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Universitat Autònoma de Barcelona

Facultat de Medicina

Departament de Pediatria, d'Obstetrícia i Ginecologia, i de Medicina Preventiva

"Maneig farmacològic del dolor agut a urgències. Compendi d'evidències"

TESI DOCTORAL

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Doctorat en Salut Pública i Metodologia de la Recerca Biomèdica

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Xavier Basurto Oña

Memòria de Tesi presentada per Xavier Basurto Oña per optar al grau de Doctor en Medicina per la Universitat Autònoma de Barcelona i realitzada sota la direcció del Dr. Xavier Bonfill i Cosp.

Barcelona, Setembre 2014

Agraïments

A tots els professionals del Centre Cochrane Iberoamericà per l'oportunitat, el temps i l'esforç dedicat a les publicacions presentades en aquesta tesi.

A la Laura Robles Perea.

ÍNDEX

- *Basurto Ona X, Uriona Tuma SM, Martínez García L, Solà I, Bonfill Cosp X. Drug therapy for preventing post-dural puncture headache. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD001792. DOI: 10.1002/14651858.CD001792.pub3.*
http://www.update-software.com/BCP/WileyPDF/EN/CD001792.pdf

- *Basurto Ona X, Martínez García L, Solà I, Bonfill Cosp X. Drug therapy for treating post-dural puncture headache. Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD007887. DOI: 10.1002/14651858.CD007887.pub2.*
http://www.update-software.com/BCP/WileyPDF/EN/CD007887.pdf

- *Basurto Ona X, Rigau Comas D, Urrútia G. Opioids for acute pancreatitis pain. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD009179. DOI: 10.1002/14651858.CD009179.pub2.*
http://www.update-software.com/BCP/WileyPDF/EN/CD009179.pdf

1.- RESUM

1.- RESUM

Antecedents

La medicina d'urgències és un camp de la medicina clínica d'importància creixent al nostre sistema sanitari actual, convertint-se en una porta d'accés al sistema sanitari de primera magnitud. El dolor agut als serveis d'urgències suposa un repte important pels professionals sanitaris donada l'elevada prevalença, l'etiologia multifactorial, la percepció subjectiva, la dificultat en l'avaluació clínica, la monitorització i la variada oferta d'arsenal terapèutic farmacològic i no farmacològic. Ferides, contusions, esquinços, lumbàlgia, cervicàlgia, dolor abdominal, fractures, luxacions i la cefalea, representen el 50% de les causes de dolor en un servei d'urgències. La cefalàlgia per punció dural i el dolor abdominal de la pancreatitis aguda són dues de les entitats que cursen amb dolor agut presents als serveis d'urgències. Amb excessiva freqüència el maneig del dolor a urgències no és prou satisfactori per al pacient i una de les possibles raons és la manca de coneixement científic existent a mans dels actors implicats en el maneig del dolor agut.

Mètodes

S'han portat a terme tres revisions sistemàtiques seguint la metodologia Cochrane amb l'objectiu d'identificar i avaluar els beneficis i riscs dels fàrmacs emprats en la prevenció i tractament el dolor agut. 1) Fàrmacs per a la prevenció de la cefalàlgia per punció dural, 2) Fàrmacs per al tractament de la cefalàlgia per punció dural i 3) Opioides per a la pancreatitis aguda.

Resultats

1) En la prevenció de la cefalàlgia per punció dural, la morfina epidural, la cosintropina intravenosa i l'administració intravenosa d'aminofil·lina, redueixen el risc de cefalàlgia amb un NNT de 2,8 (IC95% 1,7-7,9), 3,1 (IC95% 1,9-7,3) i 5,5 (IC95% 3,3-15,9) respectivament, especialment en aquells pacients d'alt risc com són les gestants amb anestèsia espinal durant el part.

2) En el tractament de la cefalàlgia per punció dural, la cafeïna intravenosa redueix la persistència de cefalàlgia i la necessitat d'altres intervencions complementàries; NNT de 1,6 (IC95% 1,2-2,7). La gabapentina oral, la teofil·lina oral i la hidrocortisona intravenosa redueixen la intensitat del dolor agut en 2-3 punts sobre 10.

3) En el tractament amb opioides del dolor abdominal de la pancreatitis aguda, la morfina subcutània i la pentazocina intravenosa, disminueixen la necessitat d'altres mesures analgèsiques complementàries; NNT de 2,4 (IC95% 1,7-3,7).

1.- RESUM

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Discussió

Les revisions sistemàtiques presentades en aquesta tesi han intentat, seguint una metodologia rigorosa i sistemàtica, identificar les investigacions disponibles sobre el tema que s'està estudiant i sintetitzar els resultats dels estudis inclosos.

Una de les principals limitacions identificades en aquestes revisions sistemàtiques són l'escàs número d'estudis inclosos en cada revisió; un total de 22 assajos clínics en les 3 revisions. L'escàs nombre de participants en els assajos és una altre limitació; un total de 2043 persones en les 3 revisions amb una mediana de 55 participants. Una pobre qualitat en la publicació dels assajos en limita l'avaluació del risc de biaix. També l'heterogeneïtat clínica entre estudis dificulta el procés de síntesi de resultats.

Conclusions

En relació al tractament farmacològic del dolor a urgències, s'incorpora nou coneixement científic disponible per al personal sanitari sobre el benefici i risc de diferents estratègies farmacològiques per a dues entitats que cursen amb dolor agut; la cefalàlgia per punció dural i la pancreatitis aguda.

- ✓ La morfina epidural, la cosintropina intravenosa i l'administració intravenosa d'aminofil·lina redueixen el risc de cefalàlgia per punció dural, especialment en pacients d'alt risc.

- ✓ La cafeïna intravenosa redueix la persistència de cefalàlgia per punció dural i la necessitat d'altres intervencions complementàries. La gabapentina oral, la teofil·lina oral i la hidrocortisona intravenosa disminueixen la intensitat del dolor agut.

- ✓ La morfina subcutània i la pentazocina intravenosa, disminueixen la necessitat d'altres mesures analgèsiques complementàries en el tractament del dolor abdominal de la pancreatitis aguda.

- ✓ S'aconsella als investigadors que en futurs assajos clínics utilitzin variables de resultat clínicament rellevants i amb definicions estandarditzades que permetin fer síntesi de resultats en futures revisions.

- ✓ Es recomana als futurs investigadors d'assajos a utilitzar una grandària de mostra suficient per a donar resposta a les hipòtesis plantejades.

- ✓ S'aconsella a tots els investigadors a seguir les directrius de la declaració CONSORT per millorar la qualitat de la publicació d'assajos clínics, facilitant-ne la lectura crítica i l'avaluació més acurada del risc de biaix.

- ✓ S'anima als autors de revisions sistemàtiques a utilitzar el sistema GRADE per classificar la qualitat de l'evidencia i poder elaborar les recomanacions amb més rigor.

1.- RESUMEN

Antecedentes

La medicina de urgencias es un campo de la medicina clínica de importancia creciente en nuestro sistema sanitario actual, convirtiéndose en una puerta de acceso al sistema sanitario de primera magnitud. El dolor agudo en los servicios de urgencias supone un reto importante para los profesionales sanitarios dada la elevada prevalencia, la etiología multifactorial, la percepción subjetiva, la dificultad en la evaluación clínica, la monitorización y la variada oferta de arsenal terapéutico farmacológico y no farmacológico. Heridas, contusiones, esguinces, lumbago, cervicalgia, dolor abdominal, fracturas, luxaciones y la cefalea, representan el 50% de las causas de dolor en un servicio de urgencias. La cefalea pospunción de la duramadre y el dolor abdominal de la pancreatitis aguda son dos de las entidades que cursan con dolor agudo presentes en los servicios de urgencias. Con excesiva frecuencia el manejo del dolor en urgencias no es suficientemente satisfactorio para el paciente y una de las posibles razones es la falta de conocimiento científico existente en manos de los actores implicados en el manejo del dolor agudo.

Métodos

Se han llevado a cabo tres revisiones sistemáticas siguiendo la metodología Cochrane con el objetivo de identificar y evaluar los beneficios y riesgos de los fármacos utilizados en la prevención y tratamiento del dolor agudo. 1) Fármacos para la prevención de la cefalea pospunción de la duramadre, 2) Fármacos para el tratamiento de la cefalea pospunción de la duramadre y 3) Opioides para la pancreatitis aguda.

Resultados

1) En la prevención de la cefalea pospunción de la duramadre, la morfina epidural, la cosintropina intravenosa y la administración intravenosa de aminofilina, reducen el riesgo de cefalea con un NNT de 2,8 (IC95% 1,7-7,9), 3,1 (IC95% 1,9-7,3) y 5,5 (IC95% 3,3-15,9) respectivamente, especialmente en aquellos pacientes de alto riesgo como son las gestantes con anestesia espinal durante el parto.

2) En el tratamiento de la cefalea pospunción de la duramadre, la cafeína intravenosa reduce la persistencia de cefalea y la necesidad de otras intervenciones complementarias; NNT de 1,6 (IC95% 1,2-2,7). La gabapentina oral, la teofilina oral y la hidrocortisona intravenosa reducen la intensidad del dolor agudo en 2-3 puntos sobre 10.

3) En el tratamiento con opioides del dolor abdominal de la pancreatitis aguda, la morfina subcutánea y la pentazocina intravenosa, disminuye la necesidad de otras medidas analgésicas complementarias; NNT de 2,4 (IC95% 1,7-3,7).

Discusión

Las revisiones sistemáticas presentadas en esta tesis han intentado, siguiendo una metodología rigurosa y sistemática, identificar las investigaciones disponibles sobre el tema que se está estudiando y sintetizar los resultados de los estudios incluidos.

Una de las principales limitaciones identificadas en estas revisiones son el escaso número de estudios incluidos en cada revisión; un total de 22 ensayos en las 3 revisiones. El escaso número de participantes en los ensayos es otra limitación; un total de 2.043 personas en las 3 revisiones con una mediana de 55 participantes. Una pobre calidad en la publicación de los ensayos limita la evaluación del riesgo de sesgo. También la heterogeneidad clínica entre los estudios dificulta el proceso de síntesis de resultados.

Conclusiones

En relación al tratamiento farmacológico del dolor en urgencias, se incorpora nuevo conocimiento científico disponible para el personal sanitario sobre el beneficio y riesgo de diferentes estrategias farmacológicas para dos entidades que cursan con dolor agudo; la cefalea pospunción de la duramadre y la pancreatitis aguda.

- ✓ La morfina epidural, la cosintropina intravenosa y la administración intravenosa de aminofilina reducen el riesgo de cefalea pospunción de la duramadre, especialmente en pacientes de alto riesgo.

- ✓ La cafeína intravenosa reduce la persistencia de cefalea pospunción de la duramadre y la necesidad de otras intervenciones complementarias. La gabapentina oral, la teofilina oral y la hidrocortisona intravenosa disminuye la intensidad del dolor agudo.

- ✓ La morfina subcutánea y la pentazocina intravenosa, disminuye la necesidad de otras medidas analgésicas complementarias en el tratamiento del dolor abdominal de la pancreatitis aguda.

- ✓ Se aconseja a los investigadores que en futuros ensayos clínicos utilicen variables de resultado clínicamente relevantes y con definiciones estandarizadas que permitan hacer síntesis de resultados en futuras revisiones.

- ✓ Se recomienda a los futuros investigadores de ensayos clínicos a utilizar un tamaño de muestra suficiente para dar respuesta a las hipótesis planteadas.

- ✓ Se aconseja a todos los investigadores a seguir las directrices de la declaración CONSORT para mejorar la calidad de la publicación de ensayos clínicos, facilitando la lectura crítica y la evaluación más precisa del riesgo de sesgo.

- ✓ Se anima a los autores de revisiones sistemáticas a usar el sistema GRADE para clasificar la calidad de la evidencia y poder elaborar las recomendaciones con más rigor.

1.- ABSTRACT

Background

Emergency medicine is a field of clinical medicine increasingly important in our current healthcare system, becoming a gateway to the health system of the first order. Acute pain in emergency services represents a major challenge for health professionals given the high prevalence, multifactorial etiology, subjective perception, difficulty in clinical assessing, monitoring and varied range of pharmacological and non-pharmacological armamentarium. Wounds, bruises, sprains, back pain, neck pain, abdominal pain, fractures, dislocations and headache, represent 50% of the causes of pain in an emergency department. The post-dural puncture headache and the abdominal pain of acute pancreatitis are two entities with acute pain presents to the emergency services. Too often pain management is not satisfactory to the emergency patient and one of the possible reasons is the lack of existing scientific knowledge in the hands of those involved in the management of acute pain.

Methods

Carried out three systematic reviews using the Cochrane methodology in order to identify and evaluate risks and benefits of drugs used to prevent and treat acute pain. 1) Drugs for preventing post-dural puncture headache, 2) Drugs for treating post-dural puncture headache and 3) Opioids for acute pancreatitis.

Results

1) In the prevention of post-dural puncture headache, epidural morphine, intravenous cosyntropin and the intravenous aminophylline, reduce the risk of headache with a NNT of 2,8 (95%CI 1,7-7,9), 3,1 (95%CI 1,9-7,3) and 5,5 (95%CI 3,3-15,9) respectively, particularly in high-risk patients such as pregnant women with spinal anesthesia during labor.

2) In the treatment of post-dural puncture headache, intravenous caffeine reduces the persistence of headache and the need for other complementary interventions; NNT of 1,6 (95%CI 1,2-2,7). Oral gabapentin, oral theophylline and intravenous hydrocortisone reduced the intensity of acute pain in 2-3 out of 10.

3) In the treatment of abdominal pain from acute pancreatitis with opioids, subcutaneous morphine and intravenous pentazocine, reduce the need for other measures complementary analgesic; NNT of 2,4 (95%CI 1,7-3,7).

Discussion

Systematic reviews presented in this thesis have attempted, following a rigorous and systematic methodology, to identify the available research on the topic being discussed and summarize the results of the included studies.

One of the main limitations identified in these systematic reviews are the limited number of studies included in each review; 22 trials in 3 reviews. The small number of participants in trials is another limitation; 2043 people in 3 reviews with a median of 55 participants. Poor quality publishing trials limits the risk assessment bias. Also the clinical heterogeneity between studies difficults the process of synthesizing the results.

Conclusions

Regarding the pharmacological treatment of pain in the emergency department, new scientific knowledge is available to the medical staff on the benefits and risks of different pharmacological strategies for both entities that present with acute pain; the post-dural puncture headache and acute pancreatitis.

- ✓ The epidural morphine, intravenous cosyntropin and intravenous aminophylline reduce the risk of post-dural puncture headache, especially in high-risk patients.

- ✓ Intravenous caffeine reduces the persistence of post-dural puncture headache and the need for other complementary interventions. Oral gabapentin, oral theophylline and intravenous hydrocortisone reduced the intensity of acute pain.

- ✓ Subcutaneous morphine and intravenous pentazocine, reduce the need for other complementary analgesic in the treatment of abdominal pain from acute pancreatitis.

- ✓ It is recommended that researchers in future clinical trials use a clinically relevant outcomes and standardized definitions that allow synthesis of results in future reviews.

- ✓ It is recommended that future researchers use a sample size sufficient to respond to the hypotheses.

- ✓ It is recommended to all researchers to follow the CONSORT statement to improve the quality of publication of clinical trials, facilitating critical reading and more accurate assessment of risk of bias.

- ✓ The review authors are encouraged to use the GRADE system in order to classify the quality of the evidence and to develop recommendations with more rigor.

2.- INTRODUCCIÓ

2.- INTRODUCCIÓ

2.1.- El dolor agut a urgències

La medicina d'urgències és un camp de la medicina clínica d'importància creixent al nostre sistema sanitari actual, i possiblement a la resta del món occidental. Els motius d'aquest progressiu creixement i desenvolupament dels serveis d'urgències són multifactorials: han augmentat les plantilles de professionals dedicats, ha millorat la qualificació acadèmica d'aquest professionals, les infraestructures han crescut i s'han modernitzat i també el nivell tecnològic emprat es molt més elevat. Tot això ha permès ampliar el ventall de tècniques, procediments, diagnòstics i tractaments que es realitzen a urgències, amb el conseqüent augment de la capacitat resolutiva aconseguida. Això podria estar relacionat amb un altre dels motius fonamentals del creixement global de la medicina d'urgències i emergències, que és la concepció i ús per part dels ciutadans. La facilitat d'accés (atenció ininterrompuda les 24 hores del dia, tot l'any), la disponibilitat immediata, la capacitat resolutiva i a la seva gratuïtat universal, facilita que els serveis d'urgències s'hagin convertit en una porta d'accés al sistema sanitari de primera magnitud per una part important de la societat. A Catalunya, durant el 2012 el 31,7% (IC95% 30,4-33,0) de la població general ha visitat o consultat un servei d'urgències en els darrers 12 mesos (1).

El dolor agut als serveis d'urgències suposa un repte important pels professionals sanitaris i per la medicina en general. L'elevada prevalença, l'etiologia multifactorial, el seu caràcter subjectiu, la dificultat en l'avaluació clínica, la monitorització periòdica i la variada oferta d'arsenal terapèutic farmacològic i no farmacològic, converteixen el dolor agut en un dels símptomes més complexes pel que fa a la seva prevenció, avaluació i tractament.

Anys enrere, el dolor s'acceptava com una situació inevitable i era freqüent la resignació, tant per al professional sanitari com per al pacient, quan el maneig resultava subòptim. Actualment el maneig del dolor és concebut com un dret humà fonamental i part integral de la pràctica mèdica moderna, ètica, cost-efectiva i centrada en el pacient (2).

El dolor és una experiència individual i multifactorial, influenciada per la cultura, les experiències anteriors de dolor, les creences, l'estat d'ànim i la capacitat individual per a fer-hi front. La definició de dolor més acceptada actualment és la de la *International Association for the Study of Pain* (IASP), que va definir el dolor com

"una experiència sensorial i emocional desagradable associada amb dany tissular real o potencial o descrita en termes d'aquesta lesió" (3). Amb la creació de la IASP el 1974, es va impulsar l'abandonament del concepte unidimensional del dolor i es va produir un apropament al concepte multidisciplinari. El dolor és per definició una experiència subjectiva (2)*,* i per tant variable, igual que serà variable la resposta al maneig d'aquest dolor. Es important que els clínics i els investigadors tinguin en compte els factors físics (somàtics), psicològics i contextuals (situació i cultura), en el maneig (avaluació i tractament) del dolor. Aquest mateix organisme, la IASP, va impulsar la Declaració de Montreal del 2010 (4), on representants de més de 60 països van acordar una sèrie de drets per les persones amb dolor; drets humans universals, que obliga als governs, les institucions sanitàries i als professionals de la salut a seguir unes recomanacions per garantir l'accés de les persones a un correcte maneig del dolor.

Quan aquest dolor percebut per una persona és de caràcter agut, es defineix com aquell dolor de recent començament, de probable durada limitada i que en general té una relació temporal i causal identificable amb una lesió o malaltia. Dolor agut i crònic s'haurien d'interpretar com un contínuum i no com entitats independents. El dolor agut és el símptoma més freqüent referit a urgències. S'estima que en el 78-86% (5) dels pacients que consulten a un servei d'urgències, el dolor es el principal motiu de consulta. Aquest dolor agut, que ha motivat a una persona a consultar a un servei d'urgències pot estar ocasionat o desencadenat per múltiples causes: ferides, contusions, esquinços, lumbàlgia, cervicàlgia, dolor abdominal, fractures, luxacions i la cefalea, representen aproximadament el 50% de les causes de dolor que es consulten en un servei d'urgències, tal i com es pot veure a la taula 1.

Taula 1. Principals diagnòstics a l'alta d'urgències relacionats amb el dolor (6)

	N (%)
Wound, abrasion or contusion	91 (11)
Sprain or strain	90 (11)
Back or neck pain	85 (10)
Abdominal pain	71 (9)
Fracture or dislocation	48 (6)
Headache	47 (6)
Chest pain (noncardiac)	40 (5)
Upper respiratory infection	30 (4)
Abscess or cellulitis	25 (3)
Toothache	19 (2)
Urinary tract infection	16 (2)
Renal colic	14 (2)
Other diagnoses	243 (30)
Total with ICD-9 diagnosis	819 (100)

Maneig efectiu del dolor agut

El maneig efectiu del dolor a urgències requereix, per part del professional sanitari, molt més que el simple domini dels fàrmacs analgèsics. Per un correcte i efectiu maneig del dolor es necessari seguir les següents 3 fases consecutives (2,7):

a. Avaluació clínica del dolor

b. Administració d'analgèsia

c. Reavaluació constant i periòdica

a. Avaluació clínica del dolor

L'avaluació clínica del dolor cal fer-la seguint un model biopsicosocial, ja que tant els aspectes fisiològics, psicològics com ambientals poden influir en l'experiència de dolor agut. Aquesta valoració integral del dolor és important per un maneig posterior segur, efectiu i individualitzat. Ens permet identificar la causa del dolor i discriminar entre dolor somàtic, visceral o neuropàtic per tal de seleccionar el tractament analgèsic més adequat. L'avaluació del dolor ha d'incloure l'anamnesi, l'exploració física i la història del dolor.

Com s'ha comentat anteriorment, el dolor és una experiència individual i subjectiva modulada per factors fisiològics, psicològics i ambientals: experiències prèvies, la cultura, el pronòstic, la por i l'ansietat són factors que jugaran un paper molt important en la percepció individual del dolor (8,9). Donades aquestes característiques, la manera més habitual de mesurar el dolor és utilitzant sistemes autoinformats per al pacient, com les escales o qüestionaris. Altres eines o sistemes que poden aportar informació sobre el dolor que experimenta una persona i que en ocasions cal tenir en compte són: les respostes hormonals (p.ex. concentració de cortisol plasmàtic), l'alteració en el comportament (p.ex. l'expressió facial), les manifestacions funcionals (p.ex. la tos o el caminar), la neuroanatomia o neurofisiologia del dolor (p.ex. imatges d'una tomografia per emissió de positrons, una ressonància magnètica funcional, un SPECT o un electroencefalograma) o les alteracions fisiològiques (p.ex. la freqüència cardíaca) (10,11). Aquests altres sistemes ens poden aportar informació important o complementària a les escales o qüestionaris autoinformats.

Les escales utilitzades per a mesurar el dolor han de ser apropiades a cada pacient i per això cal considerar factors com l'estat cognitiu, el llenguatge, l'estat de desenvolupament i els factor culturals (2). La majoria d'escales utilitzades a la pràctica clínica mesuren la intensitat del dolor, tot i que hi ha escales que mesuren el grau d'alleugeriment del dolor després d'una intervenció. Aquestes darreres escales són menys usades a la pràctica clínica, però són molt útils quan volem comparar la resposta de diferents tractaments; p. ex. en assajos clínics, on tots els pacients parteixen d'un nivell basal "0" d'alleugeriment.

Disposem de moltes escales diferents per mesurar el dolor agut però les més freqüentment utilitzades són les unidimensionals, es a dir, aquelles que només valoren un determinat aspecte del dolor, normalment la intensitat. En aquest grup hi trobem les escales categòriques o descriptives simples, les numèriques i les

d'expressió facial (12).

Les escales categòriques o descriptives simples són les escales de descripció verbal, de tipus likert, en les quals la persona ha d'escollir aquella paraula que millor defineix la intensitat del dolor que està experimentant, p.ex.: cap, lleu, moderat o sever. Normalment cada paraula va associada a un número, p.ex.: cap=0, lleu=1, moderat=2 i sever=3 per tal de facilitar el registre i anàlisi. Són escales molt usades i es correlacionen bé amb les escales visuals analògiques (EVA). Són ràpides, senzilles i aplicables a nens, vells o persones amb deficiències visuals i amb trastorn cognitiu lleu o moderat. Com a limitació caldria dir que són menys sensibles per detectar petites diferències i els seus termes descriptors (p.ex.: no dolor, lleu, moderat, intens o insuportable) en ocasions poden ser difícils d'interpretar degut a limitacions culturals, lingüístiques o personals del pacient (13,14). En trobem diferents versions: Keele, Morrison, Dundee, Anderson i Melzack (Figura 1).

Figura 1. Escales verbals descriptives de Melzack i Keele

Les escales numèriques són possiblement més utilitzades. L'escala verbal numèrica és la més utilitzada a la pràctica clínica. Útil per l'avaluació d'adults i també per a nens a partir de 6-8 anys. Es pot ser escrita o parlada i complimentada per al propi pacient o per al personal sanitari. Una puntuació de 0/10 es considera "sense dolor" i un 10/10 "el pitjor dolor imaginable". És un eina senzilla d'administrar, consistent i amb bona correlació amb les EVA. És una escala categòrica i per tant en el seu anàlisi estadístic es faran servir proves no paramètriques.

L'EVA o escala visual analògica (15), és la més utilitzada en recerca. També es pot usar per mesurar altres aspectes del dolor, com els components afectius, la satisfacció dels pacients, efectes secundaris... Els seus mínims i màxims van de 0 a 100. El valor referit per la persona (0-100) pot categoritzar-se en 4 nivells: no dolor (0-5), lleu (5-44), moderat (45-74) i sever (>74). Una reducció del voltant de 30 punts sobre 100 (IC95% 36,4-23.6) en l'EVA es pot considerar una disminució d'intensitat

de dolor clínicament significativa i percebuda per al pacient com un adequat control del dolor en un servei d'urgències (16). A la literatura científica trobem discòrdia en el fet de considerar si es tracta d'una escala ordinal o no; la recomanació més acceptada és tractar-la com una escala ordinal, i per tant, en l'anàlisi estadístic caldria utilitzar proves no paramètriques. Aquesta recomanació no es segueix de manera generalitzada. És relativament simple d'utilitzar per la persona avaluada, ràpida i evita la imprecisió de les escales descriptives (17), però requereix concentració i coordinació per part de la persona entrevistada. Són exemples a destacar l'EVA (Figura 2), l'escala de Scott Huskinson (Figura 3), l'escala de grisos de Luesher (Figura 4) i l'escala lluminosa analògica de Nayman (Figura 5).

Figura 2. Escala visual analògica o EVA

Figura 3. Escala de Scott Huskinson. Obtingut de: www.fisioterapiasinred.com. Data: 07/07/2014
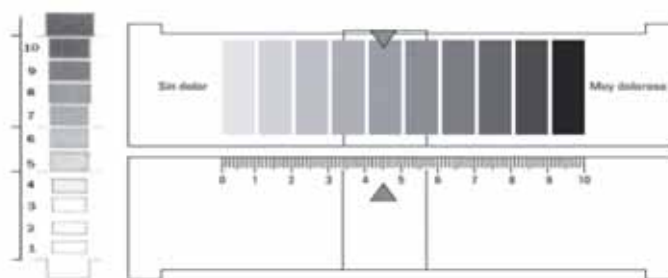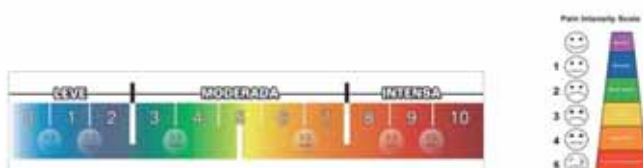

Figura 4. Escala de grisos de Luesher. Obtingut de: www.fisioterapiasinred.com. Data: 07/07/2014

Figura 5. Escala lluminosa analògica (Nayman). Obtingut de: www.fisioterapiasinred.com. Data: 07/07/2014

Disposem de moltes altres eines per a mesurar la intensitat del dolor, com la d'expressió facial i la d'impressió de milloria global del pacient. Les d'expressió facial són molt útils en nens entre 3 i 7 anys i que siguin col·laboradors però també es poden usar en adults (18).

Figura 6. Escala d'expressió facial de Wong-Baker. Obtingut de http://www.nursingconsult.com. Data: 07/07/2014

L'escala d'impressió de milloria global del pacient, en anglès *Patient Global Impression of Improvement Scale* (PGI-I), consisteix en una sola pregunta en la qual es sol·licita al pacient que classifiqui l'alleugeriment obtingut amb el tractament segons una escala de Likert de set punts. Es consideren tractaments "amb èxit" si responen "Moltíssim millor" o "Molt millor". Totes les altres opcions de resposta es defineixen com fallada de tractament.

Figura 7. Patient Global Impression of Improvement Scale (PGI-I). Obtingut de http://sedolor.es. Data: 07/07/2014

La majoria d'escales utilitzades a la practica clínica estan centrades en avaluar la intensitat del dolor percebuda per al pacient, són unidimensionals com s'ha comentat, ja que no tenen en compte altres aspectes importants del dolor, com són la freqüència d'aparició, la localització o l'afectació en les activitats quotidianes. Però també existeixen diferents eines de caràcter multidimensionals per a mesurar el dolor. Una de les més usades és el Qüestionari Breu del Dolor, en anglès *Wisconsin Brief Pain Inventory* (BPI) (19,20) que mesura la intensitat del dolor i la discapacitat que produeix, referint-se al dolor experimentat en les darreres 24 hores. També s'utilitza el Qüestionari de McGill, en anglès McGill Pain Questionnaire (MPQ), creat per Melzack el 1975 i validat en espanyol per Masedo el 2000 i Lázaro el 1994

(21,22). És una de les eines més usades per avaluar el dolor, en la qual a més de valorar la intensitat d'aquest, es procura fer una avaluació multidimensional de l'experiència dolorosa fent una descripció verbal de les característiques del dolor.

En el camp de la recerca, per exemple en un assaig clínic, s'utilitzen diferents mesures de resultat per expressar l'efecte d'una intervenció analgèsica sobre la intensitat del dolor percebut pels participants a l'estudi (23), com són:

- o Grau o intensitat de l'efecte analgèsic

  Es pot expressar com la diferència d'intensitat o d'alleugeriment del dolor entre abans i després de la intervenció. En ocasions també pot expressar-se com la necessitat de dosis d'analgèsia de rescat durant un període de temps determinat.

- o Temps fins aconseguir un efecte analgèsic

  Temps fins aconseguir un efecte analgèsic concret predeterminat o fins aconseguir l'efecte analgèsic màxim.

- o Duració del efecte

  Temps fins que el dolor torna a estar al 50% o 100% del dolor basal o el temps transcorregut fins que el pacient sol·licita analgèsia de rescat.

- o Nombre de persones que cal tractar o NNT, de l'anglès *"number needed to treat"*

  És el número de pacients que cal tractar per aconseguir com a mínim un 50% de reducció de dolor en un pacient durant 4-6 hores, comparat amb placebo (23). Es calcula 1/P1-P2, on P1 és la proporció de pacients amb un 50% mínim de reducció de dolor amb analgèsics i P2 és la proporció de pacients amb un 50% mínim de reducció de dolor amb la intervenció de control.

Altres variables de resultat que podrien ser rellevants de mesurar per avaluar el dolor d'una manera multidimensional, sobretot en un projecte d'investigació, són:

- o Estat funcional del pacient

  Avaluar el son, la ingesta alimentària, les activitats de la vida diària o les activitats d'oci entre d'altres mesures de l'estat funcional del pacient. Per aquesta finalitat es poden utilitzar escales com la *Short Form 36 of Medical Outcomes Study* (SF-36) o la *Quality of life* (QOL).

- o Estat emocional

  Avaluar els efectes del dolor a curt termini (angoixa, depressió,

irritabilitat) i a llarg termini (pèrdua d'autoconfiança o estrès posttraumàtic).

  o Esdeveniments adversos dels fàrmacs analgèsics

    Avaluar els tipus d'efectes adversos identificats en els estudis, amb la seva freqüència, intensitat o gravetat. Es pot expressar de manera similar al NNT, però en aquesta ocasió amb el nombre necessari per danyar, de l'anglès *"number needed to harm"* o NNH.

b. Administració d'analgèsia

Un cop avaluat el dolor, com a mínim la seva intensitat, i abans d'iniciar qualsevol intervenció analgèsica, és important determinar la causa del dolor ja que això pot condicionar la selecció del fàrmac més adequat. El maneig del dolor ha de respondre a una estratègia individualitzada, multidimensional, revisada periòdicament i no només a l'administració de fàrmacs. Els fàrmacs es seleccionaran de manera racional segons l'Escala Analgèsica de la OMS (24) (Figura 8). Aquesta escala determina el grup de fàrmacs més adequat segons la intensitat del dolor.

Figura 8. Escala analgèsica de la OMS

Per un correcte maneig del dolor no s'hauria d'oblidar mai les mesures analgèsiques no farmacològiques. Un ambient tranquil i calmat a urgències junt amb unes tècniques psicològiques en el moment adequat, p.ex. la distracció, poden tenir un efecte beneficiós en un moment puntual. Que el professional sanitari mantingui una bona comunicació amb el pacient durant la seva assistència, p.ex. explicant les causes d'aquest dolor amb els efectes beneficiosos i perjudicials de l'analgèsia administrada, també pot contribuir a un millor maneig del dolor. Tècniques com la immobilització, l'elevació de la zona afectada i l'aplicació tòpica de fred, s'utilitzen freqüentment a la pràctica mèdica com a mesura analgèsica no farmacològica.

c. Reavaluació constant i periòdica (2,7)

De manera periòdica, caldrà avaluar la resposta al tractament analgèsic administrat mitjançant la intensitat del dolor o el grau d'alleugeriment d'aquest, l'impacte funcional i els efectes adversos del tractament. Aquesta avaluació periòdica ens ha de permetre modificar el tractament, en funció de la resposta inicial i posterior, per tal d'aconseguir un maneig més efectiu del dolor agut.

Realitat actual del maneig del dolor agut

El dolor es pot considerar com a dolor sever quan aquest rep una puntuació ≥7/10 per part del pacient (7). Tot i que el dolor a urgències sol ser d'intensitat servera, alguns estudis estimen una mediana de 8/10 (6), només el 15% d'aquests pacients que consulten a un servei d'urgències són tractats amb opioides. Això no és tot, aquesta analgèsia necessària es administrada tard amb excessiva freqüència, amb una mediana de 90 minuts des de l'ingrés a urgències. Només un 29% dels pacients que necessiten analgèsia, la reben durant la primera hora d'ingrés a urgències i es calcula que el 41% dels pacients visitats a urgències per dolor, aquest símptoma no ha disminuït al moment de l'alta. Només un 50% pels pacients experimenten un descens de ≥2 punts en una escala numèrica, que es considera com el mínim descens clínicament significatiu segons (6). Totes aquestes dades ens indiquen que amb excessiva freqüència el maneig del dolor a urgències no és tan satisfactori com caldria esperar (25).

És important tenir en compte la importància i les conseqüències d'aquest maneig subòptim del dolor. Immediatament després d'una lesió, un traumatisme, una intervenció quirúrgica, és a dir, qualsevol situació que pugui desencadenar dolor a la persona, l'organisme respondrà de manera sistèmica a aquesta lesió (Figura 9 i Taula 2). El dolor agut és un més dels factors que desencadenen la cascada metabòlica, humoral, neural i bioquímica que donaran lloc a la resposta lesional. La magnitud i duració del dolor està associat a la magnitud i duració d'aquesta resposta lesional sistèmica. Una intervenció efectiva sobre el dolor agut podria modificar aquesta associació (2).

Figura 9. Desencadenants de la resposta lesional (7)

Figure 1.2   The injury response

		Injury response
Postoperative pain	Acute phase 'cytokines' (eg Interleukins 1,6)	Inflammation
Surgical trauma	Neural	Hyperalgesia
Psychological, environmental and social factors	Humoral	Catabolism
Other factors (eg drugs)	Metabolic	Other systemic adaptations
	Immune	Physical, mental deactivation

Note: Pain is only one of the factors, including psychological and environmental factors, that trigger complex intermediates (neural, humoral etc) leading to the 'injury response'. Thus acute pain and the injury response are inevitably inter-related. The end result is physical and mental deactivation.

Source: *Acute Pain Management: the Scientific Evidence* (NHMRC 1999); © Commonwealth of Australia, reproduced with permission.

Taula 2. La resposta sistèmica, metabòlica i endocrina (7)

Table 1.6   Metabolic and endocrine responses to injury

Endocrine	↑ Catabolic hormones	↑ ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons, IL-1, TNF, IL-6
	↓ Anabolic hormones	↓ Insulin, testosterone
Metabolic		
carbohydrate	Hyperglycaemia, glucose intolerance, insulin resistance	↑ Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids)
		↓ Insulin secretion/activation
protein	Muscle protein catabolism, ↑ synthesis of acute phase proteins	↑ Cortisol, adrenaline, glucagons, IL-1, IL-6, TNF
lipid	↑ Lipolysis and oxidation	↑ Catecholamines, cortisol, glucagon, growth hormone
Water and electrolyte flux	Retention of water and sodium, ↑ excretion of potassium and ↓ functional ECF with shifts to ICF	↑ Catecholamine, aldosterone, ADH, cortisol, angiotensin II, prostaglandins and other factors

Note: ACTH: adrenocorticotrophic hormone; ADH: antidiuretic hormone; ECF: extracellular fluid; ICF: intracellular fluid; IL: interleukin; TNF: tumour necrosis factor.

Source: *Acute Pain Management: the Scientific Evidence* (NHMRC 1999); copyright Commonwealth of Australia, reproduced with permission.

És possible que en cas de que el dolor sigui persistent, a través de mecanismes psicològics, pugui alterar-se la percepció del dolor. No controlar bé aquest dolor pot augmentar l'angoixa, l'insomni, la desmoralització, la sensació d'impotència, la pèrdua de control, la dificultat per interaccionar amb els altres i la pèrdua d'autonomia. Aquestes respostes psicològiques i ambientals poden condicionar la progressió a un dolor crònic (26). Un dolor infratractat pot disminuir la qualitat i l'esperança de vida i traduir-se en un cost més elevat pels sistemes de salut, cosa que ho converteix en un problema de salut pública (27).

El caràcter multifactorial del dolor fa que una gran part de l'èxit del seu maneig recaigui en la implicació de tot el personal sanitari involucrat, en la formació específica o coneixements del personal assistencial implicat i en l'organització del sistema sanitari concret que dona assistència a la persona amb dolor. Possiblement aquests tres factors siguin més importants o determinants que la pròpia tècnica analgèsica utilitzada (2,7).

Trobem molta informació i evidencies relacionades amb el tractament del dolor agut

a urgències, amb guies de pràctica clínica (GPC) que ofereixen recomanacions als professionals sanitaris. Però un dels principals problemes d'aquestes eines és la dificultat en la implementació de les seves recomanacions, i també en moltes ocasions, les limitacions observades amb molta freqüència en la qualitat metodològica de les GPC publicades (28).

Per tant, millorant tot l'entorn organitzatiu, la formació del professional sanitari i facilitant un accés a fonts de coneixement vàlides, rellevants i aplicables, p.ex. GPC elaborades seguint una sistemàtica científica (29), caldria esperar una millora en l'avaluació del dolor, el control d'aquest i la pràctica prescriptora. Si es pretén millorar el maneig actual del dolor agut, serà necessari destinar suficients recursos econòmics per implementar unitats de tractament del dolor, per la formació dels professionals sanitaris i també per a desenvolupar camps d'investigació sobre el dolor (27).

Dues de les entitats que cursen amb dolor agut que sovint hem de fer front als serveis d'urgències són la cefalàlgia per punció dural (CPPD), ja sigui amb l'objectiu de la seva prevenció com del seu tractament, i el dolor abdominal que manifesten els pacients amb una pancreatitis aguda (PA).

Cefalàlgia per punció dural

La punció lumbar (PL), tècnica invasiva que consisteix en l'extracció de líquid cefaloraquidi (LCR) penetrant a l'espai subaracnoïdal, és realitza freqüentment als serveis d'urgències amb l'objectiu d'analitzar aquest líquid i facilitar d'aquesta manera el diagnòstic de patologies potencialment greus, com la meningitis bacteriana o l'hemorràgia subaracnoïdal. La PL també es realitza per raons terapèutiques, p. ex. en l'administració de fàrmacs (antibiòtics o quimioteràpics), per l'administració de contrast radiològic o com a via d'administració de l'anestèsia regional (opioides o anestèsics locals).

Les complicacions importants d'una PL correctament realitzada són molt poc freqüents (30) i la cefalea és possiblement la més habitual (31,32). L'anomenada CPPD, es caracteritza per ser una cefalea constant que s'inicia després d'una PL i que apareix o empitjora als 15 minuts d'estar assegut o dempeus i s'alleuja en 15 minuts d'estar estirat (33,34).

Els mecanismes fisiopatològics de la CPPD no es coneixen completament. Sembla cert que la punció en la duramàter permet que el LCR surti de l'espai subaracnoïdal, el que resulta en una disminució de volum i pressió en aquest espai (35). A partir d'aquest punt són vàries les hipòtesis fisiopatològiques que s'especulen. La pèrdua de volum de LCR pot conduir a una tracció sobre estructures sensibles al dolor i aquesta tracció provocaria la cefalea (32,36–39). Alternativament, la pèrdua de LCR pot condicionar un augment en el flux sanguini cerebral, donant lloc a vasodilatació arterial i venosa, i aquesta finalment, provocar la CPPD. Una tercera explicació fa

referència al paper de la substància P, neuropèptid que actua como neuromodulador i neurotransmissor i al paper de la regulació dels receptors de la neurocinina-1 (NK1R) (40). Una altre possible mecanisme responsable d'aquest procés són l'existència d'agulles de PL amb imperceptibles defectes de fabricació que ocasionen forats a la duramàter més grans dels previstos (41).
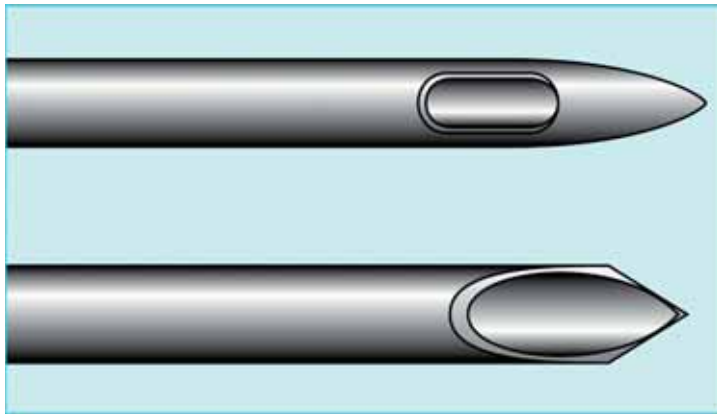
La prevalença de CPPD és molt variable i està condicionada per múltiples paràmetres, sobretot per les característiques basals de la persona i per les característiques o condicions tècniques de la PL; el calibre de l'agulla utilitzada en la PL, l'orientació de l'agulla, l'habilitat del professional sanitari i l'edat o història prèvia de CPPD són factors que condicionen el risc de desenvolupar una CPPD (42). Es presenta en un 30-50% dels pacients després d'una PL realitzada per motius diagnòstics (43–45), a menys d'un 10% com a conseqüència d'una anestèsia espinal (45,46) i fins a un 80% en cas d'una punció dural inadvertida en el curs d'una anestèsia epidural en les pacients obstètriques amb treball de part (47). El risc reportat d'una una punció dural inadvertida durant l'anestèsia epidural en població obstètrica oscil·la entre el 0,04% i el 6% (48,49). Per tant, possiblement l'analgèsia obstètrica és la principal font de pacients amb CPPD.

La clínica de la CPPD s'inicia en la majoria del casos (90%) durant els 3 primers dies després de la PL i en el 60% dels casos es resol espontàniament en 5 dies (50). Les manifestacions clíniques que acompanyen a aquest tipus de cefalea són molt variades; pot acompanyar-se de rigidesa de nuca, acúfens, pèrdua d'audició, fotofòbia o nàusees. Altres característiques com la localització del dolor o la durada són poc previsibles (50). Aquesta important variabilitat de símptomes fa que la CPPD hagi de ser considerat un diagnòstic d'exclusió. Altres diagnòstics alternatius que cal descartar són, una meningitis vírica, una sinusitis o una hemorràgia intracranial (42).

Tot i que no es tracta d'una entitat que posi en perill la vida del pacient, si que limita l'activitat física de la persona, forçant-la a enllitar-se durant dies i augmentant l'estada hospitalària i d'atenció mèdica (51). Aquesta limitació en les activitats de la vida diària pot tenir gran rellevància clínica en els cas de les dones durant el postpart. Cal destacar també la importància o les conseqüències medicolegals que pot suposar una CPPD; aquesta complicació de la PL és la tercera causa de denuncies relacionada amb l'anestèsia obstètrica (52).

En moltes ocasions, després d'una PL els professionals sanitaris posem en marxa algunes estratègies per disminuir el risc de desenvolupar una CPPD. Aquestes mesures són el repòs al llit i la hidratació oral, que tot i ser recomanacions molt habituals (53), no es disposa de proves científiques concloents sobre el seu benefici (54). Altres mesures de prevenció utilitzades a la pràctica clínica és la selecció del tipus d'agulla i el seu calibre, aconsellant-se les agulles atraumàtiques, que tenen la punta en forma de punta de llapis, i aquelles amb un menor diàmetre extern.

Figura 10. Agulles de PL atraumàtica (superior) i estàndard (inferior) (43)

En el cas d'una persona amb un diagnòstic de CPPD, el tractament inicial acostuma incloure mesures conservadores, com el repòs al llit i analgèsics. Si la CPPD continua durant més de 72 hores, pot estar indicat un tractament més específic (36) o tècniques més invasives com l'aplicació d'un pegat hemàtic epidural (PHE) (44).

Un dels principals problemes per investigar possibles noves estratègies terapèutiques i preventives de la CPPD és que encara no es coneixen amb certesa els mecanismes fisiopatològics implicats en el desenvolupament d'aquest problema de salut. Per aquesta raó és fàcil trobar un important ventall d'intervencions usades a la pràctica clínica i en els assajos clínics: els PHE per bloquejar la sortida de LCR de l'espai subaracnoïdal, mantenir al pacient en posició de decúbit pron per intentar reduir la pressió a l'espai subaracnoïdal, seroteràpia d'hidratació per augmentar la producció de LCR (36), les metilxantines, el sumatriptan i la cafeïna per augmentar la vasoconstricció dels vasos sanguinis cerebrals, o l'hormona adrenocorticotròpica (corticotropina o ACTH) (55) per augmentar el volum intravascular són algunes de les opcions farmacològiques.

L'objectiu que es pretén amb la prevenció i el tractament de la CPPD ha de ser disminuir la freqüència o prevalença de desenvolupar una CPPD després de qualsevol PL, reduir la intensitat de la cefalea tant com sigui possible en cas de no haver-se evitat la seva aparició, evitar la necessitat d'estratègies terapèutiques invasives, p.ex. el PHE, retornar a l'activitat diària habitual, reduir la durada de l'estada hospitalària i disminuir l'ocurrència d'esdeveniments adversos.

No són gaires les revisions sistemàtiques (RS) publicades per la Col·laboració Cochrane sobre la CPPD. Una d'elles tracta les estratègies de prevenció de la CPPD amb tècniques posturals i seroteràpia (54) i l'altre és sobre prevenció i tractament de la CPPD amb els PHE (56), però en aquest darrer cas la revisió ha estat retirada per manca d'actualització. També trobem dues altres revisions que estan en procés d'elaboració; una sobre la substitució del catèter epidural i tècniques de catèter intratecal (57) i l'altre sobre el diàmetre i tipus d'agulla de PL (41). En canvi, si que trobem una gran quantitat d'investigació publicada sobre el tractament farmacològic de la CPPD. La majoria d'aquests estudis publicats són petits assajos clínics i sèries de casos molt heterogenis entre ells i on s'avaluen

diversos fàrmacs: analgèsics, cafeïna, teofil·lina, sumatriptan, ACTH, morfina, clorur sòdic al 0,9% o dextrà entre altres fàrmacs (42,58).

Donada la manca d'evidències científiques rigoroses i de qualitat, resulta necessària la realització d'una RS que sintetitzi l'eficàcia i seguretat de les intervencions farmacològiques per la prevenció i tractament de la CPPD.

Una altre entitat freqüentment avaluada als serveis d'urgències que també es manifesta principalment per dolor, en aquest cas per dolor abdominal, és la PA.

Pancreatitis Aguda a Urgències

És definida com un procés inflamatori del pàncrees i és conseqüència en un 80% dels casos a litiasi biliar o al consum crònic d'alcohol (59). La majoria dels pacients acudeixen als serveis d'urgències per un quadre de dolor abdominal d'instauració ràpida, localitzat a l'hemiabdomen superior, irradiat a l'esquena i molt sovint acompanyat de nàusees i vòmits.

La PA va ser definida el 1992 al Simposi d'Atlanta (60) com un procés inflamatori agut del pàncrees que pot involucrar també els teixits adjacents i/o òrgans remots. En general s'accepta que un diagnòstic de PA requereix almenys dues de les tres característiques següents: 1) dolor abdominal característic de PA, 2) amilasa i/o lipasa en sèrum superior a tres vegades el límit superior de la normalitat i 3) troballes característiques de PA a la tomografia computada (TC) abdominal (61). La sensibilitat de la lipasa sèrica és de 96,6% i l'especificitat del 99,4%, en comparació amb una sensibilitat del 78,6% i una especificitat del 99,1% per a l'amilasa sèrica. La TC amb contrast es recomana realitzar-la en el moment de l'ingrés hospitalari per confirmar el diagnòstic de la malaltia (87-90% de sensibilitat i 90-92% d'especificitat) o després de quatre dies, per avaluar les complicacions locals i definir la gravetat del procés.

La taxa d'incidència de la PA varia entre 5 i 80 per cada 100.000 persones a l'any, amb la incidència més alta registrada en els Estats Units i Finlàndia (62). A Espanya la incidència és de 40 casos/100.000 habitants/any i pot representar fins a un 5% dels casos de dolor abdominal agut en un servei d'urgències. És una de les malalties gastrointestinals que més freqüentment requereixen ingrés hospitalari.

En el 75-80% dels casos és possible identificar l'etiologia de la PA. Als països desenvolupats, les causes més freqüents són l'obstrucció del conducte biliar per litiasis (38%) i l'abús d'alcohol (36-44%). Els mecanismes pels quals l'obstrucció del conducte biliar o el consum d'alcohol s'associen al desenvolupament de la PA són complexes i no hi ha una teoria acceptada per unanimitat. Sembla però, que un procés patològic comú estaria relacionat amb l'activació inapropiada de tripsinogen a tripsina i per una lenta eliminació de la tripsina activa a l'interior del pàncrees (63–65); és el que es coneix per la teoria de l'autodigestió. Després de la litiasi biliar i

l'alcohol, la següent causa de PA són els procediments endoscòpics, com la colangiopancreaticografia retrògrada endoscòpica (CREP); la PA n'és la complicació més freqüent i la seva prevalença s'estima entre un 1-10% dels pacients sotmesos a una CREP. Altres causes menys freqüents de pancreatitis són els nivells elevats de triglicèrids, càncer, infeccions víriques i bacterianes, cirurgia, úlceres pèptiques, pàncrees divisum, medicaments i altres causes genètiques, metabòliques i autoimmunes. Entre un 10-20% de les PA són idiopàtiques (66)

El dolor abdominal és el símptoma més comú de la PA i en general s'acompanya de nàusees, vòmits i febre. El dolor abdominal agut, constant i intens pot durar diversos dies, es localitza majoritàriament a la regió epigàstrica o hipocondri dret i sovint s'irradia a l'esquena. L'examen físic revela adoloriment abdominal superior intens, de vegades associada amb la defensa abdominal (67,68).

La majoria dels casos de PA són lleus i autolimitats, però el 20% dels casos desenvolupen una malaltia greu, amb complicacions locals, com la necrosi, el pseudoquist o l'abscés de la glàndula, i/o complicacions extrapancreàtiques (60). La seva gravetat bé determinada per les seves complicacions, ja siguin sistèmiques com la insuficiència respiratòria aguda, la insuficiència renal aguda, la disfunció multiorgànica, la sèpsia i la coagulació intravascular disseminada, o les complicacions locals, com la necrosi, l'abscés i el pseudoquist pancreàtic (69). La PA lleu es defineix com l'associada amb una disfunció mínima de l'òrgan, mentre la PA greu es va definir com l'associada a la insuficiència d'òrgans i/o complicacions locals (necrosi, abscés o pseudoquist) acompanyat de puntuacions pronòstiques adverses (61).

La mortalitat general s'estima al voltant del 2-3%, però pot arribar al 80% (70,71). Si bé la mortalitat a la necrosi pancreàtica estèril és del 10%, les necrosis pancreàtiques sèptiques tenen una mortalitat del 25%. Gairebé la meitat de la mortalitat es produeixen durant la primera setmana, el 36% en el nostre àmbit segons la tesi de Roser Farré (72) o durant la segona setmana del seu ingrés a causa d'una fallida multiorgànica per una resposta inflamatòria sistèmica. La mortalitat més enllà d'aquest període temporal també és deguda a una insuficiència multiorgànica, però en aquest cas és secundària a la necrosi pancreàtica infectada. En el nostre medi, la mortalitat de les PA d'origen biliar és del 17% mentre que la mortalitat de les PA d'origen enòlic és del 4,21%, en tractament conservador a la unitat de cures intensives (UCI), segons la tesi de Roser Farré (72).

Diverses escales de risc, generals o específiques, s'utilitzen per classificar la gravetat de la malaltia i la supervivència. Entre els sistemes més habituals trobem els criteris radiològics precoços de gravetat segons la TC abdominal dinàmica realitzada durant les primeres 72 hores d'ingrés (TC grau D o E de Balthazar), el *Computed Tomography Severity Index* (Índex de TC), els criteris de Ranson, el sistema de puntuació Imrie, el *Acut Physiology And Chronic Health Evaluation* (APACHE II) i el *Sequential Organ Failure Assessment* (SOFA) (67,68). La proteïna C reactiva (PCR) és un reactant de fase aguda que en les PA pot usar-se com a

marcador pronòstic i de gravetat. El valor de tall establert és de 150 mg/l, però valors superiors 200 mg/l indiquen una forma greu amb un 90% de precisió i es correlaciona amb el desenvolupament de complicacions, sobretot respiratòries.

El tractament de la PA depèn principalment de la gravetat de la progressió però gairebé tots casos necessiten tractament de suport, com ara analgèsics, seroteràpia, antibiòtics en cas d'infeccions documentades i suport nutricional. En la majoria de pancreatitis s'aconsella l'alimentació enteral tan aviat com sigui possible per protegir la mucosa intestinal de l'atrofia i disminuir d'aquesta manera el risc de translocació bacteriana i la conseqüent resposta inflamatòria sistèmica.

Hi ha diversos tipus d'opioides dins el grup N02A de la Classificació ATC (*Anatomic Therapeutic Chemical*). Aquest grup comprèn analgèsics opioides i analgèsics amb estructura o acció semblant. Els opioides es poden classificar per les seves accions en: agonista (p.ex. morfina, hidromorfona o fentanil), agonista parcial (p.ex. buprenorfina), agonista-antagonista (p.ex. pentazocina) i antagonistes opioides (p.ex. naloxona). Els primers, els agonistes opioides purs, són els analgèsics més potents (73). Aquests fàrmacs són analgèsics més potents que els no opioides; 650 mg de paracetamol oral o aspirina és una dosi equianalgèsica de 30 mg de codeïna, 50 mg meperidina o 5 mg de morfina via oral.

Un opioide és una substància química psicoactiva que actua mitjançant la seva unió als receptors opioides; els receptors Mu (μ) amb els subtipus Mu1 i Mu2 estimulats per agonistes opioides purs, els receptors Kappa (κ) i els Delta (δ). Aquests receptors es troben principalment en el sistema nerviós central i perifèric i en el tracte gastrointestinal. Els fàrmacs opioides produeixen analgèsia per les accions en diversos nivells del sistema nerviós, en particular, la inhibició de l'alliberament de neurotransmissors en les terminals neuronals presinàptiques a la medul·la espinal, que es considera el principal mecanisme d'acció responsable dels efectes clínics dels opioides. També actuen inhibint les neurones postsinàptiques, prevenint la transmissió ascendent del senyal de dolor

Els opioides s'utilitzen de manera habitual per tractar el dolor en la PA. No obstant això, s'ha suggerit que, a banda de la meperidina, els opioides poden emmascarar la resolució de la PA, augmentar el dolor a causa del seu efecte espasmogènic, i a conseqüència d'aquest espasme, augmentar la pressió intraluminal de l'esfínter d'Oddi (74). Aquest augment de la pressió del sistema biliar sembla estar relacionada a la dosi i la concentració plasmàtica de l'opioide i la participació del receptor Mu (μ). No obstant això, la importància clínica d'aquest augment de la pressió és incerta ja que molts estudis que han avaluat aquest fenomen són observacions anecdòtiques, amb reduït nombre de participants i sense malaltia pancreàtica coneguda; no hi ha evidència d'assajos clínics controlats que sustenti aquesta teoria (75). El tractament amb analgèsics per al dolor abdominal en la PA, probablement no modifica el curs de la malaltia o la mortalitat. No obstant això, el tractament del dolor, millora la comoditat i l'experiència subjectiva dels pacients.

Totes les persones amb dolor abdominal agut per una PA requereixen algun un tipus d'analgèsic, p. ex. paracetamol, antiinflamatoris no esteroïdals o opioides, però no s'ha demostrat cap avantatge clar per a qualsevol de les opcions analgèsiques investigades (61). Atès que no hem identificat cap metanàlisi o RS que compari els opioides contra altres fàrmacs en aquest problema de salut, resulta necessària la realització d'una RS per avaluar l'eficàcia i seguretat dels opioides per al tractament del dolor abdominal en la PA.

2.2.- L'avaluació dels tractaments i intervencions terapèutiques

La medicina basada en l'evidència

Tot i la percepció generalitzada de la medicina com la d'una ciència exacta sòlidament fonamentada en el coneixement científic, és possible que la realitat no sigui d'aquesta manera, tal com remarcava fa uns anys un article publicat a la revista *The Lancet* (76): *"la medicina clínica més aviat sembla consistir en unes poques coses que sabem, unes quantes que creiem saber (i que molt possiblement no sabem !) i moltes altres que desconeixem en absolut".* Més recentment, l'agost de 2013, a la revista *Mayo Clinic Proceedings* publicaven un article interessant (77) on després d'analitzar tots els articles sobre intervencions terapèutiques publicats a la revista *New England Journal of Medicine* durant 10 anys, del 2001 al 2010, els autors constataven que només el 38% de la pràctica mèdica habitual disposava d'evidències científiques que demostressin la seva eficàcia. Les causes d'aquesta manca de pràctica assistencial basada en clares evidències científiques és multifactorial; en part per la manca d'homogeneïtat en les recomanacions dels diferents experts, organismes o societats científiques i també per la dificultat que tenim els clínics a identificar, avaluar i utilitzar els resultats de les investigacions biomèdiques. Aportar les eines necessàries per a fer front a aquestes limitacions és l'objectiu de la Pràctica Basada en l'Evidència (PBE).

Els fonaments del que són avui en dia els assajos clínics, l'epidemiologia i l'origen de la PBE es remunten a principis del segle XIX amb Pierre Louis (78), metge francès, i posteriorment amb les reflexions d'Archie Cochrane, metge escocès, publicades el 1972 en el llibre *"Effectiveness and Efficiency: Random Reflections on Health Services"* (79) i la posterior creació de la Col·laboració Cochrane el 1993. Més recentment, amb Sackett, Haynes, Tugwell, Guyatt i altres investigadors es va elaborar i definir el concepte i definició actual de la Medicina Basada en l'Evidència (MBE) com la integració de les millors evidències de la investigació amb l'experiència clínica i els valors dels pacients. Aquest concepte queda plasmat en la tríada de la MBE (Figura 11) i en el seu procés per aplicar aquest concepte a la pràctica clínica (Taula 3).

Figura 11. *The Evidence-based Medicine Triad.* Obtingut de Florida State University, College of Medicine. Data 22/11/2012

Taula 3. Procés de pràctica de la MBE

1. *Ask*: Definir clarament el problema, fent preguntes contestables
2. *Acquire*: Buscar i aconseguir els articles necessaris
3. *Appraise*: Lectura crítica dels estudis seleccionats: Avaluar la validesa, els resultats i la seva aplicabilitat
4. *Apply*: Aplicar els coneixements adquirits segons la pròpia experiència i les preferències del pacient
5. *Assess*: Avalua els resultats d'aplicar la teva nova pràctica

A la pràctica assistencial, quan es tracta de seleccionar un tractament per criteris científics, l'assaig clínic resulta el millor disseny per avaluar els seus efectes; tant els beneficis com els riscos que comporten, de manera objectiva i amb confiança. Per aquesta objectivitat i fiabilitat, l'assaig clínic constitueix el patró d'or (*gold standard*) per a validar la utilitat de les intervencions sanitàries, ja siguin intervencions farmacològiques o d'altre tipus.

L'assaig clínic

L'assaig clínic aleatoritzat (ACA) és un experiment planificat, prospectiu i longitudinal, on comparem els efectes d'una intervenció sanitària entre grups de persones distribuïdes a l'atzar amb l'objectiu d'avaluar l'eficàcia i la seguretat d'aquestes intervencions. L'ACA es considera el mètode epidemiològic més rigorós per confirmar o descartar les hipòtesis plantejades. Per les seves propietats, és el disseny d'investigació clínica amb menys risc de biaix (80,81).

Un ACA és un experiment pel fet que es realitza una intervenció que difereix de la intervenció habitual o les condicions d'ús habituals, i a més, aquesta intervenció està

controlada o condicionada seguint les indicacions descrites en el protocol del projecte d'investigació aprovat i no segons la pràctica mèdica habitual. Si parlem d'ACA amb medicaments, la intervenció serà una substància no autoritzada com a especialitat farmacèutica o bé emprada en condicions d'ús diferents de les autoritzades. En ser un experiment, els investigadors controlen la intervenció estudiada i la intervenció de comparació, però també es controla les condicions en què s'aplica cada la intervenció. Les mesures de resultat han d'estar definides en el protocol abans d'iniciar l'assaig i registrar-les abans i després de la intervenció (82).

Tot ACA ha de seguir un protocol adequat i aprovat oficialment. Això pretén garantir la validesa científica i els drets dels participants. El Comitè Ètic d'Investigació Clínica (CEIC) de referència en cada assaig són els organismes independents encarregats de protegir els drets dels participants en els ACA i garantir les bones pràctiques ètiques i científiques dels ACA i de qualsevol estudi científic en el qual hi participen persones.

Els participants en un assaig són inclosos i posteriorment són sotmesos a un seguiment al llarg d'un període de temps predeterminat en el protocol o fins a l'aparició de l'esdeveniment que pretenem observar. Els esdeveniments que pretenem identificar encara no han ocorregut en el moment de la inclusió del participant en l'estudi ni en el moment de recollir les característiques basals dels participants inclosos en l'estudi. Per això diem que els ACA són estudis prospectius.

En un ACA és important que tots els individus que hi participen siguin distribuïts aleatòriament. Quan tots els pacients inclosos a l'estudi són assignats a l'atzar (aleatòriament) als grups d'intervenció previstos a l'estudi, s'aconsegueix que les variables pronòstiques conegudes es distribueixin de manera similar o equilibrada entre els grups, i el que és més important, que també les variables pronòstiques no conegudes o no registrades es distribueixin de manera similar. Això fa que els grups siguin comparables (sempre que el mètode d'aleatorització hagi estat correcte i el nombre de participants suficient) i que només es diferenciïn per la intervenció rebuda. Aquesta comparabilitat i el control estricte de la intervenció per part dels investigadors fa de l'ACA el millor disseny per a poder interpretar les associacions trobades com causals.

Segons l'objectiu de l'assaig, aquests es dissenyen amb un objectiu explicatiu o pragmàtic (83,84). L'explicatiu s'utilitza quan es vol avaluar noves intervencions, amb molt pocs estudis previs, on l'experiment ha d'estar molt controlat. El pragmàtic s'utilitza per posar a prova una intervenció en condicions reals, habituals; és la prova final d'una intervenció. Els límits que diferencien un ACA explicatiu d'un de pragmàtic no sempre són nítids; en moltes ocasions trobem ACA on es barregen característiques d'ambdós dissenys (Taula 4).

Taula 4. Característiques dels ACA amb disseny explicatiu i pragmàtic

	Explicatiu	Pragmàtic
Objectiu	-Eficàcia	-Efectivitat
	-Informació sobre mecanismes biològics	-Definir estratègies terapèutiques i valoracions econòmiques sanitàries
Fase desenvolupament del fàrmac	Inicial (I-II-III)	Avançada (IV)
Criteris inclusió/exclusió	Estrictes	Laxes
Àmbit de reclutament	Concret	Múltiple
Mostra	Homogènia	Heterogènia
Grandària de la mostra	Limitada	Àmplia
Seguiment	Estricte	Condicions habituals
Duració	Mínima necessària	Suficient per detectar efectes clínics importants
Validesa	Menor risc de biaix	Més risc de biaix
Generalitzable	No	Si
Mesures de resultat	-Biològiques	-Clínicament rellevants
	-Objectives	-Objectives i subjectives
Anàlisi	Per protocol	Per intenció de tractar

Tot i que l'ACA és el disseny epidemiològic considerat com a patró d'or per establir amb certa seguretat i confiança els efectes d'una intervenció, sabem que aquest disseny també implica certes limitacions, com per exemple:

- o L'elevat cost econòmic i alta complexitat organitzativa
- o Els condicionants ètics que limiten en moltes ocasions la possibilitat de realitzar determinats experiments
- o Generalització de conclusions a la població diana és limitada en moltes ocasions pels criteris d'inclusió i exclusió previstos

Les revisions sistemàtiques

Els professionals sanitaris, investigadors o gestors sanitaris així com els propis usuaris del sistema sanitari necessitem reconèixer la informació clínica rellevant sobre la qual fonamentar les seves pròpies decisions. Això no sempre resulta fàcil, bé perquè les necessitats d'informació són sempre noves i canviants, bé perquè la quantitat de la mateixa la fa difícilment manejable. En aquest sentit, l'objectiu dels professionals de la salut consistirà en identificar aquelles intervencions que permetin maximitzar la quantitat i qualitat de vida de la població. A mesura que augmenta la pressió sobre uns recursos sanitaris limitats, es fa més palesa la necessitat de racionalitzar el seu ús. No obstant això, sovint ens veurem desbordats per una quantitat d'informació impossible de manejar i que dificulta enormement aquesta tasca.

Les revisions de la literatura científica, produïdes per autoritats o experts en la matèria i àmpliament difoses en revistes i llibres de medicina, juguen avui un paper central en la pràctica clínica. Tanmateix, encara avui moltes d'aquestes revisions pateixen serioses limitacions que qüestionen els seus resultats i les conclusions que

se'n deriven, especialment en les anomenades revisions "narratives", dependents de la subjectivitat del revisor i en què no se sol explicitar els mètodes de recerca i selecció de les fonts. Entre altres limitacions, es poden destacar les següents:

- o Dificultat per identificar tots els assaigs clínics rellevants existents, resultant així un material esbiaixat (biaixos de publicació i de selecció)
- o Qualitat variable, per una baixa o desigual qualitat dels estudis originals inclosos, amb dissenys metodològics inadequats i/o escàs nombre de pacients per obtenir resultats fiables (heterogeneïtat)
- o Manca de sistematització, en no existir un protocol previ on s'estableixin de forma precisa els passos a seguir en la revisió
- o Manca de transparència, en no ser explícits els criteris que han guiat els autors en cadascuna de les seves decisions durant l'execució de la revisió, per exemple, inclusió i exclusió d'estudis
- o Manca d'actualització de les dades, quedant ràpidament obsoletes en no poder incorporar els avenços i controvèrsies que se susciten al voltant de la qüestió que s'analitza

Una possible conseqüència d'aquestes limitacions és que els clínics, en ocasions, no recomanen alguns tractaments fins i tot molts anys després que s'hagi demostrat la seva eficàcia, o per contra, continuen recomanant alguns tractaments molts anys després que s'hagi demostrat la seva ineficàcia. Com a exemple tenim el cas del tractament trombolític en els pacients amb un infart agut de miocardi. Tot i que ja en la dècada dels 70 existia una sòlida evidència científica favorable a l'eficàcia d'aquest tractament, aquesta pràctica es va demorar durant més d'una dècada fins a la seva efectiva aplicació en la pràctica clínica (85).

Per tal d'evitar aquestes limitacions pròpies de l'excés d'informació, concepte conegut com a *infoxicació*, i les limitacions pròpies de les revisions narratives esmentades prèviament, disposem del recurs de les RS. Una RS és un "estudi d'estudis" amb l'objectiu de contestar una pregunta clínica concreta i ben definida utilitzant mètodes sistemàtics i explícits. S'inicia a partir d'una recerca sistemàtica, és a dir, protocol·litzada i exhaustiva dels d'estudis per identificar tota l'evidència disponible en el moment d'iniciar la RS (86). Finalitza amb una síntesi i anàlisi de les dades obtingudes orientant-se a un enfocament pràctic. Els resultats de la revisió es poden presentar de dues formes: si una variable de resultat present en ≥2 dels ACA inclosos es poden combinar i resumir de manera conjunta, aleshores es realitza una anàlisi estadística quantitativa i s'elabora una metanàlisi de la RS. Si aquesta síntesi de resultats entre diferents ACA inclosos no és possible, es realitza una anàlisi descriptiva o també anomenat anàlisi qualitatiu sense la possibilitat de presentar els resultats mitjançant una metanàlisi (87).

Si la RS està correctament realitzada es converteix en un article científic rigorós i exhaustiu, amb intenció informativa i divulgativa, per la qual cosa haurien de ser redactades de forma explícita i clara per facilitar la lectura i comprensió. Les RS són

investigacions científiques en sí mateixes (recerca secundària o recerca sobre la recerca), amb mètodes específics preestablerts a un protocol per dur a terme l'assemblatge dels estudis originals, que sintetitzen els resultats d'aquests. Les característiques bàsiques que millor defineixen una RS es podrien resumir en les següents (88):

- o Són síntesis i anàlisis de la informació amb un enfoc pràctic
- o Es basen en la millor evidència científica disponible
- o Formulen preguntes clarament definides
- o Utilitzen mètodes sistemàtics i explícits per identificar i seleccionar els estudis pertinents, avaluar-los críticament, extraure'n les dades d'interès i analitzar-los

Conseqüentment, les RS pretenen ser:

- o Rigoroses, quant als estudis inclosos (amb criteris de qualitat)
- o Informatives, és a dir, enfocades cap a problemes reals, tractant de contestar una pregunta clarament delimitada o específica, i idealment analitzant i presentant les dades de la forma que millor ajudi a la presa de decisions
- o Exhaustives: el seu objectiu és identificar i utilitzar la major quantitat possible d'informació pertinent, sense introduir biaixos (de publicació, de selecció)
- o Explícites, ja que tots els mètodes utilitzats a la revisió han d'escriure's amb el detall suficient

El procés d'elaboració d'una RS és una tasca més complexa del que en principi podria semblar; una prova d'això són els 23 mesos de mediana que cal invertir des de la publicació del protocol de la revisió fins a la publicació final (89). Aquest procés d'elaboració el podem sintetitzar en 9 etapes successives:

1. Crear l'equip investigador
2. Fer una pregunta clínica
3. Aprovar un protocol d'investigació
4. Cerca sensible d'estudis
5. Selecció dels estudis elegibles
6. Anàlisi de la validesa dels estudis inclosos, extracció i anàlisi de dades
7. Interpretació
8. Difusió (publicació)
9. Actualització

1. Crear l'equip investigador

Abans d'iniciar qualsevol projecte investigador, és important saber si es disposa de l'equip humà necessari. L'equip mínim es compon de tres persones:

1. El clínic, que sol ser l'instigador del projecte

2. El documentalista o coordinador de cerca d'assajos, que dissenya l'estratègia de recerca electrònica en les principals bases de dades

3. L'estadista, que assessora sobre l'anàlisi quantitativa dels resultats

2. Formular la pregunta clínica

Formular la pregunta d'investigació i respondre-la es converteix en l'objectiu de la RS. És important que aquesta pregunta sigui descrita de forma precisa i explícita per tal de centrar i concretar tots els següents passos. Aquest és un punt important en tota revisió, tal i com apuntava Counsell el 1997 *"Ask a poor question and you'll get a poor review"* (90).

3. Aprovar un protocol

Com en tot projecte investigador, és vital atorgar molta importància al protocol. Iniciar una RS sense tenir clar i detallat el mètode de recerca d'estudis, els criteris d'inclusió i exclusió d'aquests, el mètode d'analitzar els possibles biaixos, l'extracció de dades i la seva posterior anàlisi i síntesi, i totes les fases i detalls en l'elaboració d'una RS, pot induir fàcilment a una RS esbiaixada. És recomanable que abans de continuar, els autors facin públic un protocol aprovat. Aquests són els quatre motius pels quals la Col·laboració Cochrane demana als autors de les seves revisions que preparin i publiquin el protocol (87):

1. Un cop el protocol està aprovat, la resta de la RS continua més fàcilment

2. El biaix es redueix

3. El protocol es sotmet a la revisió per parells que en garanteix la qualitat

4. La publicació de protocols redueix la duplicació d'esforços; qualsevol persona interessada en el mateix tema es donarà compte dels treballs en curs.

4. Cerca sensible d'estudis

Seguint el que s'ha escrit en el protocol, es procedeix a la recerca d'estudis potencialment elegibles a les fonts d'informació predeterminades i amb l'estratègia de cerca també predeterminada. Aquesta recerca ha de ser molt sensible per intentar que cap estudi elegible passi desapercebut.

5. Selecció dels estudis elegibles

Es seleccionen els articles recuperats en la recerca segons els criteris d'inclusió/exclusió preestablerts en el protocol.

6. Anàlisi de la validesa dels estudis inclosos, extracció i anàlisi de dades

Cal analitzar el risc de biaix de cada estudi inclòs, extreure la informació i analitzar-sintetitzar els resultats de tots els estudis, ja sigui mitjançant una síntesi narrativa (qualitativa) o numèrica (quantitativa).

Per analitzar el risc de biaix de cada assaig clínic inclòs en una RS, la Cochrane proposa una "*avaluació basada en dominis*" (87). Aquest mètode consisteix en que per cada estudi inclòs a la RS, els autors analitzen els principals aspectes metodològics o dominis que poden influir en la presència de biaix en aquests assajos. Aquests dominis són:

1. Generació de la seqüència aleatoritzada > biaix de selecció
2. Ocultació de l'assignació > biaix de selecció
3. Cegament dels participants i del personal > biaix de realització
4. Cegament dels avaluadors > biaix de detecció
5. Maneig de les dades de resultat incomplets > biaix de desgast
6. Notificació selectiva > biaix de notificació

Per a cada un d'aquests dominis, Cochrane descriu els criteris per considerar si el mètode descrit en l'assaig clínic és suggestiu d'alt risc de biaix, baix risc de biaix o risc poc clar.

7. Interpretació

Interpretar els resultats de la RS per donar resposta a la pregunta clínica en forma de conclusions.

8. Difusió (publicació)

Publicar els resultats seguint un estàndard internacional, que permeti a tot lector d'una RS fer-ne una lectura crítica, i en cas de considerar-la vàlida, rellevant i aplicable, incloure aquests nous coneixements a la pràctica clínica diària.

Actualment l'estàndard a seguir per a la publicació d'una RS és la declaració PRISMA. Publicada el 2009 (91,92), és una eina per als autors de RS que pretén contribuir a millorar la claredat i la transparència en la publicació de RS. No és un instrument per valorar la qualitat d'una RS. La seva aplicació per part dels autors de RS suposa un benefici per als lectors d'aquest tipus de publicacions: disposar de tota la informació necessària, de manera clara i transparent per poder jutjar la força, les limitacions i la rellevància dels resultats per respondre a la pregunta clínica que

la RS pretén abordar. En contra cal dir que la seva aplicació implica un augment de l'extensió del text.

La Declaració PRISMA consta d'una llista de comprovació i un diagrama de flux. La llista de comprovació inclou 27 ítems. Cada un fa referència a un apartat o aspecte concret de la RS en els quals s'especifica quina informació han d'explicitar els autors i com s'ha de reportar perquè la publicació sigui clara i transparent. El diagrama de flux pretén descriure el procés d'elaboració de la RS, des de la identificació inicial dels estudis potencialment rellevants, fins a la selecció definitiva d'aquests en la síntesi qualitativa (RS) i quantitativa (metanàlisi). A la web de la xarxa EQUATOR, *http://www.espanol.equator-network.org*, podem accedir a aquesta eina de manera gratuïta i en espanyol.

9. Actualització

Una RS pot tenir escàs valor al cap de pocs anys de la seva publicació si no s'actualitza periòdicament. La periodicitat d'aquesta actualització dependrà del volum estimat d'estudis que es realitzen sobre el tema tractat a la RS. Una bona RS s'ha d'elaborar tenint en compte aquesta circumstància i preveure la seva actualització. Les RS Cochrane s'elaboren amb previsió d'actualitzar-les cada 2 anys.

De manera gràfica, la Figura 12 pretén il·lustrar tot aquest complex procés d'elaboració d'una RS:

Figura 12. Procés d'elaboració d'una RS. Obtingut de http://navigatingeffectivetreatments.org.au/exploring_systematic_reviews.html. Data. 07/07/2014

Al final de tot aquest procés d'elaboració, totes les revisions Cochrane es publiquen seguint un mateix format editorial que s'il·lustra a la Figura 13.

Figura 13. Estructura d'una RS Cochrane publicada.
http://navigatingeffectivetreatments.org.au/exploring_systematic_reviews.html. Data. 07/07/2014

2.3.- Justificació de la tesi

Aquesta tesi doctoral titulada "*Maneig farmacològic del dolor agut a urgències. Compendi d'evidències*", que es presenta com a conjunt de publicacions, es basa fonamentalment en 3 RS publicades que tracten sobre l'eficàcia i seguretat de diferents estratègies farmacològiques utilitzades en l'àmbit de la medicina d'urgències per al maneig de dues entitats clíniques que cursen amb dolor agut. Dues d'aquestes revisions avaluen el tractament i la prevenció de la CPPD i la darrera és referent al dolor abdominal en la PA. Les tres publicacions presentades en aquesta tesi han esta publicades a *The Cochrane Library*; revista electrònica, periòdica, indexada a Medline, que prepara i elabora The Cochrane Collaboration i que amb un factor d'impacte (FI) de 5,785 al 2012 està dins el primer decil de les revistes de "Medicina General i Interna".

Totes les revisions han estat realitzades per un equip multidisciplinari procedents del Centre Cochrane Iberoamericà, membre de l'Institut d'Investigació Biomèdica Sant Pau, ubicat a l'Hospital de la Santa Creu i Sant Pau de Barcelona. L'autor de la tesi hi ha participat en totes les revisions com a metodòleg i com a clínic en el camp del dolor agut.

3.-OBJECTIUS

3.-OBJECTIUS

3.1.- Objectius generals

Reunir i sintetitzar les evidències científiques disponibles sobre el maneig farmacològic del dolor agut en relació a diferents problemes de salut dins l'àmbit de la medicina d'urgències.

3.2.- Objectius específics

Els objectius específics de la tesi són els propis de cadascuna de les publicacions que la conformen:

- o Avaluar l'eficàcia i seguretat dels medicaments per a prevenir la CPPD
- o Avaluar l'eficàcia i seguretat dels fàrmacs per tractar la CPPD
- o Avaluar l'eficàcia i la seguretat dels opioides per al dolor abdominal en la PA, en comparació amb altres analgèsics, opioides o no

4.-MÈTODES

4.-MÈTODES

Els mètodes de la tesi són els propis de cadascuna de les publicacions que la conformen.

Una RS és la revisió d'una pregunta clínica (en aquest cas, una pregunta terapèutica) formulada clarament, que utilitza mètodes sistemàtics i explícits per a identificar, seleccionar i avaluar críticament la investigació rellevant (els estudis originals pertinents), així com per a obtenir i analitzar les dades dels estudis inclosos a la revisió. Poden utilitzar o no mètodes estadístics (metanàlisi) per analitzar i resumir els resultats dels estudis inclosos.

Les revisions presentades en aquesta tesi estan elaborades i presentades seguint la metodologia establerta per la Col·laboració Cochrane, metodologia que es pot consultar al manual Cochrane. Aquest manual es pot consultar lliurement en la versió anglesa, *"Cochrane Handbook for Systematic Reviews of Interventions"* (93), a la web http://handbook.cochrane.org i també podem accedir de manera gratuïta la mateixa versió 5.1.0 traduïda a l'espanyol, el *"Manual Cochrane de Revisiones Sistemáticas de Intervenciones"* (87), a la web http://es.cochrane.org. La metodologia més específica (especialment pel que fa als criteris de selecció i l'estratègia de cerca) cal consultar-la directament a les publicacions.

En resum, les tres revisions presentades en aquesta tesis inclouen les següents seccions:

1) Antecedents

Consisteix en una breu justificació de la importància i necessitat de dur a terme la revisió. En resum, una revisió es justifica per la importància del problema de salut de que tracta i la polèmica sobre les intervencions que s'analitzen.

2) Objectiu/s de la revisió

En totes elles es tracta de l'avaluació de l'eficàcia i seguretat de les diverses intervencions terapèutiques identificades per al maneig farmacològic del dolor agut.

3) Criteris de selecció dels estudis

Condicions que han de complir els estudis de recerca original per ser seleccionats i inclosos a la revisió. Concretament, els estudis han de complir uns requisits que tenen a veure amb: i) la població d'estudi, ii) les intervencions avaluades, iii) les comparacions que són d'interès per la revisió, iv) els resultats que són d'interès (segons una jerarquització establerta a priori en funció de la seva importància clínica per als clínics i els pacients), i v) el tipus d'estudi (disseny).

Els estudis se seleccionen si compleixen tots els criteris abans esmentats, i es descarten si no en satisfan algun d'ells. En conseqüència, la decisió sobre la selecció dels estudis de recerca primaris és completament independent dels seus resultats.

4) Estratègia de cerca

La revisió, si ha de ser sistemàtica i exhaustiva, ha d'explicitar les bases bibliogràfiques que s'han emprat a la cerca. Obligatòriament sempre es fa la cerca a *Medline, Embase* i al *Cochrane Central Register of Controlled Trials* (CENTRAL), i en la majoria d'ocasions, a altres bases més específiques segons l'àrea temàtica de la revisió. Cal elaborar una estratègia de cerca sensible (paraules clau i termes *MeSH*), sense restriccions idiomàtiques i altres estratègies emprades, com seguiment de les referències o contacte amb experts.

5) Mètodes de la revisió

Cal explicitar com (i qui) ha aplicat els criteris de selecció d'estudis, com (i qui) ha portat a terme l'avaluació de la qualitat dels estudis (a les revisions d'aquesta tesi s'ha aplicat l'eina de la Col·laboració Cochrane per avaluar el risc de biaix), com (i qui) ha dut a terme l'extracció de dades dels estudis seleccionats i l'anàlisi de resultats (especificant els models estadístics emprats per la combinació de resultats, si procedeix, l'anàlisi de l'heterogeneïtat, i les mesures de l'efecte emprades per variables dicotòmiques i contínues). Donat que moltes de les decisions que cal prendre en el procés d'una RS poden tenir algun grau de subjectivitat o error (p. ex. selecció d'estudis, extracció de dades o avaluació de la qualitat dels estudis), cal que tots aquests processos siguin realitzats per dos revisors de forma independent, i en el cas d'haver-hi discrepància, aquesta ha de ser resolta per consens.

6) Descripció dels estudis

La revisió ha de proporcionar una descripció dels estudis seleccionats, resumida en forma de taula, per tal que els lectors puguin copsar a cop d'ull les característiques bàsiques de les poblacions d'estudi, els mètodes emprats, la modalitat específica d'intervenció i control aplicades i les variables de resultat (amb la seva definició o mètodes de mesura emprats) analitzades a cada estudi.

7) Qualitat dels estudis

Una part molt important de la revisió consisteix en avaluar el risc de biaix dels estudis seleccionats, a partir de la valoració de les dimensions metodològiques essencials del disseny i execució d'un assaig clínic. Bàsicament, aquestes tenen relació amb l'assignació dels tractaments, l'ocultació de la seqüència de les assignacions, l'emmascarament de les intervencions als participants i/o als avaluadors dels resultats, la similitud de les característiques basals dels grups d'estudi, les pèrdues i abandonaments i el seu maneig a l'anàlisi dels resultats, l'aplicació d'un mateix cronograma de les avaluacions, o l'adequat compliment terapèutic.

8) Resultats

D'una banda, hi ha els resultats obtinguts d'aplicar la cerca bibliogràfica, i d'altra banda, els resultats de l'anàlisi de l'impacte (efecte) dels tractaments en els subjectes d'estudi. Quant als primers, la revisió ha d'informar del flux d'estudis al

llarg del procés de cerca, reportant el número d'estudis inicialment detectats, els motius d'exclusió i el número d'estudis finalment seleccionats. Quant als segons, la revisió ha d'informar de manera clara i concisa quina és la direcció i magnitud de l'efecte dels tractaments sobre cada variable de resultat analitzada per la revisió, presentant aquesta informació de forma resumida quantitativament mitjançant la combinació de resultats (metanàlisi) o bé de forma qualitativa quan no es compleixen les condicions per dur a terme aquesta combinació de dades.

9) Discussió dels resultats

A partir dels resultats, i evitant en tot el possible transferir els valors i preferències personals, cal interpretar els resultats cenyint-se estrictament als mètodes i criteris prefixats al protocol de la revisió. També cal posar en context els resultats, especialment des del punt de vista de la seva rellevància clínica.

10) Conclusions

Finalment, els autors han d'arribar a emetre les seves conclusions, les quals tindran implicacions a dos nivells diferents i complementaris: 1) les implicacions per a la pràctica clínica serien aquelles recomanacions que es poden derivar d'uns resultants prou clars (a favor o en contra) de l'ús de la intervenció analitzada, amb graus variables de certesa; 2) les implicacions per a la investigació, que identifiquen llacunes del coneixement o deficiències en la recerca prèvia, i que justificarien la necessitat de dur a terme nous estudis de recerca focalitzats a suplir aquestes mancances i aportar nova informació rellevant.

11) Referències

La revisió, com tota investigació formal, ha d'aportar les referències bibliogràfiques bàsiques, que han d'incloure sobretot la referències dels estudis inclosos sobre la qual aquesta es basa.

12) Taules, figures i annexos

La revisió ha d'incloure taules i figures on, de forma resumida, es presenta la descripció dels estudis, el flux d'estudis al llarg del procés de revisió, l'avaluació de la seva qualitat o risc de biaix i els resultats en el cas d'haver-hi metanàlisi.

5.-RESULTATS

5.-RESULTATS

5.1.- Publicacions presentades per aquesta tesi

Publicació nº1:

- *Basurto Ona X, Uriona Tuma SM, Martínez García L, Solà I, Bonfill Cosp X. Drug therapy for preventing post-dural puncture headache. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD001792. DOI: 10.1002/14651858.CD001792.pub3.*

Factor d'impacte (2012): 5.785

Publicació nº2:

- *Basurto Ona X, Martínez García L, Solà I, Bonfill Cosp X. Drug therapy for treating post-dural puncture headache. Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD007887. DOI: 10.1002/14651858.CD007887.pub2.*

Factor d'impacte (2012): 5.785

Publicació nº3:

- *Basurto Ona X, Rigau Comas D, Urrútia G. Opioids for acute pancreatitis pain. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD009179. DOI: 10.1002/14651858.CD009179.pub2.*

Factor d'impacte (2012): 5.785

5.2.- Publicació nº1

Basurto Ona X, Uriona Tuma SM, Martínez García L, Solà I, Bonfill Cosp X

Drug therapy for preventing post-dural puncture headache

Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD001792

Resum de la publicació nº1

Objectiu: Avaluar l'eficàcia i seguretat dels medicaments per a prevenir la CPPD en adults i nens.

Resultats: Es van incloure 10 ACA (1611 participants) en aquesta revisió amb una majoria de dones (72%), la majoria (913) dones en treball de part després d'una PL per l'anestèsia regional. Els fàrmacs avaluats van ser la morfina epidural i espinal, el fentanil espinal, la cafeïna per via oral, la indometacina rectal, la cosintropina intravenosa, l'aminofil·lina intravenosa i la dexametasona intravenosa.

Tots els ACA inclosos presentaven dades sobre el resultat primari, és a dir, el nombre de participants afectats per CPPD de qualsevol gravetat després d'una PL. La morfina epidural i cosintropina intravenosa van reduir el nombre de participants afectats per CPPD de qualsevol gravetat després d'una PL, en comparació amb el placebo. També l'aminofil·lina intravenosa va reduir el nombre de participants afectats per CPPD de qualsevol gravetat després d'una PL en comparació amb la no intervenció, mentre que la dexametasona intravenosa el va augmentar. La morfina espinal va augmentar el nombre de participants afectades per pruïja en comparació amb el placebo, i la morfina epidural va augmentar la nombre de participants afectats per nàusees i vòmits, en comparació amb el placebo. La cafeïna oral augmenta el nombre de participants afectats per insomni, en comparació amb el placebo. La resta de les intervencions analitzades no va mostrar cap efecte rellevant per a cap dels resultats. Cap dels ACA inclosos informen del nombre de dies que els pacients van romandre a l'hospital.

Conclusions: Morfina i cosintropina han demostrat eficàcia per reduir el nombre de participants afectats per CPPD de qualsevol gravetat després d'una PL, en comparació amb el placebo, especialment en pacients amb alt risc de CPPD, com les pacients obstètriques que han rebut una punció dural accidental. L'aminofil·lina també va reduir el nombre de participants afectats per CPPD de qualsevol gravetat després d'una PL en comparació amb cap intervenció, en pacients sotmeses a cesària electiva. La dexametasona augmenta el risc de CPPD, després de l'anestèsia espinal per la cesària, en comparació amb el placebo. La morfina també va augmentar el nombre de participants afectats per esdeveniments adversos (pruïja i nàusees i vòmits). Hi ha una falta de proves concloents per a les altres drogues avaluades (fentanil, cafeïna, indometacina i dexametasona). Aquestes conclusions s'han d'interpretar amb precaució a causa de la manca d'informació publicada en els articles seleccionats, que dificulta la correcta avaluació del risc de biaix, i també a causa de l'escassa grandària de la mostra dels ACA inclosos a la revisió.

Drug therapy for preventing post-dural puncture headache (Review)

Basurto Ona X, Uriona Tuma SM, Martínez García L, Solà I, Bonfill Cosp X

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[Intervention Review]

Drug therapy for preventing post-dural puncture headache

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A B S T R A C T

Background

Post-dural (post-lumbar or post-spinal) puncture headache (PDPH) is one of the most common complications of diagnostic, therapeutic or inadvertent lumbar punctures. Many drug options have been used to prevent headache in clinical practice and have also been tested in some clinical studies, but there are still some uncertainties about their clinical effectiveness.

Objectives

To assess the effectiveness and safety of drugs for preventing PDPH in adults and children.

Search methods

The search strategy included the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2012, Issue 5), MEDLINE (from 1950 to May 2012), EMBASE (from 1980 to May 2012) and CINAHL (from 1982 to June 2012). There was no language restriction.

Selection criteria

We considered randomised controlled trials (RCTs) that assessed the effectiveness of any drug used for preventing PDPH.

Data collection and analysis

Review authors independently selected studies, assessed risks of bias and extracted data. We estimated risk ratios (RR) for dichotomous data and mean differences (MD) for continuous outcomes. We calculated a 95% confidence interval (CI) for each RR and MD. We did not undertake meta-analysis because participants' characteristics or assessed doses of drugs were too different in the included studies. We performed an intention-to-treat (ITT) analysis.

Main results

We included 10 RCTs (1611 participants) in this review with a majority of women (72%), mostly parturients (women in labour) (913), after a lumbar puncture for regional anaesthesia. Drugs assessed were epidural and spinal morphine, spinal fentanyl, oral caffeine, rectal indomethacin, intravenous cosyntropin, intravenous aminophylline and intravenous dexamethasone.

All the included RCTs reported data on the primary outcome, i.e. the number of participants affected by PDPH of any severity after a lumbar puncture. Epidural morphine and intravenous cosyntropin reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to placebo. Also, intravenous aminophylline reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to no intervention, while intravenous dexamethasone increased it. Spinal morphine increased the number of participants affected by pruritus when compared to placebo, and epidural morphine increased the number of participants affected by nausea and vomiting when compared to placebo. Oral caffeine increased the number of participants affected by insomnia when compared to placebo.

The remainder of the interventions analysed did not show any relevant effect for any of the outcomes.

None of the included RCTs reported the number of days that patients stayed in hospital.

Authors' conclusions

Morphine and cosyntropin have shown effectiveness for reducing the number of participants affected by PDPH of any severity after a lumbar puncture, when compared to placebo, especially in patients with high risk of PDPH, such as obstetric patients who have had an inadvertent dural puncture. Aminophylline also reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to no intervention in patients undergoing elective caesarean section. Dexamethasone increased the risk of PDPH, after spinal anaesthesia for caesarean section, when compared to placebo. Morphine also increased the number of participants affected by adverse events (pruritus and nausea and vomiting)

There is a lack of conclusive evidence for the other drugs assessed (fentanyl, caffeine, indomethacin and dexamethasone).

These conclusions should be interpreted with caution, owing to the lack of information, to allow correct appraisal of risk of bias and the small sample sizes of studies.

PLAIN LANGUAGE SUMMARY

Drugs for preventing headache after a lumbar puncture

Lumbar puncture is an invasive procedure that medical personnel use to get a sample of cerebrospinal fluid for diagnostic purposes (e.g. to diagnose meningitis or subarachnoid haemorrhage) by inserting a needle into the lower spinal region. It can also be used to inject medications such as anaesthetics and analgesics (to perform regional anaesthesia), chemotherapy or radiological contrast agents.

Post-dural puncture headache (PDPH) is the most common complication of a lumbar puncture. The symptoms are a constant headache that worsens in the upright position and improves when lying down and resolves spontaneously within five to seven days. Several interventions have been used before, during or immediately after lumbar puncture to prevent PDPH, but there are still uncertainties about their clinical effectiveness, especially regarding drug treatments. Therefore, the aim of this review was to determine the effectiveness of these medications to prevent PDPH in children and adults.

We included 10 randomised clinical trials (RCTs), with a total of 1611 participants, that assessed seven medications (epidural and spinal morphine, spinal fentanyl, oral caffeine, rectal indomethacin, intravenous cosyntropin, intravenous aminophylline and intravenous dexamethasone). Epidural morphine and intravenous cosyntropin proved to be effective at reducing the number of participants affected by PDPH of any severity after lumbar puncture compared to placebo. Aminophylline also reduced the number of participants affected by PDPH of any severity after a lumbar puncture compared to no intervention. Dexamethasone increased the risk of PDPH when compared to placebo after spinal anaesthesia for caesarean section.

Morphine also increased the number of participants affected by adverse events such as itching, nausea and vomiting. The other interventions (fentanyl, caffeine, indomethacin and dexamethasone) did not show conclusive evidence of effectiveness.

Combining data was possible only for subgroups of one study comparing different dosages of caffeine to placebo, because the other RCTs appraised diverse drugs, outcomes or populations.

A meta-analysis (combining of data) was not possible because all the included RCTs assessed different drugs, different doses, different outcomes or different baseline participants' characteristics.

These conclusions should be interpreted carefully, given the lack of information to evaluate the risk of bias properly, and the small number of participants in the included studies.

BACKGROUND

Description of the condition

Post-dural (post-lumbar or post-spinal) puncture headache (PDPH) is one of the most common complications of diagnostic, therapeutic or inadvertent lumbar puncture (Bezov 2010; Davignon 2002). PDPH is defined as any headache after a lumbar puncture that worsens within 15 minutes of sitting or standing and is relieved within 15 minutes of lying down (International Headache Society 2004). Ninety per cent of PDPHs occur within three days of the procedure and 66% start in the first 48 hours (Turnbull 2003).

The pathophysiology of PDPH has not been fully described. It is well known that the puncture in the dura allows cerebrospinal fluid (CSF) to leak from the subarachnoid space, resulting in a decrease of CSF volume and pressure (Grande 2005). This CSF volume loss may cause a downwards pull on pain-sensitive structures resulting in a headache (Ahmed 2006; Baumgarten 1987; Davignon 2002; Denny 1987; Harrington 2004). Alternatively, the loss of CSF may cause an increase in blood flow, resulting in arterial and venous vasodilation and PDPH. A third explanation involves the role of substance P and the regulation of neurokinin-1 receptors (NK1R) (Clark 1996).

Occurrence of PDPH varies from 1% to 40%, according to the needle gauge, needle orientation, operator skill level and presence of risk factors such as age group or history of PDPH (Turnbull 2003). This frequency is related to the type of lumbar puncture. During anaesthetic procedures, such as epidural anaesthesia, PDPH is most commonly caused by an unintentional dural puncture (Thew 2008; Turnbull 2003). In contrast, in diagnostic or therapeutic lumbar puncture, the need for adequate CSF flow requires an intentional lesion that may generate the PDPH phenomenon (Kuczkowski 2006). Estimated frequencies vary from less than 10% following spinal anaesthesia (Hafer 1997; Vallejo 2000) to 36% for diagnostic lumbar puncture (Lavi 2006; Vallejo 2000) and up to 81% (Banks 2001) in obstetric patients with inadvertent dural puncture during active labour. Reported risk of inadvertent dural puncture placement during epidural anaesthesia in an obstetric population ranges from 0.04% to 6% (Berger 1998; Choi 2003). Therefore, obstetric analgesia is probably the main source of PDPH patients.

The features of PDPH are often variable. PDPH may be accompanied by neck stiffness, tinnitus, hearing loss, photophobia or nausea; other features, such as the location and duration, are also unpredictable (Lybecker 1995). Although PDPH is not a life-threatening condition, physical activity is often restricted. Likewise patients are usually required to stay in bed the whole day, and length of stay and medical care increases (Angle 2005).

The variability of symptoms makes PDPH a diagnosis of exclusion. Other alternative diagnoses should be ruled out (e.g. viral meningitis, sinus headache or intracranial haemorrhage) (Turnbull 2003). Once PDPH is diagnosed, the initial treatment involves conservative measures such as bed rest and analgesics. If PDPH continues for more than 72 hours, a more specific treatment is indicated (Ahmed 2006). Severe PDPH may respond to some therapeutic drugs and administration of an epidural blood patch (EBP) (Lavi 2006).

How the intervention might work

Owing to the fact that no clear pathophysiology has been asserted for PDPH, many drugs options are used to prevent headache in clinical practice and in clinical trials: for example EBP mechanically blocking the leakage of CSF, postures such as a prone position, reducing pressure in the subarachnoid space and allowing a seal to form over the dura, hydration increasing CSF production (Ahmed 2006), methylxanthines, sumatriptan and caffeine increasing vasoconstriction of cerebral blood vessels or adrenocorticotropic hormone (ACTH) (Kuczkowski 2006), or epidural saline infusion (Morewood 1993) increasing intravascular volume. Preventive drugs should help to decrease the frequency of patients with PDPH, reduce the headache severity as much as possible, avoid the need for any therapeutic option, improve daily activity, reduce the length of hospital stay and decrease the occurrence of adverse events overall.

Why it is important to do this review

Two Cochrane systematic reviews about treatment and management of PDPH have been published using EBP (Boonmak 2010) and drugs (Basurto 2011). One Cochrane systematic review about prevention of PDPH with epidural catheter replacement and intrathecal catheter techniques is also in production (Newman 2010), alongside two published reviews using EBP (Boonmak 2010), and posture and fluids (Arevalo-Rodriguez 2011).

Numerous preventive drugs have been proposed for treating this condition based on limited randomised controlled trials (RCTs) and case series, including: caffeine, morphine, paracetamol, fentanyl, vasopressin (Turnbull 2003) and epidural saline infusion (Morewood 1993). Therefore, there is weak evidence to support the preventive treatment of PDPH with drugs and the existing uncertainties require a systematic review to clarify their potential benefits. In addition, this review would like to inspire future guidelines as well as future good-quality studies regarding this topic.

OBJECTIVES

To assess the effectiveness and safety of drugs for preventing PDPH in adults and children.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We included RCTs (parallel or cross-over) conducted in any setting. We excluded studies using alternation, date of birth, hospital record number or other quasi-randomised methods of allocation of treatment.

Types of participants

Participants undergoing lumbar puncture for any of the reasons outlined: CSF sampling or pressure measurement, or both; spinal anaesthesia; myelography; intrathecal drug administration or accidental puncture of the dura during epidural anaesthesia. We included individuals of all ages and any gender.

The use of a standardised diagnostic criteria for PDPH was not required, but it should at least have been described as an orthostatic headache that worsened on standing and improved by lying down. We described the specific diagnostic criteria used in each included study.

Types of interventions

We considered any drug used for preventing PDPH. We considered interventions at any dose, formulation or route of administration given before, during or immediately after lumbar puncture. Acceptable control groups included: placebo, no intervention, any other drug treatments, behavioural and physical therapies.

Types of outcome measures

Primary outcomes

Number of participants affected by PDPH of any severity after a lumbar puncture.

Secondary outcomes

1. Number of participants with severe PDPH (based on the author's definition of severity).
2. Number of participants with any headache, not only those explicitly described as PDPH.
3. Number of days that patients stayed in hospital.
4. Any possible adverse events of drugs taken to prevent PDPH.
5. Missing data (withdrawals, drop-outs and participants lost to follow-up).

Search methods for identification of studies

We designed the search in the context of an extensive review about prevention and treatment drugs used for PDPH. The Cochrane Central Register of Controlled Trials (CENTRAL) was our primary source for identifying studies. Our search terms were a combination of thesaurus-based and free-text terms covering both the procedure of interest (dural puncture performed for diagnosis, anaesthesia or myelography) and headache. For MEDLINE, EMBASE and CINAHL we used a modified version of the strategy used to search CENTRAL. We considered articles written in any language.

In addition, we searched the reference lists of all studies and review articles identified by electronic searching. We requested information about any potentially relevant studies when we contacted trialists from every included study.

Electronic searches

We searched:
- CENTRAL (*The Cochrane Library* 2012, Issue 5);
- MEDLINE (from 1950 to May 2012);
- EMBASE (from 1980 to May 2012);
- CINAHL (from 1982 to June 2012).

We include the complete search strategies designed for CENTRAL, MEDLINE, EMBASE and CINAHL in Appendix 1, Appendix 2, Appendix 3 and Appendix 4 respectively.

Data collection and analysis

Selection of studies

Two independent review authors (XB, SU) screened titles and abstracts of studies identified by the literature search for eligibility. We resolved disagreements through discussion. We retrieved eligible studies in full to confirm whether or not they fulfilled the inclusion criteria. Review authors were not blinded to the authors' names and institutions, journal of publication or study results at this or any stage of the review.

Data extraction and management

For included studies, we used specially designed, pre-tested data forms to extract information from the original studies on participants, methods of randomisation and blinding, the comparison(s) of interest, the number of participants originally randomised in each arm of the study, any losses to follow-up and the occurrence in each arm of the outcomes of interest. If information on any of these was incomplete, we attempted to obtain it by writing to the study author concerned. One review author (XB) extracted the data from studies and a second review author (SU) checked

data for accuracy, resolving any disagreement by discussion. We entered data into Review Manager 5.1 (RevMan 2011).

When efficacy outcomes were reported in dichotomous form (e.g. number of people with severe PDPH, number of people with any headache, any possible adverse events of drug and missing data), we recorded the number of participants assigned to each treatment arm and the number with each outcome. For outcomes reported on a continuous scale (e.g. number of days participants stayed in hospital), we recorded data on the variance associated with their means.

If reported we recorded the frequency and type of adverse events for each treatment arm.

Assessment of risk of bias in included studies

We used The Cochrane Collaboration's tool for assessing risk of bias in the studies included in this review, which addresses six specific domains (Higgins 2011) summarised in a specific table. For this review we assessed five of the domains (sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting). Each domain has a description of what was reported. One review author (XB) completed the 'Risk of bias' judgements for each study and a second review author (SU) checked them for accuracy. Any disagreement was resolved by discussion.

Assessment of heterogeneity

This review did not include a meta-analysis.

We would have assessed heterogeneity of effect sizes by means of the Q (Chi^2 statistic) using the methods of Peto and Mantel-Haenszel. If statistical evidence had existed for homogeneity of effect sizes, the analysis would have used a fixed-effect model.

If significant heterogeneity had been present (Chi^2 test with P value < 0.1 or I^2 statistic value $> 50\%$), we would have made an attempt to explain the differences based on the clinical characteristics of the included studies. We would not have combined studies that were dissimilar in terms of interventions and participants. However, if a group of studies with heterogeneous results had appeared to be similar, we would have combined the study estimates using a random-effects model (Higgins 2002; Higgins 2003).

Data synthesis

The differences between the studies included in this review, in terms of participants' characteristics, interventions assessed and outcomes measured, only permitted a combined analysis in one of the comparisons (caffeine plus paracetamol versus placebo). For the other comparisons we presented a narrative summary.

We analysed the results for different drugs separately, except for caffeine plus paracetamol versus placebo, using Review Manager 5.1 (RevMan 2011). We performed analysis on an intention-to-treat (ITT) basis (i.e. all participants remained in their original trial arm, whether or not they actually received the intervention allocated).

We used dichotomous data to calculate risk ratios (RR) with 95% confidence intervals (CI). In future updates of this review, we hope to be able to calculate the numbers needed to treat for an additional beneficial outcome (NNTB) with 95% CI, as the reciprocal of the risk difference (RD) (McQuay 1998). We will use data on the proportion of participants reporting adverse events to calculate RD and numbers needed to treat for an additional harmful outcome (NNTH) with 95% CI for significant differences.

For continuous outcomes reported using the same scale, we calculated mean differences (MD) with 95% CI. In future updates of this review, we hope to be able to calculate standardised mean differences (SMD) for pooling results of continuous outcomes measured with different scales.

Subgroup analysis and investigation of heterogeneity

In future updates of this review, if sufficient data are available, we plan to carry out the following subgroup analyses:

Follow-up time subgroup analyses

When possible, we will assess the impact of the assessed interventions at short-term (< 24 hours), medium-term (24 to 48 hours) or long-term time periods (> 48 hours) for the preventive drugs.

Population subgroup analyses

Where data allow in the future, we plan to conduct separate outcome analyses to test the following null hypotheses:

1. there is no difference between obstetric participants and all other participants;
2. there is no difference between men and non-obstetric women participants;
3. there is no difference between young participants (18 to 35 years old) and all other adult participants.

Sensitivity analysis

In future updates of this review, and depending on study availability, we will conduct a sensitivity analyses formulated a priori:

- We will examine the effect on the primary outcome of excluding any study judged to be at a high risk of bias by two of the domains, sequence generation and allocation concealment.
- If applicable we will also perform a sensitivity analysis excluding those trials with a cross-over design.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

See the 'Characteristics of included studies', 'Characteristics of excluded studies' and 'Characteristics of ongoing studies' tables.

Results of the search

We identified 1894 references in primary electronic databases up to May 2012 from our extended search strategy for prevention and treatment with drugs for PDPH. We excluded 1768 references af-ter a detailed reading of the title and abstract. We obtained the full-text reports for the remainder of the studies (137 papers) to check if they strictly fulfilled all the inclusion criteria. We finally excluded 127 studies after a complete full-text review and we contacted the study authors by email in some cases when more information was needed to decide eligibility. Ten studies completely fulfilled the inclusion criteria for this review (Abboud 1992; Al-metwalli 2008; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Flaatten 1987; Hakim 2010; Sadeghi 2012; Strelec 1994; Yousefshahi 2012). See Figure 1.

Figure 1. Study flow diagram.

Included studies

Included studies are described in detail in the 'Characteristics of included studies' table.

Study design

All 10 included studies (involving a total of 1611 participants) were RCTs with a parallel design. Most of them were placebo-controlled, except Devcic 1993 and Sadeghi 2012, which used a

control group without an intervention.

Setting

All included studies were single-centre studies. Three studies were conducted in the US (Abboud 1992; Devcic 1993; Strelec 1994), three studies in Iran (Doroudian 2011; Sadeghi 2012; Yousefshahi 2012) and the remainder in Norway (Flaatten 1987), Turkey (Esmaoglu 2005), Egypt (Hakim 2010) and Saudi Arabia (Al-metwalli 2008).

All the studies recruited the participants from hospital settings and the intervention took place while they were admitted.

Sample size

The studies included a total of 1611 participants. The smallest study had 50 participants (Al-metwalli 2008) and the largest had 372 (Yousefshahi 2012).

Participants

The majority of participants were women (1160/1611; 72%), mostly parturients (woman in labour) (913) that required a lumbar puncture for regional anaesthesia (Abboud 1992; Al-metwalli 2008; Devcic 1993; Hakim 2010; Sadeghi 2012; Yousefshahi 2012). There were four studies that included men (451); three with surgical patients after a spinal anaesthesia (Doroudian 2011; Esmaoglu 2005; Flaatten 1987) and one with lumbar puncture for myelography (Strelec 1994).

The median age among participants from all studies ranged from 26.1 to 48.5 years old.

Intervention

Three included studies assessed two different opioid drugs to prevent PDPH; morphine (administered into the subarachnoid space (Abboud 1992) or into the epidural space (Al-metwalli 2008)) and fentanyl (administered into the subarachnoid space (Devcic 1993)) .

Two studies used caffeine as an intervention to prevent PDPH. Strelec 1994 compared oral caffeine 300 mg to placebo. Esmaoglu 2005 assessed oral caffeine 75 mg and 125 mg, combined with paracetamol, compared to placebo.

Two studies used intravenous dexamethasone compared to placebo to prevent PDPH (Doroudian 2011; Yousefshahi 2012).

One study compared rectal indomethacin, a non-steroidal anti-inflammatory drug, to placebo (Flaatten 1987). Intravenous cosyntropin, a synthetic derivative of ACTH, was compared to placebo in one study (Hakim 2010) and intravenous aminophylline, a

xanthine derivative, was compared to no intervention in another study (Sadeghi 2012).

Follow-up was short in general terms and differed between the included trials at 48 hours (Sadeghi 2012), three days (Abboud 1992; Flaatten 1987; Yousefshahi 2012) and three weeks (Devcic 1993).

Outcomes of interest

The number of participants affected by PDPH of any severity after a lumbar puncture (primary outcome) was reported in all included studies. Missing data were reported in six studies (Devcic 1993; Doroudian 2011; Flaatten 1987; Hakim 2010; Strelec 1994; Yousefshahi 2012). Adverse events related to study drugs were reported in five studies (Abboud 1992; Al-metwalli 2008; Esmaoglu 2005; Hakim 2010; Strelec 1994).

The number of participants with severe PDPH was reported in five studies (Al-metwalli 2008; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Yousefshahi 2012).

The number of participants with any headache was detailed in two studies (Esmaoglu 2005; Yousefshahi 2012).

The number of days that participants stayed in hospital was the only outcome not reported in the included studies.

Conflict of interest

Only three studies reported any conflict of interest. Flaatten 1987 stated that Dumex-Norway supplied the intervention drugs and placebo, Hakim 2010 stated that support was provided solely from institutional or departmental (or both) sources and Yousefshahi 2012 stated no conflict of interest.

Excluded studies

A total of 127 studies did not fulfil the inclusion criteria and were excluded.

The most frequent reasons for exclusion were that the study did not focus on PDPH (45% of studies) or describe the orthostatic component of headache (35% studies). Other less frequent reasons(20% of the excluded studies) were: was not a RCT, intervention did not aim to prevent PDPH, allocation was not randomised or did not assess an individual drug.

For a summary of the reasons for exclusion see the 'Characteristics of excluded studies' table.

Risk of bias in included studies

Risk of bias in the included studies is summarised in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

Allocation

Sequence generation

Allocation sequence was adequately generated in three studies (Al-metwalli 2008; Hakim 2010; Yousefshahi 2012) that reported a computer-generated random number sequence explicitly.
The other seven included studies were described as randomised but no information was provided, so we judged them as having an unclear risk of selection bias (Abboud 1992; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Flaatten 1987; Sadeghi 2012; Strelec 1994).

Allocation concealment

Two studies reported the method used to conceal the randomisation sequences (Al-metwalli 2008; Hakim 2010) and we judged them as having a low risk of selection bias.
The other eight studies did not provide information regarding allocation concealment (Abboud 1992; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Flaatten 1987; Sadeghi 2012; Strelec 1994; Yousefshahi 2012) and we judged them as having an unclear risk of selection bias.

Blinding

Blinding of participants and personnel (performance bias)

The blinding method was adequate in five of the studies (Al-metwalli 2008; Doroudian 2011; Hakim 2010; Sadeghi 2012; Yousefshahi 2012). The rest of the studies (Abboud 1992; Devcic 1993; Esmaoglu 2005; Flaatten 1987; Strelec 1994) did not report detailed data to allow assessment of performance bias.

Blinding of outcome assessment (detection bias)

Blinding of outcome assessment was adequate in four of the included studies (Al-metwalli 2008; Devcic 1993; Hakim 2010; Yousefshahi 2012). The six remaining studies (Abboud 1992; Doroudian 2011; Esmaoglu 2005; Flaatten 1987; Sadeghi 2012; Strelec 1994) did not report information to allow assessment of detection bias.

Incomplete outcome data

Seven studies presented results for all randomised patients or reported the number of participants lost in follow-up with reasons

explicitly stated and we judged them as having a low risk of attrition bias (Abboud 1992; Al-metwalli 2008; Doroudian 2011; Esmaoglu 2005; Hakim 2010; Sadeghi 2012; Yousefshahi 2012). The remainder of the studies stated explicitly the number of participants lost to follow-up without detailed data to allow assessment of attrition bias; Devcic 1993 with six participants lost out of 194, Flaatten 1987 with three out of 250 and Strelec 1994 with two out of 60. Gender of participants lost to follow-up in Flaatten 1987 and Strelec 1994 was not reported.

Selective reporting

Four studies presented outcomes according to objectives stated in the methods section and we judged them as having a low risk of reporting bias (Al-metwalli 2008; Hakim 2010; Strelec 1994; Yousefshahi 2012). We judged three studies as having an unclear risk of bias because no information was provided (Abboud 1992; Esmaoglu 2005; Flaatten 1987). We judged Devcic 1993, Doroudian 2011 and Sadeghi 2012 as having a high risk as they did not report outcomes about adverse effects.

Effects of interventions

We present in this section a narrative synthesis of the results for the different outcomes of interest.

Number of participants affected by post-dural puncture headache (PDPH) of any severity

Opioids

Opioids were assessed in three studies for this primary outcome. Epidural morphine (Al-metwalli 2008) showed a significant risk reduction of the number of participants affected by PDPH of any severity compared to placebo (15 events in 50 participants; risk ratio (RR) 0.25; 95% confidence interval (CI) 0.08 to 0.78; Analysis 2.1).
In contrast, spinal morphine and spinal fentanyl showed no differences compared to placebo in Abboud 1992 (17 events in 82 participants; RR 1.18; 95% CI 0.51 to 2.76; Analysis 1.1) or no intervention in Devcic 1993 (11 events in 194 participants; RR 1.79; 95% CI 0.54 to 5.91; Analysis 3.1) respectively, in the number of participants affected by PDPH of any severity.
We did not undertake meta-analysis of these three studies (Abboud 1992; Al-metwalli 2008; Devcic 1993). The Al-metwalli 2008 results were not combined with other studies because baseline incidence of PDPH was much higher in obstetric patients with inadvertent dural puncture during active labour than following spinal anaesthesia for caesarean section. We did not combine the results

from Abboud 1992 and Devcic 1993 because opioid interventions were not dose equivalent; Devcic 1993 assessed 20 μg of fentanyl, which is dose equivalent of morphine 2 mg, which is 10 times higher than the morphine 0.2 mg used in Abboud 1992.

Intravenous cosyntropin

Intravenous cosyntropin (Hakim 2010) showed a significant risk reduction of the number of participants affected by PDPH of any severity (46 events in 95 participants; RR 0.49; 95% CI 0.31 to 0.79; Analysis 8.1) compared to placebo.

Oral caffeine

Oral caffeine plus paracetamol was assessed by Esmaoglu 2005 with two different doses of caffeine, 75 mg and 125 mg, and compared to placebo. The combined analysis from these two doses of caffeine, compared to placebo, showed no significant risk reduction (42 events in 280 participants; RR 0.91; 95% CI 0.52 to 1.59; Analysis 11.1). Neither comparison showed a significant result: caffeine 75 mg versus placebo (21 events in 140 participants; RR 0.91; 95% CI 0.41 to 2.00; Analysis 4.1), caffeine 125 mg versus placebo (21 events in 140 participants; RR 0.91; 95% CI 0.41 to 2.00; Analysis 5.1) or 75 mg caffeine versus caffeine 125 mg (20 events in 140 participants; RR 1.00; 95% CI 0.44 to 2.25; Analysis 6.1). Strelec 1994 also showed no significant risk reduction (18 events in 60 participants; RR 2.00; 95% CI 0.86 to 4.63; Analysis 9.1) when comparing oral caffeine 300 mg to placebo.
We did not undertake meta-analysis of these two studies (Esmaoglu 2005; Strelec 1994) because the caffeine doses used were too different (75 mg/125 mg and 300 mg, respectively) and also because the intervention was different; caffeine plus paracetamol in Esmaoglu 2005 while Strelec 1994 used caffeine alone.

Rectal indomethacin

Rectal indomethacin (Flaatten 1987) showed no significant risk reduction when compared to placebo (51 events in 250 participants; RR 0.70; 95% CI 0.42 to 1.15; Analysis 7.1).

Intravenous dexamethasone

Intravenous dexamethasone was assessed in two studies for this primary outcome. Doroudian 2011 showed no significant risk reduction when compared to placebo (34 events in 178 participants; RR 0.79; 95% CI 0.43 to 1.45; Analysis 10.1). Yousefshahi 2012 showed a significant risk of increasing the number of participants affected by PDPH of any severity compared to placebo (39 events in 372 participants; RR 2.55; 95% CI 1.31 to 4.96; Analysis 10.1). We did not undertake a meta-analysis of these two studies (Doroudian 2011; Yousefshahi 2012) because participants' characteristics were too different in terms of age, gender, length of ges-

tation and spinal needle size used, and also because of statistical evidence of significant heterogeneity of effect sizes (Chi^2 test with P value = 0.01 and I^2 statistic value = 85%).

Intravenous aminophylline

Intravenous aminophylline (Sadeghi 2012) showed a significant risk reduction of the number of participants affected by PDPH of any severity at 24 and 48 hours after umbilical cord clamping compared to no intervention (at 24 hours: 22 events in 120 participants; RR 0.16; 95% CI 0.05 to 0.51; Analysis 12.1; at 48 hours: 17 events in 120 participants; RR 0.21; 95% CI 0.06 to 0.71; Analysis 12.1).

Number of participants with severe PDPH (based on the author's definition of severity)

Opioids

Opioids were assessed in two studies for this outcome. Epidural morphine (Al-metwalli 2008) showed no significant risk reduction compared to placebo (six events in 50 participants; RR 0.08; 95% CI 0.00 to 1.30; Analysis 2.2). Spinal fentanyl (Devcic 1993) also showed no significant risk reduction when compared to no intervention (four events in 194 participants; RR 3.06; 95% CI 0.32 to 28.93; Analysis 3.2).
We did not undertake meta-analysis of these two studies (Al-metwalli 2008; Devcic 1993) because of the difference between participants' characteristics.

Oral caffeine

Data for oral caffeine doses plus paracetamol assessed in Esmaoglu 2005 were analysed in combination, caffeine 75 mg and 125 mg, showing no significant risk reduction compared to placebo (15 events in 280 participants; RR 0.88; 95% CI 0.33 to 2.35; Analysis 11.2). Individual comparisons showed no significant risk reduction in any of the reported comparisons: caffeine 75 mg compared to placebo (10 events in 140 participants; RR 1.50; 95% CI 0.44 to 5.09; Analysis 4.2), caffeine 125 mg compared to placebo (five events in 140 participants; RR 0.25; 95% CI 0.03 to 2.18; Analysis 5.2) or caffeine 75 mg compared to caffeine 125 mg (seven events in 140 participants; RR 6.00; 95% CI 0.74 to 48.55; Analysis 6.2).

Intravenous dexamethasone

Intravenous dexamethasone was assessed in two studies. Doroudian 2011 showed no significant risk reduction compared to placebo (10 events in 178 participants; RR 0.25; 95% CI 0.05 to 1.14; Analysis 10.2). Yousefshahi 2012 could not estimate this outcome because none of the participants experienced a severe

PDPH. For this reason and because of clinical differences these two studies could not be combined.

Number of participants with any headache, not only those explicitly described as PDPH

Oral caffeine

A combined analysis of caffeine 75 mg with 125 mg in Esmaoglu 2005 showed no significant risk reduction compared to placebo (61 events in 280 participants; RR 0.79; 95% CI 0.51 to 1.24; Analysis 11.3). All other comparisons showed no significant risk reduction: 75 mg caffeine compared to placebo (10 events in 140 participants; RR 0.67; 95% CI 0.20 to 2.26; Analysis 4.3), 125 mg caffeine compared to placebo (nine events in 140 participants; RR 0.50; 95% CI 0.13 to 1.92; Analysis 5.3) or caffeine 75 mg compared to caffeine 125 mg (seven events in 140 participants; RR 1.33; 95% CI 0.31 to 5.74; Analysis 6.3).

Dexamethasone

Dexamethasone was assessed in Yousefshahi 2012 and showed no significant risk reduction compared to placebo (16 events in 372 participants; RR 2.20; 95% CI 0.78 to 6.21; Analysis 10.3).

Number of days that patients stayed in hospital

None of the included studies reported this outcome.

Any possible adverse events of drugs taken to prevent PDPH

Opioids

Opioids were assessed in two studies for this outcome. Spinal morphine (Abboud 1992) showed a significant risk for increasing the number of participants affected by pruritus (28 events in 82 participants; RR 8.75; 95% CI 2.86 to 26.72; Analysis 1.2) compared to placebo, but a non-significant result for the number of participants affected by nausea and vomiting (41 events in 82 participants; RR 0.82; 95% CI 0.53 to 1.27; Analysis 1.2).
Epidural morphine (Al-metwalli 2008) significantly increased the number of participants affected by nausea and vomiting (15 events in 50 participants; RR 2.75; 95% CI 1.01 to 7.48; Analysis 2.3) compared to placebo. This study (Al-metwalli 2008) showed three participants affected by pruritus, all of them in the morphine group, with a non-significant result (three events in 50 participants; RR 7.00; 95% CI 0.38 to 128.87; Analysis 2.3).
We did not undertake meta-analysis of these two studies (Abboud 1992; Al-metwalli 2008) for this outcome because of the difference between participants' characteristics.

Caffeine

Oral caffeine 300 mg (Strelec 1994) showed a significant risk for increasing the number of participants affected by insomnia (11 events in 60 participants; RR 4.50; 95% CI 1.06 to 19.11; Analysis 9.2) compared to placebo. Esmaoglu 2005 reported no adverse events in either the caffeine 75 mg plus paracetamol group or in caffeine 125 mg plus paracetamol group. The study did not report this outcome in the placebo group.

Intravenous cosyntropin

Intravenous cosyntropin compared to placebo (Hakim 2010) showed two participants affected by mild hypersensitivity reaction (urticaria) in the cosyntropin group, with a non-significant result (two events in 95 participants; RR 5.10; 95% CI 0.25 to 103.57; Analysis 8.2).

Missing data (withdrawals, drop-outs and participants lost to follow-up)

Opioids

Spinal fentanyl (Devcic 1993) showed no significant risk of losing participants to follow-up (six events in 194 participants; RR 2.04; 95% CI 0.38 to 10.89; Analysis 3.3) when compared to no intervention.

Rectal indomethacin

Rectal indomethacin (Flaatten 1987) showed no significant risk of losing participants to follow-up (three events in 250 participants; RR 0.14; 95% CI 0.01 to 2.74; Analysis 7.2) when compared to placebo.

Intravenous cosyntropin

Intravenous cosyntropin (Hakim 2010) show no significant risk of losing participants to follow-up (five events in 95 participants; RR 0.68; 95% CI 0.12 to 3.89; Analysis 8.3) when compared to placebo.

Oral caffeine

Oral caffeine (Strelec 1994) showed no significant risk of losing participants to follow-up when comparing 300 mg oral caffeine to placebo (two events in 60 participants; RR 0.20; 95% CI 0.01 to 4.00; Analysis 9.3).

Intravenous dexamethasone

Intravenous dexamethasone was assessed in Yousefshahi 2012 and showed no significant risk of losing participants to follow-up (12 events in 372 participants; RR 0.50; 95% CI 0.15 to 1.63; Analysis 10.4) compared to placebo. Doroudian 2011 could not estimate this outcome because none of the participants were lost to follow-up.

We did not undertake meta-analysis of the six RCTs included in this outcome because of the different intervention drugs assessed.

DISCUSSION

Summary of main results

This systematic review identified three randomised controlled trials (RCTs) assessing opioids for preventing post-dural puncture headache (PDPH): epidural morphine (Al-metwalli 2008), spinal morphine (Abboud 1992) and spinal fentanyl (Devcic 1993). Two studies assessed oral caffeine (Esmaoglu 2005; Strelec 1994) and two studies assessed intravenous dexamethasone (Doroudian 2011; Yousefshahi 2012). Three other studies assessing different drugs for preventing PDPH were identified: rectal indomethacin (Flaatten 1987), intravenous cosyntropin (Hakim 2010) and intravenous aminophylline (Sadeghi 2012).

All the included studies reported data on the primary outcome, the number of participants affected by PDPH of any severity after a lumbar puncture. For this outcome, epidural morphine (Al-metwalli 2008) and intravenous cosyntropin (Hakim 2010) reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to placebo. In both RCTs participants were obstetric patients who had an inadvertent dural puncture. Also intravenous aminophylline (Sadeghi 2012) reduced the number of participants affected by PDPH of any severity after a lumbar puncture when compared to no intervention in patients undergoing elective caesarean section. Intravenous dexamethasone after caesarean section increased the risk of PDPH in Yousefshahi 2012 and showed no significant effect in adults with lower extremity surgery (Doroudian 2011). The rest of the interventions assessed for this outcome, spinal morphine (Abboud 1992) and spinal fentanyl (Devcic 1993), oral caffeine (Esmaoglu 2005; Strelec 1994) and rectal indomethacin (Flaatten 1987), did not show any relevant effect.

When assessing any possible adverse events of drugs taken to prevent PDPH, spinal morphine (Abboud 1992) increased the number of participants affected by pruritus when compared to placebo and epidural morphine (Al-metwalli 2008) increased the number of participants affected by nausea and vomiting when compared to placebo. Also three participants in the epidural morphine group experienced pruritus. Two participants in the cosyntropin group

and none in the placebo group (Hakim 2010) were affected by a mild self limiting hypersensitivity reaction (urticaria) that required no treatment. Oral caffeine 300 mg every eight hours for three days increased the number of participants affected by insomnia (Strelec 1994); however, Esmaoglu 2005 found no relevant adverse effect.

The drugs assessed in the included studies did not show any relevant effect for the rest of the outcomes of interest for this review. The number of participants with severe PDPH was similar between the interventions and their controls in five studies (Al-metwalli 2008; Devcic 1993; Doroudian 2011; Esmaoglu 2005; Yousefshahi 2012). The number of participants with any headache, not just that explicitly described as PDPH, was reported in two studies (Esmaoglu 2005; Yousefshahi 2012) without relevant effect. Missing data (withdrawals, drop-outs and participants lost to follow-up) were reported in five studies (Devcic 1993; Flaatten 1987; Hakim 2010; Strelec 1994; Yousefshahi 2012), which showed no significant differences between the interventions and their controls. None of the included studies reported data showing the number of days participants stayed in hospital.

Three studies (Abboud 1992; Al-metwalli 2008; Devcic 1993) compared opioids versus placebo but we did not undertake meta-analysis because of the difference between participants' characteristics or because the opioid doses were not equivalent. The baseline incidence of PDPH was much higher in obstetric patients with inadvertent dural puncture during active labour than following spinal anaesthesia for caesarean section in the Al-metwalli 2008 study. Data from Abboud 1992 and Devcic 1993 could not be combined because the opioids used were not dose equivalents. In Devcic 1993, fentanyl 20 μg was the dose equivalent of morphine 2 mg and this was different from the 0.2 mg dose of morphine that was used in Abboud 1992.

Two studies (Esmaoglu 2005; Strelec 1994) compared caffeine to placebo but we chose not to combine results because the range of caffeine doses used was too wide (75 mg, 125 mg and 300 mg) and also the intervention was different; caffeine plus paracetamol was used in Esmaoglu 2005 while Strelec 1994 used caffeine alone. The two intervention groups in Esmaoglu 2005 were analysed in combination (i.e. caffeine 75 mg and caffeine 125 mg) compared to placebo, showing no relevant effect.

Two studies (Doroudian 2011; Yousefshahi 2012) compared dexamethasone to placebo but could not be combined because participants' characteristics were too varied in terms of age, gender, length of gestation and spinal needle size used, and also because of statistical evidence of significant heterogeneity of effect sizes.

In future updates of this review, if sufficient data are available, we plan to carry out the subgroup and sensitivity analyses formulated a priori.

Overall completeness and applicability of evidence

All participants included in this review were recruited from acute care hospitals and their characteristics seemed to be similar to patients seen in usual clinical practice.

The lumbar punctures were performed during hospital stay, which is the most common setting for this technique. Most of the participants in the included studies underwent lumbar puncture to administer regional anaesthesia (spinal and epidural anaesthesia), which is the most common reason for lumbar puncture. No lumbar puncture in the included studies was done for diagnostic purposes.

The opioids (morphine and fentanyl), indomethacin, aminophylline and dexamethasone, used in the included studies, are widely marketed and frequently used. Caffeine and cosyntropin are also commercialised but for more specific indications and therefore they are less widely available.

Outcomes reported from the included studies were patient-relevant. In fact, all included studies reported on the primary effectiveness outcome, that is the number of participants affected by PDPH of any severity after a lumbar puncture. The second most reported outcome was a safety issue, that is any possible adverse events of drugs taken to prevent PDPH.

Quality of the evidence

The outlined results should be interpreted with caution owing to the diversity of drugs and doses assessed, and outcomes measured, the small sample sizes of the studies included, and the bias presented. There was a lack of data reported to allow a complete appraisal of the risk of bias; review authors' judgements about each 'Risk of bias' item were unclear in around 50% across all included studies (Figure 2). We judged three included studies (Abboud 1992; Flaatten 1987; Strelec 1994) as having an unclear risk of bias in at least five out of the six items evaluated. We judged three other included studies (Al-metwalli 2008; Hakim 2010; Yousefshahi 2012) as having a low risk of bias in at least five out of the six items evaluated (Figure 3). We judged three studies (Devcic 1993; Doroudian 2011; Sadeghi 2012) as having a high risk of bias in only one item each.

Potential biases in the review process

This review was conducted in accordance with the previously published protocol. We are unaware of any biases in the review process. To minimise bias, the selection, assessment for inclusion eligibility, risk of bias and data extraction were done independently by more than one review author. We also contacted study authors for clarification of study data. None of the review authors have been involved in any of the included studies and none have any commercial or other conflict of interest.

Agreements and disagreements with other studies or reviews

We have found no other systematic review specifically assessing the efficacy of drugs for preventing PDPH. In one systematic review (Apfel 2010) analysing any treatment options to prevent PDPH after accidental dural puncture (e.g. prophylactic EBP, epidural morphine, intrathecal catheters, and epidural or intrathecal saline) no strong evidence was found to make a clinical recommendation but, as in this review, epidural morphine was the only drug with proven efficacy, based on a study also included in this review (Al-metwalli 2008). One narrative review (Bezov 2010) about PDPH concluded, as we do, that caffeine was not helpful in preventing PDPH based on a study that we also included (Esmaoglu 2005). Other Cochrane reviews (Arevalo-Rodriguez 2011; Boonmak 2010) have investigated measures other than drugs to prevent PDPH (e.g. posture, fluids and EBP), without reaching strong recommendations. One published guideline (Verma 2011) only considers the use of smaller gauge ($\geq$ 25 G) and pencil-point needles for regional anaesthesia in day-surgery patients.

A U T H O R S '   C O N C L U S I O N S

Implications for practice

Available studies show that morphine, cosyntropin and aminophylline could be a first-line drug therapy when trying to prevent post-dural puncture headache (PDPH) after a lumbar puncture.

Epidural morphine and intravenous cosyntropin decreased the number of patients affected by PDPH of any severity after a lumbar puncture compared to placebo, especially in those patients with a high risk of PDPH, such as woman giving birth who have had an inadvertent dural puncture during administration of regional anaesthesia. Pruritus, nausea and vomiting due to morphine and urticaria due to cosyntropin are the adverse events reported but these are less frequent than the benefits, are not severe or life-threatening and, if necessary, efficacious and safe drugs exist to treat them.

Aminophylline also provides the same benefit, reducing the number of participants affected by PDPH of any severity, but in this case when compared to no intervention and in patients undergoing spinal anaesthesia for elective caesarean section.

Dexamethasone increased the risk of PDPH, after spinal anaesthesia for caesarean section, when compared to placebo.

These conclusions should be interpreted with caution, owing to the lack of information to allow a complete appraisal of risk of bias and the small sample sizes of studies.

There is a lack of conclusive results for the other drugs assessed (fentanyl, caffeine, indomethacin and dexamethasone).

Implications for research

Future research in this field should focus on the design of trials with larger samples (including the reporting of how sample size was determined) in order to provide more sound and accurate information on the effectiveness of drugs in this setting and situation.

The reporting of trials could also be improved by endorsing the CONSORT statement (Schulz 2010), which would allow a better appraisal of them for their potential inclusion into systematic reviews.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abboud 1992

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: US (Los Angeles) Setting: hospital Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: double-blind Follow-up period: 3 days
Participants	Randomised: 82 (intervention group: 40; control group: 42) Excluded (post-randomisation): not described Gender (women): 82 (100%) Age (years): mean (SD): intervention group: 30.3 (6.3); control group: 29.6 (5.8) Inclusion criteria: healthy pregnant women at term, ASA I or II with no medical complications, who underwent caesarean delivery with spinal anaesthesia Exclusion criteria: not described
Interventions	Intervention group: intraspinal administration of morphine 0.2 mg in 0.2 mL solution Control group: intraspinal administration of 0.2 mL of normal saline Co-interventions: spinal anaesthesia with 0.75% bupivacaine in 8.25% dextrose plus 0.2 mL of 1:1000 epinephrine. Hydration with 1500 mL lactated Ringer's solution
Outcomes	• Number of participants affected by PDPH of any severity • Number of any possible adverse effects from the drug taken to prevent PDPH
Notes	PDPH defined as: quote: "PDPH if it occurred after the patient became ambulatory, was aggravated by sitting or standing position, was relieved by lying supine, and was mostly occipital or frontal" (Page 34) Sample size calculation: quote: "Consultation with a statistician determined the sample size of the study. The statistical approach was analysed to ensure that the power of these data was adequate to decrease below the level of statistical probability that a Type II error could have been made" (Page 35)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Quote: "Patients were randomly assigned to receive, in a double-blind fashion, either 0.2 mg of morphine (Group 1, n = 40) or saline (Group 2, n = 42)..."

Abboud 1992 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results presented for all 82 randomised patients
Selective reporting (reporting bias)	Unclear risk	No information available

Al-metwalli 2008

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Saudi Arabia (Al-Khobar) Setting: hospital Study design: parallel Randomisation: computer-generated random number table Allocation concealment: opaque envelope labelled with the study subject number Blinding: double-blind Follow-up period: minimum 5 days in those without PDPH and 3 days after resolution of the headache in those with PDPH
Participants	Randomised: 50 (intervention group: 25, control group: 25) Excluded (post-randomisation): not described Gender (women): 50 (100%) Age (years): mean (SD): intervention group 28.4 (6.0); control group 29.6 (5.4) Inclusion criteria: postpartum woman with inadvertent dural puncture during epidural analgesia in labour Exclusion criteria: temperature > 37.8 ºC, coagulopathy and delivering by caesarean section
Interventions	Intervention group: epidural morphine 3 mg in 10 mL saline and repeated the same treatment after 24 h Control group: epidural 10 mL saline and repeated the same treatment after 24 h Co-interventions: 3 mL of lidocaine 2% with fentanyl 15 μg administered to all patients before delivery to test correct epidural placement. Next, 10 mL bupivacaine 0.25% with 50 μg of fentanyl was injected followed by a continuous infusion of bupivacaine 0.125% with 1 μg/mL of fentanyl at 10 mL/h
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of any possible adverse effects from the drug taken to prevent PDPH

Al-metwalli 2008 *(Continued)*

Notes	PDPH defined as: quote "PDPH was defined as the presence of a headache or neck ache that improved significantly or completely when the subject assumed the supine position" Sample size calculation: 24 participants calculated estimating an incidence decrease of PDPH from 75% to 35%. Significance level of 0.05 and power of 80% VRSP: 0 = no pain and 10 = worst possible pain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised (via a computer-generated random number table) to treatment (morphine) group or control (saline) group" (Page 848)
Allocation concealment (selection bias)	Low risk	Quote: "Group assignment was determined by opening an opaque envelope labelled with the study subject number" (Page 848)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "An anaesthetist, who was blind to the study drug, injected 10 ml saline (control group) or 3 mg of morphine in 10 ml saline (morphine group)" (Page 848)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An anaesthetist unaware of the treatment group evaluated the subjects postpartum to ascertain the presence of PDPH" (Page 848)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results presented for all 50 randomised patients
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

Devcic 1993

Methods	Randomised, blinded, controlled trial
	Study type: single-centre study
	Location: US (Milwaukee)
	Setting: hospital
	Study design: parallel
	Randomisation: not described
	Allocation concealment: not described
	Blinding: blinding of patients and outcome assessors
	Follow-up period: 3 weeks
Participants	Randomised: 194 (Sprotte needle with fentanyl: 47; Sprotte needle without fentanyl: 49; Quincke needle with fentanyl: 49; Quincke needle without fentanyl: 49)
	Excluded (post-randomisation): not described
	Gender (women): 194 (100%)
	Age (years): mean (SD): Sprotte needle with fentanyl: 28.2 (5.8); Sprotte needle without fentanyl: 29.5 (4.4); Quincke needle with fentanyl: 28.3 (5.6), Quincke needle without fentanyl: 28.7 (5.5)
	Inclusion criteria: healthy obstetric patients requiring caesarean delivery who consented to spinal anaesthesia
	Exclusion criteria: previously attempted or performed labour epidural analgesia or spinal anaesthesia attempted with other kind of needles
Interventions	Intervention group: subarachnoid fentanyl 20 μg through a 24-gauge Sprotte needle or through a 25-gauge Quincke needle
	Control group: subarachnoid anaesthesia without fentanyl through a 24-gauge Sprotte needle or through a 25-gauge Quincke needle
	Co-interventions: all patients received 1000 to 1500 mL of 0.9% normal saline or Ringer's lactate solution before spinal anaesthesia and continued for 48 h
	Spinal anaesthesia with hyperbaric bupivacaine 0.75% to all patients. The total dose was decided by the anaesthesiologist performing the spinal anaesthesia
	Opioids via patient-controlled pump during the first 24 h postoperative and followed the next day by oral analgesics as needed
Outcomes	• Number of participants affected by PDPH of any severity
	• Number of participants with severe PDPH
	• Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: quote: "If the headache occurring on mobilization was aggravated by an erect position and was relieved by lying flat, it was considered to be a PDPH" (Page 223)
	Sample size calculation: not described
	PDPH severity: mild (annoying, but tolerable on ambulation, requiring oral analgesics); moderate (very annoying, very uncomfortable on ambulation, requiring bed rest, scheduled analgesia with intravenous fluids); severe (bedridden requiring EBP)
	Email contact

Risk of bias

Devcic 1993   *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All patients were evaluated daily during the first 4 postoperative days by the designated nurse, who was blinded to the type of needle and medication used... Investigators conducting telephone follow-up were blinded to the type of needle and anaesthetic solution used" (Page 223)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 lost to follow-up described (4 in fentanyl group, 2 in control group), but is unlikely that this loss may influence the outcomes
Selective reporting (reporting bias)	High risk	Adverse events not reported

Doroudian 2011

Methods	Randomised, blinded, controlled trial Study type: single-centre study Location: Iran (Kerman) Setting: admitted to hospital Study design: parallel Randomisation: computer-generated random allocation Allocation concealment: not described Blinding: blinding of patients and the spinal anaesthesia staff Follow-up period: 7 days
Participants	Randomised: 178 (intervention group: 89; control group: 89) Excluded (post-randomisation): none Gender (women): 61 (34.3%) Age (years): mean (range): intervention group 41.7 (31 to 53); control group 40 (30 to 50) Inclusion criteria: all adults admitted to hospital for lower-extremity surgery Exclusion criteria: hypo/hypertension, diabetes, dexamethasone intolerance or past hypersensitivity reaction, intake of any analgesic or anti-inflammatory agent during the week prior to admission, past history of chronic headache, recent-onset acute headache, contraindication for LP, a surgical procedure estimated to last longer than 90 minutes, current pregnancy, past/active peptic ulcer disease, active systemic fungal infection, any

Doroudian 2011 *(Continued)*

	kind of addiction, more than 2 attempts at spinal anaesthesia, any history of cardiopulmonary disorder, long-term admission, severe post-spinal haemodynamic changes and strong dependency to tea or caffeine
Interventions	Intervention group: intravenous dexamethasone 8 mg (2 mL) of before spinal anaesthesia Control group: 2 mL of intravenous normal saline before spinal anaesthesia Co-interventions: all patients received 500 mL of normal saline intravenously before intervention and spinal anaesthesia
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: an exclusion criteria was: quote: "long term admission which does not permit patient to resume the upright position within the first 7 days" (Page 144) and Class I intensity headache was: quote: "Patient suffers from a mild headache while sitting or walking" (Page 144) Sample size calculation: not described PDPH severity: Class I: "Patient suffers from a mild headache while sitting or walking", Class II: "Patient suffers from a moderate to severe headache while sitting or walking" and Class III: "Patient suffers from a moderate to severe headache even in supine position which impedes his/her daily activities"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization process was performed using Random Allocation Software®" (Page 143)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "For all injections, the anesthetic staff was blind with respect to the group allocation whereas patients were also unaware regarding the content of the study injectate" (Page 144)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results presented for all 178 randomised patients

Selective reporting (reporting bias)	High risk	Adverse events not reported

Esmaoglu 2005

Methods	Randomised, blinded, controlled trial Study type: single-centre study Location: Turkey (Kayseri) Setting: admitted to hospital Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: outcome assessors and probably patients Follow-up period: 7 days
Participants	Randomised: 210 (caffeine 75 group: 70; caffeine 125 group: 70; control group: 70) Excluded (post-randomisation): not described Gender (women): 83 (39.5%) Age (years): mean (SD): caffeine 75 group: 38 (12); caffeine 125 group: 38 (11); control group: 37 (14) Inclusion criteria: patients scheduled for elective lower extremity surgery, ASA I-II Exclusion criteria: hypertension, diabetes mellitus, caffeine consumption > 250 mg/day, intolerance to caffeine, chronic headache, contraindication to spinal anaesthesia
Interventions	Caffeine 75 group: paracetamol 500 mg + caffeine 75 mg orally Caffeine 125 group: paracetamol 500 mg + caffeine 125 mg orally Control group: placebo orally All 3 groups received intervention 1 h before the spinal anaesthesia and the same doses repeated every 6 hours for 3 days. Spinal anaesthesia with 3 mL of hyperbaric bupivacaine 0.5% Co-interventions: all patients hydrated with at least 0.5 L of intravenous crystalloid solution before the procedure
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of participants with any headache • Number of any possible adverse effects from the drug taken to prevent PDPH
Notes	PDPH defined as: quote: "headache was categorized as a PDPH if it was worse on sitting or standing and relieved or reduced by lying flat" (Page 59) PDPH severity: quote: "class I, mild headache when sitting or ambulating; class II, moderate to severe headache when sitting or ambulating; and class III, moderate to severe headache when supine" (Page 60) Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement

Esmaoglu 2005   (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The interviewer was blinded as to study group assignment" (Page 59)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No explicit information but it seems that no patients were lost
Selective reporting (reporting bias)	Unclear risk	No information available

Flaatten 1987

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Norway (Bergen) Setting: admitted to hospital Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: double-blind Follow-up period: 3 days
Participants	Randomised: 250 (intervention group: 125; control group: 125) Excluded (post-randomisation): not described Gender (women): 85 (34%) Age (years): mean: intervention group 34.2; control group 33.0 Inclusion criteria: young (< 55 years old) hospitalised patients of either sex of ASA groups I and II, receiving spinal anaesthesia Exclusion criteria: not described
Interventions	Intervention group: indomethacin 100 mg per rectum 4 hours post operation Control group: placebo per rectum 4 hours post operation Co-interventions: all spinal anaesthesia were performed using a 25-G spinal needle
Outcomes	• Number of participants affected by PDPH of any severity • Number of missing data (participants lost to follow-up)
Notes	PDPH defined as: quote "occurred after mobilisation, aggravated by the erect or sitting position, relieved by lying flat, mostly occipital or frontal, accompanied by dizziness, vomiting, rigidity of the neck and visual disturbances" (Page 202)

Flaatten 1987 (*Continued*)

	Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Quote: "following this they were randomly allocated in a double-blind manner to receive either indomethacin 100mg or a placebo per rectum 4 hours postoperatively" (Page 202)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Three patients were lost to follow-up and their results are not included in the study." (Page 202). All 3 patients from placebo group, and not reasons stated. Unlikely to produce bias, but incomplete information available
Selective reporting (reporting bias)	Unclear risk	No information available

Hakim 2010

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Egypt (Cairo) Setting: admitted to hospital Study design: parallel Randomisation: computer-generated random number list Allocation concealment: yes Blinding: blinding of patients, hospital health personnel and outcome assessors Follow-up period: 14 days
Participants	Randomised: 95 (intervention group: 47; control group: 48) Excluded (post randomisation): 5 (intervention group: 2; control group: 3) Gender (women): 95 (100%) Age (years): mean (SD): intervention group: 31.3 (4.8); control group: 29.7 (4.9) Inclusion criteria: parturients who had epidural analgesia for normal vaginal delivery and

	who suffered an inadvertent dural tap Exclusion criteria: contraindication to steroid or ACTH therapy (e.g. hypertension or diabetes mellitus), pre-eclampsia, or contraindication to EBP (e.g. fever or leukocytosis)
Interventions	Intervention group: cosyntropin 1 mg (Cortrosy®, Amphastar Pharmaceuticals Inc) in 1 mL solution, intravenously over 5 min Control group: 1 mL of normal saline intravenously Co-interventions: epidural analgesia: test with 3 mL of 2% lidocaine with 1:200,000 epinephrine. Loading dose of 8 to 15 mL of bupivacaine 0.125% plus fentanyl 50 μg. Continuous infusion of bupivacaine 0.125% with fentanyl 2 μg/mL at 8 to 15 mL/h. Patients with accidental dural puncture were encouraged to ambulate and to drink plenty of fluids, with prescription of stool softeners
Outcomes	- Number of participants affected by PDPH of any severity - Number of any possible adverse effects from the drug taken to prevent PDPH - Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: quote: "PDPH if they developed headache within 5 days after dural puncture, which worsened within 15 min of sitting or standing, and improved within 15 min after lying, with at least one of the following criteria: neck stiffness, tinnitus, hypacusia, photophobia, or nausea" (Page 414) Sample size calculation: estimated 44 patients in each group for detecting at least a 30% difference between the groups the incidence of PDPH, a beta error of 0.2, 2-tailed alfa-error of 0.05 and degree of freedom of 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to one of two groups using a computer-generated random number list. The list was created using the GraphPad StatMate version 1.01i software" (Page 414)
Allocation concealment (selection bias)	Low risk	Quote: "The list... was accessible to anaesthesiologist attending to patients in labor through the computer database" (Page 414)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Injections were prepared by assistants not participating in the study, and both the patients and those involved in the study were blinded as to the patients' group" (Page 414)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Nurses and anaesthesiologists involved in headache assessment were

Hakim 2010   (*Continued*)

		blinded as to the patients' group" (Page 414)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Flowchart showing incidence of accidental dural puncture, patient recruitment and randomisation, incidence of PDPH and need for EBP and repeat EBP" (Page 415)
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

Sadeghi 2012

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Iran (Shiraz) Setting: admitted to hospital Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: double-blind (patient and researcher) Follow-up period: 48 hours after elective caesarean section
Participants	Randomised: 120 (intervention group: 60; control group: 60) Excluded (post-randomisation): not described Gender (women): 120 (100%) Age (years): mean (SD): intervention group 26.11 (4.4); control group 26.35 (5.3) Inclusion criteria: patients undergoing elective caesarean section Exclusion criteria: headache, psychiatric problems, back pain, pre-eclampsia, coagulation disorders, convulsion background, spinal anaesthesia history and those who used any kinds of opiates
Interventions	Intervention group: after the child birth and umbilical cord clamping, aminophylline 1 mg/kg intravenously Control group: no intervention Co-interventions: 2 mL lidocaine 1% used for skin anaesthesia. A combination of 55 mg lidocaine 5% (dose and concentration as cited in the publication) and meperidine 5 mg were used for spinal anaesthesia. Needle nº 23 used for the spinal anaesthesia. In case of hypotension in both groups, ephedrine 5 mg intravenously. In both groups, the patients rested 24 h after the operation and then started walking
Outcomes	• Number of participants affected by PDPH of any severity
Notes	PDPH defined as: quote "Post dural puncture headache (PDPH) is a kind of headache that worsens by standing up and dwindles with recumbency" (Page 13) Sample size calculation: not described

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly divided into two groups with an accidental allocation" (Page 14)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind randomised study (patient and researcher)" (Page 14) Quote: "data collection performed by a trained nurse that did not know anything about the intervention, the other stages of the study were performed by the doctors who knew the whole project and it may cause bias in the study" (Page 15)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "data collection performed by a trained nurse that did not know anything about the intervention, the other stages of the study were performed by the doctors who knew the whole project and it may cause bias in the study" (Page 15)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No explicit information but it seems that no patients were lost
Selective reporting (reporting bias)	High risk	Adverse events not reported

Strelec 1994

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: US (Pittsburgh) Setting: hospital Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: described as double-blind Follow-up period: 4 days
Participants	Randomised: 60 (intervention group: 30; control group: 30) Excluded (post randomisation): 2 (intervention group: 0; control group: 2) Gender (women): 18 (31%) Age (years): mean (SD): intervention group: 40.2 (13.3); control group: 48.5 (13)

Strelec 1994 (*Continued*)

	Inclusion criteria: participants who have had a lumbar myelography Exclusion criteria: not described
Interventions	Intervention group: oral anhydrous caffeine capsules, 300 mg every 8 hours for 3 days Control group: placebo capsules every 8 hours for 3 days Co-interventions: all other caffeinated substances were forbidden
Outcomes	• Number of participants affected by PDPH of any severity • Number of any possible adverse effects from the drug taken to prevent PDPH • Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: quote: "PDPH criteria included postural headache, associated N/V, photophobia and neck stiffness" (Page 79) Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 lost. No information provided about the reasons or the moment, but unlikely this is a cause of bias
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

Yousefshahi 2012

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Iran (Tehran) Setting: admitted to hospital Study design: parallel Randomisation: computer-generated random number list Allocation concealment: not described Blinding: described as double-blind Follow-up period: 3 days
Participants	Randomised: 372 (intervention group: 186; control group: 186) Excluded (post randomisation): 12 (intervention group: 4; control group: 8) Gender (women): 372 (100%) Age (years): mean: intervention group: 28.5; control group: 28.9 Inclusion criteria: parturient after spinal anaesthesia for caesarean section Exclusion criteria: patients ASA class higher than II, sensitive to local anaesthetics, anti-coagulant therapy, pre-eclampsia or skin infection at the site of needle insertion
Interventions	Intervention group: intravenous dexamethasone 8 mg (2 mL) after clamping the umbilical cord Control group: 2 mL of intravenous normal saline after clamping the umbilical cord Co-interventions: all patients received 500 mL of normal saline or Ringer's solution intravenously before spinal anaesthesia. Ondansetron, metoclopramide and H2-blockers as needed
Outcomes	• Number of participants affected by PDPH of any severity • Number of participants with severe PDPH • Number of participants with any headache • Number of missing data (withdrawals, drop-outs and participants lost to follow-up)
Notes	PDPH defined as: quote: "PDPH was defined as a headache located in the occipital and/or frontal areas which was worsened by standing or sitting, and alleviates by lying down" (Page 2) Sample size calculation: quote: "The study was designed to achieve 80 % power to detect a 15 % difference in the population, in which the prevalence of the condition was 8.9 % based on previous studies. The level of statistical significance was reported to be 5 %" (Page 3) Email contact with Fardin Yousefshahi MD on April 2012 for clarification about missing data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were divided into two groups based on a computer random number generator" (Page 2)

Yousefshahi 2012   *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each patient received a specific row number for grouping into the dexamethasone or placebo group, corresponding to a computerized randomization system; grouping was not reflected in the patient's data sheet" (Page 2)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Trained nurses, who were unaware of the objectives of the study, asked the patients about any occurrence of headache every 24 h for 72 h. The patients complaining of possible PDPH were then visited by an anesthesiologist, similarly unaware of the study objectives, to rule out other causes of headache" (Page 2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twelve patients were excluded from the study due to missing data" (Page 2). 4 patients from the intervention group and 8 from the control group
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

ACTH: adrenocorticotropic hormone; ASA: American Society of Anesthesiologists; EBP: epidural blood patch; LP: lumbar puncture; PDPH: post-dural puncture headache; SD: standard deviation; VRSP: Verbal Rating Score for Pain.

Characteristics of excluded studies   *[ordered by study ID]*

Study	Reason for exclusion
Ackerman 2004	No individual drug assessed
Altunkaya 2005	The study did not focus on PDPH
Aziz 1968	The orthostatic component of headache not described
Balestrieri 2003	The study was not a RCT (letter)
Beilin 2003	The orthostatic component of headache not described

Breebaart 2003	The study did not focus on PDPH
Caldwell 1994	The orthostatic component of headache not described
Camann 1992	The orthostatic component of headache not described
Camann 1993	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Campbell 1995	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Cesur 2009	The study was not a RCT (retrospective observational study)
Chalmers 1988	The study did not focus on PDPH Intervention was not aimed at preventing PDPH
Chilvers 1997	Intervention was not aimed at preventing PDPH
Cho 2008	The study did not focus on PDPH
Clarke 2009	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Colonna-Romano 1989	No individual drug assessed
Cowan 1980	The orthostatic component of headache not described
D'Angelo 1994	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Danelli 2004	The study did not focus on PDPH
Dayioglu 2009	The orthostatic component of headache not described
De Pietri 2006	The orthostatic component of headache not described
Delfino 2001	The orthostatic component of headache not described
Dijkstra 2008	The orthostatic component of headache not described Intervention was not aimed to prevent PDPH
Dilli 2008	The study did not focus on PDPH
Dominguez-Hervella 1993	The orthostatic component of headache not described
Edström 1986	The orthostatic component of headache not described

Elkhodair 2010	The study was not a RCT (Critically Appraised Topics)
Fogarty 1993	The study did not focus on PDPH
Fogarty 1995	The study did not focus on PDPH
Frey 1998	The orthostatic component of headache not described
Frizelle 1997	The orthostatic component of headache not described
Fu 2008	The study did not focus on PDPH
Fujii 1998	The study did not focus on PDPH
Förster 2006	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Gangopadhyay 2010	The orthostatic component of headache not described
Ganzi 1995	No individual drug assessed
Garg 2010	The study did not focus on PDPH
Gielen 1986	The study did not focus on PDPH
Ginsberg 1996	The study did not focus on PDPH
Girgin 2008	The study did not focus on PDPH
Gogarten 2004	The study did not focus on PDPH
Gurbet 2008	The study did not focus on PDPH
Hansen 1979	The orthostatic component of headache not described
Hansen 1980	The study was not a RCT (letter)
Harsten 1997	The orthostatic component of headache not described
Hein 2010	The orthostatic component of headache not described
Hendriks 2009	The orthostatic component of headache not described
Ilioff 1990	The orthostatic component of headache not described

Imbelloni 2003	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Imbelloni 2009	Intervention was not aimed at preventing PDPH
Imbelloni 2010	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Jacobsohn 2005	The orthostatic component of headache not described
Kallio 2004	The study did not focus on PDPH
Kallio 2005	The study did not focus on PDPH
Kaukinen 1981	Allocation was not randomised
Kouri 2004	The study did not focus on PDPH
Lanz 1982	The study did not focus on PDPH
Lauretti 1999	The study did not focus on PDPH
Lauretti 1999b	The study did not focus on PDPH
Lauretti 2000	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Lauretti 2000b	The study did not focus on PDPH
Lee 2005	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Lewis 1992	The study did not focus on PDPH
Lierz 2004	The study did not focus on PDPH
Luck 2008	The study did not focus on PDPH
López-Soriano 2002	The orthostatic component of headache not described
Manaa 2005	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Martlew 2009	The study was not a RCT (letter)
Massou 2008	The study was not a RCT (letter)

Meininger 2003	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Michalek-Sauberer 2008	The orthostatic component of headache not described
Morrison 1994	The study did not focus on PDPH
Mosavy 1975	Allocation was not randomised
Murto 1999	The orthostatic component of headache not described
Møller 1984	The orthostatic component of headache not described
Neilson 2008	The study did not focus on PDPH
Ogun 2003	The study did not focus on PDPH
Paech 1993	The orthostatic component of headache not described
Palahniuk 1979	Allocation was not randomised No individual drug assessed
Pan 2001	The study did not focus on PDPH
Patra 2005	The study did not focus on PDPH
Phero 1987	The orthostatic component of headache not described
Plaja 2000	The study did not focus on PDPH
Prusinski 1974	Allocation was not randomised
Radpay 2003	The study did not focus on PDPH
Reinhart 1985	The study did not focus on PDPH
Rivera-Ordonez 2005	The study did not focus on PDPH
Roux 1983	The orthostatic component of headache not described
Rucci 1985	The study did not focus on PDPH
Ryan 1983	The study did not focus on PDPH
Sakaguchi 2000	The study did not focus on PDPH
Sangarlangkarn 1987	The orthostatic component of headache not described

Sanli 2005	Intervention was not aimed at preventing PDPH
Santos 1986	The study was not a RCT (no control group) The orthostatic component of headache not described
Sawhney 2004	The study did not focus on PDPH
Sengupta 1989	No individual drug assessed
Seyhan 2005	The study was not a RCT (no control group)
Shah 2003	The study did not focus on PDPH
Singh 2006	The study did not focus on PDPH
Smith 2004	The study did not focus on PDPH
Soni 2001	The study did not focus on PDPH
Sudarshan 1995	The study did not focus on PDPH
Tekin 2007	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Thomas 2006	The study did not focus on PDPH
Trivedi 1993	Epidural saline infusion was not used as a pharmacological agent
Tsen 2001	The orthostatic component of headache not described
Tucker 2004	The study did not focus on PDPH
Tuncer 2005	The study did not focus on PDPH
Turan 2006	The study did not focus on PDPH
Turker 2003	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Unlugenc 2006	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Unlugenc 2009	The orthostatic component of headache not described Intervention was not aimed at preventing PDPH
Usubiaga 1967	Allocation was not randomised No individual drug assessed

Vaghadia 1997	Intervention was not aimed at preventing PDPH
Vale 1995	The study did not focus on PDPH
Vichitvejpaisal 1992	Intervention was not aimed at preventing PDPH
Viscusi 2005	The study did not focus on PDPH
Waxler 2004	The study did not focus on PDPH
Wells 2004	The study did not focus on PDPH
Whiteside 2003	Intervention was not aimed at preventing PDPH
Widerlöv 1979	The orthostatic component of headache not described
Wilder-Smith 1998	The study did not focus on PDPH
Wood 1993	The study did not focus on PDPH
Yanagidate 2004	The study did not focus on PDPH
Yeh 2000	The study did not focus on PDPH
Yücel 1999	The orthostatic component of headache not described
Zackova 2000	The study did not focus on PDPH

PDPH: post-dural puncture headache; RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Spinal morphine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.1 Pruritus	1		Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Nausea and vomiting	1		Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Epidural morphine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3.1 Pruritus	1		Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Nausea and vomiting	1		Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Spinal fentanyl versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 4. Caffeine 75 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants with any headache	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 5. Caffeine 125 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants with any headache	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 6. Caffeine 75 mg versus caffeine 125 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants with any headache	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 7. Indomethacin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 8. Cosyntropin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 9. Caffeine 300 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Number of any possible adverse effects from the drug taken to prevent PDPH	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 10.   Dexamethasone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Number of participants with severe PDPH	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Number of participants with any headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 11.   Caffeine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1	280	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.52, 1.59]
2 Number of participants with severe PDPH	1	280	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.33, 2.35]
3 Number of participants with any headache	1	280	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.51, 1.24]

Comparison 12.   Aminophylline versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants affected by PDPH of any severity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Number of participants affected by PDPH of any severity at 24 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Number of participants affected by PDPH of any severity at 48 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Spinal morphine versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 1 Spinal morphine versus placebo

Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Spinal morphine n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Abboud 1992	9/40	8/42		1.18 [0.51, 2.76]

```
           0.01   0.1    1    10   100
        Favours spinal morphine    Favours placebo
```

Analysis 1.2. Comparison 1 Spinal morphine versus placebo, Outcome 2 Number of any possible adverse effects from the drug taken to prevent PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 1 Spinal morphine versus placebo

Outcome: 2 Number of any possible adverse effects from the drug taken to prevent PDPH

Study or subgroup	Favours spinal morphine n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
1 Pruritus				
Abboud 1992	25/40	3/42		8.75 [2.86, 26.72]
2 Nausea and vomiting				
Abboud 1992	18/40	23/42		0.82 [0.53, 1.27]

```
           0.01   0.1    1    10   100
        Favours spinal morphine    Favours placebo
```

Analysis 2.1.   Comparison 2 Epidural morphine versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 2 Epidural morphine versus placebo

Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Epidural morphine n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Al-metwalli 2008	3/25	12/25		0.25 [0.08, 0.78]

```
                                              0.01   0.1    1    10   100
                                        Favours epidural morphine   Favours placebo
```

Analysis 2.2.   Comparison 2 Epidural morphine versus placebo, Outcome 2 Number of participants with severe PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 2 Epidural morphine versus placebo

Outcome: 2 Number of participants with severe PDPH

Study or subgroup	Epidural morphine n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Al-metwalli 2008	0/25	6/25		0.08 [0.00, 1.30]

```
                                              0.01   0.1    1    10   100
                                        Favours epidural morphine   Favours placebo
```

Analysis 2.3. Comparison 2 Epidural morphine versus placebo, Outcome 3 Number of any possible adverse effects from the drug taken to prevent PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 2 Epidural morphine versus placebo

Outcome: 3 Number of any possible adverse effects from the drug taken to prevent PDPH

Study or subgroup	epidural morphine n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
1 Pruritus				
Al-metwalli 2008	3/25	0/25		7.00 [0.38, 128.87]
2 Nausea and vomiting				
Al-metwalli 2008	11/25	4/25		2.75 [1.01, 7.48]

0.01   0.1   1   10   100

Favours epidural morphine   Favours placebo

Analysis 3.1. Comparison 3 Spinal fentanyl versus no intervention, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 3 Spinal fentanyl versus no intervention

Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Spinal fentanyl n/N	No intervention n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Devcic 1993	7/96	4/98		1.79 [0.54, 5.91]

0.01   0.1   1   10   100

Favours spinal fenatanyl   Favours no intervention

Analysis 3.2. Comparison 3 Spinal fentanyl versus no intervention, Outcome 2 Number of participants with severe PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 3 Spinal fentanyl versus no intervention

Outcome: 2 Number of participants with severe PDPH

Study or subgroup	Spinal fentanyl n/N	No comparison n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Devcic 1993	3/96	1/98		3.06 [0.32, 28.93]

```
                                                          0.01    0.1    1    10    100
                                                     Favours spinal fentanyl   Favours no comparison
```

Analysis 3.3. Comparison 3 Spinal fentanyl versus no intervention, Outcome 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 3 Spinal fentanyl versus no intervention

Outcome: 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)

Study or subgroup	Spinal fentanyl n/N	No intervention n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Devcic 1993	4/96	2/98		2.04 [0.38, 10.89]

```
                                                          0.01    0.1    1    10    100
                                                     Favours spinal fentanyl   Favours no intervention
```

Analysis 4.1. Comparison 4 Caffeine 75 mg versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 4 Caffeine 75 mg versus placebo

Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Caffeine 75 mg n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	10/70	11/70		0.91 [0.41, 2.00]

```
                  0.01    0.1      1      10    100
                  Favours caffeine 75 mg    Favours placebo
```

Analysis 4.2. Comparison 4 Caffeine 75 mg versus placebo, Outcome 2 Number of participants with severe PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 4 Caffeine 75 mg versus placebo

Outcome: 2 Number of participants with severe PDPH

Study or subgroup	Caffeine 75 mg n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	6/70	4/70		1.50 [0.44, 5.09]

```
                  0.01    0.1      1      10    100
                  Favours caffeine 75 mg    Favours placebo
```

Analysis 4.3.   Comparison 4 Caffeine 75 mg versus placebo, Outcome 3 Number of participants with any headache.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 4 Caffeine 75 mg versus placebo

Outcome: 3 Number of participants with any headache

Study or subgroup	Caffeine 75 mg n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	4/70	6/70		0.67 [0.20, 2.26]

```
          0.01    0.1       1    10   100
       Favours caffeine 75 mg    Favours placebo
```

Analysis 5.1.   Comparison 5 Caffeine 125 mg versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 5 Caffeine 125 mg versus placebo

Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Caffeine 125 mg n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	10/70	11/70		0.91 [0.41, 2.00]

```
          0.01    0.1       1    10   100
      Favours caffeine 125 mg    Favours placebo
```

Analysis 5.2. Comparison 5 Caffeine 125 mg versus placebo, Outcome 2 Number of participants with severe PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 5 Caffeine 125 mg versus placebo

Outcome: 2 Number of participants with severe PDPH

Study or subgroup	Caffeine 125 mg n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	1/70	4/70		0.25 [0.03, 2.18]

```
            0.01   0.1    1    10   100
         Favours caffeine 125 mg   Favours placebo
```

Analysis 5.3. Comparison 5 Caffeine 125 mg versus placebo, Outcome 3 Number of participants with any headache.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 5 Caffeine 125 mg versus placebo

Outcome: 3 Number of participants with any headache

Study or subgroup	Caffeine 125 mg n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	3/70	6/70		0.50 [0.13, 1.92]

```
            0.01   0.1    1    10   100
         Favours caffeine 125 mg   Favours placebo
```

Analysis 6.1. Comparison 6 Caffeine 75 mg versus caffeine 125 mg, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 6 Caffeine 75 mg versus caffeine 125 mg

Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Caffeine 75 mg n/N	Caffeine 125 mg n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	10/70	10/70		1.00 [0.44, 2.25]

```
                          0.01   0.1    1    10   100
                        Favours caffeine 75 mg    Favours caffeine 125 mg
```

Analysis 6.2. Comparison 6 Caffeine 75 mg versus caffeine 125 mg, Outcome 2 Number of participants with severe PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 6 Caffeine 75 mg versus caffeine 125 mg

Outcome: 2 Number of participants with severe PDPH

Study or subgroup	Caffeine 75 mg n/N	Caffeine 125 mg n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	6/70	1/70		6.00 [0.74, 48.55]

```
                          0.01   0.1    1    10   100
                        Favours caffeine 75 mg    Favours caffeine 125 mg
```

Analysis 6.3. Comparison 6 Caffeine 75 mg versus caffeine 125 mg, Outcome 3 Number of participants with any headache.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 6 Caffeine 75 mg versus caffeine 125 mg

Outcome: 3 Number of participants with any headache

Study or subgroup	Caffeine 75 mg n/N	Caffeine 125 mg n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	4/70	3/70		1.33 [0.31, 5.74]

```
                                    0.01   0.1      1    10   100
                              Favours caffeine 75 mg   Favours caffeine 125 mg
```

Analysis 6.4. Comparison 6 Caffeine 75 mg versus caffeine 125 mg, Outcome 4 Number of any possible adverse effects from the drug taken to prevent PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 6 Caffeine 75 mg versus caffeine 125 mg

Outcome: 4 Number of any possible adverse effects from the drug taken to prevent PDPH

Study or subgroup	Caffeine 75 mg n/N	Caffeine 125 mg n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Esmaoglu 2005	0/70	0/70		0.0 [0.0, 0.0]

```
                                    0.01   0.1      1    10   100
                              Favours caffeine 75 mg   Favours caffeine 125 mg
```

Analysis 7.1. Comparison 7 Indomethacin versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 7 Indomethacin versus placebo

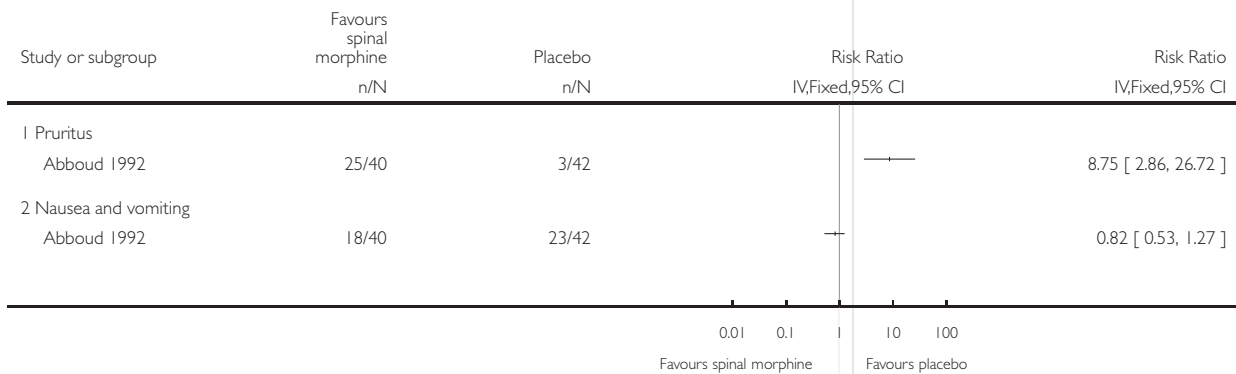Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Indomethacin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Flaatten 1987	21/125	30/125		0.70 [0.42, 1.15]

0.01   0.1   1   10   100

Favours indomethacin   Favours placebo

Analysis 7.2. Comparison 7 Indomethacin versus placebo, Outcome 2 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 7 Indomethacin versus placebo

Outcome: 2 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)

Study or subgroup	Indometacin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Flaatten 1987	0/125	3/125		0.14 [0.01, 2.74]

0.01   0.1   1   10   100

Favours indometacin   Favours placebo

Analysis 8.1.   Comparison 8 Cosyntropin versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 8 Cosyntropin versus placebo

Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Cosyntropin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Hakim 2010	15/47	31/48		0.49 [0.31, 0.79]

```
            0.01   0.1    1    10   100
         Favours cosyntropin   Favours placebo
```
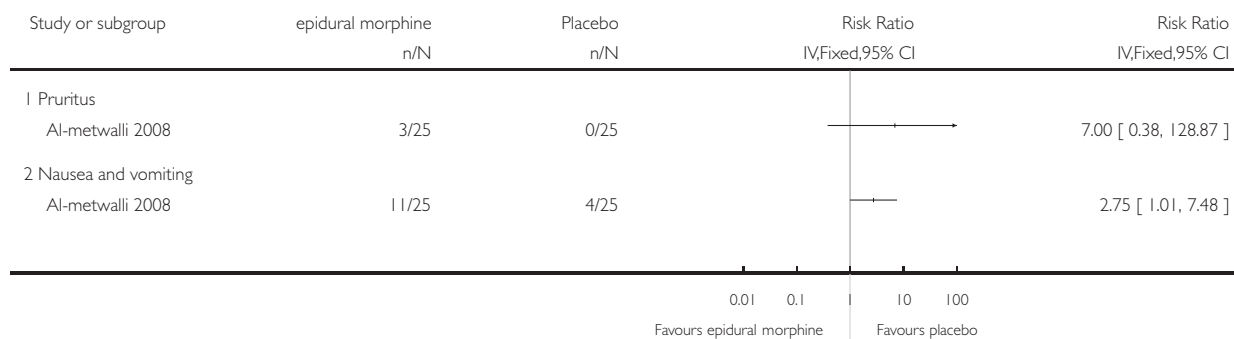
Analysis 8.2.   Comparison 8 Cosyntropin versus placebo, Outcome 2 Number of any possible adverse effects from the drug taken to prevent PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 8 Cosyntropin versus placebo

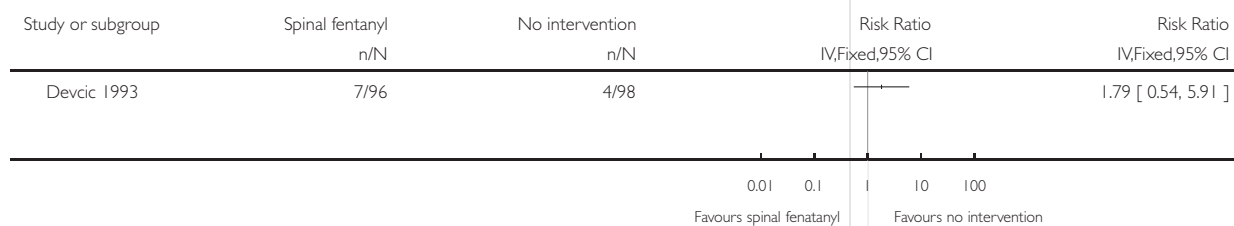Outcome: 2 Number of any possible adverse effects from the drug taken to prevent PDPH

Study or subgroup	Cosyntropin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Hakim 2010	2/47	0/48		5.10 [0.25, 103.57]

```
            0.01   0.1    1    10   100
         Favours cosyntropin   Favours placebo
```

Analysis 8.3. Comparison 8 Cosyntropin versus placebo, Outcome 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 8 Cosyntropin versus placebo

Outcome: 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)

Study or subgroup	Cosyntropin	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI	IV,Fixed,95% CI
Hakim 2010	2/47	3/48		0.68 [0.12, 3.89]

0.01   0.1   1   10   100

Favours cosyntropin   Favours placebo

Analysis 9.1. Comparison 9 Caffeine 300 mg versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 9 Caffeine 300 mg versus placebo

Outcome: 1 Number of participants affected by PDPH of any severity

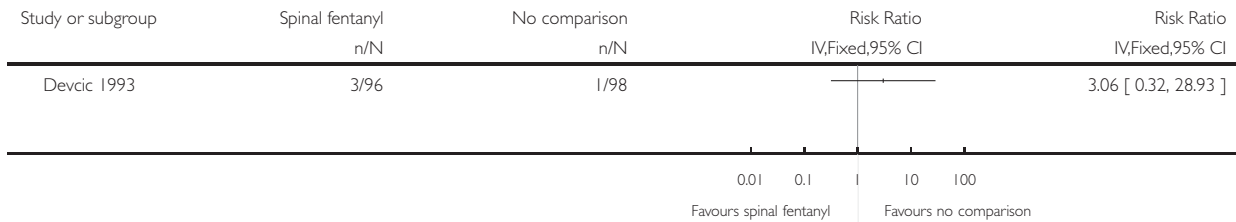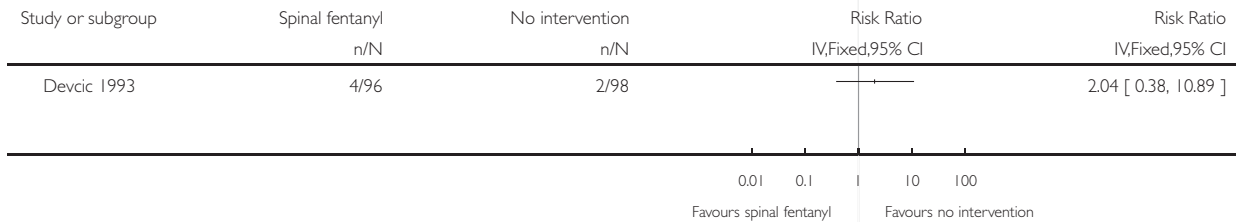| Study or subgroup	Caffeine 300 mg	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI	IV,Fixed,95% CI
Strelec 1994	12/30	6/30		2.00 [0.86, 4.63]

0.01   0.1   1   10   100

Favours caffeine 300 mg   Favours placebo

Analysis 9.2.   Comparison 9 Caffeine 300 mg versus placebo, Outcome 2 Number of any possible adverse effects from the drug taken to prevent PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 9 Caffeine 300 mg versus placebo

Outcome: 2 Number of any possible adverse effects from the drug taken to prevent PDPH

Study or subgroup	Caffeine 300 mg	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI	IV,Fixed,95% CI
Strelec 1994	9/30	2/30		4.50 [1.06, 19.11]

```
                    0.01    0.1      1      10    100
              Favours caffeine 300 mg    Favours placebo
```

Analysis 9.3.   Comparison 9 Caffeine 300 mg versus placebo, Outcome 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 9 Caffeine 300 mg versus placebo

Outcome: 3 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)

Study or subgroup	Caffeine 300 mg	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI	IV,Fixed,95% CI
Strelec 1994	0/30	2/30		0.20 [0.01, 4.00]

```
                    0.01    0.1      1      10    100
              Favours caffeine 300 mg    Favours placebo
```
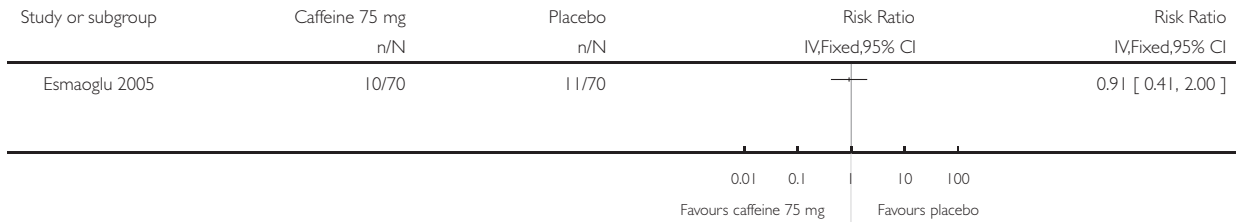
Analysis 10.1.   Comparison 10 Dexamethasone versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 10 Dexamethasone versus placebo

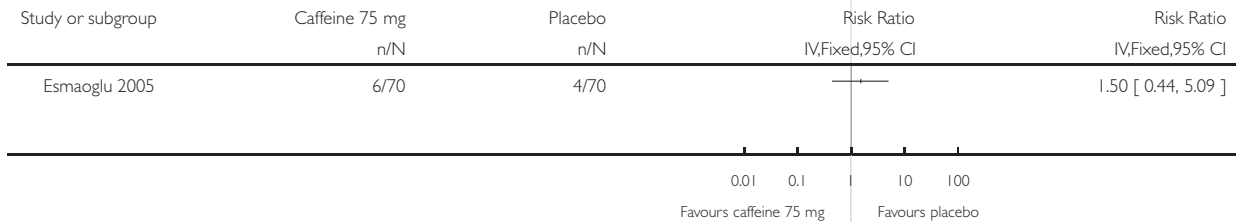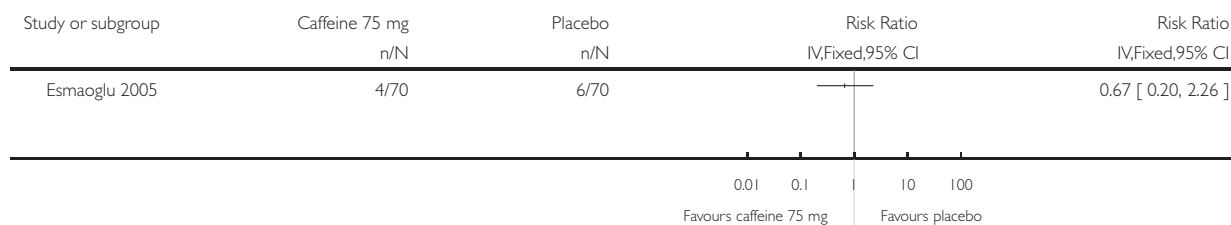Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Dexamethasone n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Doroudian 2011	15/89	19/89		0.79 [0.43, 1.45]
Yousefshahi 2012	28/186	11/186		2.55 [1.31, 4.96]

0.01   0.1   1   10   100

Favours dexamethasone   Favours placebo

Analysis 10.2.   Comparison 10 Dexamethasone versus placebo, Outcome 2 Number of participants with severe PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 10 Dexamethasone versus placebo

Outcome: 2 Number of participants with severe PDPH

Study or subgroup	Dexamethasone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Doroudian 2011	2/89	8/89		0.25 [0.05, 1.14]
Yousefshahi 2012	0/186	0/186		0.0 [0.0, 0.0]

0.01   0.1   1   10   100

Favours dexamethasone   Favours placebo

Analysis 10.3. Comparison 10 Dexamethasone versus placebo, Outcome 3 Number of participants with any headache.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 10 Dexamethasone versus placebo

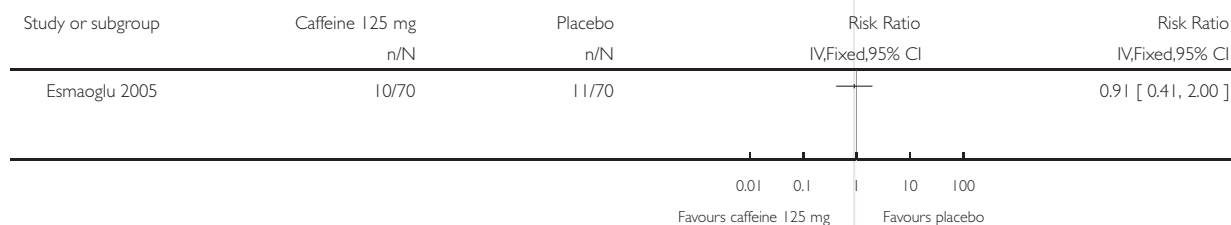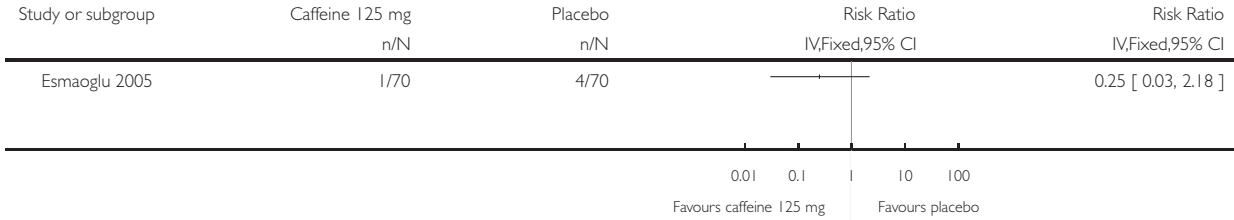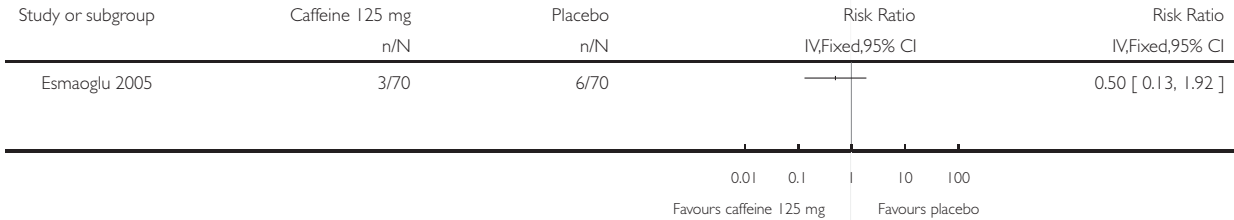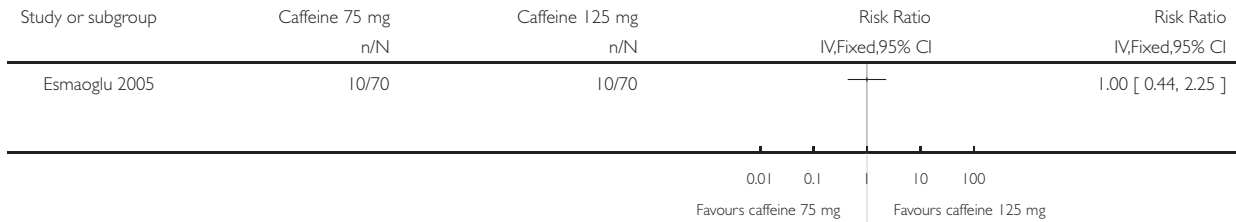Outcome: 3 Number of participants with any headache

Study or subgroup	Dexamethasone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Yousefshahi 2012	11/186	5/186		2.20 [0.78, 6.21]

```
                    0.01   0.1        1      10    100
                  Favours dexamethasone   Favours placebo
```

Analysis 10.4. Comparison 10 Dexamethasone versus placebo, Outcome 4 Number of missing data (withdrawals, drop-outs and participants lost to follow-up).

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 10 Dexamethasone versus placebo

Outcome: 4 Number of missing data (withdrawals, drop-outs and participants lost to follow-up)

Study or subgroup	Dexamethasone n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Doroudian 2011	0/89	0/89		0.0 [0.0, 0.0]
Yousefshahi 2012	4/186	8/186		0.50 [0.15, 1.63]

```
                    0.01   0.1        1      10    100
                  Favours dexamethasone   Favours placebo
```

Analysis 11.1. Comparison 11 Caffeine versus placebo, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 11 Caffeine versus placebo

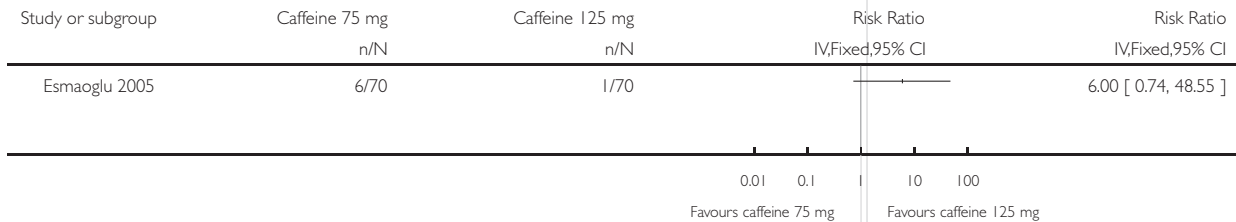Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Caffeine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Esmaoglu 2005	10/70	11/70		50.0 %	0.91 [0.41, 2.00]
Esmaoglu 2005	10/70	11/70		50.0 %	0.91 [0.41, 2.00]
Total (95% CI)	**140**	**140**		**100.0 %**	**0.91 [0.52, 1.59]**

Total events: 20 (Caffeine), 22 (Placebo)
Heterogeneity: Chi² = 0.0, df = 1 (P = 1.00); I² =0.0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
        Favours caffeine   Favours placebo
```

Analysis 11.2. Comparison 11 Caffeine versus placebo, Outcome 2 Number of participants with severe PDPH.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 11 Caffeine versus placebo

Outcome: 2 Number of participants with severe PDPH

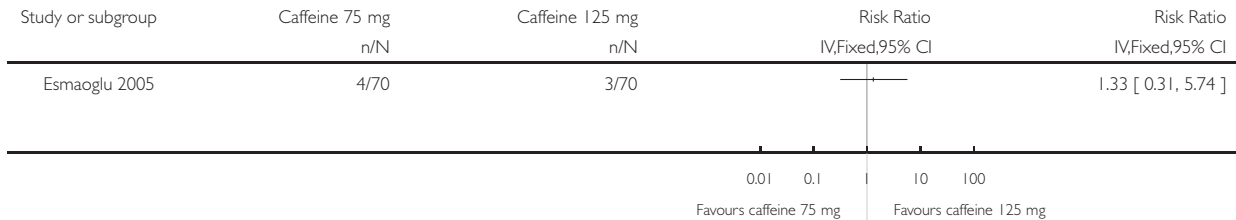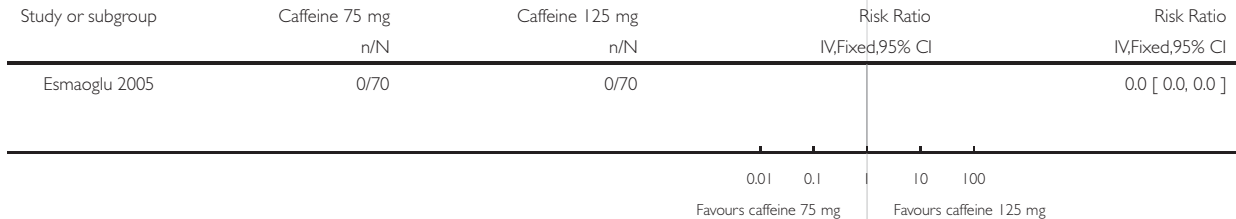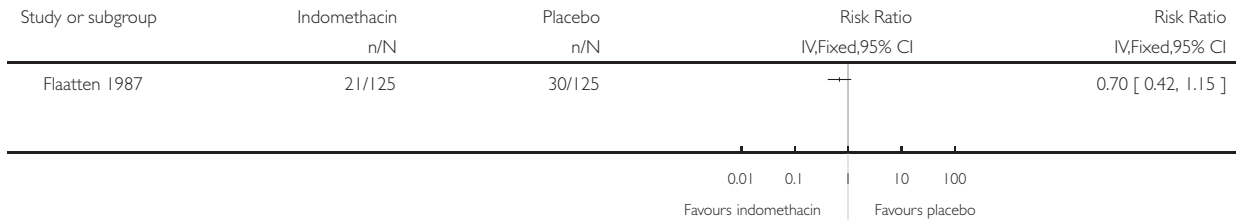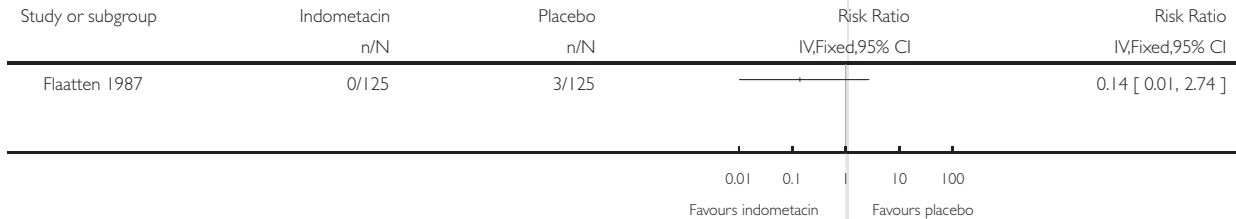| Study or subgroup	Caffeine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Esmaoglu 2005	1/70	4/70		50.0 %	0.25 [0.03, 2.18]
Esmaoglu 2005	6/70	4/70		50.0 %	1.50 [0.44, 5.09]
Total (95% CI)	**140**	**140**		**100.0 %**	**0.88 [0.33, 2.35]**

Total events: 7 (Caffeine), 8 (Placebo)
Heterogeneity: Chi² = 2.03, df = 1 (P = 0.15); I² =51%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
        Favours caffeine   Favours placebo
```

Analysis 11.3. Comparison 11 Caffeine versus placebo, Outcome 3 Number of participants with any headache.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 11 Caffeine versus placebo

Outcome: 3 Number of participants with any headache

Study or subgroup	Caffeine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Esmaoglu 2005	14/70	17/70		50.0 %	0.82 [0.44, 1.54]
Esmaoglu 2005	13/70	17/70		50.0 %	0.76 [0.40, 1.45]
Total (95% CI)	**140**	**140**		**100.0 %**	**0.79 [0.51, 1.24]**

Total events: 27 (Caffeine), 34 (Placebo)

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² =0.0%

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

```
     0.01   0.1    1    10   100
     Favours caffeine    Favours placebo
```

Analysis 12.1. Comparison 12 Aminophylline versus no intervention, Outcome 1 Number of participants affected by PDPH of any severity.

Review: Drug therapy for preventing post-dural puncture headache

Comparison: 12 Aminophylline versus no intervention

Outcome: 1 Number of participants affected by PDPH of any severity

Study or subgroup	Aminophylline n/N	No intervention n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Number of participants affected by PDPH of any severity at 24 hours				
Sadeghi 2012	3/60	19/60		0.16 [0.05, 0.51]
2 Number of participants affected by PDPH of any severity at 48 hours				
Sadeghi 2012	3/60	14/60		0.21 [0.06, 0.71]

```
        0.01   0.1    1    10   100
     Favours aminophylline   Favours no intervention
```

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 explode 'Anesthesia, Epidural' / all subheadings
#2 explode 'Anesthesia, Spinal' / all subheadings
#3 explode 'Injections, Spinal' / all subheadings
#4 explode 'Myelography' / all subheadings
#5 explode 'Spinal Puncture' / all subheadings
#6 (spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) near/10 (puncture* or inject* or anesth* or anaesth* or needle*)
#7 myelogra*
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 explode 'Headache disorders' / all subheadings
#10 headach* or cephalgia or (head near/2 pain) or (cranial adj2 pain)
#11 #9 or #10
#12 #8 and #11

Appendix 2. MEDLINE search strategy

#1 explode 'Anesthesia, Epidural' / all subheadings
#2 explode 'Anesthesia, Spinal' / all subheadings
#3 explode 'Injections, Spinal' / all subheadings
#4 explode 'Myelography' / all subheadings
#5 explode 'Spinal Puncture' / all subheadings
#6 (spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) adj10 (puncture* or inject* or anesth* or anaesth* or needle*)
#7 myelogra*
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 explode 'Headache disorders' / all subheadings
#10 headach* or cephalgia or (head adj2 pain) or (cranial adj2 pain)
#11 #9 or #10
#12 #8 and #11
The MEDLINE search strategy above was combined with the following highly sensitive search strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format.

Cochrane Highly Sensitive Search Strategy for identifying randomised trials

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. humans.sh.
11. 9 and 10

Appendix 3. EMBASE search strategy

#1 explode 'Spinal Anesthesia' / all subheadings
#2 explode 'Lumbar Puncture' / all subheadings
#3 explode 'Myelography' / all subheadings
#4 (spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) adj10 (puncture* or inject* or anesth* or anaesth* or needle*)
#5 myelogra*
#6 #1 or #2 or #3 or #4 or #5
#7 explode 'Headache and facial pain' / all subheadings
#8 headach* or cephalgia or (head adj2 pain) or (cranial adj2 pain)
#9 #7 or #8
The above EMBASE search strategy was combined with the following filter developed for EMBASE to identify randomised trials.

Search filter for EMBASE (Ovid format) 2008

1. random*.ti,ab.
2. factorial*.ti,ab. (5987)
3. (crossover* or cross over* or cross-over*).ti,ab.
4. placebo*.ti,ab.
5. (doubl* adj blind*).ti,ab.

6. (singl* adj blind*).ti,ab.
7. assign*.ti,ab.
8. allocat*.ti,ab.
9. volunteer*.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 15 and 16
18. 15 not 17
19. 14 not 18

Appendix 4. CINAHL search strategy

1 anaesthesia, epidural/ or analgesia, epidural/ or "epidural analgesia administration (iowa nic)"/ or exp injections, epidural/
2 exp injections, intraspinal/
3 myelography/
4 spinal puncture/ or anaesthesia, spinal/
5 ((spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) and (puncture* or inject* or anesthe* or anaesthe* or needle*)).ti,ab
6 myelogra*.ti,ab
7 1 or 2 or 3 or 4 or 5 or 6
8 *headache/
9 (headach* or cephalgi* or cephalalgi*).ti,ab
10 8 or 9
11 7 and 10
12 exp clinical trials/
13 (clinical and trial*).ti
14 ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti
15 (randomi?ed and control* and trial*).ti
16 random assignment/
17 (random* and allocat*).ti
18 placebo*.ti
19 placebos/
20 quantitative studies/
21 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 11 and 21

W H A T ' S   N E W

Last assessed as up-to-date: 15 October 2012.

Date	Event	Description
25 February 2013	Amended	Added link to Appendix 4.

CONTRIBUTIONS OF AUTHORS

Conceiving the review (guarantor): Xavier Basurto (XB).

Screening search results: XB, Sonia Uriona (SU).

Screening retrieved papers against inclusion criteria: XB, SU, Laura Martínez (LM), Ivan Solà (IS), Xavier Bonfill Cosp (XBC).

Appraising quality of papers: XB, LM, SU.

Extracting data from papers: XB, LM, SU.

Data management for the review: XB, LM.

Entering data into Review Manager (RevMan 5.1): XB, LM.

Interpretation of data: XB, LM, IS, XBC.

Statistical analysis: XB, LM, IS.

Writing the review: XB, LM, SU, IS.

Comment and editing of review drafts: XB, LM, SU, IS, XBC.

Responsible for reading and checking review before submission: XB, LM, IS, XBC.

Responsible for initiating and running the update of this review: XB.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Iberoamerican Cochrane Centre, Spain.
- CIBER de Epidemiología y Salud Pública (CIBERESP), Spain.

External sources

- Agencia de Calidad del Sistema Nacional de Salud, Ministerio de Salud y Consumo, Spain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Types of participants: "The use of a standardized diagnostic criteria for PDPH was not required, but it should at least be described as orthostatic headache which worsens on standing and improved by lying down." The "it should at least be" has been added to emphasise the need to include only those studies that have used an orthostatic headache criteria to include participants.

- PaPaS Review Group Specialised Register electronic search eliminated.

- CINAHL search strategy included.

- Background has been adapted with a previous published Cochrane review on treatment drugs for PDPH (Basurto 2011).

NOTES

This protocol was originally published in Issue 1, 2000 by Cathie Sudlow. The review has now been taken over by Xavier Basurto Ona and the title split into one on prevention (this present review) and another on treatment, which is being written alongside this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminophylline [administration & dosage]; Analgesics [*administration & dosage]; Caffeine [administration & dosage]; Cosyntropin [administration & dosage]; Dexamethasone [administration & dosage; adverse effects]; Drug Administration Routes; Fentanyl [administration & dosage]; Indomethacin [administration & dosage]; Morphine [administration & dosage; adverse effects]; Post-Dural Puncture Headache [*prevention & control]; Randomized Controlled Trials as Topic; Spinal Puncture [adverse effects]

MeSH check words

Adult; Child; Female; Humans; Male

5.3.- Publicació nº2

Basurto Ona X, Martínez García L, Solà I, Bonfill Cosp X

Drug therapy for treating post-dural puncture headache

Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD007887

DOI:10.1002/14651858.CD007887.pub 2.

5.3.- Publicació nº2

Resum de la publicació nº2

Objectiu: Avaluar l'eficàcia i seguretat dels fàrmacs (qualsevol substància química) per al tractament de la CPPD en adults i nens.

Resultats: Es van incloure 7 ECA (200 participants) en aquesta revisió. Entre un 88-90,5% eren dones, la majoria parteres (84-87%) després d'una PL per l'anestèsia regional. Els fàrmacs avaluats van ser la cafeïna oral i intravenosa, el sumatriptan subcutani, la gabapentina oral, la teofil·lina oral, la hidrocortisona intravenosa i l'ACTH intramuscular.

Un ACA va informar dades sobre la persistència de CPPD de qualsevol gravetat durant el seguiment (resultat primari); cafeïna redueix el nombre de participants amb CPPD en una o dues hores quan es compara amb placebo. El tractament amb cafeïna també va reduir la necessitat de tractament complementari conservador. El tractament amb gabapentina en comparació amb placebo va informar millors puntuacions a l'EVA després d'un, dos, tres i quatre dies. El tractament amb hidrocortisona més el tractament convencional va demostrar millors puntuacions a l'EVA que el tractament convencional sol només a les 6, 24 i 48 hores. El tractament amb teofil·lina va mostrar una mitjana de "suma de dolor" menor en comparació amb el placebo. El sumatriptan i l'ACTH no van mostrar cap efecte rellevant per a aquest resultat. No hi va haver esdeveniments adversos clínicament significatius als fàrmacs utilitzats. La resta dels resultats no es van informar als ACA o no va mostrar cap efecte rellevant .

Conclusions: La cafeïna ha demostrat eficàcia en el tractament de la CPPD, disminuint la proporció de participants amb persistència CPPD i d'aquells que requereixen analgèsia complementària, en comparació amb el placebo. La gabapentina, la teofil·lina i la hidrocortisona també han demostrat una disminució de la puntuació de la intensitat del dolor en comparació amb placebo o tractament convencional. Hi ha una falta de proves concloents per a les altres drogues avaluades (sumatriptan i ACTH). Aquestes conclusions s'han d'interpretar amb cautela a causa de la manca d'informació que permet la correcta avaluació del risc de biaix, l'escassa grandària de les mostres dels estudis i també la limitada possibilitat de generalitzar, ja que la majoria dels participants eren dones durant el postpart.

Drug therapy for treating post-dural puncture headache (Review)

Basurto Ona X, Martínez García L, Solà I, Bonfill Cosp X

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Drug therapy for treating post-dural puncture headache

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ABSTRACT

Background

Post-dural puncture headache (PDPH) is the most common complication of lumbar puncture, an invasive procedure frequently performed in the emergency room. Numerous pharmaceutical drugs have been proposed to treat PDPH but there are still some uncertainties about their clinical effectiveness.

Objectives

To assess the effectiveness and safety of drugs for treating PDPH in adults and children.

Search methods

The search strategy included the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2011, Issue 2), MEDLINE (from 1950 to June 2011), EMBASE (from 1980 to June 2011) and CINAHL (from 1982 to June 2011). There was no language restriction.

Selection criteria

We considered randomised controlled trials (RCTs) assessing the effectiveness of any pharmacological drug used for treating PDPH.

Data collection and analysis

Review authors independently selected studies, assessed risks of bias and extracted data. We estimated risk ratios (RR) for dichotomous data and mean differences (MD) for continuous outcomes. We calculated a 95% confidence interval (CI) for each RR and MD. We did not undertake meta-analysis because the included studies assessed different sorts of drugs or different outcomes. We performed an intention-to-treat (ITT) analysis.

Main results

We included seven RCTs (200 participants) in this review (between 88% and 90.5% were women; mostly parturients (84% to 87%) after a lumbar puncture for a regional anaesthesia). Pharmacological drugs assessed were oral and intravenous caffeine, subcutaneous sumatriptan, oral gabapentin, oral theophylline, intravenous hydrocortisone and intramuscular adrenocorticotropic hormone (ACTH).

One RCT reported data about PDPH persistence of any severity at follow up (primary outcome); caffeine reduced the number of participants with PDPH at one to two hours when compared to placebo. Treatment with caffeine also decreased the need for a

conservative supplementary therapeutic option. Treatment with gabapentin versus placebo reported better visual analogue scale (VAS) scores after one, two, three and four days; treatment with hydrocortisone plus conventional treatment showed better VAS scores than conventional treatment alone at six, 24 and 48 hours and treatment with theophylline showed a lower mean "sum of pain" when compared with placebo. Sumatriptan and ACTH did not show any relevant effect for this outcome.

There were no clinically significant drug adverse events.

The rest of the outcomes were not reported by the RCTs or did not show any relevant effect.

Authors' conclusions

Caffeine has shown effectiveness for treating PDPH, decreasing the proportion of participants with PDPH persistence and those requiring supplementary interventions, when compared with placebo. Gabapentin, theophylline and hydrocortisone have also shown a decrease in pain severity scores when compared with placebo or conventional care.

There is a lack of conclusive evidence for the other drugs assessed (sumatriptan and ACTH).

These conclusions should be interpreted with caution, due to the lack of information to allow correct appraisal of risk of bias, the small sample sizes of studies and also the limited generalisability, as most participants were post-partum women in their 30s.

PLAIN LANGUAGE SUMMARY

Drugs for treating headache after a lumbar puncture

Lumbar puncture is an invasive procedure by which medical personnel try to get a sample of cerebrospinal fluid though a needle inserted into the lower lumbar area for diagnostic purposes (i.e. meningitis or subarachnoid haemorrhage). It is also used to inject medications such as anaesthetics and analgesics to perform a regional anaesthesia or chemotherapy. Post-dural puncture headache (PDPH) is the most common complication of a lumbar puncture. The symptoms are a constant headache that worsens in the upright position and improves when lying down and resolves spontaneously within five to seven days. Numerous medications are used in clinical practice to treat PDPH, so the aim of this review was to assess the effectiveness of these drugs.

We included seven randomised clinical trials (RCTs), with a total of 200 participants, that assessed six medications (caffeine, sumatriptan, gabapentin, hydrocortisone, theophylline and adrenocorticotropic hormone). Caffeine proved to be effective in decreasing the proportion of participants with PDPH persistence and those requiring supplementary interventions. Gabapentin, theophylline and hydrocortisone also proved to be effective, decreasing pain severity scores better than placebo or conventional treatment alone, respectively. A meta-analysis (combining of data) was not possible because all the included RCTs assessed different drugs or different outcomes. Lack of information to allow correct appraisal of the risk of bias and the small sample sizes (number of patients) of the RCTs may limit the conclusions of this review.

BACKGROUND

Description of the condition

Post-dural (post-lumbar or post-spinal) puncture headache (PDPH) is one of the most common complications of diagnostic, therapeutic or inadvertent lumbar punctures (Bezov 2010; Davignon 2002). PDPH is defined as any headache after a lumbar puncture that worsens within 15 minutes of sitting or standing and is relieved within 15 minutes of lying down (International Headache Society 2004). Ninety percent of PDPHs occur within three days of the procedure and 66% start in the first 48 hours (Turnbull 2003).

The pathophysiology of PDPH has not been fully described. It is well known that the puncture in the dura allows cerebrospinal fluid (CSF) to leak from the subarachnoid space, resulting in a decrease of CSF volume and pressure (Grande 2005). This CSF volume loss may cause a downward pull on pain-sensitive structures resulting in a headache (Ahmed 2006; Baumgarten 1987; Davignon 2002;

Denny 1987; Harrington 2004). Alternatively, the loss of CSF may cause an increase in blood flow, resulting in arterial and venous vasodilatation and PDPH. A third PDPH explanation involves the role of P substance and the regulation of neurokinin-1 receptors (NK1R) (Clark 1996).

Occurrence of PDPH varies from 1% to 40%, according to the needle gauge, needle orientation, operator skill level and presence of risk factors such as age group or history of PDPH (Turnbull 2003). This frequency is related to the type of lumbar puncture. During anaesthetic procedures, such as epidural anaesthesia, PDPH is most commonly caused by an unintentional dural puncture (Thew 2008; Turnbull 2003). In contrast to the aforementioned, in diagnostic or therapeutic lumbar punctures, the need for adequate CSF flow requires an intentional lesion that may generate the PDPH phenomenon (Kuczkowski 2006). Estimated frequencies vary from less than 10% following spinal anaesthesia (Hafer 1997; Vallejo 2000) to 36% for diagnostic lumbar punctures (Lavi 2006; Vallejo 2000) and up to 81% (Banks 2001) in obstetric patients with inadvertent dural puncture during active labour. Reported risk of inadvertent dural puncture placement during epidural anaesthesia in an obstetric population ranges from 0.04% to 6% (Berger 1998; Choi 2003). Therefore, obstetric analgesia is probably the main source of PDPH patients.

The features of PDPH are often variable. PDPH may be accompanied by neck stiffness, tinnitus, hearing loss, photophobia or nausea; other features, such as the location and duration, are also unpredictable (Grande 2005). Although PDPH is not a life-threatening condition, physical activity is often restricted. Likewise patients are usually required to stay in bed the whole day and length of stay as well as medical attendance increases (Angle 2005).

The variability of symptoms makes PDPH a diagnosis of exclusion. Other alternative diagnoses should be ruled out (e.g. viral meningitis, sinus headache or intracranial haemorrhage) (Turnbull 2003). Once PDPH is diagnosed, the initial treatment involves conservative measures such as bed rest and analgesics. If PDPH continues for more than 72 hours, a more specific treatment is indicated (Ahmed 2006). Severe PDPH may respond to some therapeutic drugs and administration of epidural blood patch (Lavi 2006).

How the intervention might work

Due to the fact that no clear pathophysiology has been asserted for PDPH, many therapeutic options are used to relieve headache in clinical practice and also essayed in clinical trials: epidural blood patch (EBP) mechanically blocking the leakage of CSF, postures such as a prone position, reducing pressure in the subarachnoid space and allowing a seal to form over the dura, hydration increasing CSF production (Ahmed 2006), methylxanthines, sumatriptan and caffeine increasing vasoconstriction of cerebral blood vessels or adrenocorticotropic hormone (ACTH) increasing intravascular volume (Kuczkowski 2006).

Treatment drugs should help to decrease the duration of headache, reduce the headache severity as much as possible, avoid the need for any other therapeutic option (e.g. EBP), improve daily activity, reduce the length of hospital stay and decrease the occurrence of adverse events overall.

Why it is important to do this review

Three Cochrane systematic reviews about prevention of PDPH are in process (Arévalo-Rodríguez 2011; Basurto 2009; Newman 2010) alongside with one published review (Boonmak 2010). Treatment and management of PDPH is also focused on in Boonmak 2010.

Numerous therapeutic drugs have been proposed, based on limited randomised controlled trials (RCTs) and case series, including: analgesics, caffeine, theophylline, sumatriptan, epidural route administration of adrenocorticotropic hormones, morphine, 0.9% sodium chloride or dextran (Choi 1996; Turnbull 2003). Most of these trials' sample sizes are small and there is inconsistency among them, therefore there is weak evidence to support the drug treatment of PDPH.

Current uncertainties about the clinical effectiveness of treatment drugs require a systematic review to clarify their potential benefits and inspire future guidelines on the topic.

O B J E C T I V E S

The objectives of this review were to assess the effectiveness and safety of drugs (in the form of any chemical substance) for treating PDPH in adults and children.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) (parallel, crossover or factorial) in any setting. We excluded studies using alternation, date of birth, hospital record number or other quasi-random methods of allocation of treatment.

Types of participants

Participants undergoing lumbar punctures for any of the reasons outlined: CSF sampling or pressure measurement, or both, spinal

anaesthesia, myelography, intrathecal drug administration, or accidental puncture of the dura during epidural anaesthesia. We included individuals of all ages and either sex.

The use of a standardised diagnostic criteria for PDPH will not be required, but it should at least be described as orthostatic headache which worsens on standing and is improved by lying down. We described the specific diagnostic criteria used in each included study.

Types of interventions

We considered any pharmacological drug used for treating PDPH. Acceptable control groups included: placebo, no intervention, any other drug treatments, behavioural and physical therapies. We considered interventions at any dose, formulation or route of administration given after lumbar puncture.

Types of outcome measures

Primary outcomes

PDPH persistence of any severity at follow up. We considered the rate of persistent PDPH at short (< 12 hours), medium (< 24 hours) or long-term (≥ 24 hours) follow up.

Secondary outcomes

1. Daily activity limited by headache.
2. Conservative supplementary therapeutic option offered when trial drug intervention fails to relieve headache and following trial protocol (e.g. bed rest, fluid consumption, analgesics).
3. Epidural blood patch performed, administered when intervention drug and conservative option fail to relieve headache and following trial protocol.
4. Change in pain severity scores as defined by the trialist.
5. Improvements in pain severity scores as defined by the trialist.
6. Number of days participants stay in hospital.
7. Any possible adverse events of pharmacological drugs taken to treat PDPH.
8. Missing data (withdrawals, drop-outs and participants lost to follow up).

Search methods for identification of studies

We designed the search in the context of an extensive review about the prevention and treatment drugs used for PDPH.

The Cochrane Central Register of Controlled Trials (CENTRAL) was our primary source for identifying studies.

Our search terms were a combination of thesaurus-based and free-text terms covering both the procedure of interest (dural puncture performed for diagnosis, anaesthesia or myelography) and headache. For MEDLINE, EMBASE and CINAHL we used a modified version of the strategy used to search CENTRAL.

We considered articles written in any language.

In addition, we searched the reference lists of all studies and review articles identified by electronic searching. We requested information about any potentially relevant studies when we contacted trialists from every included study.

Electronic searches

We searched:
- CENTRAL (*The Cochrane Library*, 2011, Issue 2);
- MEDLINE (from 1950 to June 2011);
- EMBASE (from 1980 to June 2011); and
- CINAHL (from 1982 to June 2011).

The search strategies for CENTRAL, MEDLINE and EMBASE can be found in Appendix 1, Appendix 2 and Appendix 3, respectively.

Data collection and analysis

Selection of studies

Two independent review authors (XB, IS) screened titles and abstracts of studies identified by the literature search for eligibility. We resolved disagreements through discussion. We retrieved eligible studies in full to confirm whether or not they fulfilled the inclusion criteria. Review authors were not blinded to the authors' names and institutions, journal of publication or study results at this or any stage of the review.

Data extraction and management

For included studies, we used specially designed, pre-tested data forms to extract information from the original studies on participants, methods of randomisation and blinding, the comparison(s) of interest, the number of participants originally randomised in each arm of the study, any losses to follow up, and the occurrence in each arm of the outcomes of interest. If information on any of these was incomplete, we attempted to obtain it by writing to the study author concerned.

One review author (XB) extracted the data from studies and a second review author (LM) checked data for accuracy, resolving any disagreement by discussion. We entered data into Review Manager 5.1.

When efficacy outcomes were reported in dichotomous form (primary outcome and all secondary outcomes except change in pain

severity (outcome number 4) and number of days participants stay in hospital (outcome number 6)), we recorded the number of participants assigned to each treatment arm and the number with each outcome.

For outcomes reported on a continuous scale (change in pain severity (outcome number 4) and number of days participants stay in hospital (outcome number 6)), we recorded data on the variance associated with their means.

In future updates of this review, when a study reports pre and post-treatment group means, without reporting data on the variance associated with these means, we will attempt to calculate or estimate variances based on primary data or test statistics, if these are reported. When a study uses pre and post-treatment scores to calculate a change score for each participant, and then uses these within-patient change scores to calculate a group mean change score, we will record and analyse these group mean change scores. When only post-treatment data are available, we will use these, relying on allocation to achieve between-group balance. If these calculations are needed, we will perform a sensitivity analyses excluding the studies involved, to assess the impact of the calculations.

We recorded the proportion of participants reporting adverse events for each treatment arm wherever possible. We recorded the identity and rates of specific adverse events.

Assessment of risk of bias in included studies

We used the Cochrane Collaboration's tool for assessing risk of bias in the studies included in this review, which addresses six specific domains (Higgins 2009) summarised in a specific table. For this review we assessed five of the domains (sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting). Each domain has a description of what was reported. One review author (XB) completed the risk of bias judgements for each study and a second review author (LM) checked these for accuracy, resolving any disagreement by discussion.

Assessment of heterogeneity

This review did not include a meta-analysis.

In future updates of this review, if needed, we will assess heterogeneity of effect sizes by means of the Q (Chi^2 statistic) using the methods of Peto and Mantel-Haenszel. If statistical evidence exists for homogeneity of effect sizes, the planned analysis will use a fixed-effect model.

When significant heterogeneity is present (Chi^2 test with P value < 0.1 or I^2 statistic value greater than 50%), we will make an attempt to explain the differences based on the clinical characteristics of the included studies. We will not statistically combine studies that are dissimilar in terms of interventions and participants. However, when a group of studies with heterogeneous results appears to

be similar, we will combine the study estimates using a random-effects model (Higgins 2002; Higgins 2003).

Data synthesis

The differences between the studies included in this review, in terms of interventions assessed and outcomes measured, only permitted a narrative summary.

We analysed the results for different drugs separately using Review Manager 5.1. We performed analysis on an intention-to-treat (ITT) basis, i.e. all participants remained in their original trial arm, whether or not they actually received the intervention allocated. We used dichotomous data to calculate risk ratios (RR) with 95% confidence intervals (CI). In future updates of this review, we hope to calculate the numbers needed to treat for an additional beneficial outcome (NNT) with 95% CI, as the reciprocal of the risk difference (RD) (McQuay 1998). We will use data on the proportion of participants reporting adverse events to calculate RD and numbers needed to treat for an additional harmful outcome (NNH) with 95% CI for significant differences.

For continuous outcomes reported using the same scale, we calculated mean differences (MD) with 95% CI. In future updates of this review, we hope to calculate standardised mean differences (SMD) for pooling results of continuous outcomes measured with different scales.

Subgroup analysis and investigation of heterogeneity

In future updates of this review, when sufficient data are available, we plan to carry out the following subgroup analyses:

Follow-up time subgroup analyses

When possible, we will assess the impact of the assessed interventions at short (< 12 hours), medium (12 to 24 hours) or long-term time periods ($\geq$ 24 hours) for the treatment drugs.

Population subgroup analyses

Where data allow in the future, we plan to conduct separate outcome analyses to test the following null hypotheses:
- there is no difference between obstetric participants and all other participants;
- there is no difference between men and non-obstetric women participants;
- there is no difference between young participants (18 to 35 years old) and all other adult participants.

Sensitivity analysis

In future updates of this review, we will conduct a sensitivity analyses formulated *a priori*:

- We will examine the effect on the primary outcome of excluding any study judged to be at a high risk of bias by two of the domains, sequence generation and allocation concealment.
- If applicable we will also perform a sensitivity analysis excluding those studies with a cross-over design.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
See the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Results of the search

We identified 1615 references in primary electronic databases on June 2011 from our extended search strategy for prevention and treatment drugs for PDPH. We excluded 1588 references after a detailed reading of the title and abstract. We obtained the full text report for the rest of the studies (27 papers) to check if they strictly fulfilled all the inclusion criteria. We finally excluded 18 studies after a complete full-text review and we contacted the study authors by email in some cases when more information was needed to decide eligibility. Seven studies in nine articles published completely fulfilled the inclusion criteria for this review (Camann 1990; Connelly 2000; Dogan 2006; Feuerstein 1986; Noyan 2007; Rucklidge 2004; Sechzer 1978).

Included studies

Included studies are detailed in the 'Characteristics of included studies' table.

Study design

All seven included studies (involving a total of 200 participants) were RCTs with a parallel design. Most of them were placebo-controlled except Noyan 2007 who used a control group.

Setting

Only Rucklidge 2004 was a multicentric study with five hospitals involved.
Three studies were conducted in the USA (Camann 1990; Connelly 2000; Sechzer 1978), one in the UK (Rucklidge 2004), one in Germany (Feuerstein 1986), one in Turkey (Dogan 2006) and one in Iran (Noyan 2007).

All the studies recruited the participants from hospital settings and the intervention took place while they were admitted.

Sample size

The studies included a total of 200 participants suffering from PDPH. The smallest study had 10 participants (Connelly 2000) and the largest one 60 (Noyan 2007).
Rucklidge 2004 was the only RCT that described how the sample size was calculated.

Participants

The majority of participants were women (at least 140/159), mostly parturient after a lumbar puncture for a regional anaesthesia (at least 118/140). There were three RCTs that included men (at least 19/159) (Connelly 2000; Dogan 2006; Feuerstein 1986). Sechzer 1978 did not report statistics about gender. The median age among participants ranged from 24 to 46.6 years old.

Intervention

Six of the seven studies compared placebo with different drugs: oral theophylline (Feuerstein 1986), oral (Camann 1990) or intravenous (Sechzer 1978) caffeine, subcutaneous sumatriptan (Connelly 2000), oral gabapentin (Dogan 2006) or intramuscular adrenocorticotropic hormone (ACTH) (Rucklidge 2004). Intravenous hydrocortisone was compared with conventional care (bed rest, hydration, acetaminophen and pethidine) in Noyan 2007.
Caffeine was assessed in two RCTs by different routes of administration but at equipotent doses; Camann 1990 with 300 mg anhydrous caffeine orally and Sechzer 1978 with 500 mg of caffeine sodium benzoate intravenously.
Four included studies (Camann 1990; Connelly 2000; Noyan 2007; Rucklidge 2004) used an epidural blood patch (EBP) as a supplementary analgesic in case the intervention drug failed to resolve the headache.
Follow up differed between studies but the most common length of follow up was 48 hours in three studies (Connelly 2000; Noyan 2007; Rucklidge 2004). The shortest one was Camann 1990 with 24 hours and the longest was Dogan 2006 with four days. Two studies (Feuerstein 1986; Sechzer 1978) did not report length of follow up.

Outcomes of interest

Sechzer 1978 reported data on the primary outcome and proportion of participants with PDPH persistence of any level of severity at follow up.
The most reported secondary outcome, described by six included RCTs (Camann 1990; Connelly 2000; Dogan 2006; Feuerstein 1986; Noyan 2007; Rucklidge 2004), was a change in the pain severity scores. The outcome was reported directly or could be

calculated with the results on pain severity scores documented during the follow up.

Four RCTs reported data regarding proportion of participants with EBP performed (Camann 1990; Connelly 2000; Noyan 2007; Rucklidge 2004) and five studies reported the number of any possible adverse events of pharmacological drug (Camann 1990; Connelly 2000; Feuerstein 1986; Noyan 2007; Rucklidge 2004). The proportion of participants showing improvements in pain severity scores were detailed in two RCTs (Camann 1990; Connelly 2000).

The proportion of participants with a conservative supplementary therapeutic option offered when the trial drug intervention failed was reported in two RCTs (Feuerstein 1986; Sechzer 1978).

Only Feuerstein 1986 reported the number of missing data (drop-out participants) but without specifying to which intervention group they belonged.

There were two secondary outcomes not reported in the included RCTs: proportion of participants with daily activity limited by existence of headache and the number of days participants stayed in hospital.

Conflict of interest

Only one study stated that it had been funded with a grant from Glaxo (Connelly 2000).

Excluded studies

Eighteen studies did not fulfil the inclusion criteria and were excluded. The two most frequent reasons for exclusion were not being a RCT in five studies (Aguilera 1988; De las Heras 1997; Eldor 1990; Hakim 2005; Hodgson 1997) and not assessing an individual pharmacological drug intervention in five studies (Bart 1978; Naja 2009; Oedit 2005; Sandesc 2005; van Kooten 2008). In four studies (Basso 1985; Flaatten 1987; Widerlöv 1979; Zenglein 1978) the reason for exclusion was because the intervention was not aiming to treat PDPH. In three RCTs (Lang 1993; Schwalbe 1991; Torres 1986) the reason was not describing the orthostatic component of headache. Finally, in one case the reason was that the study used quasi-randomisation (Ergün 2008). For a summary of the reasons for exclusion please see the 'Characteristics of excluded studies' table.

Risk of bias in included studies

Risk of bias in the included studies is summarised in Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Sequence generation

Allocation sequence was adequately generated in three RCTs (Connelly 2000; Rucklidge 2004; Sechzer 1978). Connelly 2000 did not report the method used to generate the sequence but after contacting the study author, a computer random series was confirmed. Rucklidge 2004 explicitly reported a computer-generated random numbers sequence and Sechzer 1978 used a table of random numbers.

The other three studies did not report the method used for sequence generation (Camann 1990; Dogan 2006; Feuerstein 1986; Noyan 2007).

Allocation concealment

Three studies had adequately concealed randomisation sequences: Connelly 2000 by sealed containers (confirmed by e-mail), Rucklidge 2004 via an independent office (confirmed by e-mail) and Sechzer 1978 by pharmacy-controlled randomisation.

The other four included studies did not provide information regarding allocation concealment (Camann 1990; Dogan 2006; Feuerstein 1986; Noyan 2007).

Blinding

The blinding method was adequate in all of the included studies (Camann 1990; Connelly 2000; Feuerstein 1986; Noyan 2007; Rucklidge 2004; Sechzer 1978) except in Dogan 2006 that did not report detailed data to allow assessment of this issue.

Incomplete outcome data

All RCTs included in this review, except one (Feuerstein 1986), had a low risk of attrition bias. The studies detailed data for all the participants that were randomised at the beginning of the trials. Feuerstein 1986 was judged as at high risk of attrition bias.

Selective reporting

All included RCTs (Camann 1990; Connelly 2000; Dogan 2006; Feuerstein 1986; Noyan 2007; Rucklidge 2004; Sechzer 1978) did not report results for key outcomes (PDPH persistence of any severity at follow up and number of any possible adverse events) that would be expected to have been reported for such a study.

Effects of interventions

We present in this section a narrative synthesis of the results for the different outcomes of interest.

Post-dural puncture headache (PDPH) persistence of any severity at follow up

One study included data for the primary outcome of the review. Sechzer 1978 showed a statistically significant risk ratio when comparing intravenous caffeine sodium benzoate with placebo (23 events in 41 participants; risk ratio (RR) 0.29, 95% confidence interval (CI) 0.13 to 0.64; see Analysis 7.1).

Conservative supplementary therapeutic option offered when trial drug intervention fails to relieve headache

Two studies reported this outcome. Sechzer 1978 showed a statistically significant risk ratio for conservative supplementary therapeutic option when comparing intravenous caffeine sodium benzoate with placebo (23 events in 41 participants; RR 0.29, 95% CI 0.13 to 0.64; see Analysis 7.2). Feuerstein 1986 also reported this outcome, showing a non-significant risk ratio when comparing theophylline with placebo (six events in 11 participants; RR 0.42, 95% CI 0.12 to 1.40; see Analysis 4.1).

Epidural blood patch (EBP) performed

The studies that reported this outcome did not show significant differences (Camann 1990; Connelly 2000; Noyan 2007; Rucklidge 2004).

Camann 1990 showed that the risk ratio for EBP performed was statistically non-significant when comparing caffeine with placebo (18 events in 40 participants; RR 0.64, 95% CI 0.31 to 1.30; see Analysis 1.1).

Connelly 2000 showed a non-significant risk ratio when comparing sumatriptan with placebo (nine events in 10 participants; RR 0.82, 95% CI 0.49 to 1.38; see Analysis 2.1).

Noyan 2007 showed a non-significant risk ratio when comparing hydrocortisone with control group (one event in 60 participants; RR 0.33, 95% CI 0.01 to 7.87; see Analysis 5.1).

Finally, Rucklidge 2004 showed a non-significant risk ratio when comparing adrenocorticotropic hormone (ACTH) with placebo (13 events in 18 participants; RR 0.86, 95% CI 0.48 to 1.53; see Analysis 6.1).

Change in pain severity scores as defined by the trialist

Six studies included in the review measured pain severity by means of visual analogue scale (VAS) scores (Camann 1990; Connelly 2000; Dogan 2006; Noyan 2007; Rucklidge 2004) or by mean sum of pain (Feuerstein 1986).

Camann 1990 reported statistically similar baseline VAS scores for the caffeine group and for the placebo group (40 participants; mean difference (MD) 9.00, 95% CI -0.80 to 18.80; see Analysis 1.2). At four hours, pain scores decreased in both groups, but did not show a significant difference (40 participants; MD -16.00, 95% CI -34.07 to 2.07; see Analysis 1.2). This result was also shown at 24 hours post-treatment (40 participants; MD 7.00, 95% CI -18.10 to 32.10; see Analysis 1.2).

Connelly 2000 showed statistically similar VAS scores at baseline (10 participants; MD -26.00, 95% CI -55.14 to 3.14; see Analysis 2.2), and when comparing sumatriptan with placebo after one hour (10 participants; MD -18, 95% CI -55.73 to 19.73; see Analysis 2.2).

Dogan 2006 also reported a statistically similar baseline VAS score (20 participants; MD 0.20, 95% CI -0.17 to 0.57; see Analysis 3.1). Gabapentin showed a significant decrease in VAS scores when compared with placebo. The study showed a progressive reduction in VAS scores for participants receiving gabapentin after one, two and three days of follow up (20 participants; one day: gabapentin 4.1 (SD 0.31), placebo 5.7 (SD 0.42), MD -1.60, 95% CI -1.92 to -1.28; two days: gabapentin 1.8 (SD 0.29), placebo 4.4 (SD 0.33), MD -2.60, 95% CI -2.87 to -2.33; three days: gabapentin 0.3 (SD 0.15), placebo 3.2 (SD 0.29), MD -2.90, 95% CI -3.10 to -2.70; see Analysis 3.1). The effect was reduced after four days of follow up (20 participants; gabapentin 0.1 (SD 0.1), placebo 1.7 (SD 0.21), MD -1.60, 95% CI -1.74 to -1.46; see Analysis 3.1).

Noyan 2007 reported a statistically similar baseline VAS score (60 participants; MD 0.13, 95% CI -0.22 to 0.48; see Analysis 5.2). Hydrocortisone showed a significant decrease in VAS scores when compared with conventional care. The studies showed a progressive reduction in pain scores for the participant receiving hydrocortisone at six hours and 24 hours of follow up (60 participants; six hours: hydrocortisone 2.77 (SD 1.07), conventional treatment 6.63 (SD 1.35), MD -3.86, 95% CI -4.48 to -3.24; 24 hours: hydrocortisone 0.73 (SD 0.74), conventional treatment 3.87 (SD 1.63), MD -3.14, 95% CI -3.78 to -2.50; see Analysis 5.2). The effect was reduced at 48 hours of follow up (60 participants; hydrocortisone 0.63 (SD 0.61), conventional treatment 1.87 (SD 0.93), MD -1.24, 95% CI -1.64 to -0.84; see Analysis 5.2).

Rucklidge 2004 (18 participants) reported no significant differences for this outcome, but all the results were reported in a figure. In Feuerstein 1986 a mean sum of pain among the participants during the treatment period was used to compare both groups. Treatment with theophylline showed a significant lower mean sum of pain when compared with placebo (11 participants; theo-

phylline 16 (SD 3.91), placebo 28 (SD 4.73), MD -12.00, 95% CI -17.19 to -6.81; see Analysis 4.2).

Improvements in pain severity scores

Camann 1990 showed a marginal significant difference in the rate of participants with an improvement when receiving caffeine compared to placebo (30 events in 40 participants; RR 1.50, 95% CI 1.02 to 2.21; see Analysis 1.3).

Connelly 2000 reported an improvement for two participants, one in each group (two events in 10 participants; RR 1.00, 95% CI 0.08 to 11.93; see Analysis 2.3). While the effect of sumatriptan was maintained until the end of follow up (48 hours), the participant in the placebo group worsened after 13 hours from the injection.

Any possible adverse events of pharmacological drug taken to treat PDPH

Camann 1990 reported one participant in each group with transient flushing and anxiety. Feuerstein 1986 reported one participant in each group with gastric pain. Dogan 2006, Noyan 2007 and Rucklidge 2004 reported no adverse events.

Missing data (withdrawals, drop-outs and participants lost to follow up)

Feuerstein 1986 did not report sufficient information about participants randomised who dropped out (5/16).

D I S C U S S I O N

This systematic review identified two randomised controlled trials (RCTs) assessing caffeine for treating post-dural puncture headache (PDPH) (Camann 1990; Sechzer 1978) and five RCTs assessing other different drugs for treating PDPH: theophylline (Feuerstein 1986), sumatriptan (Connelly 2000), gabapentin (Dogan 2006) and adrenocorticotropic hormone (ACTH) (Rucklidge 2004). Some data were available for PDPH persistence of any severity at follow up (only in Sechzer 1978) and for changes in pain severity scores derived from visual analogue scale (VAS) measures.

For PDPH persistence (primary outcome), intravenous caffeine sodium benzoate showed a significant decrease in the proportion of participants with PDPH persistence when compared with placebo in Sechzer 1978.

For the changes in pain severity scores outcome, gabapentin showed a significant decrease in pain scores when compared to placebo in Dogan 2006, with differences at one, two and three

days and decreased after four days of the intervention. Hydrocortisone showed a significant decrease in pain scores when compared with conventional care in Noyan 2007, with differences that were sustained at six and 24 hours and decreased after 48 hours of the intervention. Theophylline showed a significant lower mean sum of pain when compared with placebo in Feuerstein 1986.

The minimum clinically significant difference in acute pain VAS score has been poorly investigated, although some published studies (Gallagher 2002; Kelly 1998; Kelly 2001; Mark 2009; Todd 1996) have estimated it to be around 9 to 17 on a 0 to 100 VAS score. RCTs included in this review with statistically significant mean differences in VAS scores reported numbers around 2 to 4 on a 0 to 10 VAS score, giving to these values a clinically significant difference.

For the conservative supplementary therapeutic option, intravenous caffeine sodium benzoate showed a significant decrease in the proportion of participants needing supplementary interventions when compared with placebo in Sechzer 1978.

The drugs assessed in the included studies did not show any relevant effect for the rest of outcomes of interest for this review. The proportion of participants that required an epidural blood patch (EBP) was similar between the interventions and their controls in four studies (Camann 1990; Connelly 2000; Noyan 2007; Rucklidge 2004), and only two studies showed a marginal effect favouring caffeine (Camann 1990) and sumatriptan (Connelly 2000) over placebo in the proportion of participants that reported an improvement in pain scores.

The studies did not report any clinically significant adverse event derived from any of the assessed drugs (Camann 1990; Dogan 2006; Feuerstein 1986; Noyan 2007; Rucklidge 2004).

Two RCTs (Camann 1990; Sechzer 1978) used equipotent doses of caffeine but we did not undertake meta-analysis because they reported different outcomes.

The outlined results should be interpreted with caution due to the limited number of studies identified, the diversity of drugs assessed and outcomes measured, the small sample sizes of the studies included and the bias presented. The reporting bias risk was judged high in all the included RCTs and there is also an important lack of data reported to allow correct appraisal of the risk of other sources of bias. Most of the studies included labouring women (between 84% and 87% of the total sample derived from the included studies) experiencing PDPH after having received regional anaesthesia. The short duration of the included studies does not allow us to know the effect of the drugs that showed some effects at a mid-term. This lack of applicability of the results is similar to that observed in another Cochrane Review assessing EBP for treating PDPH (Boonmak 2010).

Larger studies (reporting how sample size was determined) with an extended duration, similar to the follow up in the study involving gabapentin (at least four days) (Dogan 2006), and the use of more pragmatic outcomes such as the persistence of pain at follow up and possible adverse events of pharmacological drugs, should provide more information on the impact of the assessed drugs in this setting and situation.

AUTHORS' CONCLUSIONS

Implications for practice

From the studies available caffeine shows a significant decrease in the proportion of participants with post-dural puncture headache persistence and in those needing supplementary interventions, when compared with placebo. Gabapentin, theophylline and hydrocortisone have shown a decrease in pain severity scores when compared with placebo or conventional care.

However, this conclusion should be interpreted with caution because this result comes from studies with limited sample sizes (seven studies involving a total of 200 participants).

The other drugs assessed (sumatriptan and adrenocorticotropic hormone) have not shown a significant effect.

Implications for research

Future research in this field should focus on the design of trials with larger samples (reporting how sample size was determined), extended follow-up periods (at least four days) and the measurement of relevant outcomes for decision-making, such as the persistence of pain at follow up and possible adverse events of pharmacological drugs. The reporting of these trials should also be improved (i.e. using the CONSORT statement (Schulz 2010)) to allow medical literature users to appraise the results of these studies accurately.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Camann 1990

Methods	Randomised, double-blind, placebo-controlled trial Study type: single-centre study Location: USA (Massachusetts) Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: blinding of participants and key study personnel. Investigational pharmacist was not blinded Follow-up period: 24 hours
Participants	Randomised: 40 (intervention group: 20; control group: 20) Excluded (post-randomisation): not described **Gender** (women): 40 (100%) **Age** (years); mean (standard deviation - SD): intervention group 29.8 (6.26), control group 30.6 (5.36) **Baseline VAS score**; mean (SD): intervention group 69 (13.42), control group 60 (17.89) **Inclusion criteria:** Post-partum woman **Exclusion criteria:** Hypertension, pre-eclampsia, seizure disorder, intolerance to caffeine or consumed beverages containing caffeine within the previous 4 hours
Interventions	**Intervention group:** once oral capsule with 300 mg of caffeine **Control group:** once oral placebo capsule with lactose **Co-interventions:** • Fail to resolve headache within 4 h: rest, increase fluid consumption and analgesics • If previous fail to relieve headache: EBP
Outcomes	1. Number of participants with EBP performed 2. Change in pain severity VAS score after 4 and 24 hours 3. Number of participants showing improvements in pain severity VAS score at 4 hours 4. Number of any possible adverse events
Notes	Post-dural puncture headache (PDPH): Quote "Frontal and/or occipital discomfort worsened by upright posture and relieved by lying supine" (page 181) Visual analogue scale (VAS): 0 = no headache and 100 = worst headache imaginable Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement

Camann 1990 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No information provided. Reported as randomised.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Capsules, prepared by our investigational pharmacy, contained either anhydrous caffeine powder (USP 300 mg, Spectrum Chemical Mfg. Corp., Gardena, Calif.) or placebo (lactose powder) and appeared identical." (Pages 181 to 182)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow-up) that would be expected to have been reported for such a study

Connelly 2000

Methods	Randomised, double-blind, placebo-controlled trial Study type: single-centre study Location: USA (Massachusetts) Study design: parallel Randomisation: computer random numbers series Allocation concealment: sealed container with a random code Blinding: blinding of participants and key study personnel Follow-up period: 48 hours
Participants	Randomised: 10 (intervention group: 5; control group: 5) Excluded (post-randomisation): not described **Gender** (women): 8 (80%); intervention group 3 (60%); control group 5 (100%) **Age** (years); mean (SD): intervention group 43 (12); control group 24 (8) **Baseline VAS score**; mean (SD): intervention group 61 (24), control group 87 (23) **Inclusion criteria:** Patients with severe PDPH **Exclusion criteria:** History of migraine, a contraindication to an EBP, or contraindication to sumatriptan (ischaemic heart disease, hypertension, pregnancy, pre-eclampsia or being treated with ergot medications or MAO inhibitors)
Interventions	**Intervention group:** once subcutaneous sumatriptan, 6 mg (0.5 ml) **Control group:** once subcutaneous saline (0.5 ml) **Co-interventions:** • Conservative treatment (fluid hydration, bed rest and caffeine beverages) for at

	least 12 hours prior to study participation • EBP if headache remained severe after 1 hour
Outcomes	1. Number of participants with EBP performed 2. Change in pain severity VAS score after 1 hour 3. Number of participants showing improvements in pain severity
Notes	Post-dural puncture headache (PDPH): Quote "Headache which is characterized by relieved with recumbency". (Page 316) Visual analogue scale (VAS): 0 = no headache and 100 = worst headache imaginable Sample size calculation: not described Email contact with MD Neil Roy Connelly on January 2010 for clarification about randomisation, allocation concealment, blinding and statistical questions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigator reported the use of a computer random number generator
Allocation concealment (selection bias)	Low risk	The investigator reported the use of a sealed container with a random code
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Patients received, in a randomised fashion, either subcutaneous sumatriptan, 6 mg (0.5 mL), or saline (0.5 mL) using the Glaxo injector". (Page 317) The investigator report blinding the VAS recorder
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcomes (PDPH persistence of any severity at follow-up and number of any possible adverse events) that would be expected to have been reported for such a study

Dogan 2006

Methods	Randomised, placebo-controlled trial Study type: single-centre study Location: Turkey (Afyon) Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: not described Follow-up period: 4 days
Participants	Randomised: 20 (intervention group: 10; control group: 10) Excluded (post-randomisation): not described **Gender** (women): 8 (40%); intervention group 4 (40%); control group 4 (40%) **Age** (years); mean (SD): intervention group 36.30 (9.54); control group 46.60 (17.10) **Baseline VAS score**; mean (SD): intervention group 7.5 (0.428); control group 7.3 (0.423) **Inclusion criteria:** • ASA I and II • PDPH after spinal anaesthesia **Exclusion criteria:** Known allergy or contraindications (pancreatitis, galactosaemia) to gabapentin, migraine, asthma and hepatic or renal insufficiency
Interventions	**Intervention group:** gabapentin 900 mg/day orally (300 mg every 8 hours) during 4 days **Control group:** placebo **Co-interventions:** • All patients were treated with bed rest and fluid hydration
Outcomes	1. Change in pain severity VAS score after 1, 2, 3 and 4 days 2. Number of any possible adverse events
Notes	Post-dural puncture headache (PDPH): Quote "PDPH was diagnosed by the postural component of the pain". (Page 170) Visual analogue scale (VAS): 0 = no pain and 10 = worst pain imaginable Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Described as randomised.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided

Dogan 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study

Feuerstein 1986

Methods	Randomised, double-blind, placebo-controlled trial Study type: single-centre study Location: Germany (Freiburg) Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: blinding of participants and evaluation personnel Follow-up period: until healing of the headache
Participants	Randomised: 16 (not described the number of participants initially allocated to each group) Excluded (post-randomisation): 5 (not described how many from each group). Analysed: 11 (intervention group: 6; control group: 5) **Gender** (women): 6 (54%) **Age** (years); n (%): 4 (36.4%) 10 to 30 years old (intervention group 3; control group 1); 4 (36.4%) 31 to 50 years old (intervention group 1; control group 3); 3 (27.3%) > 50 years old (intervention group 2; control group 1) **Baseline VAS score**: not evaluated **Inclusion criteria:** patients with a diagnostic lumbar puncture performed, with no headache during the last week before the lumbar puncture and a severe headache **Exclusion criteria**: not described
Interventions	**Intervention group:** orally theophylline 281.7 mg tablets (verum Euphyllin retard tablets) 3 times a day **Control group:** orally placebo tablets 3 times a day **Co-interventions:** analgesics and hypotonic saline solution as needed
Outcomes	1. Number of participants with a conservative supplementary therapeutic option offered 2. Change in pain severity ("sum of pain") during the treatment period 3. Number of any possible adverse events 4. Missing data (withdrawals, drop-outs and participants lost to follow up
Notes	Post-dural puncture headache (PDPH): Quote "Subjective severe headache occurring only after arising and ceasing within a few minutes after lying down.". (Page 217) Sum of pain: 1 = slight headache; 2 = intermediate headache and 3 = severe headache. Three values per day

Feuerstein 1986 *(Continued)*

	Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Reported as randomised
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The placebo tablets, indistinguishable from the verum Euphyllin retard tablets (281.7 mg theophylline), were kindly provided by Byk Gulden Pharmazeutika, Konstanz, FRG." (Page 217) Quote: "Verum and placebo tablets were randomised so that neither the patient nor the examining medical staff knew the real content of the administered tablets." (Page 217)
Incomplete outcome data (attrition bias) All outcomes	High risk	5 of 16 participants randomised were dropped out with insufficient information provided Quote: "Five patients of 16 dropped out (transferal to other clinical departments, dismissal before the end of the study or insufficient compliance)." (Page 217)
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study

Noyan 2007

Methods	Randomised, double-blind, controlled trial Study type: single-centre study Location: Iran (Tehran) Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: blinding of participants and key study personnel Follow-up period: 48 hours
Participants	Randomised: 60 (intervention group: 30; control group: 30) Excluded (post-randomisation): not described **Gender** (women): 60 (100%) **Age** (years); mean (SD): 27.1 (3.45) **Baseline VAS score**; mean (SD): intervention group 9.20 (0.71); control group 9.07 (0.69) **Inclusion criteria:** • 18 to 40 years • ASA I and II • Headache after spinal anaesthesia for caesarean section **Exclusion criteria:** Cluster headache, convulsion, cerebrovascular accident, pre-eclampsia, eclampsia, high intracranial pressure, coagulopathy or previous neurologic disease
Interventions	**Intervention group:** 200 mg hydrocortisone intravenously as a bolus and 100 mg hydrocortisone every 8 hours for 48 hours **Co-interventions:** • All patients were treated conventionally: complete bed rest, hydration (serum dextrose saline 3 L/4 h) and analgesics (acetaminophen 2 325 mg tablets every 6 hours and intravenous pethidine 50 mg every 12 hours)
Outcomes	1. Number of participants with EBP performed 2. Change in pain severity VAS score after 6, 24 and 48 hours 3. Number of any possible adverse events
Notes	Post-dural puncture headache (PDPH): Quote "Headache after spinal anaesthesia". (Page 416) Visual analogue scale (VAS): 0 to 1 no headache; 2 to 4 mild headache, 5 to 7 moderate headache; 8 to 10 severe headache Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Described as randomised.
Allocation concealment (selection bias)	Unclear risk	No information provided

Noyan 2007 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Parturient women and observer did not know which patient had received hydrocortisone". (Page 418)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study

Rucklidge 2004

Methods	Randomised, double-blind, placebo-controlled trial Study type: multicentre trial Location: UK Study design: parallel Randomisation: computer-generated random numbers Allocation concealment: central randomisation Blinding: blinding of participants and key study personnel Follow-up period: 48 hours
Participants	Randomised: 18 (intervention group: 9; control group: 9) Excluded (post-randomisation): not described **Gender** (women): 18 (100%) **Age** (years); mean (SD): intervention group 24.1 (3.8); control group 29.3 (4.7) **Baseline VAS score**: (graphical data) **Inclusion criteria:** Women with PDPH following deliberate or accidental dural puncture associated with obstetric regional anaesthesia or analgesia **Exclusion criteria:** Asthma, severe allergy or diabetes
Interventions	**Intervention group:** intramuscular synthetic analogue of ACTH (Synacthen Depot®) 1 mg (1 ml) **Control group:** intramuscular saline 0.9% (1 ml) **Co-interventions:** • All patients were treated with simple oral analgesics and hydration • EBP was performed if requested by the patient
Outcomes	1. Number of participants with EBP performed 2. Change in pain severity VAS score after 6, 12, 24 and 48 hours 3. Number of any possible adverse events

Rucklidge 2004   *(Continued)*

Notes	Post-dural puncture headache (PDPH): Quote "severe headache occurring within 48 h of dural puncture; exacerbation on sitting or standing with relief on lying or on abdominal compression; and the absence of focal neurological signs". (Page 138) Visual analogue scale (VAS): 0 = no pain and 10 = worst pain imaginable The study reported data on neck stiffness and nausea as 2 side effects derived from the progression of the condition. These 2 side effects were not considered as adverse events related with the assessed intervention Email contact with Dr. Steve Yentis on March 2010 for clarification about VAS numerical results Sample size calculation: estimate VAS reduction = 30%, β = 80%; α = 0.05

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Parturients were randomly allocated to receive Synacthen Depot 1 mg (1 ml) or 0.9% saline (1 ml) according to computer-generated random numbers held at the Chelsea and Westminster Hospital, London". (Page 138)
Allocation concealment (selection bias)	Low risk	Quote: "Parturients were randomly allocated to receive Synacthen Depot 1 mg (1 ml) or 0.9% saline (1 ml) according to computer-generated random numbers held at the Chelsea and Westminster Hospital, London". (Page 138)
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The study agent was dispatched from the relevant pharmacy in a prefilled syringe and the contents were blinded to the parturient, investigator and midwife administering the drug". (Page 138)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study

Sechzer 1978

Methods	Randomised, double-blind, placebo-controlled trial
	Study type: single-centre study
	Location: USA (New York)
	Study design: parallel
	Randomisation: table of random numbers
	Allocation concealment: central randomisation
	Blinding: blinding of participants and key study personnel
	Follow-up period: not described
Participants	Randomised: 41 (intervention group: 20; control group: 21)
	Excluded (post-randomisation): not described
	Gender (women): not reported
	Age (years): not reported
	Baseline VAS score: not evaluated
	Inclusion criteria: patients with PDPH after a spinal anaesthesia, with usual symptomatic treatment unsatisfactory and headache went through a 2 to 4 days course
	Exclusion criteria: not described
Interventions	**Intervention group:** Intravenous caffeine sodium benzoate (CSB) (0.5 g/2 ml)
	Control group: intravenous physiologic saline solution (2 ml)
	Co-interventions: supplementary caffeine (0.5 g/2 ml) was administered if headache was not relieved after 1 to 2 hours
Outcomes	1. PDPH persistence of any severity at 1 to 2 hours
	2. Number of participants with a conservative supplementary therapeutic option offered (CSB second dose demanded)
Notes	Post-dural puncture headache (PDPH): Quote "Aggravated by sitting or standing". (Page 308)
	Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After informed consent was obtained, the patients were treated in random fashion with initial intravenous injection A which was either: physiologic saline solution (2 ml) or CSB (0.5 gm / 2 ml)." (Page 308) Quote: "The solutions were prepared in the hospital pharmacy according to a list derived from a table of random numbers." (Page 308)
Allocation concealment (selection bias)	Low risk	Quote: "The solutions were prepared in the hospital pharmacy according to a list derived from a table of random numbers."

Sechzer 1978   (*Continued*)

		(Page 308)
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The syringes were coded so that the observers were not aware of the contents." (Page 308)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (number of any possible adverse events) that would be expected to have been reported for such a study

EBP: epidural blood patch
h: hour
PDPH: post-dural puncture headache
SD: standard deviation
VAS: visual analogue scale

Characteristics of excluded studies   *[ordered by study ID]*

Study	Reason for exclusion
Aguilera 1988	Not RCT (case series)
Bart 1978	No individual pharmacological drug assessed
Basso 1985	Intervention was not aimed to treat PDPH
De las Heras 1997	Not RCT (case report)
Eldor 1990	Not RCT (case series)
Ergün 2008	Randomisation by alternation (odd hospital record numbers assigned to intervention and even numbers to control; information provided by the trialists)
Flaatten 1987	Intervention was not aimed at treating PDPH
Hakim 2005	Not RCT (clinical trial without control group)
Hodgson 1997	Not RCT (case report)
Lang 1993	The orthostatic component of headache not described

Naja 2009	No individual pharmacological drug assessed
Oedit 2005	No individual pharmacological drug assessed
Sandesc 2005	No individual pharmacological drug assessed
Schwalbe 1991	The orthostatic component of headache not described
Torres 1986	The orthostatic component of headache not described
van Kooten 2008	No individual pharmacological drug assessed
Widerlöv 1979	Intervention was not aimed at treating PDPH
Zenglein 1978	Intervention was not aimed at treating PDPH

PDPH: post-dural puncture headache
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1.   Comparison 1: Caffeine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with EBP performed (secondary outcome 3)	1	40	Risk Ratio (IV, Fixed, 95% CI)	0.64 [0.31, 1.30]
2 Change in pain severity scores (secondary outcome 4)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Baseline VAS score	1	40	Mean Difference (IV, Fixed, 95% CI)	9.0 [-0.80, 18.80]
2.2 Change in pain severity VAS score after 4 hours	1	40	Mean Difference (IV, Fixed, 95% CI)	-16.0 [-34.07, 2.07]
2.3 Change in pain severity VAS score after 24 hours	1	40	Mean Difference (IV, Fixed, 95% CI)	7.0 [-18.10, 32.10]
3 Number of participants showing improvements in pain severity scores (secondary outcome 5)	1	40	Risk Ratio (IV, Fixed, 95% CI)	1.5 [1.02, 2.21]
3.1 Number of participants showing improvements in pain severity VAS score 4 hours	1	40	Risk Ratio (IV, Fixed, 95% CI)	1.5 [1.02, 2.21]
4 Number of any possible adverse effects (secondary outcome 7)	1	40	Risk Ratio (IV, Fixed, 95% CI)	1.0 [0.07, 14.90]

Comparison 2.   Comparison 2: Sumatriptan versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with EBP performed (secondary outcome 3)	1	10	Risk Ratio (IV, Fixed, 95% CI)	0.82 [0.49, 1.38]
2 Change in pain severity scores (secondary outcome 4)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Baseline VAS score	1	10	Mean Difference (IV, Fixed, 95% CI)	-26.0 [-55.14, 3.14]
2.2 Change in pain severity VAS score after 1 hour	1	10	Mean Difference (IV, Fixed, 95% CI)	-18.0 [-55.73, 19.73]
3 Number of participants showing improvements in pain severity scores (secondary outcome 5)	1	10	Risk Ratio (IV, Fixed, 95% CI)	1.0 [0.08, 11.93]

Comparison 3.   Comparison 3: Gabapentin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in pain severity scores (secondary outcome 4)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Baseline VAS score	1	20	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.17, 0.57]
1.2 Change in pain severity VAS score after 1 day	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-1.92, -1.28]
1.3 Change in pain severity VAS score after 2 days	1	20	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-2.87, -2.33]
1.4 Change in pain severity VAS score after 3 days	1	20	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-3.10, -2.70]
1.5 Change in pain severity VAS score after 4 days	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.6 [-1.74, -1.46]
2 Number of any possible adverse effects (secondary outcome 7)	1	20	Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4.   Comparison 4: Theophylline versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2)	1	11	Risk Ratio (IV, Fixed, 95% CI)	0.42 [0.12, 1.40]
2 Change in pain severity ("sum of pain") during the treatment period (secondary outcome 4)	1	11	Mean Difference (IV, Fixed, 95% CI)	-12.0 [-17.19, -6.81]
3 Number of any possible adverse effects (secondary outcome 7)	1	11	Risk Ratio (IV, Fixed, 95% CI)	0.83 [0.07, 10.20]

Comparison 5.   Comparison 5: Hydrocortisone versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with EBP performed (secondary outcome 3)	1	60	Risk Ratio (IV, Fixed, 95% CI)	0.33 [0.01, 7.87]
2 Change in pain severity score (secondary outcome 4)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Baseline VAS score	1	60	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.22, 0.48]

2.2 Change in pain severity VAS score after 6 hours	1	60	Mean Difference (IV, Fixed, 95% CI)	-3.86 [-4.48, -3.24]
2.3 Change in pain severity VAS score after 24 hours	1	60	Mean Difference (IV, Fixed, 95% CI)	-3.14 [-3.78, -2.50]
2.4 Change in pain severity VAS score after 48 hours	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.24 [-1.64, -0.84]
3 Number of any possible adverse effects (secondary outcome 7)	1	60	Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Comparison 6: ACTH versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with EBP performed (secondary outcome 3)	1	18	Risk Ratio (IV, Fixed, 95% CI)	0.86 [0.48, 1.53]
2 Number of any possible adverse effects (secondary outcome 7)	1	18	Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. Comparison 7: Caffeine sodium benzoate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PDPH persistence of any severity at 1 to 2 hours (primary outcome)	1	41	Risk Ratio (IV, Fixed, 95% CI)	0.29 [0.13, 0.64]
2 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2)	1	41	Risk Ratio (IV, Fixed, 95% CI)	0.29 [0.13, 0.64]

Analysis 1.1. Comparison 1 Comparison 1: Caffeine versus placebo, Outcome 1 Number of participants with EBP performed (secondary outcome 3).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 1 Comparison 1: Caffeine versus placebo

Outcome: 1 Number of participants with EBP performed (secondary outcome 3)

Study or subgroup	Favours caffeine n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Camann 1990	7/20	11/20		100.0 %	0.64 [0.31, 1.30]
Total (95% CI)	**20**	**20**		**100.0 %**	**0.64 [0.31, 1.30]**

Total events: 7 (Favours caffeine), 11 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.24 (P = 0.22)
Test for subgroup differences: Not applicable

```
         0.05   0.2      1      5    20
         Favours caffeine    Favours placebo
```

Analysis 1.2. Comparison 1 Comparison 1: Caffeine versus placebo, Outcome 2 Change in pain severity scores (secondary outcome 4).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 1 Comparison 1: Caffeine versus placebo

Outcome: 2 Change in pain severity scores (secondary outcome 4)

Study or subgroup	Caffeine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Baseline VAS score							
Camann 1990	20	69 (13.42)	20	60 (17.89)		100.0 %	9.00 [-0.80, 18.80]
Subtotal (95% CI)	**20**		**20**			**100.0 %**	**9.00 [-0.80, 18.80]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.80 (P = 0.072)							
2 Change in pain severity VAS score after 4 hours							
Camann 1990	20	33 (26.83)	20	49 (31.3)		100.0 %	-16.00 [-34.07, 2.07]
Subtotal (95% CI)	**20**		**20**			**100.0 %**	**-16.00 [-34.07, 2.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.74 (P = 0.083)							

```
        -20   -10    0    10    20
        Favours caffeine   Favours placebo
```

(*Continued* . . .)

Study or subgroup	Caffeine		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI

3 Change in pain severity VAS score after 24 hours

| Camann 1990 | 20 | 41 (35.78) | 20 | 34 (44.72) | | 100.0 % | 7.00 [-18.10, 32.10] |
| **Subtotal (95% CI)** | **20** | | **20** | | | **100.0 %** | **7.00 [-18.10, 32.10]** |

Heterogeneity: not applicable

Test for overall effect: Z = 0.55 (P = 0.58)

```
     -20   -10    0    10    20
```
Favours caffeine   Favours placebo

Analysis 1.3. Comparison 1 Comparison 1: Caffeine versus placebo, Outcome 3 Number of participants showing improvements in pain severity scores (secondary outcome 5).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 1 Comparison 1: Caffeine versus placebo

Outcome: 3 Number of participants showing improvements in pain severity scores (secondary outcome 5)

Study or subgroup	Caffeine	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI		IV,Fixed,95% CI

1 Number of participants showing improvements in pain severity VAS score 4 hours

| Camann 1990 | 18/20 | 12/20 | | 100.0 % | 1.50 [1.02, 2.21] |
| **Total (95% CI)** | **20** | **20** | | **100.0 %** | **1.50 [1.02, 2.21]** |

Total events: 18 (Caffeine), 12 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 2.06 (P = 0.040)

Test for subgroup differences: Not applicable

```
     0.5   0.7    1    1.5    2
```
Favours placebo   Favours caffeine

Analysis 1.4. Comparison 1 Comparison 1: Caffeine versus placebo, Outcome 4 Number of any possible adverse effects (secondary outcome 7).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 1 Comparison 1: Caffeine versus placebo

Outcome: 4 Number of any possible adverse effects (secondary outcome 7)

Study or subgroup	Caffeine n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Camann 1990	1/20	1/20		100.0 %	1.00 [0.07, 14.90]
Total (95% CI)	**20**	**20**		**100.0 %**	**1.00 [0.07, 14.90]**

Total events: 1 (Caffeine), 1 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)
Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
     Favours experimental   Favours control
```

Analysis 2.1. Comparison 2 Comparison 2: Sumatriptan versus placebo, Outcome 1 Number of participants with EBP performed (secondary outcome 3).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 2 Comparison 2: Sumatriptan versus placebo

Outcome: 1 Number of participants with EBP performed (secondary outcome 3)

Study or subgroup	Sumatriptan n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Connelly 2000	4/5	5/5		100.0 %	0.82 [0.49, 1.38]
Total (95% CI)	**5**	**5**		**100.0 %**	**0.82 [0.49, 1.38]**

Total events: 4 (Sumatriptan), 5 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable

```
        0.05   0.2    1    5    20
     Favours sumatriptan   Favours placebo
```

Analysis 2.2. Comparison 2 Comparison 2: Sumatriptan versus placebo, Outcome 2 Change in pain severity scores (secondary outcome 4).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 2 Comparison 2: Sumatriptan versus placebo

Outcome: 2 Change in pain severity scores (secondary outcome 4)

Study or subgroup	Sumatriptan		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Baseline VAS score							
Connelly 2000	5	61 (24)	5	87 (23)		100.0 %	-26.00 [-55.14, 3.14]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-26.00 [-55.14, 3.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.75 (P = 0.080)							
2 Change in pain severity VAS score after 1 hour							
Connelly 2000	5	47 (22)	5	65 (37)		100.0 %	-18.00 [-55.73, 19.73]
Subtotal (95% CI)	**5**		**5**			**100.0 %**	**-18.00 [-55.73, 19.73]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.94 (P = 0.35)							
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² =0.0%							

```
          -20   -10    0    10    20
      Favours sumatriptan   Favours placebo
```

Analysis 2.3.   Comparison 2 Comparison 2: Sumatriptan versus placebo, Outcome 3 Number of participants showing improvements in pain severity scores (secondary outcome 5).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 2 Comparison 2: Sumatriptan versus placebo

Outcome: 3 Number of participants showing improvements in pain severity scores (secondary outcome 5)

Study or subgroup	Sumatriptan	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI		IV,Fixed,95% CI
Connelly 2000	1/5	1/5		100.0 %	1.00 [0.08, 11.93]
Total (95% CI)	**5**	**5**		**100.0 %**	**1.00 [0.08, 11.93]**
Total events: 1 (Sumatriptan), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

```
        0.05   0.2    1    5    20
     Favours placebo    Favours sumatriptan
```

Analysis 3.1. Comparison 3 Comparison 3: Gabapentin versus placebo, Outcome 1 Change in pain severity scores (secondary outcome 4).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 3 Comparison 3: Gabapentin versus placebo

Outcome: 1 Change in pain severity scores (secondary outcome 4)

Study or subgroup	Gabapentin		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Baseline VAS score							
Dogan 2006	10	7.5 (0.428)	10	7.3 (0.423)		100.0 %	0.20 [-0.17, 0.57]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**0.20 [-0.17, 0.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.05 (P = 0.29)							
2 Change in pain severity VAS score after 1 day							
Dogan 2006	10	4.1 (0.31)	10	5.7 (0.42)		100.0 %	-1.60 [-1.92, -1.28]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**-1.60 [-1.92, -1.28]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.69 (P < 0.00001)							
3 Change in pain severity VAS score after 2 days							
Dogan 2006	10	1.8 (0.29)	10	4.4 (0.33)		100.0 %	-2.60 [-2.87, -2.33]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**-2.60 [-2.87, -2.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 18.72 (P < 0.00001)							
4 Change in pain severity VAS score after 3 days							
Dogan 2006	10	0.3 (0.15)	10	3.2 (0.29)		100.0 %	-2.90 [-3.10, -2.70]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**-2.90 [-3.10, -2.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 28.09 (P < 0.00001)							
5 Change in pain severity VAS score after 4 days							
Dogan 2006	10	0.1 (0.1)	10	1.7 (0.21)		100.0 %	-1.60 [-1.74, -1.46]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**-1.60 [-1.74, -1.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 21.75 (P < 0.00001)							
Test for subgroup differences: Chi² = 260.84, df = 4 (P = 0.00), I² =98%							

-4 -2 0 2 4

Favours gabapentin   Favours placebo

Analysis 3.2. Comparison 3 Comparison 3: Gabapentin versus placebo, Outcome 2 Number of any possible adverse effects (secondary outcome 7).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 3 Comparison 3: Gabapentin versus placebo

Outcome: 2 Number of any possible adverse effects (secondary outcome 7)

Study or subgroup	Gabapentin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Dogan 2006	0/10	0/10		0.0 [0.0, 0.0]
Total (95% CI)	**10**	**10**		**0.0 [0.0, 0.0]**

Total events: 0 (Gabapentin), 0 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

```
      0.01   0.1    I    I0   I00
   Favours experimental   Favours control
```

Analysis 4.1. Comparison 4 Comparison 4: Theophylline versus placebo, Outcome 1 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 4 Comparison 4: Theophylline versus placebo

Outcome: 1 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2)

Study or subgroup	Theophylline n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Feuerstein 1986	2/6	4/5		100.0 %	0.42 [0.12, 1.40]
Total (95% CI)	**6**	**5**		**100.0 %**	**0.42 [0.12, 1.40]**

Total events: 2 (Theophylline), 4 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable

```
      0.01   0.1    I    I0   I00
   Favours experimental   Favours control
```

Analysis 4.2.   Comparison 4 Comparison 4: Theophylline versus placebo, Outcome 2 Change in pain severity ("sum of pain") during the treatment period (secondary outcome 4).
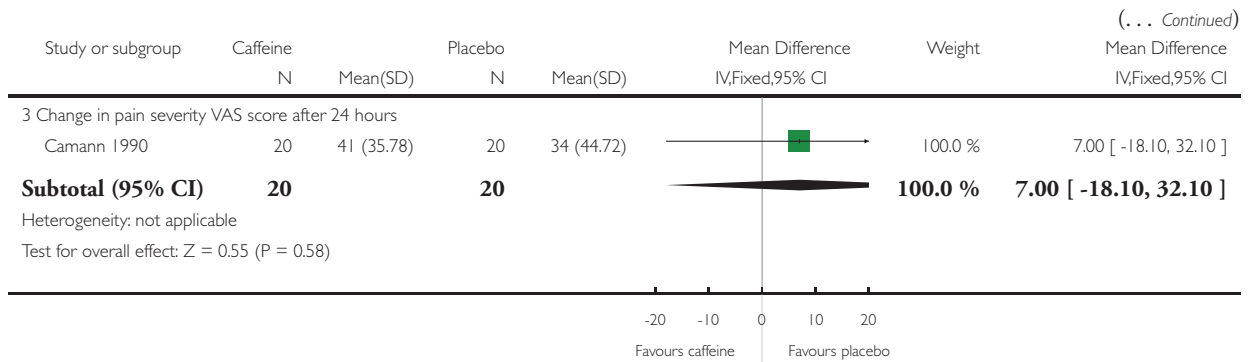
Review: Drug therapy for treating post-dural puncture headache

Comparison: 4 Comparison 4: Theophylline versus placebo

Outcome: 2 Change in pain severity ("sum of pain") during the treatment period (secondary outcome 4)

Study or subgroup	Theophylline		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Feuerstein 1986	6	16 (3.91)	5	28 (4.73)		100.0 %	-12.00 [-17.19, -6.81]
Total (95% CI)	**6**		**5**			**100.0 %**	**-12.00 [-17.19, -6.81]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.53 (P < 0.00001)

Test for subgroup differences: Not applicable

```
      -100    -50     0     50    100
      Favours experimental   Favours control
```
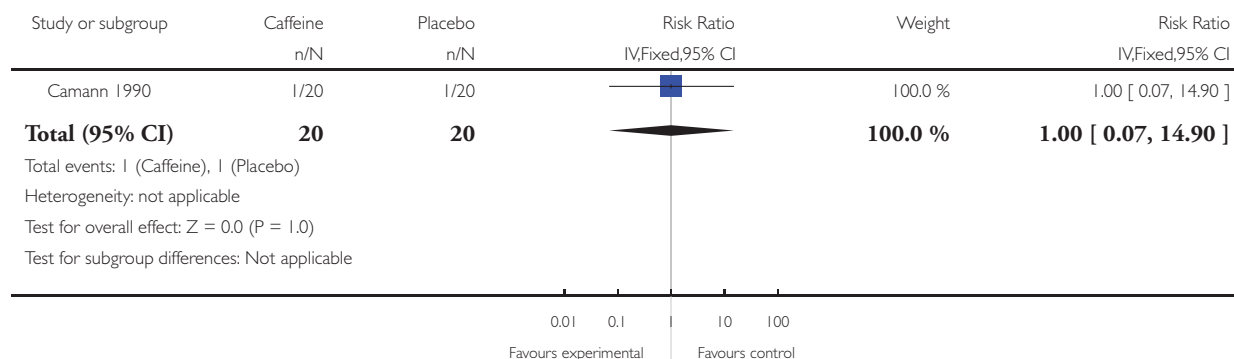
Analysis 4.3.   Comparison 4 Comparison 4: Theophylline versus placebo, Outcome 3 Number of any possible adverse effects (secondary outcome 7).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 4 Comparison 4: Theophylline versus placebo

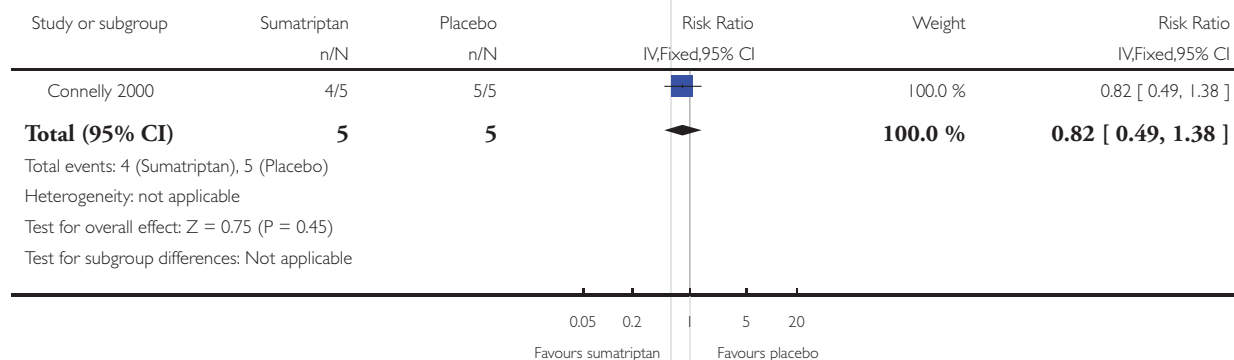Outcome: 3 Number of any possible adverse effects (secondary outcome 7)

Study or subgroup	Theophylline	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI		IV,Fixed,95% CI
Feuerstein 1986	1/6	1/5		100.0 %	0.83 [0.07, 10.20]
Total (95% CI)	**6**	**5**		**100.0 %**	**0.83 [0.07, 10.20]**

Total events: 1 (Theophylline), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable

```
     0.01    0.1     1     10    100
     Favours experimental   Favours control
```

Analysis 5.1. Comparison 5 Comparison 5: Hydrocortisone versus control, Outcome 1 Number of participants with EBP performed (secondary outcome 3).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 5 Comparison 5: Hydrocortisone versus control

Outcome: 1 Number of participants with EBP performed (secondary outcome 3)
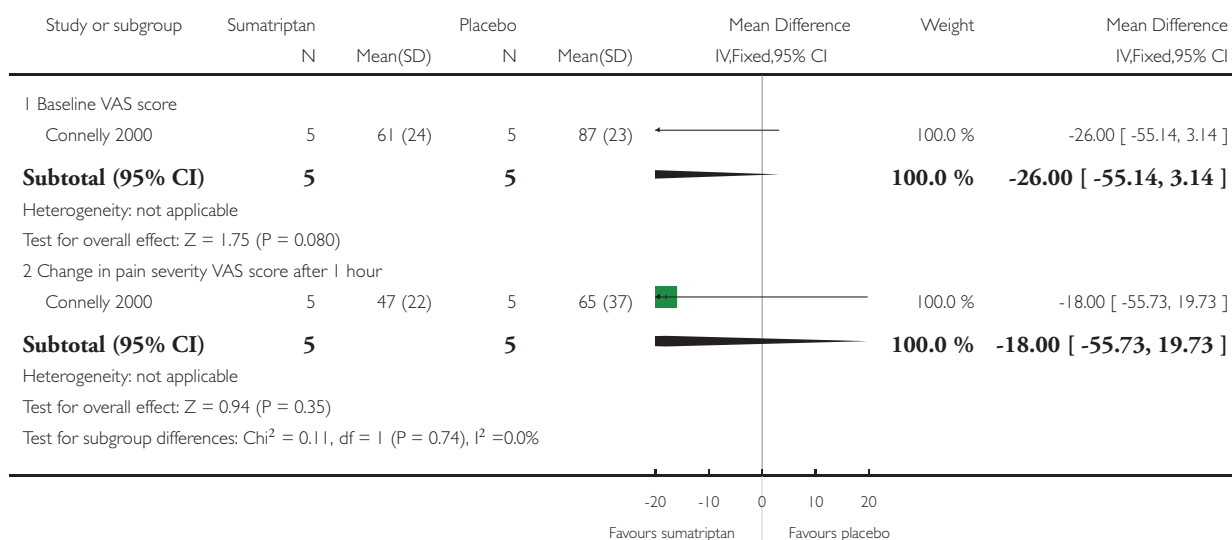
Study or subgroup	Hydrocortisone n/N	Control n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Noyan 2007	0/30	1/30		100.0 %	0.33 [0.01, 7.87]
Total (95% CI)	**30**	**30**		**100.0 %**	**0.33 [0.01, 7.87]**

Total events: 0 (Hydrocortisone), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

```
        0.05   0.2      1      5    20
      Favours hydrocortisone   Favours control
```

Analysis 5.2. Comparison 5 Comparison 5: Hydrocortisone versus control, Outcome 2 Change in pain severity score (secondary outcome 4).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 5 Comparison 5: Hydrocortisone versus control

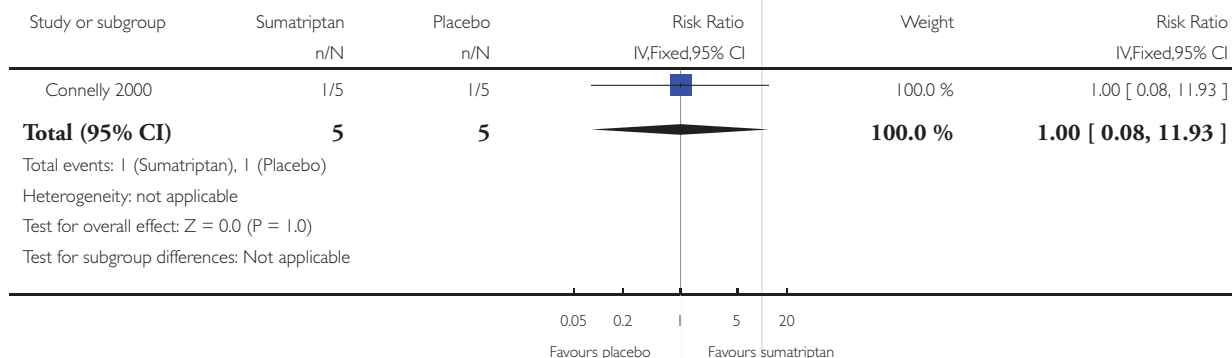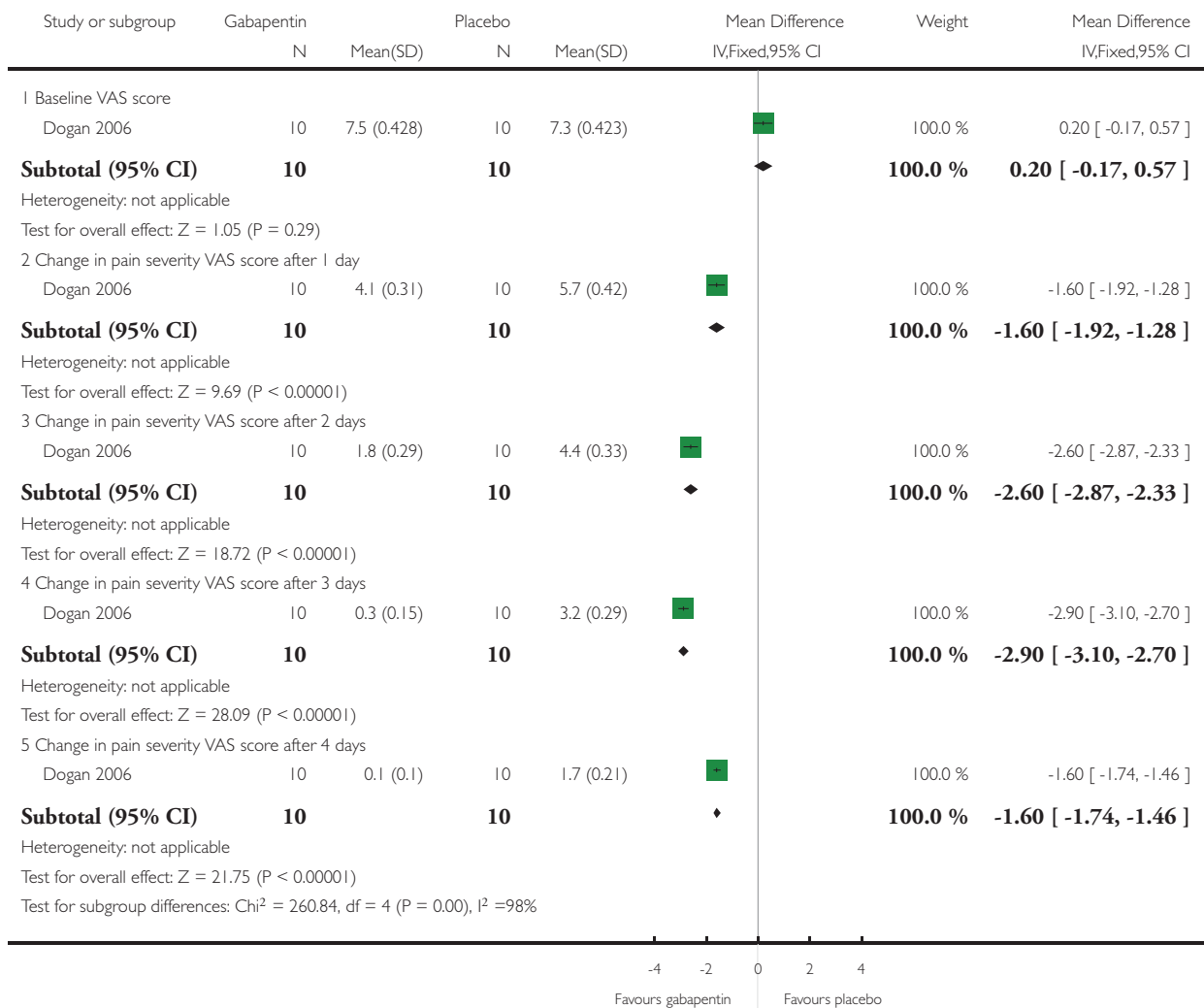Outcome: 2 Change in pain severity score (secondary outcome 4)

Study or subgroup	Hydrocortisone N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Baseline VAS score							
Noyan 2007	30	9.2 (0.71)	30	9.07 (0.69)		100.0 %	0.13 [-0.22, 0.48]
Subtotal (95% CI)	**30**		**30**			**100.0 %**	**0.13 [-0.22, 0.48]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

2 Change in pain severity VAS score after 6 hours							
Noyan 2007	30	2.77 (1.07)	30	6.63 (1.35)		100.0 %	-3.86 [-4.48, -3.24]
Subtotal (95% CI)	**30**		**30**			**100.0 %**	**-3.86 [-4.48, -3.24]**

Heterogeneity: not applicable
Test for overall effect: Z = 12.27 (P < 0.00001)

```
        -4    -2    0    2    4
    Favours hydrocortisone   Favours control
```

(*Continued* . . .)

Study or subgroup	Hydrocortisone		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
3 Change in pain severity VAS score after 24 hours							
Noyan 2007	30	0.73 (0.74)	30	3.87 (1.63)		100.0 %	-3.14 [-3.78, -2.50]
Subtotal (95% CI)	**30**		**30**			**100.0 %**	**-3.14 [-3.78, -2.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.61 (P < 0.00001)							
4 Change in pain severity VAS score after 48 hours							
Noyan 2007	30	0.63 (0.61)	30	1.87 (0.93)		100.0 %	-1.24 [-1.64, -0.84]
Subtotal (95% CI)	**30**		**30**			**100.0 %**	**-1.24 [-1.64, -0.84]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.11 (P < 0.00001)							
Test for subgroup differences: Chi² = 160.56, df = 3 (P = 0.00), I² =98%							

```
        -4    -2    0    2    4
     Favours hydrocortisone   Favours control
```

Analysis 5.3.   Comparison 5 Comparison 5: Hydrocortisone versus control, Outcome 3 Number of any possible adverse effects (secondary outcome 7).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 5 Comparison 5: Hydrocortisone versus control

Outcome: 3 Number of any possible adverse effects (secondary outcome 7)

Study or subgroup	Hydrocortisone	Control	Risk Ratio	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI	IV,Fixed,95% CI
Noyan 2007	0/30	0/30		0.0 [0.0, 0.0]
Total (95% CI)	**30**	**30**		**0.0 [0.0, 0.0]**
Total events: 0 (Hydrocortisone), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

```
    0.01   0.1    1    10   100
   Favours experimental   Favours control
```

Analysis 6.1. Comparison 6 Comparison 6: ACTH versus placebo, Outcome 1 Number of participants with EBP performed (secondary outcome 3).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 6 Comparison 6: ACTH versus placebo
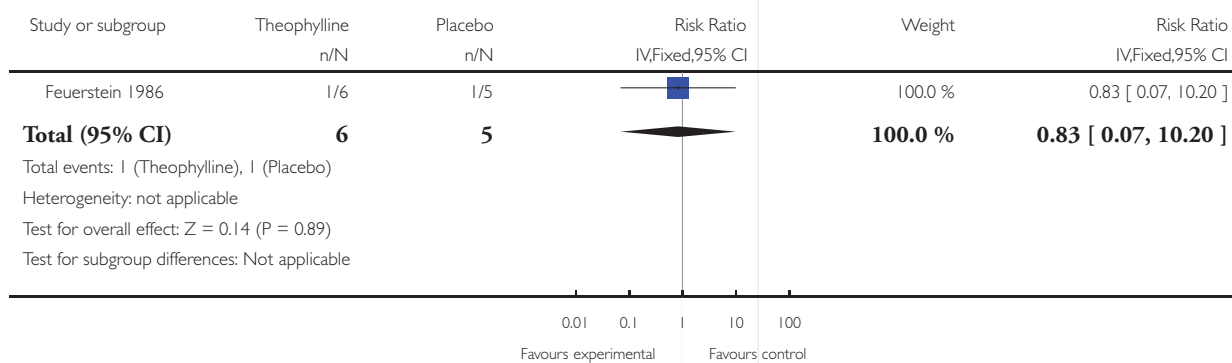
Outcome: 1 Number of participants with EBP performed (secondary outcome 3)

Study or subgroup	ACTH n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Rucklidge 2004	6/9	7/9		100.0 %	0.86 [0.48, 1.53]
Total (95% CI)	**9**	**9**		**100.0 %**	**0.86 [0.48, 1.53]**

Total events: 6 (ACTH), 7 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable

```
        0.05    0.2    I    5    20
       Favours ACTH       Favours placebo
```

Analysis 6.2. Comparison 6 Comparison 6: ACTH versus placebo, Outcome 2 Number of any possible adverse effects (secondary outcome 7).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 6 Comparison 6: ACTH versus placebo

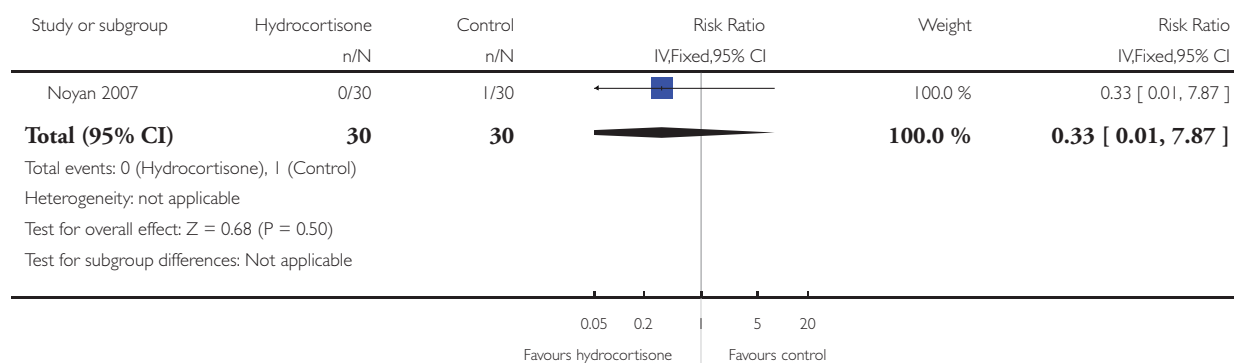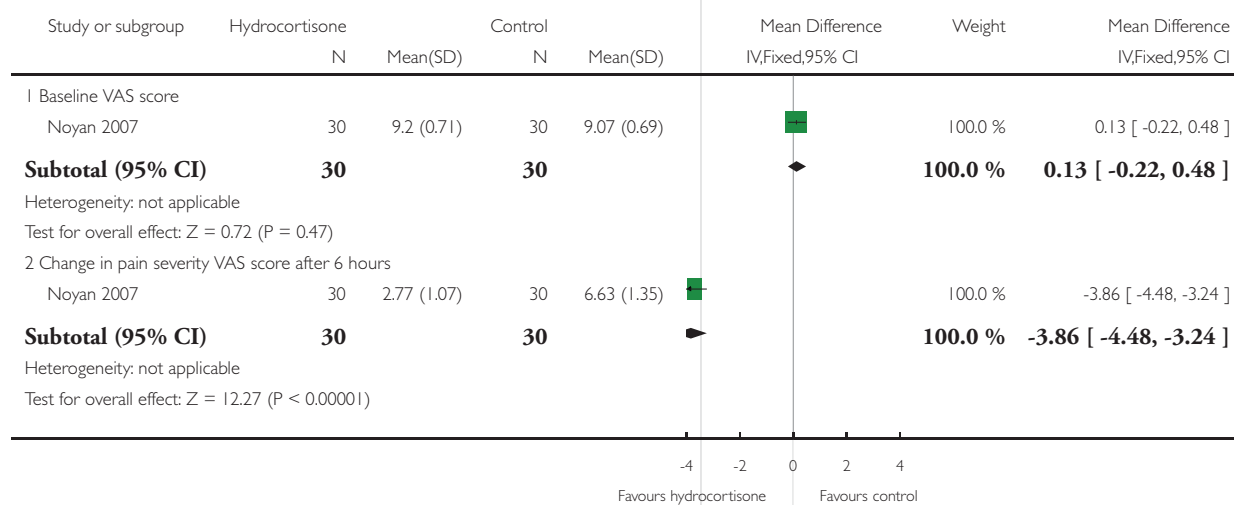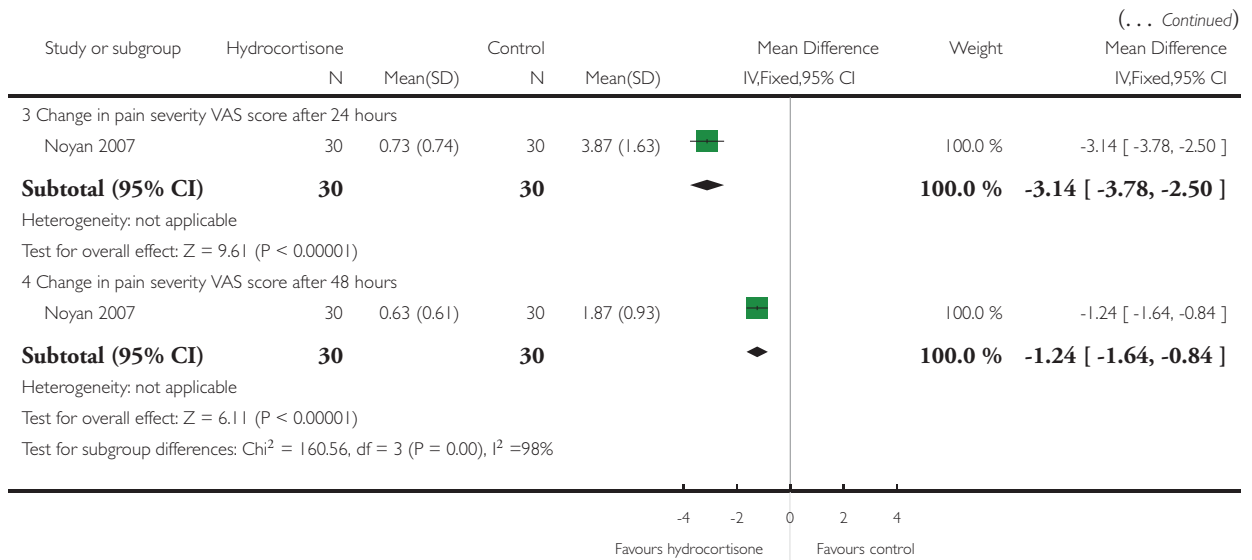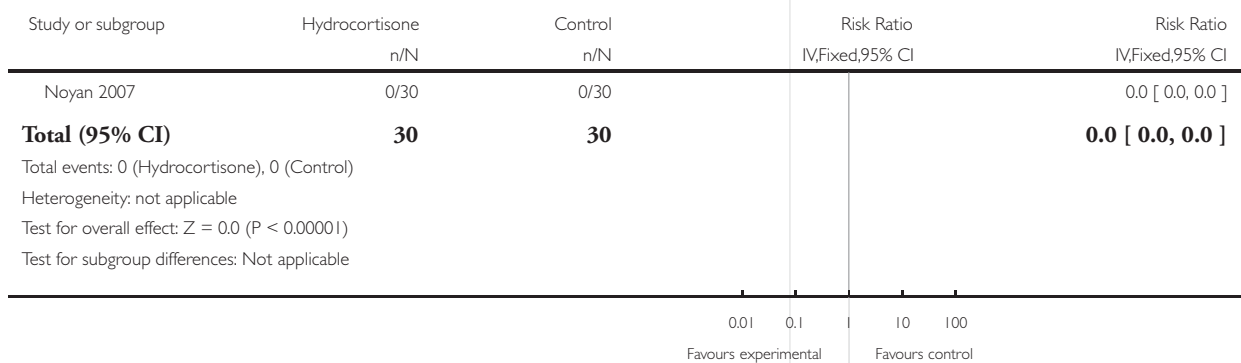Outcome: 2 Number of any possible adverse effects (secondary outcome 7)

Study or subgroup	ACTH n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Rucklidge 2004	0/9	0/9		0.0 [0.0, 0.0]
Total (95% CI)	**9**	**9**		**0.0 [0.0, 0.0]**

Total events: 0 (ACTH), 0 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

```
      0.01    0.1    I    10    100
   Favours experimental    Favours control
```

Analysis 7.1. Comparison 7 Comparison 7: Caffeine sodium benzoate versus placebo, Outcome 1 PDPH persistence of any severity at 1 to 2 hours (primary outcome).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 7 Comparison 7: Caffeine sodium benzoate versus placebo

Outcome: 1 PDPH persistence of any severity at 1 to 2 hours (primary outcome)

Study or subgroup	Caffeine sodium benzoate n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Sechzer 1978	5/20	18/21		100.0 %	0.29 [0.13, 0.64]
Total (95% CI)	**20**	**21**		**100.0 %**	**0.29 [0.13, 0.64]**

Total events: 5 (Caffeine sodium benzoate), 18 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 3.10 (P = 0.0019)
Test for subgroup differences: Not applicable

```
        0.01   0.1        1    10   100
       Favours experimental    Favours control
```

Analysis 7.2. Comparison 7 Comparison 7: Caffeine sodium benzoate versus placebo, Outcome 2 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2).

Review: Drug therapy for treating post-dural puncture headache

Comparison: 7 Comparison 7: Caffeine sodium benzoate versus placebo
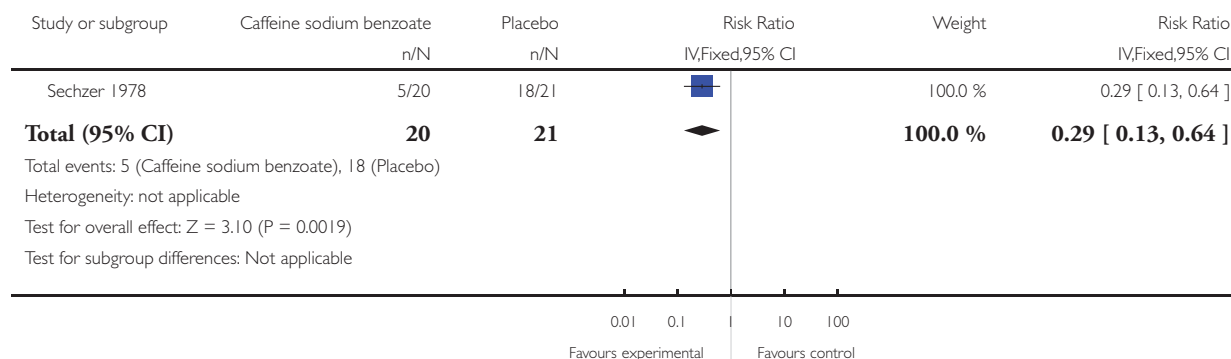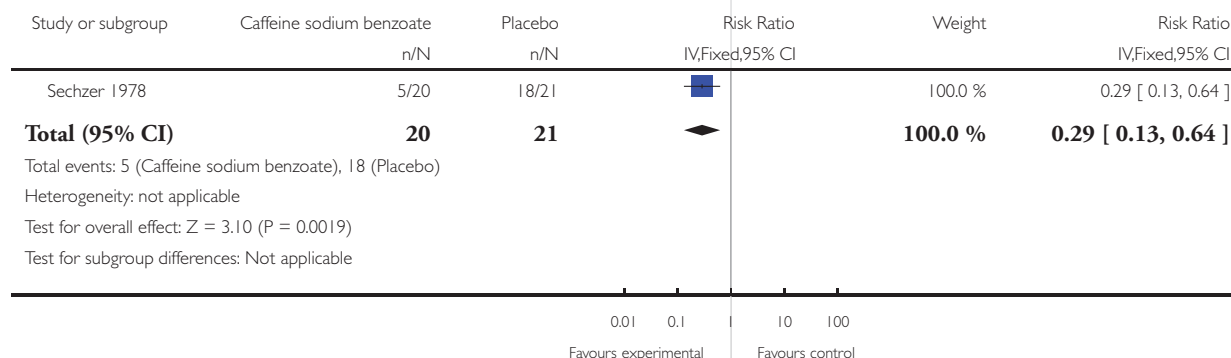
Outcome: 2 Number of participants with a conservative supplementary therapeutic option offered (secondary outcome 2)

Study or subgroup	Caffeine sodium benzoate n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Sechzer 1978	5/20	18/21		100.0 %	0.29 [0.13, 0.64]
Total (95% CI)	**20**	**21**		**100.0 %**	**0.29 [0.13, 0.64]**

Total events: 5 (Caffeine sodium benzoate), 18 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 3.10 (P = 0.0019)
Test for subgroup differences: Not applicable

```
        0.01   0.1        1    10   100
       Favours experimental    Favours control
```

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor Anesthesia, Epidural explode all trees
#2 MeSH descriptor Anesthesia, Spinal explode all trees
#3 MeSH descriptor Injections, Spinal explode all trees
#4 MeSH descriptor Myelography explode all trees
#5 MeSH descriptor Spinal Puncture explode all trees
#6 (spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) near/10 (puncture* or inject* or anesth* or anaesth* or needle*)
#7 myelogra*
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Headache Disorders explode all trees
#10 headach* or cephalgia or (head near/2 pain) or (cranial near/2 pain)
#11 (#9 OR #10)
#12 (#8 AND #11)

Appendix 2. MEDLINE Ovid search strategy

1 exp Anesthesia, Epidural/
2 exp Anesthesia, Spinal/
3 Injections, Spinal/
4 exp Myelography/
5 exp Spinal Puncture/
6 ((spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) adj10 (puncture* or inject* or anesth* or anaesth* or needle*)).mp.
7 myelogra*.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp Headache Disorders/
10 (headach* or cephalgia or (head adj2 pain) or (cranial adj2 pain)).mp.
11 9 or 10
12 8 and 11
13 randomised controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 drug therapy.fs.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 12 and 21
key:
p = title, original title, abstract, name of substance word, subject heading word, unique identifier
pt = publication type, ab = abstract, fs = floating subheading

Appendix 3. EMBASE Ovid search strategy

1 exp spinal anaesthesia/
2 exp lumbar puncture/
3 exp MYELOGRAPHY/
4 ((spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* ot theca* or intrathecal or subarachnoid*) adj10 (puncture* or inject* or anesth* or anaesth* or needle*)).mp.
5 myelogra*.mp.
6 1 or 2 or 3 or 4 or 5
7 exp "headache and facial pain"/
8 (headach* or cephalgia or (head adj2 pain) or (cranial adj2 pain)).mp.
9 7 or 8
10 6 and 9
11 random*.mp.
12 factorial*.mp.
13 (crossover* or cross over* or cross-over*).mp.
14 placebo*.mp.
15 (doubl* adj blind*).mp.
16 (singl* adj blind*).mp.
17 assign*.mp.
18 allocat*.mp.
19 volunteer*.mp.
20 crossover procedure/
21 double blind procedure/
22 randomised controlled trial/
23 single blind procedure/
24 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 10 and 24
key:
mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

Appendix 4. CINAHL search strategy

1 anaesthesia, epidural/ or analgesia, epidural/ or "epidural analgesia administration (iowa nic)"/ or exp injections, epidural/
2 exp injections, intraspinal/
3 myelography/
4 spinal puncture/ or anaesthesia, spinal/
5 ((spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or theca* or intrathecal or subarachnoid*) and (puncture* or inject* or anesthe* or anaesthe* or needle*)).ti,ab
6 myelogra*.ti,ab
7 1 or 2 or 3 or 4 or 5 or 6
8 *headache/
9 (headach* or cephalgi* or cephalalgi*).ti,ab
10 8 or 9
11 7 and 10
12 exp clinical trials/
13 (clinical and trial*).ti
14 ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti
15 (randomi?ed and control* and trial*).ti
16 random assignment/
17 (random* and allocat*).ti
18 placebo*.ti
19 placebos/

20 quantitative studies/
21 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 11 and 21

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 8, 2011

CONTRIBUTIONS OF AUTHORS

Conceiving the review (guarantor): Xavier Basurto (XB).

Screening search results: XB, Ivan Solà (IS).

Screening retrieved papers against inclusion criteria: XB, IS, Xavier Bonfill Cosp (XBC).

Appraising quality of papers: XB, IS.

Extracting data from papers: XB, IS.

Data management for the review: XB, Laura Martínez (LM).

Entering data into Review Manager (RevMan 5.1): XB, LM.

Interpretation of data: XB, IS, XBC, LM.

Statistical analysis: XB, IS, LM.

Writing the review: XB, IS, XBC, LM.

Comment and editing of review drafts: XB, IS, XBC, LM.

Responsible for reading and checking review before submission: XB, IS, XBC, LM.

Responsible for initiating and running the update of this review: XB

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- CIBER de Epidemiología y Salud Pública (CIBERESP), Spain.
- Iberoamerican Cochrane Centre, Spain.

External sources

- Agencia de Calidad para el Sistema Nacional de Salud, Ministerio de Sanidad, Política Social e Igualdad, Spain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Types of participants: "The use of a standardized diagnostic criteria for PDPH will not be required, but it should at least be described as orthostatic headache which worsens on standing and is improved by lying down." The "it should at least be" has been added to emphasise the need to include only those RCTs that have used an orthostatic headache criteria to include participants.

- PaPaS Review Group Specialised Register electronic search eliminated.

- CINAHL search strategy included.

NOTES

Protocol title split from 'Drug therapy for preventing and treating post-dural puncture headache' into two separate titles; one on prevention (Basurto 2009) and this one on treatment.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenocorticotropic Hormone [therapeutic use]; Amines [therapeutic use]; Analgesics [*therapeutic use]; Caffeine [therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Hydrocortisone [therapeutic use]; Pain Measurement [methods]; Post-Dural Puncture Headache [*drug therapy]; Randomized Controlled Trials as Topic; Spinal Puncture [*adverse effects]; Sumatriptan [therapeutic use]; Theophylline [therapeutic use]; Treatment Outcome; gamma-Aminobutyric Acid [therapeutic use]

MeSH check words

Female; Humans; Male

5.4.- Publicació nº3

Basurto Ona X, Rigau Comas D, Urrútia G

Opioids for acute pancreatitis pain

Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD009179

5.4.- Publicació nº3

Resum de la publicació nº3

Objectiu: Avaluar l'eficàcia i la seguretat dels opioides per al dolor abdominal en la PA, en comparació amb altres analgèsics, opioides o no.

Resultats: Es van incloure 5 ACA amb un total de 227 participants (rang d'edat 23-76 anys; 65% homes) amb dolor abdominal de PA. Els opioides avaluats eren la buprenorfina intravenosa i intramuscular, la petidina intramuscular, la pentazocina intravenosa, el fentanil transdèrmic i la morfina subcutània.

Un ACA, comparant morfina subcutània amb metamizol intravenós va reduir de manera no significativa el nombre de participants amb millores en la intensitat del dolor (resultat primari). Tres estudis van comparar l'analgèsia amb opioides contra els tractaments no opioides. Després d'excloure un estudi que va utilitzar opioides a través d'una infusió intravenosa contínua, hi va haver una disminució en el nombre de pacients que van requerir analgèsia suplementària. En un únic estudi, no hi va haver diferències en el nombre de pacients que van requerir analgèsia suplementària entre buprenorfina i petidina. Les complicacions de la pancreatitis no es van associar amb una diferència significativa a cap dels fàrmacs provats. No es van produir esdeveniments adversos clínicament greus o potencialment mortals en relació amb el tractament. No es van trobar diferències en aquest resultat entre els opioides i no opioides o segons el tipus d'esdeveniment advers. Una mort en el grup de la procaïna es va informar entre tots els ACA inclosos.
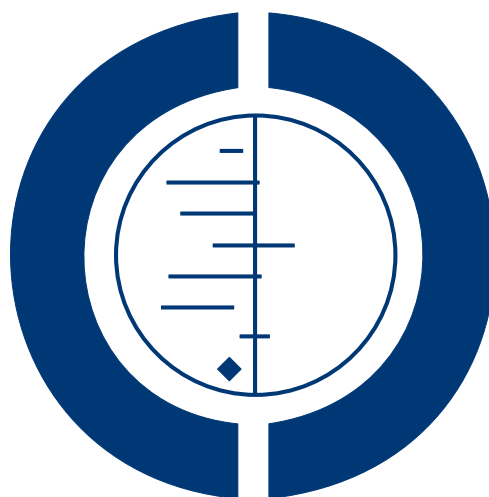
Un ACA comparant petidina amb buprenorfina intramuscular va informar diferències no significatives en l'analgèsia complementària, esdeveniments adversos o morts. Un ACA comparant fentanil amb placebo no va trobar diferències en els esdeveniments adversos.

Els resultats d'aquesta revisió estan limitats per la falta d'informació que permet la completa avaluació del risc de biaix i el mesurament de resultats rellevants i també pel petit nombre de participants i escassos esdeveniments coberts pels assajos.

Conclusions: Els opioides poden ser una opció apropiada en el tractament del dolor abdominal en la PA. En comparació amb altres opcions analgèsiques, els opioides poden disminuir la necessitat d'analgèsia suplementària. Actualment no hi ha cap diferència en el risc de complicacions de la pancreatitis o esdeveniments adversos greus entre els opioides i altres opcions d'analgèsia. La investigació futura s'ha de centrar en el disseny d'assajos amb mostres més grans i el mesurament dels resultats rellevants per a la presa de decisions, com ara el nombre de participants que mostren reduccions en la intensitat del dolor. La comunicació d'aquests ACA també s'ha de millorar per permetre als usuaris de la literatura mèdica avaluar els resultats amb precisió. Es necessiten estudis longitudinals grans per establir el risc d'efectes adversos relacionats amb els fàrmacs.

Opioids for acute pancreatitis pain (Review)

Basurto Ona X, Rigau Comas D, Urrútia G

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[Intervention Review]

Opioids for acute pancreatitis pain

Xavier Basurto Ona[1], David Rigau Comas[2], Gerard Urrútia[2]

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A B S T R A C T

Background

Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve adjacent tissues and/or remote organ systems. Abdominal pain is the main symptom and is usually accompanied by nausea, vomiting and fever. Opioids are commonly used to manage pain in acute pancreatitis but there are still some uncertainties about their clinical effectiveness and safety.

Objectives

To assess the effectiveness and safety of opioids for treating acute pancreatitis pain.

Search methods

The search strategy included the Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2013, Issue 6), MEDLINE (from 1950 to June 2013) and EMBASE (from 1980 to June 2013). There were no restrictions by language or publication status.

Selection criteria

We considered randomised clinical trials (RCTs) assessing the effectiveness of any opioid drug used for treating acute pancreatitis pain.

Data collection and analysis

Two review authors independently selected studies, assessed risks of bias and extracted data. We estimated risk ratios (RRs) for dichotomous data and calculated a 95% confidence interval (CI) for each RR. We performed an intention-to-treat (ITT) analysis. We undertook meta-analysis for some outcomes.

Main results

We included five RCTs with a total of 227 participants (age range 23 to 76 years; 65% men) with acute pancreatitis pain. The opioids assessed were intravenous and intramuscular buprenorphine, intramuscular pethidine, intravenous pentazocine, transdermal fentanyl and subcutaneous morphine.

One RCT, comparing subcutaneous morphine with intravenous metamizole reported non-significant reduction in the number of participants with improvements in pain intensity (primary outcome) (RR 0.50, 95% CI 0.19 to 1.33). Three studies compared analgesia using opioids with non-opioid treatments. After excluding one study that used opioids through continuous intravenous infusion, there

was a decrease in the number of patients requiring supplementary analgesia (RR 0.53, 95% CI 0.30 to 0.93). In a single study, there were no differences in the number of patients requiring supplementary analgesia between buprenorphine and pethidine (RR 0.82, 95% CI 0.61 to 1.10).

Pancreatitis complications were not associated with a significant difference between the drugs tested. No clinically serious or life-threatening adverse events occurred related to treatment. No differences for this outcome were found between opioid and non-opioid treatments, or for type of adverse event (nausea-vomiting and somnolence-sedation). One death in the procaine group was reported across all the trials.

One RCT comparing pethidine with intramuscular buprenorphine reported non-significant differences of supplementary analgesic, adverse events or deaths. One RCT comparing fentanyl with placebo found no difference in adverse events.

The findings of this review are limited by the lack of information to allow full appraisal of the risk of bias, the measurement of relevant outcomes and the small numbers of participants and events covered by the trials.

Authors' conclusions

Opioids may be an appropriate choice in the treatment of acute pancreatitis pain. Compared with other analgesic options, opioids may decrease the need for supplementary analgesia. There is currently no difference in the risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesia options.

Future research should focus on the design of trials with larger samples and the measurement of relevant outcomes for decision-making, such as the number of participants showing reductions in pain intensity. The reporting of these RCTs should also be improved to allow users of the medical literature to appraise their results accurately. Large longitudinal studies are also needed to establish the risk of pancreatitis complications and adverse events related to drugs.

PLAIN LANGUAGE SUMMARY

Opioids for abdominal pain in acute pancreatitis

The pancreas is a gland behind the stomach and close to the first part of the small intestine. It produces digestive juices, amylase, secreted into the small intestine and releases hormones, insulin and glucagon, into the bloodstream. Acute pancreatitis refers to a sudden inflammation of the pancreas. It happens when digestive juices become active inside the pancreas, causing swelling, bleeding and damage to the pancreas and its blood vessels. It is a serious condition and can lead to further problems. Common symptoms are severe pain in the upper abdomen, nausea, and vomiting. Treatment is usually a few days in hospital for fluids, antibiotics, and medicines to relieve pain, delivered by drip.

If there is severe pain, at least one type of pain relief (e.g. paracetamol, non-steroidal anti-inflammatory drugs, opioids) is generally used. Opioids, such as morphine and its derivatives, are commonly used, but without firm evidence for their effectiveness and safety. It is possible that they may hide the resolution of the disease, and may increase pain by causing spasms. The aim of this review is to clarify the appropriate use of opioids for abdominal pain in acute pancreatitis.

We searched a number of electronic databases up to June 2013. We include five randomised clinical trials (RCTs), with a total of 227 participants in this review. The opioids evaluated were buprenorphine, pethidine, pentazocine, fentanyl and morphine.

For participants needing additional pain relief, combined analysis of opioids (pentazocine and morphine) showed a significant benefit when compared with non-opioid treatments. Two trials showed that buprenorphine and pentazocine were each more effective than procaine. Our confidence in the stability of these effects is low, however, due to limitations in the number of studies and participants, and the low quality of the way the trials were run and reported. No serious or life-threatening adverse events were linked to the drugs being studied. One death was reported, in a procaine group, across all the included trials.

On the evidence so far, opioids may be an appropriate treatment option and might have the advantage of decreasing the need for additional pain relief. We found no clear difference in the risk of pancreatitis complications or serious adverse event between opioids and other pain relief treatments. However, the findings of this review are limited by the lack of information to allow full appraisal of the risk of bias, the measurement of relevant outcomes and the small numbers of participants covered by the trials.

S U M M A R Y   O F   F I N D I N G S   F O R   T H E   M A I N   C O M P A R I S O N   [Explanation]

Morphine compared to metamizole for acute pancreatitis pain

Patient or population: participants with acute pancreatitis pain
Settings:
Intervention: Morphine
Comparison: Metamizole

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Metamizole	**Morphine**				
Improvements in pain intensity as defined by the trialist (primary outcome) Follow-up: 2 days	38 per 100	19 per 100 (7 to 50)	**RR 0.50** (0.19 to 1.33)	16 (1 study)	⊕⊕◯◯ Low[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Few participants included, few events reported and methodological limitations.

BACKGROUND

Description of the condition

Acute pancreatitis was defined in 1992 at the Atlanta Symposium (Bradley 1993) as an acute inflammatory process of the pancreas that may also involve adjacent tissues and/or remote organ systems. Mild acute pancreatitis was defined as that associated with minimal organ dysfunction, whereas severe acute pancreatitis was defined as that associated with organ failure and/or local complications (necrosis, abscess, or pseudocyst) accompanied by adverse prognostic scores (Banks 2006).

The incidence rate of acute pancreatitis ranges between 5 and 80 per 100,000 people per year, with the highest incidence recorded in the United States and Finland (Banks 2002).

In 75% to 80% of sufferers, the aetiology of acute pancreatitis is identified. In developed countries, the most frequent causes are bile duct obstruction (38%) and alcohol abuse (36% to 44%).

The mechanisms by which bile duct obstruction or alcohol consumption initiate acute pancreatitis are not completely known. It seems, however, that a common pathogenic pathway might be related to inappropriate activation of trypsinogen to trypsin and to a lack of prompt elimination of active trypsin inside the pancreas (Wang 2009; Whitcomb 2006; Whitcomb 2008).

Other less common causes of pancreatitis are elevated triglyceride levels, cancer, viral and bacterial infections, surgery, peptic ulcers, pancreas divisum, medications and other genetic, metabolic and autoimmune causes.

Abdominal pain is the most common symptom of acute pancreatitis and is usually accompanied by nausea, vomiting and fever. Acute, constant and intense abdominal pain might last for several days, is mostly experienced in the epigastric region or the right upper quadrant and may radiate to the back. Physical examination often reveals severe upper abdominal tenderness at times associated with guarding (Carroll 2007; Frossard 2008).

It is generally accepted that a diagnosis of acute pancreatitis requires at least two of the following three features: 1) abdominal pain characteristic of acute pancreatitis; 2) serum amylase and/or lipase greater than three times the upper limit of normal; and 3) characteristic findings of acute pancreatitis on abdominal scan (Banks 2006). Contrast-enhanced computerised tomography (CECT) can be done after admission to confirm diagnosis of disease (87% to 90% sensitivity and 90% to 92% specificity), or after four days, to assess local complications and to score the disease.

Most cases of acute pancreatitis are mild and self-limiting, but 20% of cases develop severe disease with local complications, such as necrosis, pseudocyst or abscess of the gland, and/or extrapancreatic complications (Bradley 1993). Several risk scales, general or specific, are used to classify disease severity and survival, including Computed Tomography Severity Index (CTSI), Ranson's criteria, Imrie scoring system, Acute Physiology And Chronic Health Evaluation (APACHE II), and the Sequential Organ Failure Assessment (SOFA) (Carroll 2007; Frossard 2008). General mortality is estimated to be around 2% to 3%, but can reach 80% (Johnson 2005). While mortality in sterile pancreatic necrosis is 10%, infected necrosis generates a mortality of 25%. Nearly half of deaths occur during the first one to two weeks after admission because of multiple organ failure from systemic inflammatory response. Deaths beyond this time are also due to multiple organ failure, but are secondary to infected pancreatic necrosis.

Description of the intervention

Treatment of acute pancreatitis depends mainly on the severity of the progression but almost all cases will need supportive treatment, such as analgesics.

Several types of opioids exist under the N02A Anatomical Therapeutic Chemical ATC code (ATC Classification). This group comprises strong analgesics of the opiate type and analgesics with similar structure or action. Opioids can be classified by their actions: agonist (e.g. morphine, hydromorphone, fentanyl), partial agonist (e.g. buprenorphine), agonist-antagonist (e.g. pentazocine), and antagonist opioids (e.g. naloxone). Pure opioid agonists are the most potent analgesics (Trescot 2008). These drugs are stronger pain relievers than non-opioids; oral 650 mg paracetamol or aspirin is oral dose equianalgesic to 30 mg codeine, 50 mg meperidine or 5 mg morphine. Apart from pain relief, opioid uses include treatment of opioid dependence, cough suppressants, epidural analgesia or as an antispasmodic.

Opioids are commonly used to manage pain in acute pancreatitis. However, it has been suggested that, apart from meperidine, opioids may mask the resolution of the disease and increase pain due to their spasmogenic effect, which in turn increases intraluminal pressure in the sphincter of Oddi (Isenhower 1998). This increased bile pressure appears to be related to the dose and plasma concentration of the opioid, and is apparently mediated by the Mu (μ) receptor. However, the clinical significance of this increased pressure is uncertain, because many studies are anecdotal observations, with small numbers of participants without known pancreatic disease, and there is no clear evidence from controlled clinical trials that would support this theory (Cebrián 2003).

How the intervention might work

Treatment with analgesics for abdominal pain in acute pancreatitis probably does not modify the course of disease or mortality. However, the treatment of pain as a symptom improves comfort and patient-reported outcomes.

An opioid is a psychoactive chemical that works by binding to opioid receptors; Mu (μ) with Mu1 and Mu2 subtypes receptors stimulated by pure opioid agonists, Kappa (κ) and Delta (δ). These receptors are found principally in the central and peripheral nervous system and the gastrointestinal tract. The opioid drugs pro-

duce analgesia by actions at several levels of the nervous system, in particular, inhibition of neurotransmitter release on presynaptic neuronal terminals in the spinal cord, considered to be the major mechanism of action responsible for the clinical effects of opioids, and inhibition of postsynaptic neurons, preventing the ascending transmission of the pain signal.

Why it is important to do this review

All people suffering from pain with acute pancreatitis would be considered for at least one type of analgesic (e.g. paracetamol, non-steroidal anti-inflammatory drugs, opioids). No clear advantage for any particular type of analgesia has been demonstrated in the treatment of abdominal pain in people with acute pancreatitis (Banks 2006). We have been unable to identify any meta-analysis or systematic reviews comparing opioids versus other drugs for this condition.

The aim of this review is to clarify the appropriate use of opioids for abdominal pain management in acute pancreatitis.

OBJECTIVES

To assess the efficacy and safety of opioids for abdominal pain in acute pancreatitis, compared with other analgesics or different opioids.

METHODS

Criteria for considering studies for this review

Types of studies

We include randomised clinical trials (RCTs) with a parallel design, developed in any setting. We excluded quasi-randomised clinical trials.

Since abdominal pain in acute pancreatitis is not a stable and chronic condition, we excluded cross-over design trials.

Types of participants

We include studies with men or women, of any age, with abdominal pain due to acute pancreatitis. We have not used an explicit definition of acute pancreatitis, but have accepted the definition used by study authors.

Types of interventions

We considered treatment with opioids, i.e. those classified under the N02A Anatomical Therapeutic Chemical ATC code (e.g. morphine, hydromorphone, oxycodone, dihydrocodeine, diamorphine, codeine, pethidine, fentanyl, dextropropoxyphene, methadone, pentazocine, buprenorphine, tramadol, nicomorphine, meperidine, among others), used as an analgesic drug at any dose, drug-release formulation or route of administration.

Control groups included any other type of analgesic drug treatment, including other opioids, at any dose, drug-release formulation or route of administration.

Types of outcome measures

Primary outcomes

1. Number of participants showing improvements in pain intensity as defined by the trialist.
2. Number of participants requiring supplementary analgesia (offered when trial drug intervention fails to relieve pain and following trial protocol).

Secondary outcomes

1. Number of participants with pancreatitis complications.
2. Number of participants with drug-related adverse events.
3. Number of deaths from any cause.

For the first primary outcome 'Number of participants showing improvements in pain intensity' we accepted any degree of improvement reported by the authors. In the case of multiple degrees described by a trial, we took all of them into account. For meta-analysis, we combined only comparable degrees of improvement.

Search methods for identification of studies

Electronic searches

We attempted to identify all relevant trials regardless of language in the following databases:
- Cochrane Upper Gastrointestinal and Pancreatic Diseases Review Group Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*; 2013, Issue 6), Appendix 1;
- MEDLINE (via PubMed): from 1950 to June 2013, Appendix 2;
- EMBASE (via OVID): from 1980 to June 2013, Appendix 3.

We designed a search strategy through a combination of thesaurus-based terms and a broad list of free-text terms covering both the intervention and the problem of interest. The most recent search was in June 2013.

We combined our strategies with validated filters to retrieve trials (Cochrane Handbook).

Searching other resources

We checked the reference lists of all included studies in order to identify any potentially relevant RCT not found through electronic searches.

We also contacted study authors where necessary, to obtain additional information.

Data collection and analysis

Selection of studies

Two authors (XBO and GU) independently screened titles and abstracts of all references identified by the literature search for eligibility.

We obtained the full text of all potentially eligible studies and independently evaluated the for inclusion in the review. We excluded any studies that did not provide results for adults and children separately (as a subgroup analysis), or if this information could not be obtained after contacting the authors. We resolved disagreements by consensus or by contacting the authors for clarification. We document reasons for excluding studies (see Characteristics of excluded studies table).

Data extraction and management

Two authors (XBO and GU) independently extracted data using a standardised data extraction sheet. For all included studies we extracted information on the number of participants randomised and number for which outcome(s) were measured. We extracted the number of events and the number of participants in each treatment arm for dichotomous outcomes.

We resolved any inadequacies or discrepancies between the extracted data by discussion and if necessary by contacting the study authors for further details.

Assessment of risk of bias in included studies

Two authors (XBO and GU) independently assessed the risk of bias for each included trial using an assessment form outlined in Chapter 8 of the Cochrane Handbook. We resolved any disagreements by discussion or by involving a third assessor.

We assessed the following five components for each of the trials: sequence generation (selection bias), allocation concealment (selection bias), blinding (performance and detection biases), incomplete outcome data (attrition bias through withdrawals, drop-outs, protocol deviations) and selective reporting bias.

For each of these components, we assigned a judgement of low, high or unclear risk of bias (Cochrane Handbook). We recorded

the results in a standard table in Review Manager 5 (RevMan), and summarised the findings in a 'Risk of bias' table and figures.

Measures of treatment effect

We measured the effect of treatment as a dichotomous outcome using the risk ratio (RR) with a 95% confidence interval (CI).

Dealing with missing data

Due to the acute condition being assessed in this review, we did not expect a significant drop-out rate in the studies included in the review. As shown below, missing data were generally not a problem for the included trials.

Assessment of heterogeneity

We pooled data only for clinically homogeneous studies based on comparability of interventions and outcome measures. We assessed statistical heterogeneity using the I^2 statistic (Higgins 2003). I^2 values above 75% indicate substantial heterogeneity between studies.

Assessment of reporting biases

There were insufficient studies included in the review to support the use of a funnel plots or other methods to test for publication bias.

Data synthesis

Where pooling of data was possible (i.e. the trials assessed a common comparison providing adequate data for a specific outcome), we carried out a meta-analysis using the Mantel-Haenszel random-effects model.

When pooling was not possible, we provide a qualitative description of the results. All statistical analyses were performed using Cochrane Review Manager 5 (RevMan) statistical package, following the recommendations of the Cochrane Handbook.

Subgroup analysis and investigation of heterogeneity

In future updates of this review, provided that sufficient data are available, we plan to carry out the following subgroup analyses to examine the effect of opioids on specific group of participants:

- Disease severity (severe versus less severe). Severe acute pancreatitis is defined as having any of the following criteria: organ failure, local complications, Ranson's criteria > 3 or APACHE-II score $\geq$ 8;
- Disease aetiology (alcohol versus other causes);
- Opioid class (pure agonists, partial agonist, agonist-antagonists, antagonists);
- Opioid administration route (oral versus parenteral).

Sensitivity analysis

In future updates of this review, we will conduct sensitivity analyses formulated a priori to investigate the robustness of the results modified by various components of the risk of bias assessments. We will examine the effect on the primary outcome of excluding any RCT judged to be at a high risk of bias by three of the domains, i.e. sequence generation, allocation concealment and blinding. We will also carry out sensitivity analysis to compare the random-effects model with a fixed-effect model.

RESULTS

Description of studies

Results of the search

The search identified 316 references in our primary electronic databases. We excluded 302 references on the basis of title and abstract alone. We then obtained the full-text report for the remaining 14 references to check whether they met all the inclusion criteria. We finally excluded nine of these studies after a complete full-text review, and after we had contacted the study authors for more information to decide eligibility. Five studies met the inclusion criteria for this review (Blamey 1984; Jakobs 2000; Kahl 2004; Peiro 2008; Stevens 2002).
The study flow is shown in Figure 1.

Figure 1. Study flow diagram.

Included studies

A detailed description of included studies is provided in the Characteristics of included studies table.

Study design

All five studies, involving a total of 227 participants, were randomised clinical trials (RCTs) with a parallel design. All were active-control trials except Stevens 2002, which used a placebo-controlled group.

Setting

All the RCTs were single-centre trials conducted in Germany (Jakobs 2000; Kahl 2004), the UK (Blamey 1984), the USA (Stevens 2002), and Spain (Peiro 2008).

All the RCTs recruited their participants from hospital settings, with the intervention conducted while they were in acute care units.

Sample size

The smallest trial had 16 participants (Peiro 2008) and the largest 107 (Kahl 2004). Peiro 2008 was the only trial that described how the sample size was calculated.

Participants

The majority of participants were men (at least 127/195; 65%) with an age range between 23 and 76 years. Blamey 1984, with 32 participants, did not report details of gender or age of their participants.

Intervention

Five different opioids were used in the five RCTs included in this review. Two trials assessed buprenorphine, comparing it with another opioid (pethidine; Blamey 1984) and with procaine, a local anaesthetic (Jakobs 2000). Pentazocine was compared with procaine in Kahl 2004, morphine was compared with metamizole (Peiro 2008) and fentanyl with placebo (Stevens 2002).

All intervention and control groups used a parenteral route of administration. Two trials used the intravenous route (Jakobs 2000; Kahl 2004), the intramuscular route was used in Blamey 1984, the transdermal route in Stevens 2002 and subcutaneous route in Peiro 2008.

Opioids were the supplementary analgesic drugs (rescue treatment) most used when the intervention drug failed to resolve the acute abdominal pain. Four RCTs used pethidine (Blamey 1984; Jakobs 2000; Peiro 2008; Stevens 2002) and Kahl 2004 used pentazocine. A pyrazolone derivate was also used in Jakobs 2000.

Outcomes of interest

Peiro 2008 was the only trial reporting data on our first primary outcome, i.e. the number of participants showing improvements in pain intensity, assessed after 24 hours of starting treatment. Using a 100 mm Visual Analogue Scale (VAS), the treatment was considered effective when the VAS score was less than 15 mm in two consecutive VAS evaluations.

All RCTs except Stevens 2002 reported data on our second primary outcome, i.e. the number of participants with a supplementary analgesic option.

The number of participants with drug-related adverse events was reported by all the RCTs. The number of deaths from any cause was reported by all the RCTs except for Stevens 2002, and the least-reported secondary outcome was the number of participants with pancreatitis complications, reported by three trials (Jakobs 2000; Kahl 2004; Peiro 2008).

Most of the RCTs reported the results at the end of the trial. Blamey 1984 and Peiro 2008 at 24 hours, Kahl 2004 at four days, Jakobs 2000 at 72 hours and Stevens 2002 at three days after discharge. Peiro 2008 also reported results at 48 hours for pain assessment and at six months for adverse events.

Excluded studies

Five trials did not fulfil the inclusion criteria and were excluded. (Hopton 1971; Salazar 1987; Salim 1991; Santosh 2010; Spiegel 2001).

For a summary of the reasons for exclusion please see the Characteristics of excluded studies table.

Risk of bias in included studies

Our assessment of the risk of bias in the included studies is summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3.   Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Sequence generation
Allocation sequence was adequately generated in one RCT (Blamey 1984) using a computerised random numbers series. The other four RCTs did not report the method used for sequence generation (Jakobs 2000; Kahl 2004; Peiro 2008: Stevens 2002).
Allocation concealment
Three RCTs had adequately concealed randomisation sequences: Blamey 1984 and Peiro 2008 by central randomisation and Stevens 2002 by sealed envelopes. The other two included RCTs did not provide information regarding allocation concealment (Jakobs 2000; Kahl 2004).

Blinding

Blinding of participants and personnel (performance bias):

The blinding method was judged as adequate in two RCTs (Blamey 1984; Stevens 2002). The rest of the trials reported no blinding of participants or study personnel.

Blinding of outcome assessment (detection bias):

Three trials used a blinded method to assess outcomes (Blamey 1984; Peiro 2008: Stevens 2002). Outcome assessment in Jakobs 2000 and Kahl 2004 was reported as not blinded.

Incomplete outcome data

All RCTs included in this review except Stevens 2002 had a low risk of attrition bias, because of the low rate of withdrawals: 6/107 participants in Kahl 2004, 1/40 in Jakobs 2000 and none in Blamey 1984 and Peiro 2008. The principal author of one study (Stevens 2002) indicated that 38.5% of participants had withdrawn and could not report how those patients were distributed. The study was therefore judged to be at high risk of attrition bias.

Selective reporting

All RCTs included in this review except Stevens 2002 reported results for all the key outcomes that would be expected to have been reported for such a trial and were therefore judged to be at low risk of reporting bias.

Effects of interventions

See: **Summary of findings for the main comparison** Morphine compared to metamizole for acute pancreatitis pain; **Summary of findings 2** Opioids versus no opioids for acute pancreatitis pain
We present in this section a narrative synthesis of the results for the different outcomes of interest, with illustrative forest plots (not pooled, apart from Analysis 4).
Number of participants showing improvements in pain intensity as defined by the trialist
Only one RCT reported data for this primary outcome (Peiro 2008), showing non-significant differences in the number of participants with subcutaneous morphine compared with intravenously metamizole (RR 0.50, 95% CI 0.19 to 1.33; Analysis 2.1).
Number of participants with a supplementary analgesic option offered when trial drug intervention fails to relieve pain
All the RCTs reported data for this primary outcome except Stevens 2002.
Results of RCTs comparing opioids versus non-opioids (Jakobs 2000; Kahl 2004; Peiro 2008) have been combined, showing no difference in the number of participants demanding supplementary analgesia (RR 0.41, 95% CI 0.14 to 1.19; Analysis 4.1).
After excluding Jakobs 2000 in a sensitivity analysis, the combined analysis of Kahl 2004 and Peiro 2008 showed low heterogeneity (I² = 25%) with a statistically significant reduction in the number of participants demanding supplementary analgesia favouring opioids compared to non-opioids (RR 0.53, 95% CI 0.30 to 0.93). The heterogeneity contributed by Jakobs 2000 may be attributable to its continuous intravenously infusion of opioids, compared to Kahl 2004 and Peiro 2008, in which opioids were administered every six and four hours respectively.
Jakobs 2000 and Kahl 2004 both showed a statistically significant reduction in the number of participants demanding supplementary analgesia, favouring buprenorphine (RR 0.08, 95% CI 0.01 to 0.52; Analysis 4.1) and pentazocine (RR 0.47, 95% CI 0.34 to 0.65; Analysis 4.1) respectively, compared to procaine. Peiro 2008 showed no difference between groups (RR 1.00, 95% CI 0.28 to 3.54; Analysis 4.1).
The only study comparing an opioid (intramuscular buprenorphine) versus another opioid (intramuscular pethidine) (Blamey 1984) showed no difference between groups (RR 0.82, 95% CI 0.61 to 1.10; Analysis 1.1).
Number of participants with pancreatitis complications
Three RCTs reported data for this outcome (Jakobs 2000; Kahl 2004; Peiro 2008); results of all three RCTs have been combined showing no difference in the number of participants with pancreatitis complications in comparison to non-opioid treatment (RR 1.05, 95% CI 0.82 to 1.34; Analysis 4.2) without heterogeneity

(I² = 0%).

None of these trials individually showed a statistical significant difference between groups.

Number of participants with drug-related adverse events

All the RCTs included reported data for this outcome, with a total of 22 events reported.

Stevens 2002, comparing an opioid (fentanyl) versus placebo, reported that none of the participants suffered a serious adverse event related to the interventions.

Results of RCTs comparing opioids versus non-opioids with at least one event (Jakobs 2000; Peiro 2008) have been combined showing a statistically non-significant increase associated with opioids (RR 2.00, 95% CI 0.90 to 4.46; Analysis 4.3) without heterogeneity (I² = 0%).

When combining results by type of adverse events, nauseas-vomiting and somnolence-sedation, neither showed a statistical signif-
icant increase associated with opioids. Nausea or vomiting in two RCTs (RR 1.68, 95% CI 0.70 to 4.00) without heterogeneity (I² = 0%) and somnolence or sedation in two RCTs (RR 5.54, 95% CI 0.69 to 44.79) also without heterogeneity (I² = 0%).

Kahl 2004 reported that none of the participants suffered an adverse event related to the intervention.

The only study comparing an opioid (intramuscular buprenorphine) versus another opioid (intramuscular pethidine) (Blamey 1984) showed no difference between groups (RR 2.67, 95% CI 0.12 to 60.93; Analysis 1.1)

Number of deaths from any cause

All the included RCTs except Stevens 2002 reported data for this outcome. Blamey 1984, Kahl 2004 and Peiro 2008 reported that none of the participants died and Jakobs 2000 reported one death from acute pancreatitis, in the procaine group.

A D D I T I O N A L   S U M M A R Y   O F   F I N D I N G S *[Explanation]*

Opioids versus no opioids for acute pancreatitis pain

Patient or population: participants with acute pancreatitis pain
Settings:
Intervention: Opioids versus no opioids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Control	**Opioids versus no opioids**				
Supplementary analgesic option offered (primary outcome 2) Follow-up: 2 to 4 days	**73 per 100**	**30 per 100** (21 to 42)	**RR 0.41** (0.29 to 0.57)	162 (3 studies)	⊕⊕○○ **Low**[1,2]	
Pancreatitis complications (secondary outcome 1) Follow-up: 2 to 4 days	**49 per 100**	**52 per 100** (41 to 66)	**RR 1.05** (0.82 to 1.34)	162 (3 studies)	⊕⊕○○ **Low**[1,2]	
Any drug-related adverse event (secondary outcome 2) Follow-up: 2 to 3 days	**11 per 100**	**21 per 100** (10 to 48)	**RR 2** (0.9 to 4.46)	110 (2 studies)	⊕⊕○○ **low**[1,2]	
Nausea and vomiting (secondary outcome 2) Follow-up: 2 to 3 days	**21 per 100**	**36 per 100** (15 to 86)	**RR 1.68** (0.7 to 4)	55 (2 studies)	⊕⊕○○ **low**[1,2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Sedation and somnolence (secondary outcome 2) Follow-up: 2 to 3 days	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 5.54** (0.69 to 44.79)	55 (2 studies)	⊕⊕○○ **low**[1,2]
Death from any cause (secondary outcome 3) Follow-up: 1 to 4 days	**10 per 1000**	**4 per 1000** (0 to 83)	**RR 0.35** (0.02 to 8.1)	194 (4 studies)	⊕○○○ **very low**[1,3]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of performance and detection bias
[2] Low frequency of events
[3] Very low frequency of events

DISCUSSION

Summary of main results

This systematic review identified two RCTs assessing buprenorphine for treating acute pancreatitis pain; Blamey 1984 using intramuscular buprenorphine compared to the opioid pethidine, and Jakobs 2000 comparing intravenous buprenorphine compared to procaine. Three other RCTs were included assessing other opioid drugs for treating acute pancreatitis pain: pentazocine versus procaine (Kahl 2004), morphine versus metamizole (Peiro 2008), and fentanyl versus placebo (Stevens 2002).

For the number of participants showing improvements in pain intensity (primary outcome), subcutaneous morphine did not show a significant reduction in the likelihood of a reduction in pain intensity compared with metamizole (Peiro 2008).

For the number of participants requiring a supplementary analgesic option (primary outcome), the combined analysis of three RCTs (Jakobs 2000; Kahl 2004; Peiro 2008) comparing opioids versus non-opioids found no difference between groups. After excluding Jakobs 2000 in a sensitivity analysis, the combined analysis of Kahl 2004 and Peiro 2008 showed low heterogeneity (I² = 25%) with a statistically significant reduction in the number of participants demanding supplementary analgesia favouring opioids compared to non-opioids (RR 0.53, 95% CI 0.30 to 0.93). The results of the sensitivity analysis should be interpreted with caution. The confidence in this effect estimate, however, is low due to methodological limitations and the variability of results among individual studies. The large heterogeneity detected in the analysis and a so different effect size in Jakobs 2000 could be explained because this study offered continuous intravenous opioid infusion to participants, whereas in Kahl 2004 and Peiro 2008 opioids were administered every four to six hours respectively. We do not know this beneficial effect responds only to the manner of administering analgesia, continuous or intermittent, the type of opioid used or other circumstances, but it is a fact that we state and could be considered in future trials.

Blamey 1984 comparing an opioid, buprenorphine, versus another opioid, pethidine, and found no difference between groups.

Pancreatitis complications were assessed with three different opioids, buprenorphine (Jakobs 2000), pentazocine (Kahl 2004) and morphine (Peiro 2008); the combined analysis of these three RCTs did not show a significant difference.

The included RCTs did not report any clinically serious or lifethreatening adverse events for opioids compared with the control drugs.

Only one death was reported, in a procaine group, across all the included trials. None of the included trials reported opioid-induced sphincter of Oddi spasm or increased bile pressure related to opioids.

The results for pancreatitis complications and adverse effects should be interpreted with caution, because clinical trials are not the best source for establishing the risk of low-frequency events related to drug treatments.

Overall completeness and applicability of evidence

Although we cannot differentiate the severity of acute pancreatitis experienced in these trials, all participants were admitted to acute care hospitals, and none to intensive care or outpatient departments. This is the setting in which the majority of people with acute pancreatitis are managed nowadays. We noted no anomalies in gender and age reported in these trials, and would take them to be a typical patient population.

All the opioids tested in the included RCTs are widely available and frequently used, so the findings are readily generalisable.

All the RCTs included in this review included one or more outcomes relevant to patients. Only one RCT reported data on the first primary outcome: number of participants showing improvements in pain intensity, defined as a 15 mm reduction in a 100 mm VAS scale over two consecutive evaluations. Even though the outcome is of relevance for patients, 15 mm reduction in a 100 mm VAS scale might be considered as not being clinically meaningful.

The number of participants requesting supplementary analgesic options can be considered as a surrogate measure of pain relief. This was also included as a primary outcome, since it is frequently reported in studies on pain management.

Although most of the included RCTs reported data on the second primary outcome (number of participants with a supplementary analgesic option), an overall lack of information limits the possibility of evaluating accurately and comprehensively the effects of opioids for acute pancreatitis pain.

Quality of the evidence

The results should be interpreted with caution, due to the limited number of trials identified, the diversity of drugs assessed and outcomes measured, the small sample sizes, and the levels of bias in the conduct and reporting of the trials.

Potential biases in the review process

The review was conducted in accordance with a previously published protocol. We believe the search strategy used here ensures an unbiased study selection, but we did not locate any trials other than English language reports, nor any unpublished trials, and it is possible that we might have missed such studies. The selection, data collection and analyses were all performed by more than one person to minimise bias. We also contacted study authors for clarification on study data.

None of the authors of this report has been involved in any of the included trials and none has any commercial or other conflict of interest.

Agreements and disagreements with other studies or reviews

We have found no other systematic review specifically investigating the efficacy of opioids for treating acute pancreatitis pain and its possible adverse events. Despite earlier investigation and clinical recommendations advising against the use of opioids, especially meperidine (Munoz 2000), recent studies (Thompson 2001) have failed to establish an association between opioids and clinically significant adverse events related to opioid-induced sphincter of Oddi spasm and basal pressure. These studies are compatible with our conclusions that neither deaths nor serious or life-threatening adverse events have been shown to be associated with opioid treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Opioids may be an appropriate choice for the treatment of acute pancreatitis pain. Compared with other analgesic options, opioids might decrease the need for supplementary analgesia. There is no difference in the risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesic options.

Implications for research

Future research in this field should focus on the design of trials with larger samples (reporting how sample size was determined), the measurement of relevant outcomes for decision-making, such as the number of participants showing a certain level of improvement in pain intensity, different opioids or routes of delivery, and opioids versus other techniques. Effectiveness of continuous analgesic infusion in acute pancreatitis could be tested in future RCTs. The reporting of these trials should also be improved (i.e. using the CONSORT statement (Schulz 2010)) to allow users of the medical literature to accurately appraise the results of these RCTs. Large longitudinal studies are also needed to establish the risk of less frequent pancreatitis complications and adverse events related to drug treatments.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blamey 1984

Methods	**Study type**: Double-blind, randomised trial, controlled with active treatment, parallel design. Single centre. Country and setting: UK and acute care hospital
Participants	**Randomised**: 32 (17 buprenorphine; 15 pethidine) **Excluded:** None **Gender:** Not specified **Age:** Not specified **Inclusion criteria:** Consecutive participants with acute pancreatitis **Exclusion criteria**: Not specified
Interventions	Intramuscular buprenorphine (0.3 mg) versus intramuscular pethidine (100 mg) **Co-interventions**: Routine supportive treatment was used. Subsequent analgesia (pethidine 100 mg) was provided on demand
Outcomes	1. Number of participants demanding further analgesia 2. Adverse events 3. Death Follow-up was 24 hours after administration of treatment
Notes	**Acute pancreatitis defined as:** Quote: "(serum amylase activity > 1200 IU/l or urinary amylase activity >3000 IU/1) ". (Page 1494) **Sample size calculation**: Not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Quote: "randomly number coded by a computer in the hospital pharmacy". (Page 1494)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical ampoules. Quote: "identical ampoules that had been randomly number coded". (Page 1494)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical ampoules

Blamey 1984 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or incomplete outcome reporting
Selective reporting (reporting bias)	Low risk	

Jakobs 2000

Methods	**Study type**: Open, randomised trial, controlled with active treatment, parallel design. Single centre. Country and setting: Germany and acute care hospital
Participants	**Randomised**: 40 (20 buprenorphine; 20 procaine) **Excluded:** one participant in buprenorphine group lost to follow-up (2.5%) **Gender:** Men: women. buprenorphine 12:8; procaine 11:9 **Age:** Buprenorphine: mean 51.5 (range 26 - 76); procaine: mean 47.5 (range 23 - 72) **Inclusion criteria:** acute abdominal pain consistent with the clinical diagnosis of acute pancreatitis (pain localised in the epigastrium or the upper abdomen; in some cases radiating to the back), elevated levels of serum amylase or serum lipase (minimum two-fold of normal) at any time of treatment and signs of acute pancreatitis on abdominal ultrasound or contrast-enhanced computed tomography **Exclusion criteria**: < 18 or > 75 years old, pregnancy, cardiac arrhythmias on initial electrocardiogram, known severe arrhythmias in the past, allergies to any of the study medications or individual follow-up < 24 hours
Interventions	Buprenorphine initial bolus of 0.3 mg and then 2.4 mg/day as a constant i.v. infusion, versus procaine 2 g/day intravenously as a constant infusion **Co-interventions**: Besides study medication, all the participants were treated with the standard therapeutic regimen including i.v. fluids and parenteral feeding via a central venous catheter, and prophylactic antibiotics in case of necrotising pancreatitis. Participants in the procaine group who were not satisfied with the analgesic effect received pethidine (50 mg bolus i.v.), while those in the buprenorphine group received a pyrazolone derivate or pethidine if necessary
Outcomes	1. Number of participants demanding further analgesia 2. Number of participants with pancreatitis complications 3. Adverse events 4. Deaths Follow-up was 72 hours after drug administration
Notes	**Acute pancreatitis defined as:** Quote: "pain localized in the epigastrium or the upper abdomen; in some cases radiating to the back, elevated levels of serum amylase or serum lipase (minimum two-fold of normal) at any time of treatment and signs of acute pancreatitis on abdominal ultrasound or contrast-enhanced computed tomography". (Page 1319) Acute pancreatitis / acute bout of a chronic pancreatitis: 14/20 (70%) in the buprenorphine group and 13/20 (65%) in the procaine group At least one participant was 76 years old, despite the exclusion criteria **Sample size calculation**: not described

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Methods of list generation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study. Quote: "The study design was open (not blind)". (Page 1320)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study. Quote: "The study design was open (not blind)". (Page 1320)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of participants withdrawn from the analysis
Selective reporting (reporting bias)	Low risk	

Kahl 2004

Methods	**Study type**: Open, randomised trial, controlled with active treatment, parallel design. Single centre. Country and setting: Germany and acute care hospital
Participants	**Randomised**: 107 (55 procaine; 52 pentazocine) **Excluded:** 6 (5 procaine, 1 pentazocine) **Gender:** Men: women. pentazocine 38:12; procaine 34:17 **Age: p**entazocine: mean 43 (SD 11); procaine: mean 47 (SD 14) **Inclusion criteria:** Acute pancreatitis, onset of abdominal pain < 72 hours prior to hospitalisation, without analgesic treatment, written informed consent and age > 18 years **Exclusion criteria**: onset of abdominal pain > 72 hours prior to hospitalisation, any analgesic treatment, age < 18 years, pregnancy, no written informed consent
Interventions	Pentazocine 30 mg / 6 hour intravenously or Procaine 2 g/24 hours continuous intravenous infusion **Co-interventions**: Besides pain treatment, participants were under standard therapeutic regimen including intravenous fluids, enteral or parenteral nutrition and antibiotics if necessary
Outcomes	1. Number of participants demanding further analgesia 2. Number of participants with pancreatitis complications 3. Adverse events

Kahl 2004 (*Continued*)

4. Deaths
Follow-up was four days (for analysis purposes)

Notes	**Acute pancreatitis defined as:** Quote: "Acute abdominal pain of sudden onset and threefold elevation of serum pancreatic enzymes". (Page 6) **Sample size calculation**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of participants withdrawn from the analysis
Selective reporting (reporting bias)	Low risk	

Peiro 2008

Methods	**Study type**: Open, randomised trial, controlled with active treatment, parallel design. Single centre. Country and setting: Spain and acute care hospital
Participants	**Randomised**: 16 (8 metamizole; 8 morphine) **Excluded:** At 24 hours only 4 /16 participants were assessed for pain. It is not clear if for safety analysis all the participants were included **Gender:** Men: women. metamizole 3:5 ; morphine 5:3 **Age:** Metamizole: mean 54.4 (SD 13.5); Morphine: mean 55.1 (SD 18.8) **Inclusion criteria:** Acute pancreatitis with admission within 12 hours of onset of symptoms **Exclusion criteria**: significant chronic renal or hepatic insufficiency, anaemia, agranulocytosis, any contraindication for receiving morphine, metamizole, pethidine, anyone considered unable to complete the study
Interventions	Morphine 1% 10 mg/4 hours s.c or metamizole 2 g/8 hours i.v. in a slow perfusion for 3 minutes

Peiro 2008   *(Continued)*

	Co-interventions: Besides pain treatment, participants received the standard care for acute pancreatitis, including intravenous fluids, artificial nutrition or antibiotics if necessary. Pethidine was additionally administered on demand as a rescue treatment whenever required to participants of both groups
Outcomes	1. Number of participants showing improvements 2. Number of participants demanding further analgesia 3. Number of participants with pancreatitis complications 4. Adverse events 5. Deaths Follow-up was 48 hours after admission for pain assessment, and six months for adverse events
Notes	**Acute pancreatitis defined as:** Quote: "upper abdominal pain plus hyperamylasemia or hyperlipasemia three fold the normal upper limit". (Page 26) **Sample size calculation**: Quote: "16 patients were necessary to provide 80% statistical power (at a type I error rate of 0.05) to detect relevant differences of 30% on VAS between both groups". (Page 26) Email contact with Dr Juan Martínez in September 2011 for clarification about randomisation method used, follow-up period, duration of intervention and dose of supplementary pethidine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of list generation not stated
Allocation concealment (selection bias)	Low risk	Quote: "Assignments of patients were made according to a randomization list held by the Clinical Pharmacology Unit". (Page 26)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Pain score was recorded every 4 h by a blinded researcher". (Page 26)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of participants withdrawn from the analysis
Selective reporting (reporting bias)	Low risk	

Stevens 2002

Methods	**Study type**: Double-blind, randomised trial, controlled with placebo, parallel design. Single centre. Country and setting: USA and acute care hospital
Participants	**Randomised**: 32 (15 fentanyl, 17 placebo) **Excluded:** at least 9 people at some point of the trial **Gender**: 18 men; 14 women **Age**: Range: 26 - 47 years **Inclusion criteria**: participants admitted to hospital and: 1) primary diagnosis of acute pancreatitis confirmed by a gastrointestinal specialist; 2) pain as a chief complaint; 3) pain on admission measuring ≥ 2 on a verbal self-reported scale of 0 to 5; 4) English-speaking; 5) alert and oriented at admission; 6) $\geq$ 18 years old **Exclusion criteria**: acute or chronic respiratory diseases, known sensitivity to the investigational medication
Interventions	Transdermal fentanyl (Transdermal Therapeutic System, TTS) 50 mcg/hour versus transdermal placebo (TTS)) **Co-interventions**: All patients received Demerol (Meperidine) Intramuscular 50-100 mg/every 3 hours (increase dosage at rate of 25 mg every 3 hours until patient reports pain intensity is 2 or less on a 0-5 scale); antiemetics; oral acetaminophen up to 1.300 mg/d Titration algorithm to determine adjustment of TTS fentanyl (or placebo) system*: Total doses used past 24 hours: 0 - 100 mg, decrease 25 mcg; 101 - 175 mg, continue present dose; 176 - 350 mg, increase 25 mcg; 351 - 575 mg, increase 50 mcg; 576 - 800 mg, increase 75 mcg; 801 - 1025 mg, increase 100 mcg
Outcomes	1. Self-reported pain intensity 2. Satisfaction with pain management 3. Adverse events Follow-up was from 3 to 72 hours after hospital admission (for analysis purposes)
Notes	**Acute pancreatitis defined as:** Quote: "acute pancreatitis confirmed by a gastrointestinal specialist". (Page 103) **Sample size calculation**: not described **Email contact** with Gregg W. Asher, Ph.D on October 2011 for clarification about randomisation method used, allocation concealment, exclusions and outcome data not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Reported as randomised
Allocation concealment (selection bias)	Low risk	Quote: "subjects were randomly assigned by the sealed-envelope technique". (Page 104)

Stevens 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "For staff to remain blind to the patients' true experimental condition, the inducting research assistant placed the placebo system or active TTS fentanyl system on the back of the upper torso and covered it with waterproof foam adhesive tape". (Page 104)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To maintain the integrity of the study, the assistants did not participate in collecting self-reported pain intensity or satisfaction data and they did not provide direct nursing care to the subject during the course of his or her hospitalisation". (Page 104)
Incomplete outcome data (attrition bias) All outcomes	High risk	Email contact revealed 38.5% withdraw after randomization
Selective reporting (reporting bias)	High risk	Gave results for outcomes not specified in the methods section

i.v: intravenous; s.c.: sub-cutaneous

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Hopton 1971	Intervention was not aimed at treating acute pancreatitis pain
Salazar 1987	Not RCT (case series)
Salim 1991	Intervention was not an opioid
Santosh 2010	Control group was not a drug but a technique
Spiegel 2001	Not RCT (letter)

DATA AND ANALYSES

Comparison 1.   Buprenorphine versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with a supplementary analgesic option offered (primary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Number of participants with drug-related adverse events (secondary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Number of deaths from any cause (secondary outcome 3)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 2.   Morphine versus metamizole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants showing improvements in pain intensity (primary outcome 1)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Number of participants with a supplementary analgesic option offered (primary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Number of participants with pancreatitis complications (secondary outcome 1)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Number of participants with drug-related adverse events (secondary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Number of deaths from any cause (secondary outcome 3)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 3. Pentazocine versus procaine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with a supplementary analgesic option offered (primary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Number of participants with pancreatitis complications (secondary outcome 1)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Number of participants with drug-related adverse events (secondary outcome 2)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Number of deaths from any cause (secondary outcome 3)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 4. Opioids versus no opioids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with a supplementary analgesic option offered (primary outcome 2)	3	162	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.14, 1.19]
2 Number of participants with pancreatitis complications (secondary outcome 1)	3	162	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.82, 1.34]
3 Number of participants with drug-related adverse events (secondary outcome 2)	2	110	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.90, 4.46]
3.1 Nausea and vomiting	2	55	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.70, 4.00]
3.2 Sedation and somnolence	2	55	Risk Ratio (M-H, Random, 95% CI)	5.54 [0.69, 44.79]
4 Number of deaths from any cause (secondary outcome 3)	4	194	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.02, 8.10]

Analysis 1.1. Comparison 1 Buprenorphine versus pethidine, Outcome 1 Number of participants with a supplementary analgesic option offered (primary outcome 2).

Review: Opioids for acute pancreatitis pain

Comparison: 1 Buprenorphine versus pethidine

Outcome: 1 Number of participants with a supplementary analgesic option offered (primary outcome 2)

Study or subgroup	Buprenorphine n/N	Pethidine n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Blamey 1984	13/17	14/15		0.82 [0.61, 1.10]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**

Total events: 13 (Buprenorphine), 14 (Pethidine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

```
        0.5   0.7    1    1.5   2
    Favours buprenorphine   Favours pethidine
```

Analysis 1.2. Comparison 1 Buprenorphine versus pethidine, Outcome 2 Number of participants with drug-related adverse events (secondary outcome 2).

Review: Opioids for acute pancreatitis pain

Comparison: 1 Buprenorphine versus pethidine

Outcome: 2 Number of participants with drug-related adverse events (secondary outcome 2)

Study or subgroup	Buprenorphine n/N	Pethidine n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Blamey 1984	1/17	0/15		2.67 [0.12, 60.93]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**

Total events: 1 (Buprenorphine), 0 (Pethidine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

```
   0.001 0.01  0.1   1    10  100 1000
    Favours buprenorphine   Favours pethidine
```

Analysis 1.3. Comparison 1 Buprenorphine versus pethidine, Outcome 3 Number of deaths from any cause (secondary outcome 3).

Review: Opioids for acute pancreatitis pain

Comparison: 1 Buprenorphine versus pethidine

Outcome: 3 Number of deaths from any cause (secondary outcome 3)

Study or subgroup	Buprenorphine	Pethidine	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
Blamey 1984	0/17	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Buprenorphine), 0 (Pethidine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

```
          0.01   0.1    1    10   100

     Favours buprenorphine      Favours pethidine
```

Analysis 2.1. Comparison 2 Morphine versus metamizole, Outcome 1 Number of participants showing improvements in pain intensity (primary outcome 1).

Review: Opioids for acute pancreatitis pain

Comparison: 2 Morphine versus metamizole

Outcome: 1 Number of participants showing improvements in pain intensity (primary outcome 1)

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Peiro 2008	3/8	6/8		0.50 [0.19, 1.33]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**

Total events: 3 (Morphine), 6 (Metamizole)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours metamizole   Favours morphine

Analysis 2.2. Comparison 2 Morphine versus metamizole, Outcome 2 Number of participants with a supplementary analgesic option offered (primary outcome 2).

Review: Opioids for acute pancreatitis pain

Comparison: 2 Morphine versus metamizole

Outcome: 2 Number of participants with a supplementary analgesic option offered (primary outcome 2)

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Peiro 2008	3/8	3/8		1.00 [0.28, 3.54]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**

Total events: 3 (Morphine), 3 (Metamizole)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours morphine   Favours metamizole

Analysis 2.3.   Comparison 2 Morphine versus metamizole, Outcome 3 Number of participants with pancreatitis complications (secondary outcome 1).

Review: Opioids for acute pancreatitis pain

Comparison: 2 Morphine versus metamizole

Outcome: 3 Number of participants with pancreatitis complications (secondary outcome 1)

Study or subgroup	Morphine	Metamizole	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
Peiro 2008	3/8	2/8		1.50 [0.34, 6.70]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 3 (Morphine), 2 (Metamizole)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

```
              0.01    0.1     I    10    100

           Favours morphine      Favours metamizole
```

Analysis 2.4. Comparison 2 Morphine versus metamizole, Outcome 4 Number of participants with drug-related adverse events (secondary outcome 2).

Review: Opioids for acute pancreatitis pain

Comparison: 2 Morphine versus metamizole

Outcome: 4 Number of participants with drug-related adverse events (secondary outcome 2)

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Peiro 2008	4/8	1/8		4.00 [0.56, 28.40]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 4 (Morphine), 1 (Metamizole)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

```
         0.01   0.1    1    10   100
         Favours morphine    Favours metamizole
```

Analysis 2.5. Comparison 2 Morphine versus metamizole, Outcome 5 Number of deaths from any cause (secondary outcome 3).

Review: Opioids for acute pancreatitis pain

Comparison: 2 Morphine versus metamizole

Outcome: 5 Number of deaths from any cause (secondary outcome 3)

Study or subgroup	Morphine n/N	Metamizole n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Peiro 2008	0/8	0/8		0.0 [0.0, 0.0]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Morphine), 0 (Metamizole)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

```
         0.01   0.1    1    10   100
         Favours morphine    Favours metamizole
```

Analysis 3.1. Comparison 3 Pentazocine versus procaine, Outcome 1 Number of participants with a supplementary analgesic option offered (primary outcome 2).

Review: Opioids for acute pancreatitis pain

Comparison: 3 Pentazocine versus procaine

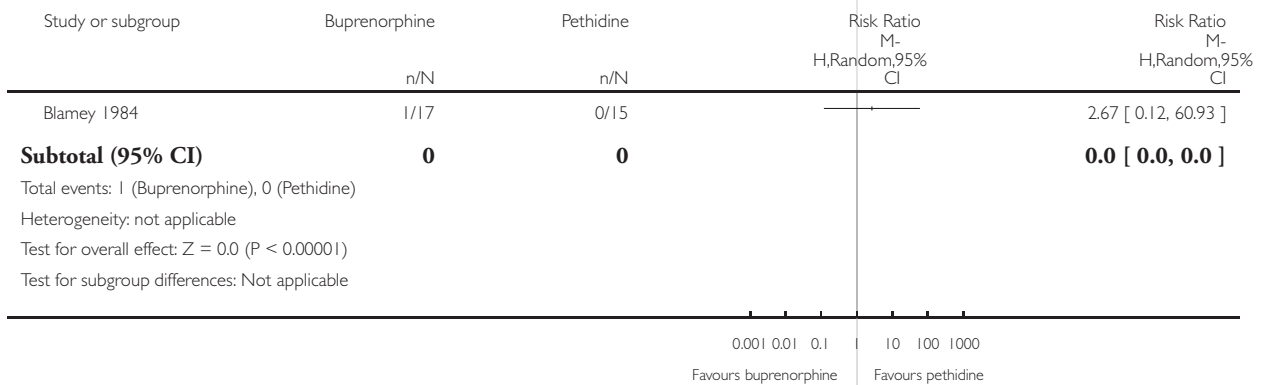Outcome: 1 Number of participants with a supplementary analgesic option offered (primary outcome 2)

Study or subgroup	Pentazocine n/N	Procaine n/N	Risk Ratio M- H,Random,95% CI	Risk Ratio M- H,Random,95% CI
Kahl 2004	22/52	50/55		0.47 [0.34, 0.65]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**

Total events: 22 (Pentazocine), 50 (Procaine)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

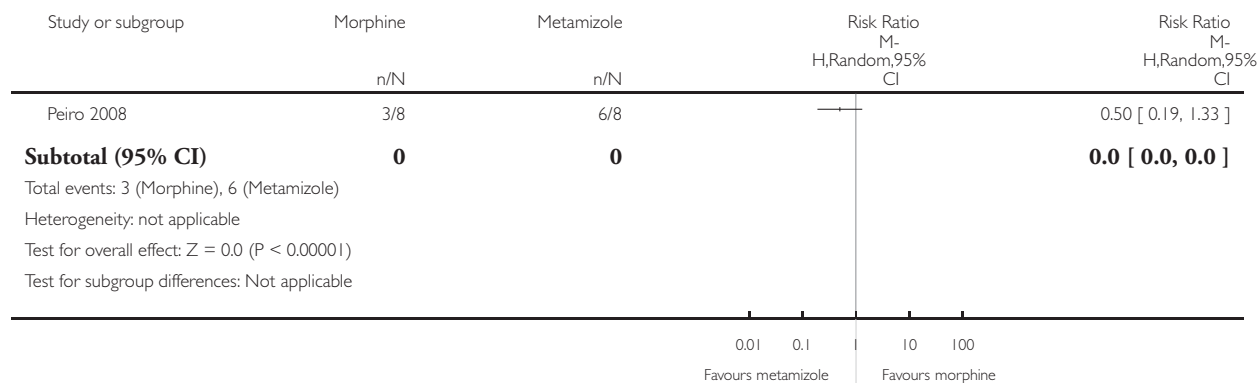Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
     Favours pentazocine   Favours procaine
```

Analysis 3.2. Comparison 3 Pentazocine versus procaine, Outcome 2 Number of participants with pancreatitis complications (secondary outcome 1).

Review: Opioids for acute pancreatitis pain

Comparison: 3 Pentazocine versus procaine

Outcome: 2 Number of participants with pancreatitis complications (secondary outcome 1)

Study or subgroup	Pentazocine n/N	Procaine n/N	Risk Ratio M- H,Random,95% CI	Risk Ratio M- H,Random,95% CI
Kahl 2004	37/52	38/55		1.03 [0.80, 1.32]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 37 (Pentazocine), 38 (Procaine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

```
         0.01   0.1    1    10   100
        Favours pentazocine   Favours procaine
```

Analysis 3.3. Comparison 3 Pentazocine versus procaine, Outcome 3 Number of participants with drug-related adverse events (secondary outcome 2).

Review: Opioids for acute pancreatitis pain

Comparison: 3 Pentazocine versus procaine

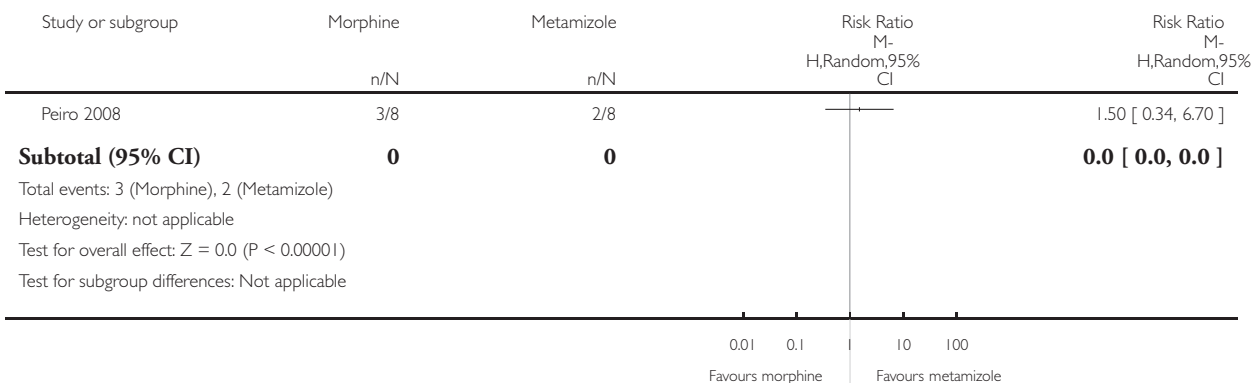Outcome: 3 Number of participants with drug-related adverse events (secondary outcome 2)

Study or subgroup	Pentazocine n/N	Procaine n/N	Risk Ratio M- H,Random,95% CI	Risk Ratio M- H,Random,95% CI
Kahl 2004	0/52	0/55		0.0 [0.0, 0.0]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Pentazocine), 0 (Procaine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

```
         0.01   0.1    1    10   100
        Favours pentazocine   Favours procaine
```
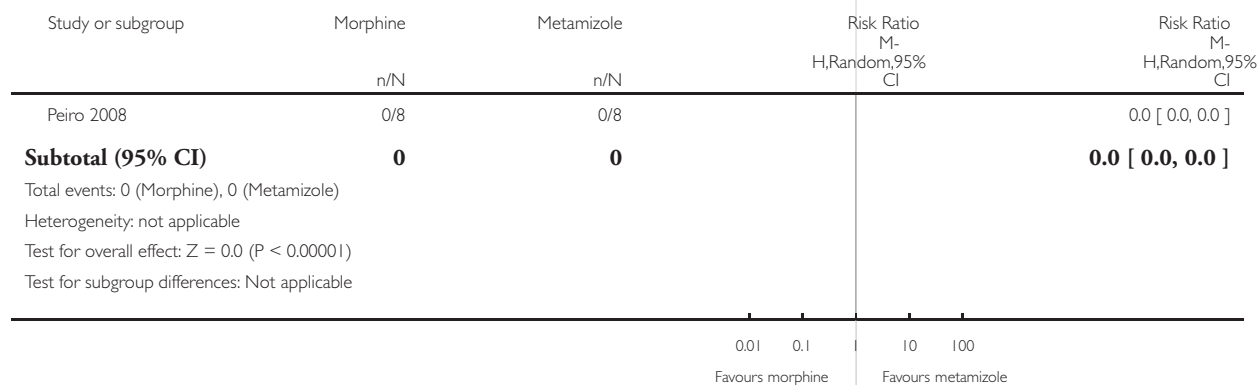
Analysis 3.4. Comparison 3 Pentazocine versus procaine, Outcome 4 Number of deaths from any cause (secondary outcome 3).

Review: Opioids for acute pancreatitis pain

Comparison: 3 Pentazocine versus procaine

Outcome: 4 Number of deaths from any cause (secondary outcome 3)

Study or subgroup	Pentazocine n/N	Procaine n/N	Risk Ratio M- H,Random,95% CI	Risk Ratio M- H,Random,95% CI
Kahl 2004	0/52	0/55		0.0 [0.0, 0.0]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Pentazocine), 0 (Procaine)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

```
        0.01    0.1      1      10    100

     Favours pentazocine      Favours procaine
```
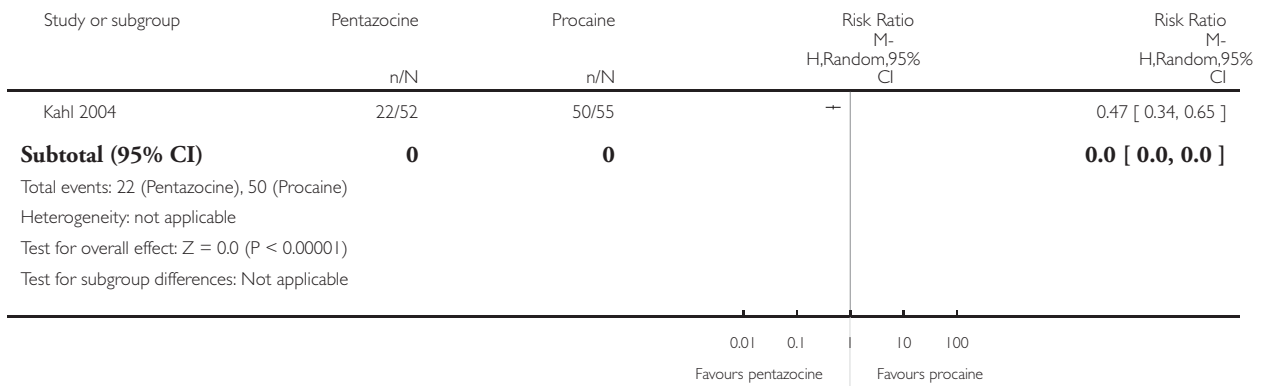
Analysis 4.1.   Comparison 4 Opioids versus no opioids, Outcome 1 Number of participants with a supplementary analgesic option offered (primary outcome 2).

Review: Opioids for acute pancreatitis pain

Comparison: 4 Opioids versus no opioids

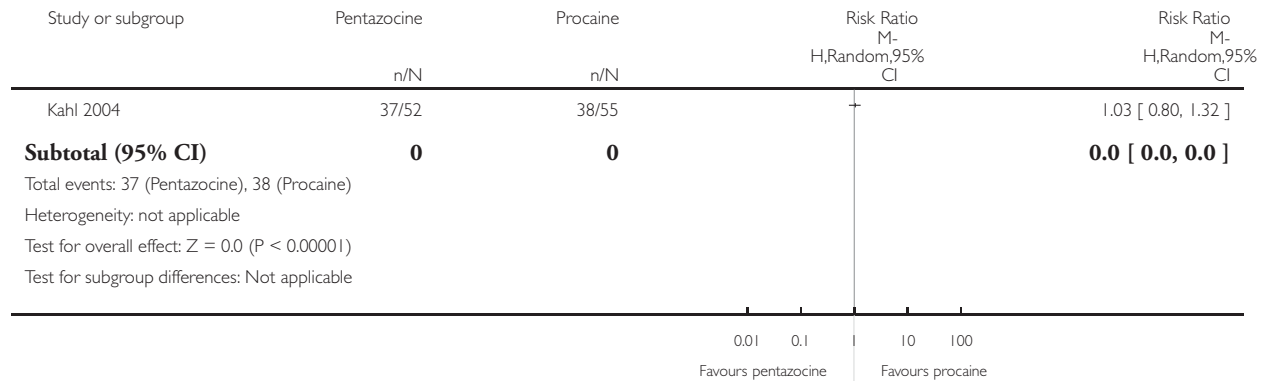Outcome: 1 Number of participants with a supplementary analgesic option offered (primary outcome 2)

Study or subgroup	Opioid n/N	No Opioid n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Jakobs 2000	1/19	14/20		19.2 %	0.08 [0.01, 0.52]
Kahl 2004	22/52	50/55		50.6 %	0.47 [0.34, 0.65]
Peiro 2008	3/8	3/8		30.2 %	1.00 [0.28, 3.54]
Total (95% CI)	**79**	**83**		**100.0 %**	**0.41 [0.14, 1.19]**

Total events: 26 (Opioid), 67 (No Opioid)

Heterogeneity: Tau^2 = 0.55; Chi^2 = 5.49, df = 2 (P = 0.06); I^2 =64%

Test for overall effect: Z = 1.64 (P = 0.10)

Test for subgroup differences: Not applicable

```
        0.005     0.1     1     10     200
        Favours Opioids    Favours No Opioids
```

Analysis 4.2. Comparison 4 Opioids versus no opioids, Outcome 2 Number of participants with pancreatitis complications (secondary outcome 1).

Review: Opioids for acute pancreatitis pain

Comparison: 4 Opioids versus no opioids

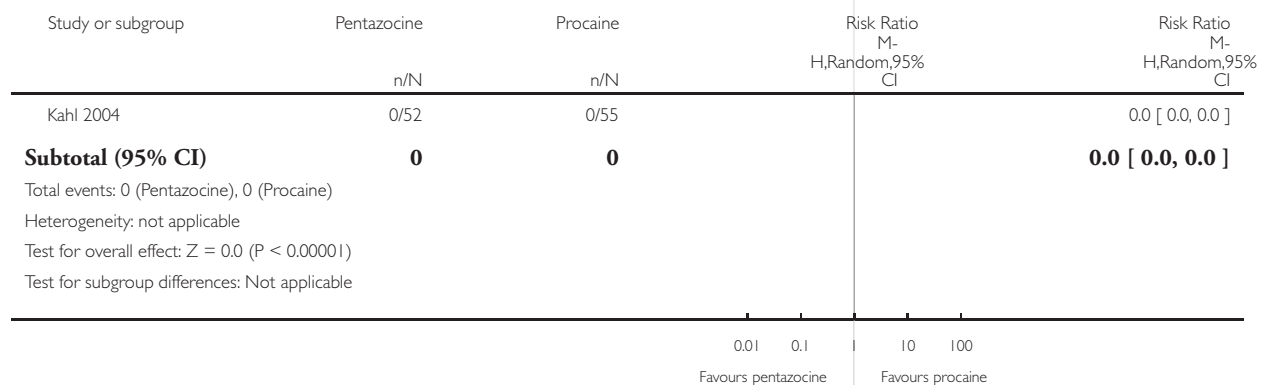Outcome: 2 Number of participants with pancreatitis complications (secondary outcome 1)

Study or subgroup	Opioid n/N	No Opioid n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Jakobs 2000	2/19	1/20		1.1 %	2.11 [0.21, 21.36]
Kahl 2004	37/52	38/55		96.3 %	1.03 [0.80, 1.32]
Peiro 2008	3/8	2/8		2.6 %	1.50 [0.34, 6.70]
Total (95% CI)	**79**	**83**		**100.0 %**	**1.05 [0.82, 1.34]**

Total events: 42 (Opioid), 41 (No Opioid)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.64, df = 2 (P = 0.72); I^2 =0.0%

Test for overall effect: Z = 0.38 (P = 0.70)

Test for subgroup differences: Not applicable

```
        0.05   0.2    1     5    20
       Favours Opioid    Favours No Opioid
```
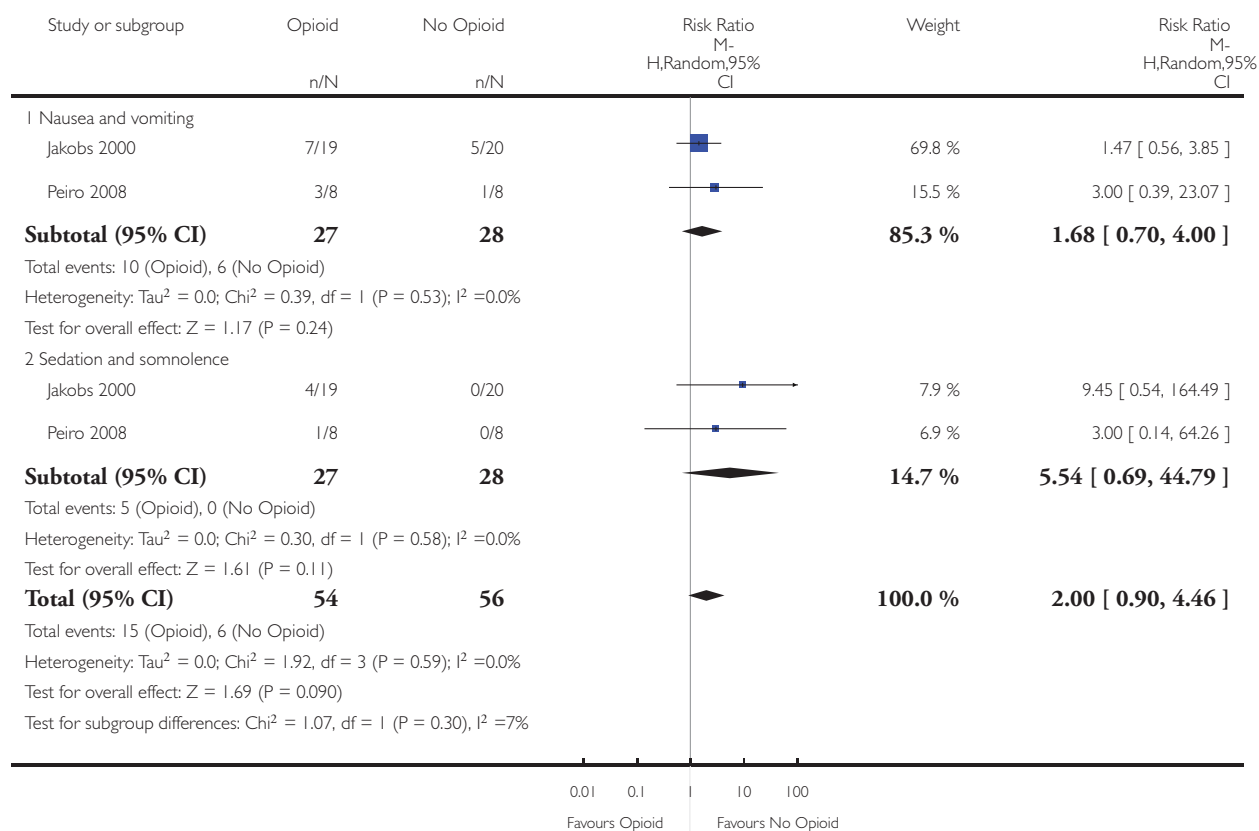
Analysis 4.3. Comparison 4 Opioids versus no opioids, Outcome 3 Number of participants with drug-related adverse events (secondary outcome 2).

Review: Opioids for acute pancreatitis pain

Comparison: 4 Opioids versus no opioids

Outcome: 3 Number of participants with drug-related adverse events (secondary outcome 2)

Study or subgroup	Opioid n/N	No Opioid n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 Nausea and vomiting					
Jakobs 2000	7/19	5/20		69.8 %	1.47 [0.56, 3.85]
Peiro 2008	3/8	1/8		15.5 %	3.00 [0.39, 23.07]
Subtotal (95% CI)	**27**	**28**		**85.3 %**	**1.68 [0.70, 4.00]**
Total events: 10 (Opioid), 6 (No Opioid)					
Heterogeneity: Tau² = 0.0; Chi² = 0.39, df = 1 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 1.17 (P = 0.24)					
2 Sedation and somnolence					
Jakobs 2000	4/19	0/20		7.9 %	9.45 [0.54, 164.49]
Peiro 2008	1/8	0/8		6.9 %	3.00 [0.14, 64.26]
Subtotal (95% CI)	**27**	**28**		**14.7 %**	**5.54 [0.69, 44.79]**
Total events: 5 (Opioid), 0 (No Opioid)					
Heterogeneity: Tau² = 0.0; Chi² = 0.30, df = 1 (P = 0.58); I² =0.0%					
Test for overall effect: Z = 1.61 (P = 0.11)					
Total (95% CI)	**54**	**56**		**100.0 %**	**2.00 [0.90, 4.46]**
Total events: 15 (Opioid), 6 (No Opioid)					
Heterogeneity: Tau² = 0.0; Chi² = 1.92, df = 3 (P = 0.59); I² =0.0%					
Test for overall effect: Z = 1.69 (P = 0.090)					
Test for subgroup differences: Chi² = 1.07, df = 1 (P = 0.30), I² =7%					

0.01   0.1   1   10   100

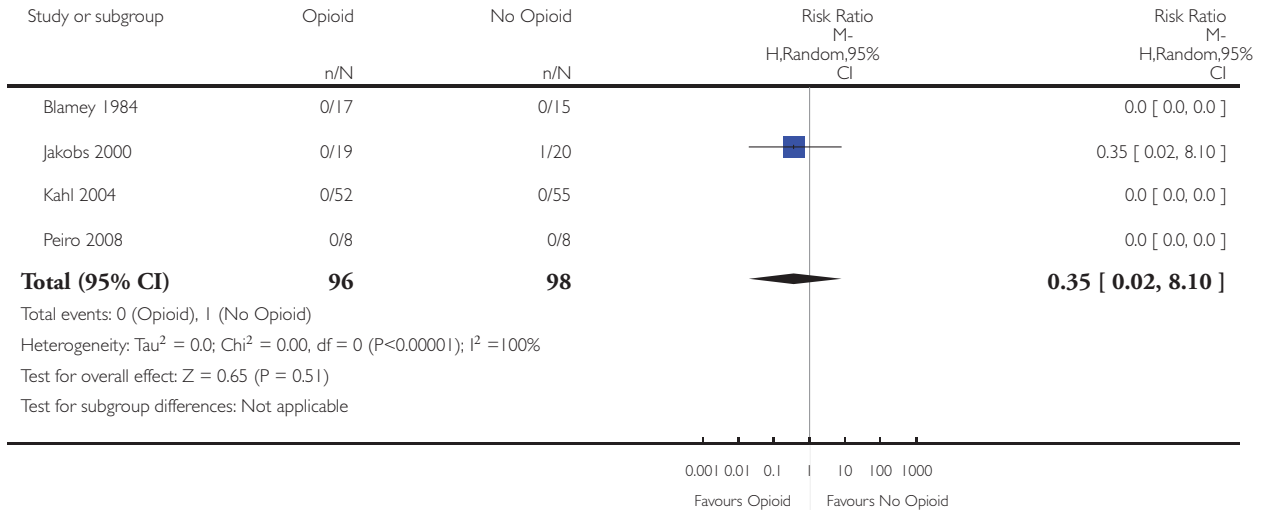Favours Opioid   Favours No Opioid

Analysis 4.4. Comparison 4 Opioids versus no opioids, Outcome 4 Number of deaths from any cause (secondary outcome 3).

Review: Opioids for acute pancreatitis pain

Comparison: 4 Opioids versus no opioids

Outcome: 4 Number of deaths from any cause (secondary outcome 3)

Study or subgroup	Opioid n/N	No Opioid n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Blamey 1984	0/17	0/15		0.0 [0.0, 0.0]
Jakobs 2000	0/19	1/20		0.35 [0.02, 8.10]
Kahl 2004	0/52	0/55		0.0 [0.0, 0.0]
Peiro 2008	0/8	0/8		0.0 [0.0, 0.0]
Total (95% CI)	**96**	**98**		**0.35 [0.02, 8.10]**

Total events: 0 (Opioid), 1 (No Opioid)

Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 0 (P<0.00001); I² =100%

Test for overall effect: Z = 0.65 (P = 0.51)

Test for subgroup differences: Not applicable

0.001 0.01 0.1   1   10   100   1000

Favours Opioid   Favours No Opioid

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials

1. exp Pancreatitis, Acute Necrotizing/
2. exp Pancreatitis, Alcoholic/
3. Pancreatitis/et [Etiology]
4. exp Pancreas/ab, de, pa [Abnormalities, Drug Effects, Pathology]
5. (acute adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. (necro* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. (Alcohol* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8. (Gallstone* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9. or/1-8
10. exp Analgesics, Opioid/
11. exp Narcotics/
12. (Opioid$ or Opiate$ or Narcotic$).mp.
13. exp Morphine/
14. (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).mp.

15. exp Opium/
16. (opium or omnopon or pantopon or papaveretum).mp.
17. exp Hydromorphone/
18. (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph$ or hydrostat or hymorphan or laudicon or novolauden or palladone).mp.
19. Nicomorphine.mp.
20. exp Oxycodone/
21. (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).mp.
22. (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).mp.
23. (Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag).mp.
24. exp Codeine/
25. (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).mp.
26. Ketobemidone.mp.
27. exp Meperidine/
28. (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).mp.
29. exp Fentanyl/
30. (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).mp.
31. exp Dextromoramide/
32. Dextromoramide.mp.
33. (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).mp.
34. exp Dextropropoxyphene/
35. (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen).mp.
36. (Bezitramide or Burgodin).mp.
37. exp Methadone/
38. (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).mp.
39. exp Benzomorphans/
40. exp Pentazocine/
41. (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin).mp.
42. exp Phenazocine/
43. (Phenazocine or Prinadol or Narphen).mp.
44. Oripavine.mp.
45. exp Buprenorphine/
46. (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).mp.
47. exp Etorphine/
48. (Etorphine or Immobilon or M99).mp.
49. exp Morphinans/
50. exp Butorphanol/
51. (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic).mp.
52. exp Tilidine/
53. (Tilidine or tilidate or Valoron or Valtran or Tilidin).mp.
54. exp Tramadol/
55. (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal$ or tramedo or ultram or zamadol or zydol).mp.
56. (Dezocine or Dalgan or 'WY-16225').mp.
57. exp Meptazinol/
58. (Meptazinol or Meptid).mp.
59. (Tapentadol or cg5503 or nucynta).mp.

60. (Remifentanil or 'gi 87084b' or remifentanyl or ultiva).mp.
61. exp Procaine/
62. (Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra).mp.
63. or/10-62
64. 9 and 63

Appendix 2. MEDLINE search strategy

1. exp Pancreatitis, Acute Necrotizing/
2. exp Pancreatitis, Alcoholic/
3. Pancreatitis/et [Etiology]
4. exp Pancreas/ab, de, pa [Abnormalities, Drug Effects, Pathology]
5. (acute adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. (necro* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. (Alcohol* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8. (Gallstone* adj3 pancrea*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9. or/1-8
10. exp Analgesics, Opioid/
11. exp Narcotics/
12. (Opioid$ or Opiate$ or Narcotic$).mp.
13. exp Morphine/
14. (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).mp.
15. exp Opium/
16. (opium or omnopon or pantopon or papaveretum).mp.
17. exp Hydromorphone/
18. (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph$ or hydrostat or hymorphan or laudicon or novolauden or palladone).mp.
19. Nicomorphine.mp.
20. exp Oxycodone/
21. (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).mp.
22. (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).mp.
23. (Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag).mp.
24. exp Codeine/
25. (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).mp.
26. Ketobemidone.mp.
27. exp Meperidine/
28. (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).mp.
29. exp Fentanyl/
30. (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).mp.
31. exp Dextromoramide/
32. Dextromoramide.mp.
33. (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).mp.
34. exp Dextropropoxyphene/
35. (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen).mp.
36. (Bezitramide or Burgodin).mp.
37. exp Methadone/

38. (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).mp.
39. exp Benzomorphans/
40. exp Pentazocine/
41. (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin).mp.
42. exp Phenazocine/
43. (Phenazocine or Prinadol or Narphen).mp.
44. Oripavine.mp.
45. exp Buprenorphine/
46. (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).mp.
47. exp Etorphine/
48. (Etorphine or Immobilon or M99).mp.
49. exp Morphinans/
50. exp Butorphanol/
51. (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic).mp.
52. exp Tilidine/
53. (Tilidine or tilidate or Valoron or Valtran or Tilidin).mp.
54. exp Tramadol/
55. (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal$ or tramedo or ultram or zamadol or zydol).mp.
56. (Dezocine or Dalgan or 'WY-16225').mp.
57. exp Meptazinol/
58. (Meptazinol or Meptid).mp.
59. (Tapentadol or cg5503 or nucynta).mp.
60. (Remifentanil or 'gi 87084b' or remifentanyl or ultiva).mp.
61. exp Procaine/
62. (Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra).mp.
63. or/10-62
64. randomised controlled trial.pt.
65. controlled clinical trial.pt.
66. randomized.ab.
67. placebo.ab.
68. drug therapy.fs.
69. randomly.ab.
70. trial.ab.
71. groups.ab.
72. or/64-71
73. exp animals/ not humans.sh.
74. 72 not 73
75. 9 and 63 and 74

Appendix 3. EMBASE search strategy

1. exp Pancreatitis, Acute Necrotizing/
2. exp Pancreatitis, Alcoholic/
3. Pancreatitis/et [Etiology]
4. (acute adj3 pancrea$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5. (necro$ adj3 pancrea$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. (Alcohol$ adj3 pancrea$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7. (Gallstone$ adj3 pancrea$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8. or/1-7
9. exp narcotic analgesic agent/

10. exp Analgesics, Opioid/
11. exp Narcotics/
12. (Opioid$ or Opiate$ or Narcotic$).mp.
13. exp Morphine/
14. (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).mp.
15. exp Opium/
16. (opium or omnopon or pantopon or papaveretum).mp.
17. exp Hydromorphone/
18. (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph$ or hydrostat or hymorphan or laudicon or novolauden or palladone).mp.
19. Nicomorphine.mp.
20. exp Oxycodone/
21. (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).mp.
22. (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).mp.
23. (Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag).mp.
24. exp Codeine/
25. (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).mp.
26. Ketobemidone.mp.
27. exp Meperidine/
28. (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).mp.
29. exp Fentanyl/
30. (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).mp.
31. exp Dextromoramide/
32. Dextromoramide.mp.
33. (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).mp.
34. exp Dextropropoxyphene/
35. (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen).mp.
36. (Bezitramide or Burgodin).mp.
37. exp Methadone/
38. (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).mp.
39. exp Benzomorphans/
40. exp Pentazocine/
41. (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin).mp.
42. exp Phenazocine/
43. (Phenazocine or Prinadol or Narphen).mp.
44. Oripavine.mp.
45. exp Buprenorphine/
46. (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).mp.
47. exp Etorphine/
48. (Etorphine or Immobilon or M99).mp.
49. exp Morphinans/
50. exp Butorphanol/
51. (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic).mp.
52. exp Tilidine/
53. (Tilidine or tilidate or Valoron or Valtran or Tilidin).mp.

54. exp Tramadol/
55. (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal$ or tramedo or ultram or zamadol or zydol).mp.
56. (Dezocine or Dalgan or 'WY-16225').mp.
57. exp Meptazinol/
58. (Meptazinol or Meptid).mp.
59. (Tapentadol or cg5503 or nucynta).mp.
60. (Remifentanil or 'gi 87084b' or remifentanyl or ultiva).mp.
61. exp Procaine/
62. (Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra).mp.
63. or/9-62
64. 8 and 63
65. Clinical trial/
66. Randomized controlled trial/
67. Randomization/
68. Single-Blind Method/
69. Double-Blind Method/
70. Cross-Over Studies/
71. Random Allocation/
72. Placebo/
73. Randomi?ed controlled trial$.tw.
74. Rct.tw.
75. Random allocation.tw.
76. Randomly allocated.tw.
77. Allocated randomly.tw.
78. (allocated adj2 random).tw.
79. Single blind$.tw.
80. Double blind$.tw.
81. ((treble or triple) adj blind$).tw.
82. Placebo$.tw.
83. Prospective study/
84. or/65-83
85. Case study/
86. Case report.tw.
87. Abstract report/ or letter/
88. or/85-87
89. 84 not 88
90. 64 and 89

CONTRIBUTIONS OF AUTHORS

Draft the protocol: All authors and M. Roqué (Iberoamerican Cochrane Center Statistician)

Develop a search strategy: Racquel Simpson (TSC Cochrane UGPD review group)

Search for trials: X Basurto

Obtain copies of trials: X Basurto

Select which trials to include: X Basurto and D Rigau

Extract data from trials (2 people): X Basurto and D Rigau (G Urrutia as arbiter)

Enter data into Review Manager 5: X Basurto

Carry out the analysis: X Basurto

Interpret the analysis: all authors

Draft the final review: all authors

Update the review: all authors

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Iberoamerican Cochrane Centre, Spain.
- CIBER de Epidemiologí y Salud Pública (CIBERESP), Spain.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the effect of the intervention related to number of participants demanding supplementary analgesia, we compared opioids versus non-opioids combining the results of three RCTs (Jakobs 2000; Kahl 2004; Peiro 2008), which demonstrated substantial heterogeneity (I^2 = 64%). We decided to do a post hoc sensitivity analysis not planned at the protocol stage, to test the origin of the heterogeneity. We excluded Jakobs 2000 because the effect size was so different from the two others RCTs, and this was attributed to its continuous intravenous infusion of opioids compared to Kahl 2004 and Peiro 2008, in which opioids were administered every six and four hours respectively. The conclusions derived from this post hoc sensitivity analysis should be interpreted with caution for clinical practice, but may be of use for the generation of new hypotheses.

6.-DISCUSSIÓ

6.-DISCUSSIÓ

6.1.- Breu discussió específica derivada de les publicacions

Fàrmacs per a la prevenció de la CPPD

Els estudis disponibles inclosos en aquesta revisió mostren que la morfina, la cosintropina i l'aminofil·lina poden considerar-se com a teràpia farmacològica de primera línia quan es tracta de prevenir la CPPD.

La morfina epidural i la cosintropina intravenosa redueixen el nombre de pacients amb CPPD de qualsevol gravetat, en comparació amb el placebo, especialment en aquells pacients amb un alt risc de CPPD, com és el cas de dones sotmeses a una anestèsia espinal durant el treball de part i que han estat víctimes d'una punció dural accidental. La pruïja, les nàusees i els vòmits a causa de la morfina i la urticària a causa de la cosintropina, són els efectes adversos reportats. Aquests efectes adversos són menys freqüents que els beneficis clínics, no són greus, i en cas d'aparèixer, es disposa d'arsenal terapèutic eficient i segur per tractar-los.

L'administració intravenosa d'aminofil·lina també proporciona el mateix benefici, la reducció del nombre dels participants afectats per CPPD de qualsevol gravetat, però en aquest cas en comparació amb no realitzar cap intervenció i en pacients sotmesos anestèsia espinal per cesària electiva.

La dexametasona intravenosa, en comparació amb el placebo, augmenta el risc de CPPD després de l'anestèsia espinal per una cesària, i no demostrava cap efecte significatiu en adults sotmesos a una cirurgia d'extremitats inferiors.

La resta d'intervencions avaluades en els estudis inclosos en aquesta RS, la morfina espinal, el fentanil espinal, la cafeïna oral i la indometacina rectal no van mostrar cap efecte rellevant en la reducció del risc de desenvolupar una CPPD.

Les tres intervencions que han demostrat reduir el risc de desenvolupar una CPPD mostren uns resultats que podem interpretar com a clínicament rellevants. L'assaig clínic de *Al-metwalli* (94) sobre la morfina epidural contra placebo, amb un risc relatiu (RR) de 0,25 (IC95% 0,08-0,78) suposa una reducció absoluta del risc de desenvolupar CPPD del 36% (IC95% 59,4-12,6) i un NNT de 2,8 (IC95% 1,7-7,9). Aquesta magnitud en la reducció del risc cal interpretar-la com a clínicament rellevant. L'escàs nombre de participants inclosos en aquest assaig fa reduir la precisió dels resultats, cosa que es manifesta amb un ampli interval de confiança en les estimacions calculades.

Taula 5. Morfina epidural contra placebo. Risc de CPPD. Obtingut de:
http://clinicalevidence.bmj.com/x/set/static/cms/statistics-calculator.html

Results				
	Point estimate	95% CIs		
RR	0.3	0.1	to	0.8
RRR / RRI	-75.0%	-92.0%	to	-22.0%
ARR / ARI	-36.0%	-59.4%	to	-12.6%
NNT / NNH**	-2.8	-1.7	to	-7.9

Similars són els resultats que s'obtenen amb la cosintropina contra placebo en l'ACA de Hakim (95). El RR calculat és de 0,49 (IC95% 0,31-0,79) que suposa una reducció absoluta del risc de desenvolupar una CPPD similar a la morfina epidural, 32,7% (IC95% 51,7-13,7) i un NNT de 3,1 (IC95% 1,9-7,3); uns resultats de magnitud clínicament rellevants tot i que d'escassa precisió atès l'escassa grandària de la mostra de l'assaig clínic.

Taula 6. Cosintropina contra placebo. Risc de CPPD
Obtingut de: http://clinicalevidence.bmj.com/x/set/static/cms/statistics-calculator.html

Results				
	Point estimate	95% CIs		
RR	0.5	0.3	to	0.8
RRR / RRI	-50.6%	-69.0%	to	-21.2%
ARR / ARI	-32.7%	-51.7%	to	-13.7%
NNT / NNH**	-3.1	-1.9	to	-7.3

Amb l'administració d'aminofil·lina en l'estudi de Sadeghi (96), l'eficàcia no sembla ser tant clínicament rellevant si ho comparem amb els resultats obtinguts amb la morfina i la cosintropina. Aquí el RR calculat a les 48 hores és de 0,21 (IC95% 0,06-0,71) que suposa una reducció absoluta del risc de desenvolupar una CPPD del 18,3% (IC95% 30,4-6,3) i un NNT de 5,5 (IC95% 3,3-15,9). En aquest cas continuem tenint el mateix problema de precisió dels resultats.

Taula 7. Aminofil·lina contra no intervenció. Risc de CPPD
Obtingut de: http://clinicalevidence.bmj.com/x/set/static/cms/statistics-calculator.html

Results					
	Point estimate	95% CIs			
RR	0.2	0.1	to	0.7	
RRR / RRI	-78.6%	-93.5%	to	-29.2%	
ARR / ARI	-18.3%	-30.4%	to	-6.3%	
NNT / NNH**	-5.5	-3.3	to	-15.9	

Cal remarcar que en aquest tres assajos clínics els participants són dones sotmeses a una PL per l'administració d'anestèsia epidural durant el treball de part. Aquest fet cal tenir-lo en compte al inferir aquests resultats a una població més amplia i diversa que l'estrictament obstètrica representada en aquests assajos. És important també remarcar que, tant en l'assaig de la morfina epidural com en el de la cosintropina, la població d'estudi tenia un alt risc de desenvolupar una CPPD ja que es tracta de participants amb una punció dural inadvertida, fet que se li atribueix un risc del 80% de desenvolupar CPDD. Cal tenir en compte aquesta incidència basal quan intentem extrapolar les dades a una població amb un notable menor risc de CPPD, sobretot si quantifiquen el benefici amb mesures de resultat relatives, com el RR, enlloc de mesures absolutes com el NNT.
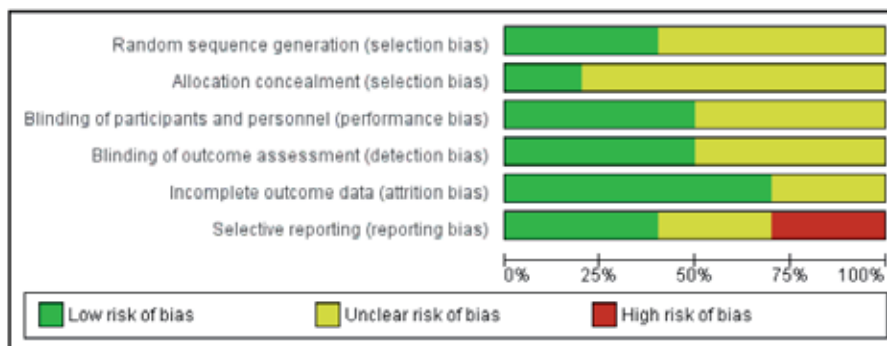
Una de les limitacions d'aquesta RS ha estat la important heterogeneïtat entre els diferents assajos inclosos pel que fa al tipus de fàrmacs emprats, en les dosis i en les vies d'administració utilitzades. Aquesta heterogeneïtat entre estudis també ha estat important pel que fa a les característiques basals de les diferents poblacions, sobretot pel que fa al risc basal de desenvolupar CPPD. La manca d'homogeneïtat, tant de les intervencions com de les poblacions tractades, ha impedit combinar els resultats numèrics dels diferents estudis inclosos on s'avaluava la mateixa intervenció, com és el cas dels opioides, la cafeïna i la dexametasona. La possibilitat de combinar aquests resultats mitjançant una metanàlisi hauria implicat disposar d'una major potència estadística i d'uns resultats més precisos.

L'escassa grandària de mostra dels 10 estudis inclosos a la revisió, amb 1611 participants en total, també és una limitació. L'estudi amb menor número de participants és el de Al-metwalli (94) amb 50 participants i el de major número és el de Yousefshahi (97) amb 372. Estudis amb escassos participants afavoreix l'error aleatori i això condiciona una major dispersió en els resultats obtinguts, que es reflecteix amb uns intervals de confiança més amplis. Un altre problema dels assajos clínics amb escassos participants és la limitació que es crea al procés d'aleatorització, que dificulta la creació de grups de participants similars pel que fa al risc basal de desenvolupar el fenomen que estem estudiant, bàsicament per un desequilibri en els factors pronòstics entre els diferents grups comparats (80).

La qualitat d'una revisió vindrà marcada en gran mesura per la qualitat dels estudis

inclosos. Un dels aspectes importants a tenir en compte al avaluar la qualitat de l'assaig és la seva validesa, que la podrem determinar segons risc de biaix estimat. Les revisions Cochrane donen molta importància a aquests anàlisi del risc de biaix, però malauradament, com passa sovint en la publicació d'assajos clínics i en altres dissenys d'estudis, els autors no descriuen amb prou detall tot aquells aspectes que per al lector són necessaris per avaluar aquest risc de biaix (98). Això és el que succeeix en aquesta revisió, on dels 6 dominis que analitzem per avaluar aquest risc, aproximadament en la meitat dels estudis inclosos hi manca informació detallada, cosa que impedeix definir si es tracta d'una situació d'alt o baix risc de biaix.

Figura 14. Avaluació del risc de biaix per dominis entre els estudis inclosos a la RS sobre prevenció de la CPPD

Aquestes limitacions relacionades amb les característiques dels estudis inclosos a la revisió ens obliguen a ser prudents a l'hora d'establir les conclusions de la RS. Aquesta revisió hauria de ser d'utilitat també per a futurs investigadors que estiguin iniciant un projecte d'investigació relacionat amb aquest tema per tal d'evitar els errors o limitacions que hem destacat. Seria important que futurs assajos clínics incloguin un major nombre de participants aleatoritzats i sobretot una descripció més detallada i explícita de tots els mecanismes que estan implicats en l'avaluació del risc de biaix, i per tant, en la validesa dels resultats. Per aconseguir millorar aquest darrer punt encoratgem als investigadors a seguir la declaració CONSORT (99), que té com objectiu millorar la publicació dels estudis i facilitar als lectors la lectura crítica. La llista de verificació i el diagrama de flux de la declaració CONSORT es poden obtenir de la seva web, http://www.consort-statement.org/.

Fàrmacs per al tractament de la CPPD

A partir dels estudis disponibles en aquesta RS, la cafeïna administrada per via intravenosa mostra una disminució significativa en la proporció de participants amb CPPD persistent i una disminució també dels participants amb CPPD que

requereixen intervencions complementàries per calmar el dolor, en comparació amb un placebo. La gabapentina oral, la teofil·lina oral i la hidrocortisona intravenosa han mostrat una disminució en les puntuacions de la intensitat del dolor en comparació amb el placebo o l'atenció habitual. Els altres fàrmacs avaluats, el sumatriptan subcutani i l'ACTH intramuscular, no han mostrat un efecte significatiu en cap de les variables de resultat proposades en aquesta revisió.

La variable de resultat principal en aquesta revisió, la persistència de CPPD de qualsevol severitat, només va ser estudiada en un dels articles inclosos. En aquest article, Sechzer (100) mostra un benefici de la cafeïna intravenosa al ser comparada amb un placebo que podem definir com a clínicament rellevant, amb un RR de 0,29 (IC95% 0,13-0,64). Aquestes dades suposen una reducció absoluta del número de participants amb CPPD del 60,7% (IC95% 84,9-36,5) i un NNT de 1,6 (IC95% 1,2-2,7). Al igual que la RS prèvia, aquí també tenim el problema de la precisió dels resultats; a l'assaig de Sechzer només hi ha 41 persones aleatoritzades.

Taula 8. Cafeïna intravenosa contra placebo. Persistència de CPPD
Obtingut de: http://clinicalevidence.bmj.com/x/set/static/cms/statistics-calculator.html

Results				
	Point estimate	95% CIs		
RR	0.3	0.1	to	0.6
RRR / RRI	-70.8%	-86.6%	to	-36.4%
ARR / ARI	-60.7%	-84.9%	to	-36.5%
NNT / NNH**	-1.6	-1.2	to	-2.7

Els mateixos resultats es van obtenir al comparar el número de persones que van necessitar alguna intervenció suplementària, amb un benefici de la cafeïna intravenosa comparada amb placebo; RR de 0,29 (IC95% 0,13-0,64).

Tres fàrmacs, la gabapentina oral, la teofil·lina oral i la hidrocortisona intravenosa han mostrat ser més beneficiosos pel que fa a la disminució de la intensitat de dolor durant el temps que els seus comparadors, el placebo o l'atenció habitual. La rellevància clínica d'aquest resultat dependrà de quin és el valor de la disminució d'intensitat que considerem clínicament rellevant. En l'àmbit d'urgències trobem estudis (16) que conclouen que reduccions de 30 punts (IC95% 36,4-23,6) d'intensitat de dolor mesurat amb una EVA de 0-100 poden considerar-se reduccions rellevants. La gabapentina en l'estudi de Dogan (101) mostra unes diferències al voltant de 2-3 en una escala de 0-10 al ser comparada amb un placebo, valors que podrien ser interpretats com a rellevants. La hidrocortisona intravenosa en l'estudi de Noyan (102) igualment mostra un benefici rellevant al comparar-la amb el tractament convencional, especialment durant les primeres 24 hores, on les diferències d'intensitat de dolor estan al voltant de 3/10. L'assaig clínic

de Feuerstein (103) de teofil·lina oral contra placebo, mostra un benefici a favor de la teofil·lina però utilitza una variable descriptiva per a valorar la intensitat del dolor que dificulta la seva interpretació clínica.

Taula 9. Resultats de gabapentina, teofil·lina i hidrocortisona contra placebo o l'atenció habitual. Disminució de la intensitat del dolor.
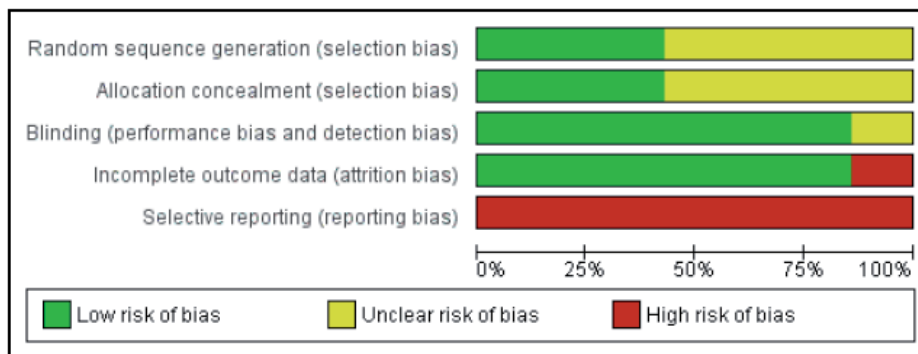
Outcome: Change in pain severity scores (secondary outcome 4)
Oral gabapentin
one day: gabapentin 4.1 (SD 0.31), placebo 5.7 (SD 0.42) ⇨ MD -1.60, 95%CI -1.92 to -1.28 two days: gabapentin 1.8 (SD 0.29), placebo 4.4 (SD 0.33) ⇨ MD -2.60, 95%CI -2.87 to -2.33 three days: gabapentin 0.3 (SD 0.15), placebo 3.2 (SD 0.29) ⇨ MD -2.90, 95%CI -3.10to -2.70 four days: gabapentin 0.1 (SD 0.1),   placebo 1.7 (SD 0.21) ⇨ MD -1.60, 95%CI -1.74 to -1.46
Intravenous hydracortisone
6 hours: hydracortisone 2.77 (SD1.07), convent. 6.63 (SD 1.35) ⇨ MD -3.86, 95%CI -4.48 to -3.24 24 hours: hydracortisone 0.73 (SD 0.74), convent. 3.87 (SD 1.63) ⇨ MD -3.14, 95%CI -3.78 to -2.50 48 hours: hydracortisone 0.63 (SD 0.61), convent 1.87 (SD 0.93) ⇨ MD -1.24, 95%CI -1.64 to -0.84
Oral theophylline
mean sum pain (theophylline 16 (SD 3.91), placebo 28 (SD 4.73) ⇨ MD -12.00, 95%CI -17.19 to -6.81
SD: Standard Deviation; MD: Mean Difference; convent. : conventional treatment

A l'avaluar l'aplicabilitat d'aquestes intervencions per al tractament de la CPPD cal tenir en compte 2 limitacions. Una té relació amb la generalització de les conclusions a una població de referència molt més àmplia que la població d'estudi dels assajos. Igual que succeïa en la RS sobre la prevenció de la CPPD, en aquest cas també la majoria (>80%) de participants inclosos en estudis que formen part de la revisió són dones sotmeses a una PL per anestèsia regional durant el treball de part. Queda en dubte de si les conclusions d'aquesta revisió podrien ser generalitzades a casos de CPPD d'etiologia més diversa com poden ser les PL diagnòstiques. L'altra limitació que dificulta l'avaluació de l'aplicabilitat és la manca de dades sobre la seguretat de les intervencions. No s'han evidenciat efectes adversos importants en les intervencions estudiades però és important remarcar que només 5 dels 7 assajos inclosos han registrat o publicat dades sobre aquest resultat i que el seguiment dels pacients no estava dissenyat per a identificar efectes adversos d'aparició tardana. Altres limitacions detectades en aquesta RS són l'escàs nombre de participants inclosos en els assajos clínics, només 200 participants en 7 ACA; l'ACA amb menor grandària de mostra constava de 10 participants (104) i el més gran 60 (102).

Hem trobat gran variabilitat entre estudis pel que fa a les intervencions avaluades i les variables de resultat emprades; en els 7 ACA inclosos s'avaluen 5 fàrmacs diferents i només un d'ells registra la variable de resultat principal escollida en aquesta revisió. Aquesta variabilitat entre estudis ha impedit combinar els resultats de diferents assajos per donar una estimació conjunta sobre l'eficàcia d'alguna de les intervencions.

El risc de biaix detectat en els assajos inclosos també és una limitació per les conclusions de la revisió. Aquesta limitació ve determinada per la manca d'informació explícita i detallada en els ACA que ha de permetre al lector avaluar críticament el risc de biaix.

Figura 15. Avaluació del risc de biaix per dominis entre els estudis inclosos a la RS sobre tractament de la CPPD

Tenint en compte les limitacions detectades en els assajos inclosos en aquesta RS i similar al què ja s'ha detallat prèviament, seria important que futurs assajos clínics incloguin un major nombre de participants aleatoritzats, una descripció més detallada i explícita de tots els mecanismes que estan implicats en l'avaluació del risc de biaix i la utilització de variables de resultat més rellevants per al pacient i més fàcils d'analitzar i interpretar pels investigadors. Encoratgem altra vegada als investigadors a seguir la declaració CONSORT (105).

Opioides per al dolor abdominal en la pancreatitis aguda

Els opioides poden ser una opció apropiada per al tractament del dolor abdominal de la PA. En comparació amb altres opcions analgèsiques avaluades en aquesta revisió, els opioides, en aquest cas la morfina subcutània i la pentazocina intravenosa, disminueixen la necessitat d'analgèsia suplementària. No hi ha diferència en el risc de complicacions de la pancreatitis o esdeveniments adversos clínicament greus entre els opioides i altres opcions analgèsiques.

En aquesta revisió s'ha pogut combinar, mitjançant una metanàlisi, el resultat de 2 ACA sobre el número de persones que reben analgèsia suplementària, que és una de les dues variables de resultat principals que es van decidir utilitzar en aquesta revisió. La combinació de l'estudi Kahl (106) (pentazocina intravenosa contra procaïna) i Peiro (107) (morfina subcutània contra metamizol) va demostrar que amb els opioides s'aconseguia una reducció significativa en el número de persones que demanen o reben analgèsia suplementària, amb un RR de 0,53 (IC95% 0,30-0,93). Aquestes dades suposen una reducció absoluta del número de participants que

sol·liciten analgèsia de rescat del 42,5% (IC95% 57,9-27,1) i un NNT de 2,4 (IC95% 1,7-3,7).

Taula 10. Opioides contra placebo. Necessitat d'analgèsia suplementària
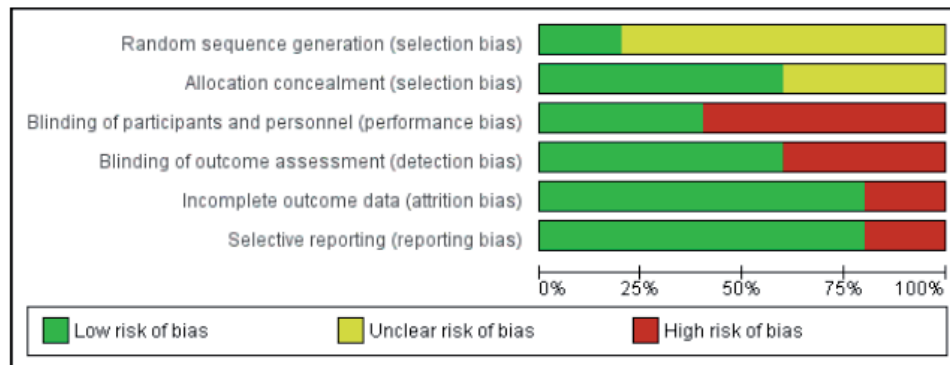Obtingut de: http://clinicalevidence.bmj.com/x/set/static/cms/statistics-calculator.html

Results				
	Point estimate	95% CIs		
RR	0.5	0.4	to	0.7
RRR / RRI	-50.5%	-64.0%	to	-31.9%
ARR / ARI	-42.5%	-57.9%	to	-27.1%
NNT / NNH**	-2.4	-1.7	to	-3.7

Els opioides en aquests ACA ha demostrat també que són una intervenció segura. Tots els estudis han valorat la freqüència d'aparició d'efectes adversos i no s'ha detectat una clara associació d'aquests pels opioides. Tampoc s'ha associat els opioides al risc de complicacions posteriors de la PA ni al risc de mortalitat. Com en la resta de revisions presentades, cal seguir remarcant que els estudis inclosos no estaven dissenyats específicament per detectar efectes adversos o complicacions molt poc freqüents o d'aparició tardana.

Similar a les altres RS incloses en aquesta tesi, són escassos el nombre d'ACA que s'han pogut incloure i també el número de persones participants en aquests assajos. S'han inclòs 5 ACA amb un total de 227 persones aleatoritzades; l'estudi més petit era de 16 participants (107) i 107 (106) el de major grandària de mostra. Aquesta escassa grandària de mostra dificulta obtenir uns resultats més precisos. La combinació de resultats entre diferents ACA només ha estat possible en la variable de resultat *"número de persones que reben analgèsia suplementària"*, i només entre 2 estudis. Aquesta dificultat la trobem relacionada amb la gran heterogeneïtat entre els estudis; les intervencions avaluades són diferents en cada estudi i les variables de resultat utilitzades també són molt diferents entre els estudis inclosos. Remarcar que només un ACA avaluava la variable de resultat principal plantejada en aquesta RS.

Una part significativa dels dominis relacionats amb l'anàlisi del risc de biaix de la RS queden fora d'estar classificats de baix risc, cosa que obliga una vegada més a ser cautelosos amb les conclusions derivades dels resultats de la RS.

Figura 16. Avaluació del risc de biaix per dominis entre els estudis inclosos a la RS sobre opioides en la PA

Una vegada més, recordar als investigadors de futurs estudis relacionats amb aquest tema les limitacions que hem detectat per tal de que els nous ACA puguin ser més vàlids, rellevants i elegibles per a futures RS o actualitzacions d'aquestes. Fer un càlcul de la grandària de mostra necessària, utilitzar variables de resultat rellevants per al pacient i descriure detallada i explícitament tota aquella informació que ens ajuda als lectors a fer una bona lectura crítica són possibles punts de millora. Tenir en compte la declaració CONSORT és una bon camí.

6.2.- Discussió dels aspectes generals

Utilitat, limitacions i reptes per dur a terme l'avaluació de les intervencions mitjançant revisions sistemàtiques

Aquesta tesi presenta 3 investigacions publicades que corresponen a recerca secundària elaborades seguint un disseny metodològic de RS. Aquest disseny basa la seva credibilitat en la qualitat i el rigor dels mètodes que utilitza, a diferència del que es coneix com a "revisió narrativa", on la credibilitat es basa en el coneixement i l'experiència d'experts en el tema, i per tant, amb un baix nivell d'evidència. Les tres revisions presentades no només estan elaborades seguint un disseny de RS sinó que corresponen a RS Cochrane. Aquestes RS segueixen estrictament una metodologia molt estandarditzada, elaborada per metodòlegs experts, i amb la participació activa en cada revisió d'un equip de professionals: clínics, metodòlegs, estadistes i documentalistes. Podem constatar moltes més diferències entre una "revisió narrativa", una RS i una RS Cochrane, tal i com s'observa a la Taula 11.

Taula 11. Comparació entre una "revisió narrativa", una RS i una RS Cochrane (108)

Comparación de revisiones narrativas, revisiones sistemáticas y revisiones Cochrane

Aspecto	Revisión narrativa[a]	Revisión sistemática	Específico de las revisiones Cochrane
Pregunta	Normalmente parte de una discusión general	Se basa en una pregunta clínica clara	La pregunta clínica es imprescindible y se discute con los editores
Protocolo	Ninguno	Finalizado antes de iniciar la revisión	Evaluado por pares y publicado
Métodos	Variables y a menudo no especificados	Claramente definidos	Métodos estandarizados, desarrollados colaborativamente por metodólogos expertos. Asesoramiento en aspectos específicos
Autores	Expertos del área	El equipo incluye a metodólogos	El equipo incluye metodólogos y expertos del área, y ocasionalmente, usuarios o pacientes
Conflictos de interés	Generalmente mal descritos	Declaración variable	Criterios estandarizados de declaración de conflictos de interés[b]
Selección de estudios	Criterios de inclusión vagos, sin descripción de los motivos de exclusión	Criterios de inclusión explícitos	Criterios de inclusión explícitos y descripción en la revisión de los estudios excluidos y sus motivos
Búsquedas de la literatura	No realizan búsquedas o no son exhaustivas	Dirigidas a identificar las publicaciones relevantes (en ocasiones solo en inglés) y datos no publicados	Métodos estandarizados en la Colaboración Cochrane, que incluyen búsquedas de estudios registrados en una base de datos central (CENTRAL)
Valoración del riesgo de sesgo	Generalmente no se tienen en cuenta las diferencias en el riesgo de sesgo de los estudios	Explora el riesgo de sesgo y las fuentes de heterogeneidad	Exploración sistemática del riesgo de sesgo y las fuentes de heterogeneidad preespecificados
Síntesis de datos	No distinguen entre estudios metodológicamente válidos y no válidos	Las conclusiones se basan solo en estudios metodológicamente válidos	Las conclusiones se basan solo en estudios metodológicamente válidos
Valoración de la fuerza de la evidencia	No se realiza	Normalmente no se realiza	Aplicación del sistema GRADE para clasificar la calidad de la evidencia e inclusión a tablas resumen y a la discusión de los resultados
Revisión por pares	Realizada por expertos del área	No siempre incluye a personas familiarizadas con las revisiones sistemáticas	Incluye especialistas en revisiones sistemáticas y, a menudo, usuarios o pacientes
Actualizaciones	Normalmente no se realiza	Normalmente no se realiza	Las revisiones se mantienen actualizadas[c]
Duplicidades	Sin mecanismos para evitar duplicaciones	Sin mecanismos para evitar duplicaciones	Mecanismos establecidos para evitar revisiones duplicadas

[a] También citadas como «revisión de autor», «punto de vista», u «opinión».
[b] www.cochrane.org/editorial-and-publishing-policy-resource/conflicts-interest-and-cochrane-reviews
[c] Desde 2014 se identificarán las revisiones que no requieren más actualizaciones, para priorizar la actualización de revisiones de temas actuales, en los que existe incertidumbre o equivalencia clínica.

Destacar el caràcter dinàmic d'aquest tipus de recerca secundària. Actualment ja estem treballant en l'actualització de la primera RS que es va publicar, la que fa referència al tractament de la CPPD, publicada l'agost de 2011. En els propers mesos està prevista la publicació de l'actualització, en la que s'inclouran entre 4 i 5 nous assajos clínics publicats recentment, més pacients inclosos i més fàrmacs avaluats.

Les RS tenen com a finalitat identificar les investigacions disponibles sobre el tema que s'està estudiant i sintetitzar els resultats dels estudis seleccionats. Finalment, com qualsevol producte derivat d'una recerca, és indispensable la seva difusió. Aquesta difusió ha de permetre que la recerca arribi a mans d'altres investigadors que estiguin treballant en projectes similars per millorar així futures investigacions relacionades. També és important que aquesta difusió permeti la transferència dels coneixements generats fins a les mans dels professionals sanitaris responsables del maneig de la salut de les persones. És important que els gestors, decisors i clínics tinguin a la seva disposició les millors evidències científiques per a prendre decisions òptimes.

Les RS incloses en aquesta tesi ja han començat el seu procés de difusió un cop publicades. Són revisions Cochrane, que són el principal producte elaborat per la *Cochrane Collaboration*. Aquestes revisions es troben incloses a *The Cochrane Database of Systematic Reviews* (CDSR), que forma part de la *Cochrane Library*, i es publiquen seguint el mètode que es coneix com a *"Publish When Ready"*. Aquest mètode permet publicar l'article tan bon punt els editors de la revista donen el vistiplau a la versió definitiva entregada pels autors, evitant així l'espera d'una data

concreta de publicació. A mesura que es van publicant les RS en la versió original anglesa es tradueixen a l'espanyol i es publiquen a la Biblioteca Cochrane Plus, la versió espanyola de la *Cochrane Library*. Aquesta és la principal font d'evidència fiable sobre els efectes de l'atenció sanitària que existeix en llengua espanyola i és totalment gratuïta a Espanya gràcies a la subscripció realitzada pel Ministeri de Sanitat i Consum (108).

És interessant que per facilitar el procés de difusió de la recerca, que aquesta es publiqui en un mitjà amb capacitat d'arribar al major nombre possible d'investigadors i professionals sanitaris. Un sistema molt utilitzat per a mesurar de manera indirecte la repercussió d'un determinat mitjà de publicació sobre la comunitat científica és el FI de la revista científica (109). Actualment la CDSR, amb un FI de 5.785 al 2012, està a la posició 11a de les 151 revistes indexades al *Journal Citation Reports*® dins la categoria "Medicina General i Interna". Amb aquestes dades del FI es podria deduir que cada revisió publicada a la CDSR durant el 2012 ha estat citada de mitjana 6 vegades per altres publicacions científiques. És evident que això és una mitjana calculada a partir de totes les RS de la CDSR. En concret, les 3 RS incloses en aquesta tesi, i fins a maig de 2014, han estat citades per múltiples estudis, tant en revistes mèdiques d'interès generalista, com d'anestèsia o del camp de la medicina d'urgències.

La RS sobre prevenció de la CPPD, publicada al març de 2013, ha estat citada per 7 estudis diferents (Taula 12) dels quals destaquem 3 RS Cochrane i un assaig clínic.

Taula 12. Cites de la RS sobre prevenció de la CPPD

Nº	Revista	Disseny estudi	Idioma	Àmbit geogràfic	Interès	FI
1	Cochrane Database of Systematic Reviews	RS	Anglès	Internacional	General	5.785
2	Cochrane Database of Systematic Reviews	RS	Anglès	Internacional	General	5.785
3	Cochrane Database of Systematic Reviews	RS	Anglès	Internacional	General	5.785
4	International Scholarly Research Notices Emergency Medicine	Revisió	Anglès	Internacional	Urgències	--
5	Anaesthesia	Editorial	Anglès	Regne Unit	Anestèsia	3.486
6	Middle East Journal of Anesthesiology	ACA	Anglès	Orient Mitjà	Anestèsia	--
7	International Journal of Obstetric Anesthesia	Transversal	Anglès	Internacional	Anestèsia	1.799

-- FI no disponible

La RS sobre el tractament de la CPPD, publicada a l'agost de 2011, és actualment la més citada de les 3 revisions amb 26 cites (Taula 13). Destaquem una RS Cochrane, 2 ACA i 9 articles de revisió narrativa. La majoria són publicacions en anglès i dirigides al camp de l'anestèsia, la neurologia, la radiologia, les urgències i també en revistes d'interès generalista.

Taula 13. Cites de la RS sobre tractament de la CPPD

Nº	Revista	Disseny estudi	Idioma	Àmbit geogràfic	Interès	FI
1	Journal of Anesthesia & Clinical Research	Cas clínic	Anglès	Internacional	Anestèsia	--
2	Canadian Journal of Emergency Medicine	Cas clínic	Anglès	Canadà	Urgències	1.514
3	Cephalalgia	Descriptiu	Anglès	Internacional	General	3.485
4	Cochrane Database of Systematic Reviews	RS	Anglès	Internacional	General	5.785
5	Anaesthesia & Intensive Care Medicine	Revisió	Anglès	Internacional	Anestèsia	--
6	Tidsskr Nor Legeforen	Revisió	Noruec	Noruega	General	--
7	Emergency radiology	Revisió	Anglès	EUA	Radiologia	--
8	Revista Medica de Costa Rica y Centroamerica	Revisió	Espanyol	Amèrica Ctr.	General	--
9	Neurological sciences	Revisió	Anglès	Itàlia	Neurologia	1.41
10	European journal of neurology	Enquesta	Anglès	Europa	Neurologia	4.16
11	The journal of ECT	Editorial	Anglès	EUA	Neurologia	1.19
12	Middle East journal of anesthesiology	ACA	Anglès	Orient Mitjà	Anestèsia	--
13	Nursing standard	?	Anglès	Regne Unit	Infermeria	--
14	Advanced biomedical research	ACA	Anglès	Índia	Anestèsia	--
15	Pain physician	Cohorts retr.	Anglès	EUA	Anestèsia	10.72
16	Der Anaesthesist	Revisió	Angl./Alem.	Alemanya	Anestèsia	0.85
17	Pediatric Hematology-Oncology in Countries with Limited Resources	Llibre	Anglès	Regne Unit	Pediatria	--
18	Danish Medical Journal	Enquesta	Danès	Dinamarca	General	--
19	International anesthesiology clinics	Guia clínica	Anglès	Internacional	Anestèsia	--
20	Anesth Pain Med	Editorial	Anglès	Iran	Anestèsia	4.16
21	Вестника муниципального здравоохранения	Revisió	Rus	Rússia	General	--
22	Pediatric Emergency Medicine Practice	Revisió	Anglès	EUA	Pediatria	--
23	Journal of Neuroscience Nursing	Revisió	Anglès	EUA	Infermeria	0.76
24	Annales françaises d'anesthèsie et de rèanimation	Cas clínic	Francès/ Anglès	França	Anestèsia	0.77
25	Emergency Radiology	Revisió	Anglès	EUA	Radiologia	--
26	Scandinavian Journal of Pain	Cas clínic	Anglès	Escandinàvia	General	_

-- FI no disponible

La darrera RS inclosa a la tesi, sobre els opioides en el tractament del dolor abdominal de la PA i publicada al juliol del 2013, no ha suscitat de moment cap cita a les revistes mèdiques tradicionals, però igual que passa amb les dues revisions sobre la CPPD, aquesta també la podem trobar citada a *UpToDate*, en el capítol *"Management of acute pancreatitis"* i a *Dynamed*, al apartat de tractament del capítol *"Acute Pancreatitis"*. *UpToDate* i *Dynamed* són dues de les fonts de coneixement més utilitzades per professionals sanitaris dels EUA, i també a Espanya en el cas de d'*UpToDate*, com a eina d'ajuda per a solucionar dubtes clínics i prendre decisions.

Les RS haurien de poder sintetitzar els resultats dels assajos clínics que inclouen, però en moltes ocasions, com ha passat també amb les RS incloses en aquesta

tesi, ens trobem amb limitacions que dificulten aquest procés de síntesi. Aquestes limitacions en el procés de síntesi fan que el resultat i les conclusions finals que hem de transmetre sobre els beneficis i riscs de les intervencions avaluades no puguin transmetre la confiança i la precisió que ens agradaria. Moltes de les limitacions que ens hem trobat en aquestes tres RS, i que són habituals en tot procés d'elaboració d'una RS, estan en relació a les característiques dels estudis que s'hi han inclòs. Diem que la qualitat d'una RS ve determinada en gran mesura per la qualitat dels estudis que hem inclòs.

Una d'aquestes limitacions són l'escàs número d'estudis que finalment podem incloure en cada revisió. En les 3 RS elaborades hi trobem un total de 22 ACA, 10 per la RS sobre prevenció de la CPPD, 7 sobre el seu tractament i 5 ACA per la RS sobre el dolor de la PA. Les causes d'aquest escàs número d'ACA inclosos són diverses. En les RS sobre la CPPD, un dels principals motius per excloure assajos que en un principi eren elegibles és degut a que l'objectiu principal de l'assaig no era específicament la prevenció o tractament de la CPPD, sinó que aquesta cefalàlgia s'estudiava com un esdeveniment advers de les PL, prenent el rol d'una variable de resultat secundària a l'assaig clínic, i per tant, amb una finalitat exploratòria. El mateix ha succeït amb la PA, on el dolor era mesurat com una variable de resultat secundària en molts dels assajos identificats com elegibles. Aquest rol secundari suposava en moltes ocasions que la variable CPPD o la variable dolor de l'ACA no estigués definida ni registrada de manera correcta, homogènia i sistemàtica. Una altre raó d'exclusió molt freqüent que hem detectat és la manca d'una definició precisa de la patologia estudiada, sobretot en el cas de la CPPD. Tot i existir una definició de CPPD per la *International Headache Society* (33), molt estudis no fan referència a aquesta definició en els criteris de selecció dels participants i en moltes ocasions, tampoc fan referència al component ortostàtic o postural de la cefalàlgia. La referència explícita a aquest component postural de la cefalàlgia el vàrem considerar com a criteri d'inclusió indispensable per tal de no incloure assajos clínics on l'objectiu fos algun altre tipus de cefalea. Tot i la prevalença i la implicació clínica i legal d'aquesta entitat, sorprèn la poca quantitat d'estudis en format ACA que s'han publicat en el qual l'objectiu principal fos la prevenció o el tractament de la CPPD, i el mateix succeeix en relació al maneig farmacològic del dolor abdominal de la PA. Podríem hipotetitzar que aquest fenomen està relacionat amb un escàs volum publicat d'assajos clínics sobre el maneig de patologia aguda en l'àmbit d'urgències i d'anestèsia comparat amb altres problemes de salut sobre els quals la investigació és molt més abundant. Les conseqüències d'aquestes limitacions són l'elaboració de RS amb pocs ACA inclosos, i per tant, amb pocs participants en el recompte global de la revisió.

L'escàs nombre de participants en cada ACA, juntament amb els pocs ACA inclosos a les RS, és una altre limitació recurrent en moltes RS; també en les 3 presentades en aquesta tesi. En els 22 ACA inclosos dins les 3 RS hi comptabilitzem un total de 2043 persones. El 80% d'aquestes (1611 persones) corresponen a la revisió sobre la prevenció de la CPPD i la resta es reparteixen a parts iguals entre les altres 2 RS,

205 per la de tractament de la CPPD i 227 per la revisió de la PA. La mediana de participants és de 55 per cada assaig clínic, amb un 25% dels ACA amb ≤29 participants i només un 25% amb ≥134 participants. En la majoria dels casos no sabem les causes que han justificat la realització d'ACA amb tant pocs participants, però si que sabem que només 6 dels 22 assajos inclosos descriuen explícitament a la publicació el sistema que han utilitzat per a calcular la grandària de mostra necessària; una de les condicions importants a tenir en compte durant la lectura crítica de qualsevol estudi. Les conseqüències d'aquests reduïts volums de participants són varies: a) estimacions poc precises, amb intervals de confiança amplis, b) una limitada potència estadística, és a dir, estudis amb risc de no detectar diferències realment existents (risc de falsos negatius) i c) dificultat en fer anàlisi de subgrups entre diferents tipus de població per explorar possibles diferències entre aquestes.

Les conclusions a les que pot arribar qualsevol RS depenen en gran mesura en el grau de confiança que tinguem en els resultats presentats pels assajos inclosos (110). L'avaluació del risc de biaix s'adreça directament a intentar delimitar el grau de confiança. Els tipus de biaixos que es pretén avaluar en cada assaig clínic inclòs en una RS Cochrane són el biaix de selecció, el de realització, el de detecció, el de desgast i el de notificació (87). Aquesta avaluació es fa seguint una eina elaborada per la Cochrane que es realitza mitjançant una avaluació basada en dominis. Els dominis avaluats són tots aquells factors propis de l'assaig clínic que més influeixen en la presència de biaixos, és a dir, la generació de la seqüència d'assignació, l'ocultació d'aquesta seqüència d'assignació, el cegament de les intervencions assignades per part dels participants, del personal o dels avaluadors, les dades de resultat incompletes, la notificació selectiva dels resultats i "altres aspectes".

Precisament una de les limitacions que afecten a moltes RS, incloent les 3 presentades aquí, és la dificultat en avaluar aquest risc de biaix. Aquesta dificultat ve determinada per una pobre qualitat en la publicació de l'estudi. És possible trobar assajos clínics en els quals els autors de l'estudi van realitzar la seva investigació amb els estàndards més alts possibles però que no han estat capaços de plasmar aquesta bona praxis en les pàgines d'una publicació. Això implica una limitació per part del lector que intenta avaluar el risc de biaix de l'estudi, és a dir, el grau en que podrem confiar o creure els resultats obtinguts. Aquesta és una de les limitacions identificades en les 3 RS presentades, on en molts assajos clínics els seus autors no descriuen explícitament ni amb suficient detall la metodologia emprada en cadascun dels dominis. Per aquest motiu i per evitar aquestes limitacions s'aconsella a tots els investigadors seguir les indicacions de la declaració CONSORT (99), que pretén guiar als investigadors a millorar la qualitat en la publicació dels assajos clínics realitzats i facilitar d'aquesta manera la lectura crítica i l'avaluació del risc de biaix per part dels lectors. Analitzant els 3 gràfics de risc de biaix de les 3 RS podem observar que el factor determinant està en la quantitat de dominis que estan marcats com a "risc de biaix poc clar", que podríem quantificar vagament en ⅓ part dels dominis. Aquesta situació ens deixa una mica insegurs pel

que fa a la validesa dels nostres resultats ja que la balança es podria decantar clarament cap a un alt o baix risc de biaix si disposéssim de tota la informació necessària per avaluar els tots els dominis etiquetats de "poc clar".

L'heterogeneïtat clínica entre estudis és una altre limitació identificada en les RS presentades que dificulta el procés de síntesi de resultats. Quan en una RS ens trobem que els assajos clínics inclosos avaluen diferents intervencions, diferents dosis o diferents vies d'administració, no té molt sentit intentar resumir o sintetitzar en un sol resultat numèric els efectes d'intervencions que d'entrada ja són molt diferents entre si. El mateix succeeix quan, entre els estudis inclosos, els participants són molt diferents, sobretot pel que fa al risc basal de presentar l'esdeveniment que intenten evitar o millorar amb la intervenció. En les 3 RS ens hem trobat en múltiples ocasions amb la necessitat d'eludir una síntesi de resultats mitjançant una metanàlisi per motius d'heterogeneïtat clínica important (111).

En tota RS, un dels primers punts a definir en les fases inicials d'elaboració són determinar quines seran les variables principals de resultat i com les definirem. És important seleccionar aquelles variables més clínicament rellevants per al pacient (112). Aquest apartat és important ja que això serà un dels factors que determinaran els criteris d'inclusió d'assajos clínics a la revisió; tots aquells assajos clínics que no registrin cap de les variables de resultat que els autors de la RS han predeterminat o que no s'ajustin a la definició proposada, no podran ser inclosos a la revisió. Aquesta és també una de les limitacions freqüents a les RS. Trobem assajos clínics que són molt correctes metodològicament, amb resultats vàlids i significatius però que no es poden integrar a la RS pel fet de no haver utilitzat cap de les variables predeterminades per l'equip que elabora la RS. Aquesta limitació suposa en molts casos reduir el número d'estudis que s'integren a la revisió, i per tant el número de participants, amb els inconvenients que això implica i que han estat descrits prèviament. En el nostre cas, un cop eliminats tots els estudis que no incorporaven cap de les variables principals, podem observar que en la RS sobre prevenció de la CPPD tots els ACA inclosos registraven la variable principal de la revisió, però en el cas de la RS sobre tractament de la CPPD, només 1 ACA (100) recull la variable principal; els altres 6 assajos s'han inclòs gràcies a que registraven alguna de les variables secundàries. En la RS de la PA, on es va decidir incloure 2 variables de resultat principals, només 1 dels 5 ACA (107) inclosos recull la primera variable principal, però 4 dels 5 ACA registren l'altre variable principal.

Aquestes limitacions detectades corresponen a les característiques dels assajos clínics que cal avaluar al fer una lectura crítica d'una RS, per així poder considerar el grau de confiança que podem tenir en les estimacions dels efectes publicats pels assajos. Aquest sistema de llegir una RS correspon al que s'exposa en un recent article publicat a la revista JAMA (113), com es pot observar a la Taula 14, on es recomana avaluar el rigor dels mètodes utilitzats pels autors de la revisió i també la qualitat dels estudis inclosos. Per aquesta darrera tasca es recomana el sistema GRADE, que és una eina de recent desenvolupament i en fase de difusió que pretén

ajudar a l'autor d'una RS a classificar la qualitat dels estudis inclosos, i per tant, a elaborar unes recomanacions amb més rigor científic.

Taula 14. Guia per avaluar i aplicar els resultats d'una RS (113)

> **Primer Criteri: va ser la metodologia de la revisió sistemàtica creïble?**
> 1. El tema està clarament definit?
> 2. La recerca bibliogràfica és exhaustiva?
> 3. La selecció i avaluació d'estudis i l'extracció de dades és reproduïble?
> 4. Els resultats de la revisió estan a punt per a la seva aplicació clínica?
> 5. Aporta tota la informació necessària per poder avaluar el segon apartat; la qualitat de les evidències?
>
> **Segon Criteri: Podem confiar en les estimacions de l'efecte?**
> Sistema GRADE:
> 1. Disseny de l'estudi: assaig clínic aleatoritzat vs observacional
> 2. Risc de biaix: eina Cochrane d'avaluació basada en dominis
> 3. Inconsistència: Heterogeneïtat
> 4. Imprecisió: nombre de persones i esdeveniments; interval de confiança
> 5. Indirecte: població, intervenció o variables són diferents a les que ens interessen
> 6. Biaix de notificació: biaix de publicació i biaix de notificació selectiva de resultats
> 7. Gran efecte de la intervenció: un gran efecte augmenta la confiança

En vistes a les 3 RS presentades, i tenint sempre en compte les limitacions i les fortaleses detectades, disposem ara de més arguments que poden ajudar al professional sanitari a prendre les decisions més òptimes sobre maneig del dolor agut, específicament del maneig farmacològic del dolor agut. Pel que fa a la prevenció i al tractament del la CPPD, durant els darrers anys s'està fent un important esforç per part de diferents grups de la Col·laboració Cochrane per tal d'actualitzar tota la informació disponible dels assajos clínics en l'elaboració de RS. Les revisions sobre la CPPD presentades en aquesta tesi es sumen al coneixement aportat per la resta de RS publicades recentment, ampliant d'aquesta manera el domini de diferents estratègies per a fer-hi front. El coneixement per part del clínic sobre quins fàrmacs poden ser més beneficiosos i segurs per prevenir o alleugerir una cefalea posterior a una PL és important. És important perquè es tracta d'un problema de salut iatrogènic, secundari a una PL, que se suma al problema de salut inicial que referia la persona; aquesta responsabilitat ens obliga a fer tot el possible per a conèixer com evitar aquest dolor o com tractar-lo en cas d'aparèixer. També és important per la seva potencial prevalença ja que la PL és una tècnica molt recorreguda, ja sigui per motius diagnòstics a l'àmbit d'urgències, a consultes o a planta d'hospitalització d'aguts, com per l'anestèsia regional per part de l'anestesista. I en darrer lloc és important per tractar-se d'un dolor agut per al qual no disposem actualment d'unes recomanacions sòlidament elaborades per al seu maneig; les RS presentades aquí pretenen aportar una mica de llum en aquest buit

de coneixement. Referent al tractament farmacològic amb opioides en el dolor abdominal de la PA és també una situació molt prevalent en l'àmbit de les urgències, on el desconeixement per part dels professionals sanitaris sobre els beneficis i riscos reals dels opioides en la PA ha dificultat el maneig apropiat del dolor agut.

Les investigacions presentades en aquesta tesi sobre la CPPD i la PA pretenen aportar coneixement útil i pràctic a disposició del clínic responsable del maneig del dolor en fases agudes; fenomen que ja em començat a percebre amb la presencia en recursos d'alt impacte com és *UpToDate*. També pretenen ser d'utilitat per a futures investigacions sobre aspectes relacionats amb la farmacopea del dolor agut, fet que intuïm ja està començant a passar si tenim en compte les cites identificades en posteriors assajos clínics o RS publicades.

7.-CONCLUSIONS

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7.1.- Implicacions per a la pràctica

En relació al tractament farmacològic del dolor agut a urgències, s'incorpora nou coneixement científic disponible per al personal sanitari sobre el benefici i risc de diferents estratègies farmacològiques per a dues entitats que cursen amb dolor agut, la CPPD i la PA:

- En la prevenció de la CPPD, la morfina epidural, la cosintropina intravenosa i l'administració intravenosa d'aminofil·lina redueixen el risc de CPPD, especialment en aquells pacients amb un alt risc de CPPD, com les gestants amb anestèsia espinal durant el part.
- En el tractament de la CPPD, la cafeïna intravenosa redueix la persistència de CPPD i la necessitat d'altres intervencions complementàries. La gabapentina oral, la teofil·lina oral i la hidrocortisona intravenosa disminueixen la intensitat del dolor agut.
- En el tractament amb opioides del dolor abdominal de la PA, la morfina subcutània i la pentazocina intravenosa disminueixen la necessitat d'altres mesures analgèsiques complementàries.

7.2.- Implicacions per a la recerca

- S'aconsella als investigadors que en futurs ACA utilitzin variables de resultat principals clínicament rellevants. Sempre que sigui possible i correcte, aquestes variables haurien de ser definides seguint l'exemple d'assajos previs, per facilitar l'homogeneïtat de les dades i d'aquesta manera la seva síntesi en futures RS.
- Es recomana als futurs elaboradors d'ACA utilitzar una grandària de mostra suficient per a donar resposta a les hipòtesis plantejades i a publicar l'estratègia utilitzada per a calcular la grandària d'aquesta mostra utilitzada.
- S'aconsella a tots els investigadors a seguir les directrius aconsellades en la declaració CONSORT que permetrà millorar la qualitat de la publicació de nous assajos clínics. Aquesta mesura facilitarà una lectura crítica més eficient per part dels lectors interessats, especialment els elaboradors de futures RS que podran avaluar de manera més acurada del risc de biaix.
- Es recomana als autors de RS l'ús del sistema GRADE per classificar la qualitat de l'evidencia i poder elaborar les recomanacions amb més rigor.

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9.-ANNEXOS

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Abreviacions utilitzades

95%CI	95% Confidential Interval
ACA	Assaig Clínic Aleatoritzat
ACTH	Hormona Adrenocorticotròpica o Corticotropina
APACHE II	Acut Physiology And Chronic Health Evaluation
ATC	Anatomic Therapeutic Chemical code
BPI	Wisconsin Brief Pain Inventory
CDSR	The Cochrane Database of Systematic Reviews
CEIC	Comitè Ètic d'Investigació Clínica
CENTRAL	Cochrane Central Register of Controlled Trials
CPPD	Cefalàlgia Per Punció Dural
CREP	Colangiopancreaticografia Retrògrada Endoscòpica
EVA	Escala Visual Analògica
FI	Factor d'impacte
GPC	Guies de Pràctica Clínica
IASP	International Association for the Study of Pain
IC95%	Interval de Confiança del 95%
LCR	Líquid Cefaloraquidi
MBE	Medicina Basada en l'Evidència
MPQ	McGill Pain Questionnaire
NNH	Number Needed to Harm
NNT	Number Needed to Treat
OMS	Organització Mundial de la Salut
p.ex.	Per exemple
PA	Pancreatitis Aguda
PBE	Pràctica Basada en l'Evidència
PCR	Proteina C Reactiva
PGI-I	Patient Global Impression of Improvement Scale
PHE	Pegat Hemàtic Epidural
PL	Punció Lumbar
QOL	Quality of life
RR	Risc Relatiu
RS	Revisió Sistemàtica
SF-36	Short Form 36 of Medical Outcomes Study
SOFA	Sequential Organ Failure Assessment
TC	Tomografia Axial Computada
UCI	Unitat de Cures Intensives

Assajos clínics elegibles per a la propera actualització de la RS sobre el tractament de la CPPD. Característiques i risc de biaix

Erol DD. The analgesic and antiemetic efficacy of gabapentin or ergotamine/caffeine for the treatment of postdural puncture headache. Adv Med Sci. 2011 Jan;56(1):25-9

Characteristics

Methods	Randomised, not-blinded, treatment-controlled trial Study type: single-centre study Location: Turkey (Afyonkarahisar) Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: not described Follow-up period: 4 days
Participants	Randomised: 42 (intervention group: 21; control group: 21) Excluded (post-randomisation): not described Gender (women): 17 (40%) Age (years); mean: intervention group 45, control group 47 Baseline VAS score;mean(SD): intervention group 7.5 (0.48), control group 7.3 (0.42) Inclusion criteria: PDPH after spinal or epidural anesthesia Exclusion criteria: known allergy to, or contraindications (pancreatitis, galactosemia) to the use of gabapentin or Cafergot, other medication use (postoperative analgesics, phenytoin, carbamazepine, valproic acid, phenobarbital, naproxen, hydrocodone, morphine, cimetidine, oral contraceptive, antacid, probenecid), migraine, asthma, coronary artery disease, and hepatic or renal insufficiency.
Interventions	Intervention group: gabapentin 900 mg/day orally (300 mg every 8 hours) x 4 days Control group: ergotamine 1 mg and caffeine 100 mg orally, every 8 hours, x 4 days Co-interventions: All patients were treated with bed rest and fluid hydration (3000cc/24h) for 4 days
Outcomes	1. Change in pain severity VAS score after 1, 2, 3 and 4 days 2. Number of any possible adverse events 3. Number of participants with EBP performed
Notes	Post-dural puncture headache (PDPH): Quote "For diagnosis we used the criteria suggested by the International Headache Society (IHS)." (page 26) Visual analogue scale (VAS): 0 (denoting no pain) to 10 (denoting worst possible imaginable pain) Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Described as randomised.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias)	Unclear risk	No information provided.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study

Zeger W, Younggren B, Smith L. Comparison of cosyntropin versus caffeine for post-dural puncture headaches : A randomized double-blind trial. 2012;3(3):10–3.

Characteristics

Methods	Randomised, double-blind, treatment-controlled trial Study type: single-centre study Location: USA (Washington) Study design: parallel Randomisation: not described Allocation concealment: Central randomization by the hospital pharmacy Blinding: blinding of participants and health care provider Follow-up period: 120 minutes or discharged from the emergency department
Participants	Randomised: 37 (intervention group: 17+x control group: 16+x) Excluded (post-randomisation): not described Gender (women): 20/33 (60.6%) Age (years); mean (standard deviation - SD): intervention group 25 (8), control group 33 (11) Baseline VAS score;mean(SD): intervention group 78 (16), control group 82 (15) Inclusion criteria: presenting to the emergency department within seven days of a lumbar puncture and meet the diagnostic criteria for a PDPH Exclusion criteria: life-threatening etiology, evidence of elevated intracranial pressure (e.g. papilledema), pregnancy, history of congestive heart failure, severe hypertension, allergy to caffeine, ACTH or its analogs or if they elected a blood patch as an initial therapeutic intervention
Interventions	Intervention group: 0.75 mg cosyntropin in 1 liter of normal saline intravenously over 60 minutes followed by 1 liter of normal saline given over 60 minutes Control group: 500 mg caffeine in 1 liter of normal saline given intravenously over 60 minutes followed by a repeated dose of 500 mg caffeine in 1 liter of normal saline over 60 minutes Co-interventions: All patients received 975 mg of acetaminophen and 2 liters of normal saline over a 2-hour period
Outcomes	1. PDPH persistence of any severity at 120 minutes 2. Change in pain severity VAS score after 60 and 120 minutes 3. Number of any possible adverse events 4. Number of participants with a conservative supplementary therapeutic option offered 5. Missing data (withdrawals, drop-outs and participants lost to follow up
Notes	Post-dural puncture headache (PDPH): Quote "headache clinically consistent with a PDPH, the presence of a postural component," (page 183) Visual analogue scale (VAS): 0 = no headache and 100 = worst headache imaginable Sample size calculation: 270 patients in each arm needed according to the calculations described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Described as randomised.
Allocation concealment (selection bias)	Low risk	Central randomization. Quote: "Each drug was premixed, coded, and randomized by the hospital pharmacy without the knowledge of the health care provider." (Page 183)
Blinding (performance bias and detection bias)	Low risk	Quote: "Each drug was premixed, coded, and randomized by the hospital pharmacy without the knowledge of the health care provider." (Page 183)
Incomplete outcome data (attrition bias)	High risk	Data from 4 patients were not available because of protocol violation (3) or withdrawal (1). Not described which group they belong.
Selective reporting (reporting bias)	Low risk	Results presented according to objectives stated in the introductory section

Mahoori A, Hassani E, Noroozinia H, Javaheri N, Hatami S. Theophylline versus acetaminophen in the treatment of post-dural puncture headache (PDPH). Middle East J Anesthesiol. 2013 Oct;22(3):289–92.

Characteristics

Methods	Randomised, single-blind, treatment-controlled trial Study type: single-centre study Location: Iran (Urmia) Study design: parallel Randomisation: computer random numbers series Allocation concealment: not described Blinding: blinding of participants Follow-up period: 12 hours
Participants	Randomised: 60 (intervention group: 30; control group: 30) Excluded (post-randomisation): not described Gender (women): 19 (31.6%) Age (years); mean (standard deviation - SD): intervention group 40.06 (5.95), control group 40 (6.43) Baseline VAS score;mean(SD): intervention group 5.46 (1.33), control group 5.96 (1.20) Inclusion criteria: ASA I patients under spinal anesthesia for various surgical procedures with PDPH according to ICDH-II definition Exclusion criteria: central nervous disorders, hypertension, ischemic heart disease, cardiac arrhythmias, hyperthyroidism, age higher than 60 years old and past history of migraine headaches
Interventions	Intervention group: 250 mg Theophylline orally, every 8 hours Control group: 500 mg Acetaminophen orally, every 8 hours Co-interventions: not described
Outcomes	1. Change in pain severity VAS score after 2, 6 and 12 hours 2. Number of any possible adverse events 3. Missing data (withdrawals, drop-outs and participants lost to follow up
Notes	Post-dural puncture headache (PDPH): Quote "subjects have experienced PDPH according to the definition of International classification of headache disorders (ICDH-II)" (page 290) Visual analogue scale (VAS): 0 (denoting no pain) to 10 (denoting worst possible imaginable pain) Sample size calculation: 54 patients needed according to the calculations described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigator reported the use of a computer random number generator
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "TDS administration to ascertain the blindness of subjects in both study groups" (Page 290)
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study

Huseyinoglu U, Huseyinoglu N, Hamurtekin E, Aygun H, Sulu B. Effect of pregabalin on post-dural-puncture headache following spinal anesthesia and lumbar puncture. J Clin Neurosci. Elsevier Ltd; 2011 Oct [cited 2014 Jun 2];18(10):1365–8.

Characteristics

Methods	Randomised, single-blind, placebo-controlled trial Study type: single-centre study Location: Turkey (Kars) Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: single-blind but not described who was blinded Follow-up period: 5 days
Participants	Randomised: 40 (intervention group: 20; control group: 20) Excluded (post-randomisation): not described Gender (women): 28 (70%) Age (years); mean (standard deviation - SD): intervention group 39.95 (12.62), control group 34.85 (10.91) Baseline VAS score;mean(SD): text reported that theres was no significant difference (p=0.947). No explicit numbers, only graphyc data. Inclusion criteria: ASA I-II patients under spinal anesthesia for various surgical procedures or diagnostic or therapeutic lumbar puncture with PDPH according to IHS criteria. Exclusion criteria: <18 years of age, weight <40 kg, renal or liver dysfunction, severe cardiovascular disease, a history of peptic ulcer and gastrointestinal system bleeding, a known allergy to any component of the treatment drugs, or glucose/lactose intolerance. Pregnancy or breast-feeding
Interventions	Intervention group: 75 mg Pregabalin orally, every 12 hours for 3 days and 150 mg Pregabalin orally, every 12 hours for 2 more days Control group: Placebo orally, every 12 hours, for 5 days Co-interventions: -75 mg diclofenac sodium intramuscularly at a dose not greater than 150 mg/day if headache. -pethidine hydrochloride at a maximum dose of 150 mg/day if PDPH symptoms persisted despite dicofenac.
Outcomes	1. Change in pain severity VAS score after 1, 2, 3, 4 and 5 days 2. Number of participants with a conservative supplementary therapeutic option offered 3. Missing data (withdrawals, drop-outs and participants lost to follow up
Notes	Post-dural puncture headache (PDPH): Quote "diagnosed with PDPH according to the International Headache Society criteria" (page 1366) Visual analogue scale (VAS): 0 = no headache and 10 = worst, unbearable headache Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Described as randomised.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	Quote: "randomized, single-blinded, placebo-controlled study" (Page 1366). No information about who was blinded and how.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study

Alam MR, Rahman MA, Ershad R. Role of very short-term intravenous hydrocortisone in reducing postdural puncture headache. J Anaesthesiol Clin Pharmacol. 2012 Apr;28(2):190–3.

Characteristics

Methods	Randomised, double-blind, placebo-controlled trial Study type: single-centre study Location: Bangladesh (Chittagong) Study design: parallel Randomisation: computer random numbers series Allocation concealment: not described Blinding: double blind, patients and observer Follow-up period: 48 hours
Participants	Randomised: 60 (intervention group: 30; control group: 30) Excluded (post-randomisation): not described Gender (women): 32 (53%) Age (years); mean (standard deviation - SD): intervention group 30.32 (5.83), control group 32.49 (4.69) Baseline VAS score;mean(SD): intervention group 9.32 (0.83), control group 9.17 (1.69) Inclusion criteria: Adult patients (ASA I and II) who developed PDPH after nonobstetric surgery Exclusion criteria: history of cluster headache, convulsion, cerebrovascular accident, preeclampsia, eclampsia, coagulopathy, or previous neurological diseases
Interventions	Intervention group: 100 mg hydrocortisone, diluted in 2 ml, intravenous 8 hourly for 48 h Control group: 2 ml of normal saline intravenously (placebo) 8 hourly for 48 hours Co-interventions: conventionally treatment: Recumbent positioning, intravenous or oral hydration, analgesics with caffeine, stool softeners, and soft diet
Outcomes	1. Change in pain severity VAS score after 6, 24 and 48 hours 2. Number of any possible adverse events 3. Number of participants with EBP performed
Notes	Post-dural puncture headache (PDPH): Quote "The mean of headache intensity was measured in all 60 patients after 1 min in upright position." (page 191) Visual analogue scale (VAS) 10 cm: 0–1, no headache; 2–4, mild headache; 5–7, moderate headache; and 8–10, severe headache Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigator reported the use of a computer random number generator
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Low risk	Quote: "The patients and the single observer were blinded to this study." (Page 191)
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study

Sen J, Sen B. Non invasive Management of Post Dural Puncture Headache –A Comparison. Bangladesh J Med Sci. 2014;13(02):114–8.

Characteristics

Methods	Randomised, placebo-controlled trial Study type: single-centre study Location: India (Faridabad) Study design: parallel Randomisation: not described Allocation concealment: not described Blinding: not described Follow-up period: 24 hours
Participants	Randomised: 40 (intervention group: 20; control group: 20) Excluded (post-randomisation): not described Gender (women): 18 (45%) Age: text reported that there was no significant difference. Quote "Groups did not differ in age" (Page 115). Baseline VAS score;mean(SD): intervention group 93.5 (5.9), control group 94.6 (4.4) Inclusion criteria: Patients of ASA I and II suffering from post dural puncture headache Exclusion criteria: not described
Interventions	Intervention group: 400 mg theophylline orally Control group: conservative treatment comprising of bed rest in supine position without a head pillow, Caffeine containing beverages, injectable Opioid and/or Non steroid anti inflammatory drug (NSAID). Co-interventions: not described
Outcomes	1. Change in pain severity VAS score after 8, 16 and 24 hours
Notes	Post-dural puncture headache (PDPH): Quote "Patients under study were asked to mark a 0 to 100 mm VAS in sitting position to facilitate a maximal score at the onset of PDPH." (page 115) Visual analogue scale (VAS) 0 to 100 mm Sample size calculation: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Described as randomised.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome (PDPH persistence of any severity at follow up) that would be expected to have been reported for such a study