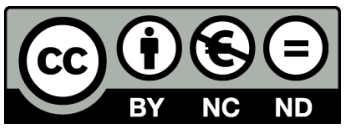
Universitat Internacional de Catalunya
Facultat de Medicina i Ciències de la Salut -
Departament de Medicina

Tesi doctoral

Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera.

Juan Victor Lorente Olazábal



Título de la Tesis:

"Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera.

Autor:

Juan Victor Lorente Olazábal

TESIS DOCTORAL

Universitat Internacional de Catalunya, 2023

Título de la Tesis:

"Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera.

Autor:

Juan Victor Lorente Olazábal

TESIS DOCTORAL

Universitat Internacional de Catalunya, 2023

Directores:

Dr. Joan Bosch Sabater

Dra. Francesca Reguant Corominas

Programa de Doctorado:

Ciencias de la Salud

Línea de Investigación:

Investigación clínica aplicada y Prevención en Salud


uic
barcelona

A María, pese a que todavía no te hemos podido abrazar, ya eres el centro de nuestras vidas.

A María Luisa, mi querida esposa, por ser mi vida, mi todo.

A mi madre, porque pese a que te fuiste demasiado pronto, siempre estás conmigo.

A mi padre, por ser uno de los referentes de mi vida.

Agradecimientos

Tuve la ocasión de disfrutar seis de los años más importantes de mi vida en Manresa. Durante este periodo temporal, se establecieron las bases de la persona y el profesional que hoy día soy. Desde el principio, aquellos aspectos de monitorización hemodinámica y fluidoterapia despertaron en mi un interés enorme en esta parcela de nuestra especialidad que por supuesto, mantengo actualmente. Además, paralelamente, pude conocer desde dentro la investigación gracias a la ayuda de la Dra. Cesca Reguant. Me dio innumerables oportunidades de colaborar a nivel asistencial, docente e investigador que valoré siempre de forma superlativa, intentando devolver su confianza con ilusión y trabajo. En este marco, surgió este proyecto de tesis doctoral que cambió mi vida, incorporé desde ese momento la investigación y docencia como una parte más de mi trabajo hasta la actualidad. Siempre estaré agradecido a Cesca, sin ella, todos los éxitos posteriores no hubieran sido posibles. Gracias.

Además, para hacerlo posible, tuve la suerte de contar con la ayuda de la Dra Anna Arnau y el Dr. Joan Bosch. Gracias también a ellos, este proyecto ha fructificado. Sois el motivo por el cual, más profesionales nos sumamos a la investigación, sin vuestro apoyo desinteresado, a deshoras, siempre disponibles, muchos investigadores nos hubiéramos quedado en el camino. Muchas mejoras, por tanto, no hubieran llegado a los pacientes sin vuestra ayuda. Gracias por vuestra calidad humana y profesional en todos los ámbitos.

Pero un investigador no es nadie sin equipo, en mi trayectoria investigadora muchos compañeros me han ayudado, desde el Dr. Esquius, que defendió la viabilidad e interés de este proyecto, hasta compañeros que colaboran cada día en el trabajo de campo y referentes de investigación y amigos, de todos ellos tengo la oportunidad de aprender a diario compartiendo experiencias asistenciales, docentes e investigadoras. Gracias a todos ellos.

Resúmen:

Objetivo: Evaluar el efecto de la terapia dirigida por objetivos guiada por monitorización hemodinámica no invasiva sobre las complicaciones perioperatorias en pacientes sometidos a cirugía de fractura de cadera, dentro de un modelo asistencial basado en un abordaje multidisciplinar.

Métodos: Estudio unicéntrico, no aleatorizado, de intervención con un grupo de control histórico y 12 meses de seguimiento. Se incluyeron pacientes intervenidos de fractura de cadera con edad igual o superior a 65 años. Los criterios de exclusión fueron pacientes con fracturas patológicas, fracturas relacionadas con el tráfico y refracturas. Los pacientes del grupo de control recibieron tratamiento estándar, en el que el manejo hemodinámico durante la cirugía fue realizado según el criterio del anestesiólogo responsable del paciente. Los pacientes del grupo de intervención recibieron un protocolo de terapia dirigida por objetivos basado en alcanzar un volumen sistólico óptimo, además de una presión arterial sistólica > 90 mmHg y un índice cardiaco individualizado. No se realizaron otros cambios entre los grupos en la trayectoria clínica durante el periodo de estudio. El resultado primario fue el número de pacientes que sufren episodios de inestabilidad hemodinámica intraoperatoria y el número de episodios de inestabilidad hemodinámica por paciente. Los resultados secundarios fueron arritmias intraoperatorias, complicaciones postoperatorias (cardiovasculares, respiratorias, infecciosas y renales), fluidos administrados, necesidad de vasopresores, transfusión perioperatoria, duración de la estancia hospitalaria, reingreso y supervivencia al año.

Resultados: Se incluyeron 551 pacientes entre ambos grupos, 272 pacientes en el grupo control y 279 en el grupo intervención. La inestabilidad hemodinámica intraoperatoria fue menor en el grupo intervención (37,5% frente a 28,0%; p=0,017). Los pacientes que recibieron terapia dirigida por objetivos, tuvieron menos complicaciones postoperatorias cardiovasculares (18,8% frente a 7,2%; p < 0,001), respiratorias (15,1% frente a 3,6%; p < 0,001) e infecciosas (21% frente a 3,9%; p < 0,001), pero no renales (12,1% frente a 33,7%; p < 0,001). Los pacientes del grupo intervención necesitaron menos vasopresores (25,5% frente a 39,7%; p<0,001) y recibieron menos líquidos [2.600 ml (RIC 1700 a 2700) frente a 850 ml (RIC 750 a 1050); p=0,001] que el grupo control. Menos pacientes requirieron transfusión en el grupo intervención (73,5% vs 44,4%; p<0,001). Para los

pacientes del grupo intervención, la mediana de la estancia hospitalaria fue más corta [11 días (RIC 8 a 16) vs 8 días; (RIC 6 a 11) $p < 0,001$] y la supervivencia a un año más alta [73,4% (95%IC: 67,7 a 78,3 vs 83,8% (95%IC: 78,8 a 87,7) $p<0,003$].

Conclusiones: El uso de un protocolo de terapia dirigida por objetivos, disminuye las complicaciones intraoperatorias y las complicaciones postoperatorias cardiovasculares, respiratorias e infecciosas, pero no las renales. Esta estrategia se asoció a una estancia hospitalaria más corta y a una mayor supervivencia un año tras la intervención quirúrgica.

Abstract:

Objective: To evaluate the effect of goal-directed therapy guided by non-invasive haemodynamic monitoring on perioperative complications in patients undergoing hip fracture surgery, within a care model based on a multidisciplinary approach.

Methods: Single-centre, non-randomised, interventional study with a historical control group and 12 months follow-up. Patients >64 years undergoing hip fracture surgery were included. The exclusion criteria were patients with pathological fractures, traffic-related fractures and refractures. Patients in the control group received standard treatment, haemodynamic management during surgery was performed at the discretion of the anaesthesiologist responsible for the patient. Patients in the intervention group received a goal-directed therapy protocol based on achieving an optimal stroke volume, in addition to a systolic blood pressure > 90 mmHg and an individualised cardiac index. No other changes were made between groups in the clinical trajectory during the study period. The primary outcome was the number of patients suffering intraoperative haemodynamic instability episodes and the number of haemodynamic instability episodes per patient. Secondary outcomes were intraoperative arrhythmias, postoperative complications (cardiovascular, respiratory, infectious and renal), fluids administered, need for vasopressors, perioperative transfusion, length of hospital stay, readmission and survival at one year.

Results: 551 patients were included in both groups, 272 patients in the control group and 279 in the intervention group. Intraoperative haemodynamic instability was lower in the intervention group (37.5% vs. 28.0%; p=0.017). Patients receiving goal-directed therapy had fewer postoperative cardiovascular (18.8% vs 7.2%; p<0.001), respiratory (15.1% vs 3.6%; p<0.001) and infectious (21% vs 3.9%; p<0.001), but not renal (12.1% vs 33.7%; p<0.001) postoperative complications. Patients in the intervention group required less vasopressors (25.5% vs. 39.7%; p<0.001) and received less fluids [2600 ml (IQR 1700 to 2700) vs. 850 ml (IQR 750 to 1050); p=0.001] than the control group. Fewer patients required transfusion in the intervention group (73.5% vs 44.4%; p<0.001). For patients in the intervention group, median hospital stay was shorter [11 days (IQR 8 to 16) vs 8 days; (IQR 6 to 11) p<0.001] and 1-year survival higher [73.4% (95%CI: 67.7 to 78.3 vs 83.8% (95%CI: 78.8 to 87.7) p<0.003].

Conclusions: The use of goal-directed therapy protocol decreases intraoperative complications and postoperative cardiovascular, respiratory and infectious complications, but not renal complications. This strategy was associated with shorter hospital stay and longer survival one year after surgery.

Índice de contenidos:

1-INTRODUCCIÓN 12

1.1. Incidencia, dependencia y mortalidad de la fractura de cadera 12

1.2. Características del paciente afecto de Fractura de Cadera y su situación al ingreso. 13

1.3. Complicaciones perioperatorias y causas de mortalidad. 14

1.4. Fundamentos fisiológicos del aporte y el consumo de oxígeno. Relación entre la macrohemodinámica y la microcirculación. 15

1.5. Bases de la optimización hemodinámica perioperatoria. Terapia dirigida por Objetivos. 16

1.6. Evidencia previa del efecto de la Terapia dirigida por Objetivos en los pacientes con Fractura de Cadera. 19

1.7. Nuevos parámetros hemodinámicos predictivos. Índice de Predicción de Hipotensión. 20

2-HIPÓTESIS 22

3-OBJETIVOS 23

4-ESTRUCTURA DE LA TESIS DOCTORAL 24

4-METODOLOGÍA Y RESULTADOS 27

4.1. Artículo 1. 27

4.2. Artículo 2 73

6-DISCUSIÓN. 101

6.1. Discusión de las características sociodemográficas y clínicas de los pacientes incluidos. 102

6.2. Discusión del tratamiento perioperatorio de los pacientes con fractura de cadera 103

6.3. Discusión de los resultados relativos a las complicaciones perioperatorias. 106

6.4. Discusión de los resultados de estancia hospitalaria y mortalidad. 109

6.5. Limitaciones y valoración global. 111

7-CONCLUSIONES 112

8-BIBLIOGRAFÍA. 113

9-ANEXOS 129

9.1. Anexo 1: Inscripción estudio "Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera" en ClinicalTrials.gov 129

9.2. Anexo 2: Hoja de información al paciente y consentimiento informado estudio "Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera" 135

9.3. Anexo 3: Aprobación Comité de Ética de la Investigación Clínica, estudio: "Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera" 139

9.4. Anexo 4: Lorente JV, Reguant F, Arnau A, Borderas M, Prieto JC, Torrallardona J, Carrasco L, Solano P, Pérez I, Farré C, Jiménez I, Ripollés-Melchor J, Monge MI, Bosch J. Effect of goal-directed haemodynamic therapy guided by non-invasive monitoring on perioperative complications in elderly hip fracture patients within an enhanced recovery pathway. Perioper Med (Lond). 2022 Aug 10;11(1):46. doi: 10.1186/s13741-022-00277-w. PMID: 35945605; PMCID: PMC9364538. 142

9.5. Anexo 5: Inscripción estudio "Manejo hemodinámico intraoperatorio mediante el índice de predicción de hipotensión (HPI) y su relación con la microcirculación. Detección del estrés renal agudo." en ClinicalTrials.gov 156

9.6. Anexo 6: Hoja de información al paciente y consentimiento informado estudio "Manejo hemodinámico intraoperatorio mediante el índice de predicción de hipotensión (HPI) y su relación con la microcirculación. Detección del estrés renal agudo." 163

9.7. Anexo 7: Aprobación Comité de Ética de la Investigación Clínica, estudio: "Manejo hemodinámico intraoperatorio mediante el índice de predicción de hipotensión (HPI) y su relación con la microcirculación. Detección del estrés renal agudo." 171

9.8. Anexo 8: Lorente JV, Jimenez I, Ripollés-Melchor J, Becerra A, Wesselink W, Reguant F, Mojarro I, Fuentes MLA, Abad-Motos A, Agudelo E, Herrero-Machancoses F, Callejo P, Bosch J, Monge MI. Intraoperative haemodynamic optimisation using the Hypotension Prediction Index and its impact on tissular perfusion: a protocol for a randomised controlled trial. The Predict H Trial. BMJ Open. 2022 Jun 2;12(6):e051728. doi: 10.1136/bmjopen-2021-051728. PMID: 35654467; PMCID: PMC9163532. 173

9.9. Anexo 9: Research Grant. The Predict H Trial. ClinicalTrials.gov: NCT04301102 181

1-INTRODUCCIÓN

La fractura no traumática de tercio proximal de fémur, también conocida usualmente como fractura de cadera, es una patología que, en un porcentaje muy elevado de casos es sufrida por pacientes con una edad mayor a 64 años, con un importante grado de dependencia y comorbilidad (Veronese & Maggi, 2018).

El mecanismo fundamental por el que se produce la fractura de cadera en los pacientes ancianos es la caída desde su propia altura (Bhandari & Swiontkowski, 2017). El riesgo de caídas aumenta con la edad y posee diversas causas, entre las que podemos destacar los cambios derivados del envejecimiento con afección a nivel neuromuscular, visual y auditivo, las patologías crónicas y los fármacos con elevada tasa de prescripción en pacientes añosos, como son los ansiolíticos y antidepresivos (Pfeiffer et al., 2020). A estos factores de riesgo intrínsecos, debemos añadir los extrínsecos o derivados del entorno del paciente (Jiménez-Sánchez et al., 2011).

1.1. Incidencia, dependencia y mortalidad de la fractura de cadera.

Tal y conforme ha sido puesto en valor en multitud de artículos científicos, la fractura de cadera constituye una patología de elevada importancia socio-sanitaria. Por un lado, por la elevada presión que la atención a esta patología genera en los Servicios Sanitarios, pero fundamentalmente, por los problemas generados en pacientes, familias y cuidadores (Veronese & Maggi, 2018).

El envejecimiento generalizado de la población y los estilos de vida son los motivos más ampliamente citados para explicar el incremento incesante de las fracturas de cadera (ref). Globalmente, durante el año 2000, se estima que se produjeron 1.6 millones de fracturas de cadera. En el año 2050, se prevé que el número de fracturas de cadera a nivel mundial pueda llegar a los 4.5 millones (Bhandari & Swiontkowski, 2017).

En España, la incidencia de fractura de cadera en pacientes mayores de 65 años varía según el territorio analizado y se sitúa entre 301 y 897/100.000 habitantes (Etxebarria-Foronda, 2015). La mortalidad intrahospitalaria en los pacientes afectos de fractura de cadera varía entre un 4% y un 8%, a los 30 días entre un 8% y un 10.5% y al año, nos

encontramos con porcentajes que varían entre un 17 y un 30%. A los 7 años, la mortalidad acumulada es del 73.6% de (Guzon-Illescas et al., 2019).

La fractura de cadera tiene además un importante impacto en el estado funcional de los pacientes ancianos (Alexiou et al., 2018). Al año de la fractura de cadera, el 20% de los pacientes perdieron la capacidad para andar, entre un 30 y un 50% presentaron una dependencia parcial y un 30% de los casos se encontraban en una situación de dependencia total (for the Fragility Fracture Network (FFN) Rehabilitation Research Special Interest Group et al., 2016). Pese a los avances técnicos y organizativos, la mortalidad es todavía elevada, la recuperación funcional relativamente escasa y los costes elevados.

El manejo basado en la evidencia de las fracturas de cadera incluye tanto diferentes opciones quirúrgicas como diferentes estrategias de cuidados perioperatorios. Las intervenciones unimodales durante el proceso quirúrgico no han mostrado un beneficio en los últimos años. En cambio, la aplicación de trayectorias clínicas basadas en la implementación de medidas de recuperación intensificada por parte de un equipo multidisciplinar especializado, se considera la aproximación con mayor evidencia en la búsqueda de mejorar los resultados quirúrgicos (Reguant et al., 2019).

1.2. Características del paciente afecto de Fractura de Cadera y su situación al ingreso.

La edad media de los pacientes con fractura de cadera en el año 2020 fue de 87 años según el Registro Nacional de Fracturas de Cadera (Registro Nacional de Fracturas de Cadera, 2021). En datos derivados de cohortes analizadas por nuestro grupo, observamos que un 43,3% de los pacientes tenían entre 75 y 85 años y un 49% fueron pacientes con 85 años o más (Reguant et al., 2019).

El envejecimiento conlleva una serie de alteraciones fisiológicas en todos los órganos y sistemas con importantes implicaciones clínicas durante todo el perioperatorio. La perdida importante de masa muscular y la aparición de un estado global pre-inflamatorio (Soysal et al., 2016) entre otros factores, tienen una gran repercusión en el sistema cardiovascular y en el endotelio vascular (Ungvari et al., 2018). La carga genética y los estilos de vida explican una parte importante de la elevada prevalencia de un envejecimiento

patológico. Los pacientes mayores de 70 años poseen una elevada prevalencia de pluri-patología y fragilidad (Arnau et al., 2016).

La evolución perioperatoria en pacientes frágiles es habitualmente tórpida y los resultados quirúrgicos obtenidos frecuentemente peores que los pacientes sin fragilidad (Sioutas & Tsoulfas, 2020). La categorización de la fractura de cadera como patología urgente es ampliamente aceptada, por lo que la posibilidad de la optimización preoperatoria de los pacientes es habitualmente muy limitada (Borges et al., 2020). En una revisión sistemática publicada en el año 2012, la prevalencia de fragilidad en personas de más de 65 años fue del 10.7% (Arnau et al., 2016). En nuestras cohortes previamente analizadas (Reguant et al., 2019), un 32% de los pacientes presentaron un índice de Charlson de 3 ó más y a un 60% de los pacientes con fractura de cadera se les otorgó una categoría III ó IV según la clasificación de la Asociación Americana de Anestesiología (ASA). Estos datos coinciden con la literatura científica previamente publicada (Azagra et al., 2014).

Casi un 90% de los pacientes presenta dolor de elevada intensidad tras la factura, con una puntuación en la escala visual analógica (EVA) mayor o igual a 8. A pesar de este elevado porcentaje se intuye un probable infradiagnóstico debido a la elevada prevalencia de alteraciones cognitivas que puede llegar a ser del 30% (Feldt & Oh, 2000). Más de un 40% de los pacientes presentan anemia en el momento del ingreso por fractura de cadera (Reguant et al., 2019), en la practica totalidad de los casos de etiología mixta y unida a hipovolemia, reflejando habitualmente, tanto la hemorragia importante tras la fractura, como la existencia de déficits y/o patologías previas (Sim et al., 2018). La aparición de dolor y sangrado secundarios a la fractura de cadera entre otras causas, provocan una situación inflamatoria aguda que se exacerba, además, con la necesidad en las siguientes 24/72 horas de una intervención quirúrgica para su tratamiento definitivo, no pudiendo por tanto ser revertida esta situación de forma completa, pese a los intentos de optimización preoperatoria (McLaughlin et al., 2006).

1.3. Complicaciones perioperatorias y causas de mortalidad.

Tal y conforme publicaron Foss y colaboradores, entre un 25 y un 50% de la mortalidad en los pacientes con fractura de cadera es probablemente inevitable (Foss & Kehlet,

2005). Se debe en gran cantidad de ocasiones a la presencia de una elevada o potencialmente grave comorbilidad previa. El porcentaje restante se asocia a la aparición de complicaciones postoperatorias, potencialmente evitables (Blanco et al., 2021).

La incidencia de complicaciones postoperatorias mayores en la fractura de cadera es elevada, existiendo una gran variabilidad entre los diferentes estudios, según los criterios usados para clasificarlas. La aparición de complicaciones postoperatorias es la principal causa de mortalidad, siendo las más frecuentes las de tipo cardiovascular, respiratorias, renales, neurológicas e infecciosas (Carpintero, 2014).

Diferentes estudios establecen un nexo de unión claro entre las complicaciones postoperatorias y las producidas durante el periodo intraoperatorio (Kinaci et al., 2016). La complicación intraoperatoria más prevalente según diferentes series analizadas es la aparición de hipotensión intraoperatoria (HIO) (Wesselink et al., 2018). Múltiples estudios han demostrado la asociación entre HIO y morbilidad postoperatoria, en términos de daño miocárdico (Ruetzler et al., 2020), disfunción renal aguda (Salmasi et al., 2017) e incluso, la aparición de ictus isquémico (Yu et al., 2020).

1.4. Fundamentos fisiológicos del aporte y el consumo de oxígeno. Relación entre la macrohemodinámica y la microcirculación.

Para el correcto funcionamiento de órganos y tejidos, es necesario que dispongan de un aporte de oxígeno acorde a sus necesidades metabólicas, que son cambiantes (Leach, 2002). Si el aporte de oxígeno es insuficiente para cubrir la demanda metabólica pueden aparecer disfunciones orgánicas de gravedad variable en función de la intensidad y la duración de la hipoxia tisular (Hardy, 1963).

La cantidad de oxígeno disponible a nivel celular es determinada por factores centrales y periféricos. Los factores centrales están relacionados con aspectos funcionales cardiorespiratorios (gasto cardiaco y presión arterial de oxígeno) y la concentración de hemoglobina. El gasto cardiaco representa el determinante central más importante del aporte de oxígeno. De hecho, una caída en la concentración de la hemoglobina o en su saturación puede ser compensada por un incremento en el gasto cardiaco, no siendo posible una respuesta compensadora opuesta. Por esta razón, el gasto cardiaco debe adaptarse a las necesidades metabólicas del organismo en condiciones fisiológicas (Vincent, 2008).

Los factores periféricos están relacionados con la redistribución del gasto cardiaco a los diferentes órganos y a la regulación de la microcirculación, cuya estructura y función juegan un papel fundamental en el mantenimiento de la perfusión tisular. El flujo capilar está regulado por el tono arteriolar en cada territorio que es modulado para garantizar una presión de entrada que se modifica en función de la demanda metabólica local del tejido (Guven et al., 2020). De tal manera que, el ajuste del tono arteriolar permite la autorregulación a nivel tisular y garantiza que siempre exista una presión de perfusión tisular adecuada, independientemente de la presión sistémica. Sin embargo, este mecanismo puede fracasar cuando la presión sistémica es superior o inferior al umbral de autorregulación, siendo la presión sistémica en estos casos la responsable directa de la presión de entrada y afectando a la perfusión tisular (Magder, 2018). Estos umbrales de autoregulación son dinámicos y presentan variabilidad intra e intersujeto, e igualmente puede variar dependiendo del tejido específico (Ripollés-Melchor et al., 2020).

1.5. Bases de la optimización hemodinámica perioperatoria. Terapia dirigida por Objetivos.

La opción terapeútica más usada para lograr un aumento del gasto cardiaco es la infusión de fluidos (Hoorn, 2017). La estrategia de fluidoterapia que seleccionemos para nuestros pacientes durante el periodo perioperatorio va a condicionar sus resultados tras la intervención quirúrgica (McLain et al., 2021). El aumento de la morbilidad perioperatoria generada por la cantidad de fluido administrado ha sido asociado tanto a un exceso de fluido como a la infusión de un volúmen insuficiente, generando una curva característica en forma de U (Bellamy, 2006). Figura 1

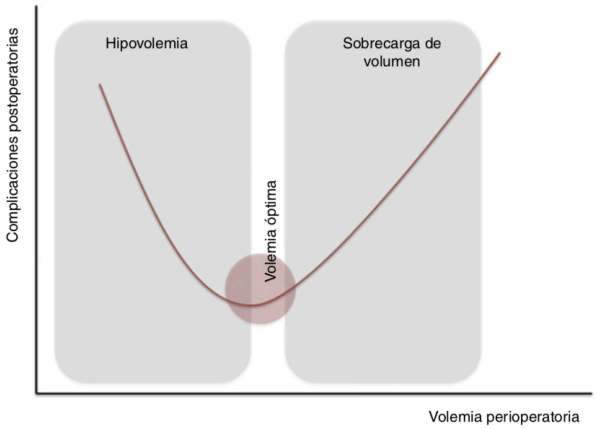


Figura 1: Asociación entre administración perioperatoria de fluidos y complicaciones postoperatorias (ref)

Los episodios de hipovolemia intraoperatoria pueden conllevar la aparición de hipoperfusión tisular e isquemia que desemboquen en disfunción orgánica (Meng, 2021). Por el contrario, un importante número de estudios han demostrado la asociación entre la hipervolemia perioperatoria con la aparición de edema a todos los niveles, fundamentalmente tisular y orgánico (Labgaa et al., 2020). Ambas condiciones por tanto, hipovolemia e hipervolemia, se han asociado en múltiples estudios a resultados adversos en términos de aparición de complicaciones postoperatorias e incluso, en un aumento de la mortalidad (Bellamy, 2006).

En sus estudios publicados entre los años 1980 y 1990, Shoemaker describió un nuevo método de optimización de la infusión de fluidos y del estado hemodinámico en pacientes de alto riesgo quirúrgico de cara a mejorar sus resultados postoperatorios (Lumb, 2016). Uno de sus objetivos prioritarios fue evitar la aparición de hipoperfusión intraoperatoria mediante el aumento del aporte de oxígeno hasta niveles incluso suprafisiológicos, mediante la utilización del catéter de arteria pulmonar (CAP). Estas publicaciones fueron el inicio de la optimización hemodinámica dentro de la cual, se acuñó posteriormente el término terapia dirigida por objetivos (TDO). Podemos definir la TDO como una serie de intervenciones focalizadas en la consecución de objetivos hemodinámicos predefinidos mediante la utilización de diferentes terapias, particularmente la infusión de fluidos, vasopresores y ionotrópicos (Chong et al., 2018). Actualmente, la optimización se enfoca como una aproximación individualizada acorde a la capacidad cardiaca del paciente, planteando objetivos adaptados a la edad y/o situación funcional previa del paciente (Kampmeier & Ertmer, 2020).

Los objetivos planteados en los algoritmos de TDO recientes son fundamentalmente dos, por un lado, un objetivo de flujo y por otro, un objetivo de presión de perfusión (Waldron et al., 2014).

Habitualmente la fluidoterapia constituye el primer pilar terapéutico de un protocolo de TDO. El reto para el clínico es el mantenimiento de la volemia de nuestros pacientes en el rango adecuado a cada momento del periodo perioperatorio.

Los parámetros de monitorización obtenidos de forma rutinaria en el paciente quirúrgico, tales como frecuencia cardiaca, presión arterial y saturación de oxígeno, han demostrado no ser medidas representativas del estado cardiovascular del paciente (Lugo et al., 1993).

Los sistemas de monitorización hemodinámica avanzada han sufrido importantes avances en las últimas décadas, fundamentalmente son menos invasivos. Sin embargo, nos ofrecen parámetros de forma continua que nos permiten la administración de fluido para lograr la obtención del objetivo de flujo marcado, generalmente volumen sistólico (VS) (Scheeren & Ramsay, 2019).

Actualmente, la práctica totalidad de algoritmos de TDO incluyen la infusión de fármacos vasoactivos e ionotropos. La utilización de fármacos vasoactivos es el segundo pilar de los algoritmos de TDO y se basa, tanto en la posibilidad de reclutar volumen no estresado, que participe del retorno venoso, como en la consecución de una adecuada presión de perfusión suficiente (Jentzer et al., 2015).

El tercer pilar terapéutico de un protocolo de TDO es habitualmente la adición de un fármaco ionotrópico positivo (Edwards et al., 2019). En caso de presencia de una contractilidad disminuida, la posibilidad de lograr un aumento suficiente de gasto cardiaco puede requerir la utilización de estos fármacos (Jentzer et al., 2015).

La aplicación de un protocolo de TDO ha demostrado disminuir tanto la morbilidad como la mortalidad en el paciente de alto riesgo quirúrgico (Giglio et al., 2016).

1.6. Evidencia previa del efecto de la Terapia dirigida por Objetivos en los pacientes con Fractura de Cadera.

Hasta el año 2019, la evidencia de la que disponíamos acerca del posible beneficio de la aplicación de un protocolo de TDO en los pacientes con fractura de cadera era limitada, En la Tabla 1, se exponen los principales estudios publicados hasta esa fecha.

ID estudio	Tipo estudio	Tamaño muestral	Monitorización hemodinámica usada	Resultado primario	Resultados
Bartha y cols. 2012	Ensayo clínico	GC: 75; GI: 74	Dilución de Litio	Riesgo relativo de complicaciones postoperatorias	Riesgo absoluto: GC 0.45; GI: 0.36. Riesgo relativo: 0.79 (0.54-1-16)
Moppett y cols. 2015	Ensayo clínico	GC: 63; GI: 51	Dilución de Litio	Estancia hospitalaria	GC: 12.2 (11.1 – 13.5) días ; GI: 13.1(11.9 – 14.5) días. p=0.31
Lewis y cols. 2016	Revisión Sistemática y Metanálisis Cochrane	5 ensayos clínicos, 403 pacientes	Análisis contorno de onda de pulso y doppler esofágico	Seguridad y efectividad de optimización hemodinámica	Ausencia de evidencia de beneficio de estrategias de optimización hemodinámica.
Davies y cols. 2019	Ensayo clínico	CG: 120; IG: 121	ClearSight (Edwards LifeSciences)	Porcentaje de pacientes con una o más complicaciones postoperatorias.	GC: 51% ; GI: 46%; O: 0.82 (95% IC 0.49-1.36, p=0.439

Tabla 1: Resúmen características principales estudios aplicando protocolo de TDO en pacientes con fractura de cadera.
GC: Grupo control; GI: Grupo intervención; IC: Intervalo de Confianza;

El primer estudio destacado acerca del potencial beneficio de la aplicación de un protocolo de TDO en pacientes con fractura de cadera fue el realizado por Bartha y colaboradores (Bartha et al., 2013). En este ensayo clínico, se incluyeron de forma aleatoria 149 pacientes con fractura de cadera, aleatorizados a un grupo control que recibieron durante el intraoperatorio un protocolo de fluidoterapia estándar o a un grupo intervención en el que recibieron un protocolo de TDO. En el grupo intervención se observó una reducción de las complicaciones postoperatorias durante la estancia hospitalaria no estadísticamente significativa, pero sí clínicamente relevante según los autores. Tampoco se observaron diferencias significativas en las complicaciones postoperatorias tardías, reingresos a los 4 ó 12 meses, ni en mortalidad. En un análisis posterior sobre la misma cohorte, los autores observaron que la implementación de un protocolo de TDO fue coste-efectiva en los pacientes de fractura de cadera, según criterio de años de vida ganados ajustados por calidad (QALYs) (Bartha et al., 2019).

Posteriormente, se publica en el año 2015 un nuevo ensayo clínico de Moppett y colaboradores (Moppett et al., 2015). Se incluyeron 114 pacientes mayores de 60 años, 63 pacientes en el grupo de tratamiento intraoperatorio estándar y 51 pacientes en el grupo que recibió un protocolo de TDO guiado también por un sistema de monitorización hemodinámica mínimamente invasiva basado en la dilución de litio. No encontraron diferencias

significativas en la estancia hospitalaria ni en las complicaciones postoperatorias, funcionalidad o mortalidad.

En el año 2016, fruto en parte de la publicación de los dos estudios comentados, *The Cochrane Collaboration* publicó una nueva revisión sistemática y metaanálisis, que actualizó por segunda vez la difundida inicialmente en el año 2004 (Lewis et al., 2016). Los autores concluyeron que no existía evidencia suficiente para rechazar o afirmar que la optimización hemodinámica reducía las complicaciones postoperatorias o la mortalidad si se utilizaba una monitorización hemodinámica avanzada o protocolos basados en medidas de monitorización rutinarias.

En el año 2019, Davies y colaboradores publicaron los resultados obtenidos en un ensayo clínico aleatorizado en el que incluyeron 240 pacientes (Davies et al., 2019). 120 pacientes del grupo control fueron tratados por el anestesiólogo durante la intervención sin la utilización de un protocolo establecido. En los 120 pacientes incluidos en el grupo intervención (TDO), se aplicó un protocolo intraoperatorio de TDO. No se obtuvo una reducción estadísticamente significativa de la aparición de complicaciones postoperatorias en el grupo intervención. No se lograron diferencias estadísticamente significativas entre ambos grupos en los resultados secundarios, tales como estancia hospitalaria y mortalidad.

Aunque los resultados de los estudios publicados no muestran mejoras estadísticamente significativas, existen indicios suficientes para observar mejoras clínicas y para establecer la conveniencia de aportar más datos para el análisis acerca del potencial beneficio de la aplicación de un protocolo de TDO en los pacientes con fractura de cadera.

1.7. Nuevos parámetros hemodinámicos predictivos. Índice de Predicción de Hipotensión.

El reconocimiento precoz de la progresión hacia un episodio hipotensivo en un paciente podría conducir a una atenuación eficaz de la hipotensión. El algoritmo del Índice de Predicción de Hipotensión (HPI), se basó en un algoritmo Machine Learning enfocado a la predicción de la aparición de hipotensión (definida como una PAM <65 mmHg) durante al menos 1 minuto. Para la confección del algoritmo, se obtuvieron características

de la onda de la presión arterial, lo que dio como resultado un modelo de regresión que pudo predecir un episodio hipotensivo, independientemente de la presión arterial, con hasta 15 minutos de antelación, con una sensibilidad y especificidad del 88% [IC del 95%: 85, 90%] y del 87% [85, 90%] (Hatib et al., 2018).

El algoritmo HPI se sometió a validación interna en 350 casos seleccionados aleatoriamente del conjunto de datos utilizado inicialmente para generar el algoritmo. Posteriormente, se validó externamente en 204 casos de pacientes de cuidados intensivos, lo que dio como resultado un algoritmo de alta precisión con un área bajo la curva característica (AUC) que oscilaba entre 0,95, 0,95 y 0,97 para 15, 10 y 5 minutos antes de un evento hipotensivo, respectivamente (Hatib et al., 2018).

La plataforma de monitorización hemodinámica proporciona cada 20 segundos un valor de HPI que oscila entre 0 y 100 y representa la probabilidad de que un paciente desarrolle un episodio hipotensivo. Su valor potencial en la práctica diaria es proporcionar información en tiempo real al clínico, permitiendo un tratamiento proactivo de los próximos episodios hipotensivos (Li et al., 2022).

2-HIPÓTESIS

La hipótesis de trabajo de este estudio fue que la optimización hemodinámica guiada por monitorización avanzada permitiría una disminución de las complicaciones cardiovasculares intraoperatorias en los pacientes intervenidos de fractura de cadera con edad igual o superior a 65 años, dentro de un modelo asistencial basado en un abordaje multidisciplinar.

3-OBJETIVOS

→ Objetivos primarios:

-Evaluar la eficacia de la optimización hemodinámica guiada por monitorización avanzada en la reducción del número de episodios de inestabilidad hemodinámica por paciente y/o en el numero de pacientes que sufren episodios de inestabilidad hemodinámica durante la intervención quirúrgica de fractura de fémur.

→ Objetivos secundarios:

-Evaluar la eficacia de la optimización hemodinámica guiada por monitorización avanzada en la reducción de la frecuencia de arritmias intraoperatorias en los pacientes intervenidos de fractura de cadera con edad igual o superior a 65 años.

-Evaluar la eficacia de la optimización hemodinámica guiada por monitorización avanzada en la reducción de la frecuencia de complicaciones postoperatorias (cardiocirculatorias, respiratorias, renales, infecciosas) en pacientes intervenidos de fractura de cadera con edad igual o superior a 65 años.

-Evaluar la eficacia de la optimización hemodinámica guiada por monitorización avanzada en la reducción de la estancia hospitalaria en pacientes intervenidos de fractura de cadera con edad igual o superior a 65 años

-Evaluar la eficacia de la optimización hemodinámica guiada por monitorización avanzada en la reducción de la mortalidad al año en pacientes intervenidos de fractura de cadera con edad igual o superior a 65 años

4-ESTRUCTURA DE LA TESIS DOCTORAL

En 2015 la Organización Mundial de la Salud (OMS) definió el concepto de capacidad intrínseca y rompió la dicotomía clásica de salud/enfermedad (Beard et al., 2016). El análisis y el concepto parten de la base del progresivo envejecimiento de la población, la cronicidad y las alteraciones de la salud durante la vida (Foster et al., 2018). La curación o el "restablecimiento de la salud" entendida como ausencia de enfermedad es cada vez más difícil o imposible. El objetivo de la medicina, aparte de curar cuando sea posible, debe ser también el de procurar que, en cada situación, las personas tengan el máximo de autonomía y conserven al máximo posible las facultades físicas, mentales y relacionales (Beard et al., 2016).

La tesis que se presenta se inscribe en este marco conceptual, entendiendo que una de las finalidades de la anestesia debe ser evitar al máximo posible las complicaciones intraoperatorias que pueden afectar a la supervivencia y/o a la funcionalidad de los pacientes.

El envejecimiento fisiológico comporta un estado general proinflamatorio, una reserva fisiológica baja y una recuperación lenta. La población sedentaria o frágil tiene riesgos sobreañadidos y una evolución más compleja (Yaffe et al., 2014).

Las intervenciones quirúrgicas mayores son una agresión que comporta dolor, pérdida de sangre, consumo de fármacos, desorientación y una inmovilización más o menos acentuada. Cuando la intervención quirúrgica es consecuencia de una situación urgente, la situación general se agrava (Turégano, 2022). En este contexto, el estudio de sistemas para prevenir o disminuir riesgos y adaptar las acciones a cada paciente es un campo de interés creciente. El desarrollo e implementación de los protocolos de TDO ha supuesto un cambio de paradigma en el manejo hemodinámico intraoperatorio, especialmente en los pacientes de alto riesgo quirúrgico (Jessen et al., 2022).

En el diseño de nuestro primer estudio se partía de la base de que si el paciente comenzaba la intervención con una volemia adecuada y ésta se mantenía durante la intervención las complicaciones cardiocirculatorias disminuirían. Estos supuestos implicaban el mantenimiento de la volemia y presión de perfusión adecuadas y de un índice cardiaco individualizado durante la intervención quirúrgica.

Esta aproximación aportaba dos novedades. La introducción del índice cardíaco como parámetro personalizable y asequible y el control del volumen sanguíneo como recurso terapéutico. Actualmente es posible la consecución de este objetivo mediante sistemas de

monitorización hemodinámica avanzada no invasivos tal y como se describe en la metodología del artículo 1. Durante la intervención se realizó una determinación contínua de la presión arterial y se utilizaban fármacos habituales incluidos dentro de nuestro protocolo de TDO.

Los resultados demostraron que las complicaciones hemodinámicas intraoperatorias y las postoperatorias disminuían, pero todavía existían entre uno y dos episodios de hipotensión en cada intervención.

El control y mantenimiento del flujo sanguíneo probablemente nos ayudaba a mantener una correcta perfusión intraoperatoria, pero la etiología de la hipotensión arterial intraoperatoria es variada y no se produce únicamente por una volemia inadecuada. Los protocolos de TDO no han sido diseñados específicamente para la reducción de la hipotensión arterial intraoperatoria ya que, pese a la incorporación de un objetivo de presión de perfusión, la estrategia aplicada en su manejo continuaba siendo reactiva. Actuábamos cuando ya se había producido la hipotensión y, existía la posibilidad de aparición de situaciones de baja perfusión tisular derivadas y, por tanto, de peores resultados postoperatorios.

Continuando con el mismo objetivo de la tesis, la disminución de las complicaciones hemodinámicas perioperatorias, se diseñó el segundo estudio, que pretendió la incorporación de un parámetro predictivo para la realización de un manejo intraoperatorio enfocado a la prevención de la hipotensión arterial. Es éste un campo de investigación activo (110 estudios y 3 revisiones de febrero 2022 a febrero 2023) y, los resultados obtenidos inicialmente derivados de su aplicación, han sido muy prometedores. Sin embargo, todos los estudios que han evaluado su utilidad son unicéntricos, por ello, planteamos la realización de un ensayo clínico multicéntrico, cuyo objetivo es evaluar la eficacia de la implementación de la optimización hemodinámica intraoperatoria guiada por monitorización avanzada que incluya el índice de predicción de hipotensión (HPI) en la reducción tanto de la duración como la severidad de la hipotensión intraoperatoria en pacientes que se someten a una cirugía abdominal mayor electiva con edad igual o superior a 65 años y el establecimiento de una posible asociación entre su implementación y una mejor perfusión durante la intervención quirúrgica, representada por la saturación tisular de oxígeno (S_tO_2) y el riesgo de insuficiencia renal aguda postoperatoria (AKIRisk). Este aspecto no ha sido evaluado hasta el momento en ningún estudio publicado.

El protocolo de este segundo estudio ha sido publicado (artículo 2 de la tesis). El manuscrito con los resultados del mismo ha sido enviado a una revista JCR para que se considere su publicación, encontrándose bajo revisión por pares en el momento de finalización de esta tesis doctoral.

4-METODOLOGÍA Y RESULTADOS

4.1. Artículo 1.

EFFECT OF GOAL-DIRECTED HAEMODYNAMIC THERAPY GUIDED BY NON-INVASIVE MONITORING ON PERIOPERATIVE COMPLICATIONS IN ELDERLY HIP FRACTURE PATIENTS WITHIN AN ENHANCED RECOVERY PATHWAY

Juan V. Lorente, Francesca Reguant, Anna Arnau, Marcelo Borderas, Juan C. Prieto, Jordi Torrallardona, Laura Carrasco, Patricia Solano, Isabel Pérez, Carla Farré, Ignacio Jiménez, Javier Ripollés-Melchor, Manuel I. Monge and Joan Bosch

Perioperative Medicine 11, 46 (2022).
Factor de Impacto 2022: 3.516
Categoría: Surgery, Segundo Cuartil

Effect of goal-directed haemodynamic therapy guided by non-invasive monitoring on perioperative complications in elderly hip fracture patients within an enhanced recovery pathway.

Juan V Lorente [1, 2, 3, *], Francesca Reguant [2, 4], Anna Arnau [5, 6, 2], Marcelo Borderas [4], Juan C Prieto [4], Jordi Torrallardona [4], Laura Carrasco [4], Patricia Solano [4], Isabel Pérez [4], Carla Farré [4], Ignacio Jiménez [7, 3], Javier Ripollés-Melchor [8, 3], Manuel I Monge [9, 3], Joan Bosch[2]

[1] Anaesthesia and Critical Care Department, Juan Ramón Jiménez Hospital. Huelva, Spain.

[2] School of Medicine and Health Sciences, International University of Catalonia (UIC), Barcelona, Spain

[3] Fluid Therapy and Hemodynamic Group of the Hemostasis, Transfusion Medicine and Fluid Therapy Section. Spanish Society of Anesthesia and Critical Care (SEDAR)

[4] Department of Anaesthesiology, Althaia Xarxa Assistencial Universitària, Manresa, Spain

[5] Central Catalonia Chronicity Research Group (C3RG). Research and Innovation Unit. Althaia Xarxa Assistencial Universitària. Manresa, Spain.

[6] Centre d'Estudis Sanitaris i Socials, (CESS), Universitat de Vic–Universitat Central de Catalunya (UVIC-UCC), Vic, Spain

[7] Clinical Management Anesthesiology Unit, Resuscitation and Pain Therapy, Virgen del Rocio Hospital, Sevilla, Spain

[8] Anesthesia and Critical Care Department, Infanta Leonor Hospital, Madrid, Spain

[9] Intensive Care Unit, Hospital Universitario SAS, Jerez de la Frontera, Spain

[*] *Corresponding author*: Anaesthesia and Critical Care Department, Juan Ramón Jiménez Hospital, Ronda Norte s/n, 21590 Huelva. Spain.

E-mail address: juanvictor.lorente@gmail.com

ABSTRACT

Background: Goal-Directed Hemodynamic Therapy (GDHT) has been shown to reduce morbidity and mortality in high-risk surgical patients. However, there is little evidence of its efficacy in patients undergoing hip fracture surgery. This study aims to evaluate the effect of GDHT guided by non-invasive haemodynamic monitoring on perioperative complications in patients undergoing hip fracture surgery.

Methods: Patients > 64 years undergoing hip fracture surgery within an Enhanced Recovery Pathway (ERP) were enrolled in this single-center, non-randomized, intervention study with a historical control group and 12-months follow-up. Exclusion criteria were patients with pathological fractures, traffic-related fractures and refractures. Control group (CG) patients received standard care treatment. Intervention group (IG) patients received a GDHT protocol based on achieving an optimal stroke volume, in addition to a systolic blood pressure > 90 mmHg and an individualised cardiac index. No changes were made between groups in the ERP during the study period. Primary outcome was percentage of patients who developed intraoperative haemodynamic instability. Secondary outcomes were intraoperative arrhythmias, postoperative complications (cardiovascular, respiratory, infectious and renal complications), administered fluids, vasopressor requirements, perioperative transfusion, length of hospital stay, readmission and one-year survival.

Results: 551 patients (CG=272; IG=279). Intraoperative haemodynamic instability was lower in the IG (37.5% vs 28.0%; p=0.017). GDHT patients had fewer postoperative cardiovascular (18.8% vs 7.2%; p < 0.001), respiratory (15.1% vs 3.6%; p<0.001) and infectious complications (21% vs 3.9%; p<0.001) but not renal (12.1% vs 33.7%; p<0.001).

IG patients had less vasopressors requirements (25.5% vs 39.7%; p<0.001) and received less fluids [2.600 ml (IQR 1700 to 2700) vs 850 ml (IQR 750 to 1050); p=0.001] than control group. Fewer patients required transfusion in GDHT group (73.5% vs 44.4%; p<0.001). For IG patients, median length of hospital stay was shorter [11 days (IQR 8 to 16) vs 8 days; (IQR 6 to 11) p < 0.001] and one-year survival higher [73.4% (95%CI: 67.7 to 78.3 vs 83.8% (95%CI: 78.8 to 87.7) p<0.003].

Conclusions: The use of GDHT decreases intraoperative complications and postoperative cardiovascular, respiratory and infectious but not postoperative renal complications. This strategy was associated with a shorter hospital stay and increased one-year survival.

Trial registration: Clinicaltrials.gov: NCT02479321

Keywords: enhanced recovery after surgery; enhanced recovery pathway; fluid therapy; goal-directed haemodynamic therapy; hip fracture; intraoperative complications; mortality; postoperative complications.

1-Background

Hip fracture represents an increasingly serious public health problem with a significant impact on life expectancy and economic burden (Veronese and Maggi 2018). Patients with hip fractures are at high risk of perioperative complications (Reguant et al. 2019) due to a limited cardiorespiratory reserve when facing the fracture and surgery-associated stress (Cowan et al. 2017). Moreover, postoperative complications related to hip fracture are a known independent risk factor for mortality (Griffiths et al. 2021).

Enhanced recovery pathways (ERP) comprise perioperative evidence-based care interventions designed to improve outcomes after surgery (Ljungqvist et al. 2017). Perioperative hemodynamic optimization is a key element of the ERP (Miller et al. 2015). The Goal-Directed Hemodynamic Therapy (GDHT) has been shown to reduce morbidity and mortality in high-risk surgical patients (Giglio et al. 2016). Nevertheless, in daily clinical practice, patients with hip fracture are usually intraoperatively monitored with routine haemodynamic parameters such as blood pressure and heart rate (Reguant et al. 2019). However, these standard physiological variables result insufficient for assessing an adequate balance between oxygen delivery (DO_2) and consumption (VO_2) (Lugo G, Arizpe D, Dominguez G 1993). This DO_2/VO_2 imbalance may eventually lead to intraoperative tissue hypoperfusion, facilitating the appearance of postoperative complications (Merry and Mitchell 2018).

Currently, there are monitoring platforms that provide advanced haemodynamic parameters to guide GDHT in a non-invasive way to avoid the complications of invasive techniques (Teboul et al. 2016).

The present study aimed to evaluate the effect of GDHT guided by non-invasive haemodynamic monitoring on perioperative complications in patients undergoing surgical hip fracture repair within an ERP.

2-Methods

This manuscript was written according to CONSORT statement. The study was approved by an independent Ethics Committee (Fundació Unio Catalana Hospitals) on 27 January 2015 (CEIC 15/03). All patients signed an informed consent to participate. The study was conducted according to the Declaration of Helsinki and all local legal and regulatory requirements. Trial registration: NCT02479321 (24/06/2015)

2.1. Study design

Single-centre, non-randomised, hospital-based intervention study with a historical control group (CG) and 12-month follow-up after hospital discharge.

2.2. Inclusion / Exclusion criteria

Patients over 64 years with hip fracture within an ERP who underwent surgical treatment were included.

Exclusion criteria were: patients with pathological fractures, traffic-related fractures, refractures, patients with known contraindication or limitations to advanced hemodynamic monitoring with ClearSight® system and EV1000 platform (Edwards Lifesciences, Irvine, USA) (Saugel et al. 2015): patients with Raynaud disease, with aortic valve prosthesis, proximal aortic aneurysm, known intra-cardiac shunts; moderate to severe mitral or aortic regurgitation; moderate to severe aortic or mitral stenosis, patients with poor quality arterial waveform signal (see below), patients with significant preoperative psychomotor agitation.

2.3. Conduct of the study

2.3.1. Perioperative management common to both groups.

Both groups were treated during the perioperative period in a multidisciplinary ERP unit created in 2010 exclusively dedicated to patients undergoing hip fracture repair (Reguant et al. 2019).

This unit's objectives were to optimize patient health status before surgery, minimize preoperative stress, prevent and/or treat electrolyte imbalance, prevent and/or treat cardiovascular, respiratory, infectious and cognitive disorders, improve nutritional status and reduce surgical delay. The team comprised orthopaedic surgeons, anaesthesiologists, internists, a nurse case manager, a social worker, a physiotherapist and a nutritionist.
The main interventions of this multidisciplinary ERP unit for patients with hip fracture are shown in Table 1.

Intraoperative period

All subjects received standard of care with a 3-lead electrocardiogram, pulse oximetry, and two peripheral intravenous lines. Patients in both groups received standard measures to maintain oxygen saturation by pulse oximetry >94% and heart rate <100 beats/min. Anaesthetic technique was at the discretion of the anesthetist.

Post-Anaesthetic Care Unit (PACU)

After surgery, patients were treated in the PACU. The attendant physician determined discharge from this unit according to the local protocol.

2.3.2. Study arms

Control group

Data from patients who underwent surgery for hip fracture between October 2010 and November 2011 with follow-up to December 2012 were used for the CG (Reguant et al. 2019).

Haemodynamic management was at the discretion of the attending anesthetist, using fluid therapy with crystalloids (0.9% saline, lactated Ringer or Isofundin®), colloids (Voluven®, Gelaspan ®), and/or cardiovascular drugs (in bolus - ephedrine – or continuous infusion – noradrenaline, dobutamine).

Non-invasive, intermittent arterial pressure measurement was obtained at least every 5 minutes using a cuff (Dahtex Ohmeda-GE S/5 Aespire ®).

Intervention group

Data from patients who underwent surgery for hip fracture between June 2015 and February 2018 with follow-up to March 2019 were used as the IG.

Pre- and intraoperative non-invasive hemodynamic monitoring was conducted using ClearSight® monitor (Edwards Lifesciences, Irvine, USA). This monitoring system is based on the volume clamp method to continuously measure arterial pressure and the Physiocal method that periodically recalibrates the system (Saugel et al. 2015). Baseline haemodynamic measurements were taken when the Physiocal value exceeded 30 (Wesseling, K H; de Wit, B; Van der Hoeven, A;Van Goudoever 1995). If a Physiocal value over 30 was not obtained after 7 minutes´ monitoring, the patient was excluded due to a poor quality arterial waveform signal (Wesseling, K H; de Wit, B; Van der Hoeven, A;Van Goudoever 1995).

Haemodynamic optimisation was performed according to the following GDHT protocol.

GDHT protocol (Figure 2):

Three groups of cardiac index (CI) goals were formed according to age and prior functional capacity expressed in metabolic equivalents (METS) (Montenij et al. 2014). Additional file 1.

Fluids were given based on a protocolized haemodynamic algorithm to achieve and maintain an adequate Indexed Stroke Volume (SVI) using crystalloids (0.9% Saline, Lactated Ringer or Isofundin ®) or colloids (if preoperative glomerular filtration rate was above 60 mL/min using Modification of Diet in Renal Disease (MDRD) equation (Ishihara 2014)- Voluven ®, Gelaspan ®). Choice of fluid type was based on anaesthesiologist criteria.

If a fluid bolus (FB) was not indicated and/or the target perfusion pressure was not been achieved with its infusion, vasopressor was administered to maintain systolic arterial pressure (SAP) above 90 mmHg (in bolus - ephedrine, phenylephrine – or continuous infusion – noradrenaline) or continuous infusion of dobutamine was added to achieve in addition, the individualized CI goal.

Phase 1: Preoperative resuscitation

On arrival in the surgical area, patients received a FB of 250 ml of 5 minutes. If SVI increased by 10% or more (*First Fluid Bolus Responder*), the fluid bolus was repeated (Cecconi et al. 2011). Fluid boluses of 250 ml were repeated until the SVI failed to increase by 10%.

Once preoperative resuscitation was completed, prophylactic antibiotic was infused. Table 1. This fluid contribution covered the estimated insensible losses during surgery (Jacob et al. 2007).

Phase 2: Post-incision optimisation

Post-incision optimisation began 15 minutes after the surgical incision, if the haemodynamic stabilisation was achieved (SAP and heart rate variation < 10% for 3 minutes); meanwhile, the haemodynamic priority was the maintenance of arterial pressure above goal set (Tassoudis et al. 2011).

Haemodynamic optimisation consisted of a 100 ml fluid bolus administered of less than 3 minutes (Guinot et al. 2015; Mallat et al. 2015; Marik 2015; Muller et al. 2011). If SVI rose >10%, the 100 ml fluid bolus was repeated. The trigger SVI during surgery was calculated by subtracting 10% from the SVI obtained from the last positive 100 ml fluid bolus (Muñoz et al. 2016).

Phase 3: Maintenance during surgery

If at least one of the following objectives, SVI>SVI trigger and /or SAP>90mmHg, were not achieved, SVI was analyzed:

-If it was lower than the trigger SVI, a 100 ml FB was administered.

-If SVI was higher than trigger SVI, we look at the CI:

-If its value was under goal level, dobutamine was added.

-When CI was above goal level, a vasopressor was chosen.

After each therapy, we re-evaluated the achievement of SAP and SVI goals.

2.4. Measurements and data handling

2.4.1. Procedure

Intraoperative haemodynamic parameters (arterial pressure, heart rate, SpO_2 in CG and also CI and SVI in IG) were registered at 15-minute intervals. Haemodynamic instability, between intervals was registered as an event in the next record. Fluids and cardiovascular drugs used from the patient's arrival in the surgical area to their admission to the PACU were collected. In both groups, the evaluation of intraoperative complications, was based on the intraoperative anesthesia charts, whereas the postoperative complications were documented in the clinical course and hospital discharge report.

Post-discharge follow-up consisted of a structured telephone interview at 1, 3, 6 and 12 months after surgery. When the information could not directly be obtained from the patients (including deceased patients), the interview was done with next of kin or carer.

2.4.2. Assessment of outcomes.

Primary outcome measures

The primary outcome was the percentage of patients who developed intraoperative haemodynamic instability, defined as one measurement of SAP < 90 mmHg in the CG and for at least one minute in the IG and/or the need for a bolus of vasoconstrictor.

Secondary outcome measures

-Intraoperative arrhythmias: defined as electrocardiographic evidence of cardiac rhythm disturbance.

-Postoperative complications, grouped as follows:

-Major cardiovascular complications*: acute myocardial infarction, acute pulmonary oedema, ischemic stroke, pulmonary thromboembolism and cardiorespiratory arrest*.

-Minor cardiovascular complications: *haemodynamic instability*, defined as one measurement of SAP < 90 and *arrhythmias*.

-Respiratory*: hypoxia*, defined as oxygen saturation <92%. Other respiratory complications: *decompensation of chronic obstructive pulmonary disease*, *acute respiratory infection* (clinical and radiological diagnosis and antibiotic treatment) and others.

-Renal*:* presence of at least one of*: oligoanuria*, defined as urine output under 0.5ml/kg per hour, including absence of urine output. *Acute renal failure*, defined as an increase in urea > 50 mg/dl and creatinine levels > 1.09 mg/dl in any analysis during admission.

-Infections: *surgical wound (*infection within 30 days after surgery that involves only skin and subcutaneous tissue of the incision)*, urinary* (positive urine culture causing patient's symptoms and which were not present on admission to hospital)*, systemic* (fever >38ºC and positive blood antigen test with appropriate antimicrobial therapy instituted by a physician)*.*

-Surgical reintervention during hospital stay.

-Total intraoperative volume and type of administered fluids, doses of cardiovascular drugs used, perioperative packed red blood cell transfusion, length of hospital stay, readmission within 30 days of surgery, and survival within 12 months after surgery.

2.5. Statistical analysis

2.5.1. Sample size

The rate of intraoperative haemodynamic instability described with standard of care was 37.5% (Reguant et al. 2019). We planned a relative risk reduction of 30% in IG.

To achieve a power of 80% using a bilateral χ^2-square test for two independent samples with a level of significance of 0.05, 538 patients had to be included (269 patients in each group). With a potential dropout of 5%, 568 patients were included.

The percentage of patients who developed one or more postoperative complications in CG was 45.2%. A meta-analysis by Grocott and colleagues suggested a RR reduction of 0.68 for complications in patients undergoing major surgery (Grocott et al. 2013). A sample size of 568 patients, 284 in each group, would have 80% power to detect a reduction of at least 22% in the number of IG patients presenting one or more postoperative complications, using a bilateral χ^2-square test for two independent samples.

2.5.2. Statistical analysis

Categorical variables were presented as absolute values and relative frequencies. Continuous variables are summarised as means and standard deviation for normal distribution and by the median and interquartile range (IQR) (25^{th} to 75^{th} percentiles) for non-normal distributions.

In the bivariate analysis, we used the Student's t-test or the non-parametric Mann-Whitney U test for continuous variables. We used the χ^2-square test for categorical variables, and Fisher's exact test or bilateral exact p-values in contingency tables when the expected frequencies were less than five.

One-year survival Kaplan–Meier curves were constructed, and the log-rank test was used to compare them. Crude and adjusted hazard ratios and confidence intervals (CI 95%) were calculated using Cox proportional regression models. The proportionality of hazards was verified by examining Schoenfeld residual plots.

Outcomes were analysed on an intention-to-treat basis. The level of statistical significance was two-sided 5% ($p < 0.05$). The IBM SPSS Statistics v.26 (IBM Corporation®, Armonk, New York) and Stata v.14 (StataCorp LP®, College Station, Texas) programs were used for statistical analysis.

3-Results

A total of 551 patients were recruited. Study flowchart is shown in figure 1. Table 2 shows the baseline characteristics of the 272 patients in CG and the 279 patients in IG. Mean age was 84.9 years (69.1% female) in the CG and 85.2 years (75.6% female) in IG. Patients in the IG had a worse health status according to the criteria of ASA (III-IV 68.8% vs 85.3%; $p < 0.001$). A higher percentage of patients with intake of more than 4 drugs (67.4% vs 75.6%; p=0.03) was observed in the IG. No significant differences between groups were observed according to type of fracture, despite this, use of intramedullary nail increased in the IG (15.8% vs 42.3%; p<0.001). Surgical time was higher in the IG (80 min vs 90 min; p<0.004). There were no differences between anesthesia techniques in two groups. Surgery was performed within 48 h of admission in 55.1% in the CG vs 68.5% of patients in the IG (p=0.001).

3.1. Primary Outcome

Details of intraoperative complications are shown in table 3. The number of patients with intraoperative haemodynamic instability was lower in IG (37.5% vs 28.0%; p=0.017). The median number of episodes of intraoperative haemodynamic instability in IG was lower than in the CG [2 (IQR 1 to 4) vs 1 (IQR 1 to 2), p<0.001].

3.2. Secondary Outcomes

3.2.1. Intraoperative arrhythmias

IG patients developed fewer arrhythmias than CG patients (2.2% vs 0.7%; p=0.172)

3.2.2. Postoperative complications.

Postoperative complications are shown in table 3. Postoperative complications rates were 42.3% in the IG versus 45.2% in CG (p=0.489). Patients in the IG had fewer cardiovascular complications (18.8% vs 7.2%; p< 0.001), fewer respiratory complications (15.1% vs 3.6%; p<0.001) and postoperative infections (21% vs 3.9%; p<0.001). However, IG patients had more renal complications (12.1% vs 33.7%; p<0.001). No differences in postoperative renal complications were observed between groups in patients with normal creatinine value at hospital admission. (Additional file 4)

3.2.3. Fluid volumes, vasopressor doses and perioperative transfusion

Details of fluid volumes and vasopressor doses in both groups are shown in table 4.

29.4% of IG patients were responders to the first fluid bolus performed. Patients in the IG received less fluid [2.600 ml (IQR 1700 to 2700) vs 850 ml (IQR 750 to 1050); p=0.001] and vasopressors (39.7% vs 25.5%; p<0.001) than CG. Lactated Ringer's was the fluid most used during the intraoperative period in CG patients (73.9% vs 4.3%; p<0.001) while saline was chosen more often in the intraoperative period in IG (25% vs 95.7%; p=0.001). Fewer patients in IG received colloids than in CG (59.2% vs 9%; p<0.001).

Fewer patients required packed red blood cells (PRBC) transfusion in IG (73.5% vs 44.4%; p<0.001), with a lower median number of PRBC among transfused patients in IG [2 (IQR 2 to 4) vs 2 (IQR 1 to 2); p<0.001].

3.2.4. Length of stay and survival within 12 months of surgery

The median length of stay was shorter for patients in the IG (median days: 11 vs 8; $p < 0.001$) (Table 3).

Demographic and clinical variables associated with one-year mortality in the bivariate analysis appear in Additional file 2. Figure 3 shows the Kaplan-Meier survival curves for both groups. The likelihood of one-year survival was higher in IG (log-rank test=9.17; $p = 0.003$) (see Figure 3), with a crude HR of 0.56 (95% CI: 0.39 to 0.82). Multivariate analysis (Additional file 3) showed that independent prognostic factors for one-year survival were: age (HR: 1.09; 95% CI: 1.05 to 1.12), male gender (HR: 2.10; 95% CI: 1.43 to 3.11), low (HR: 2.33; 95% CI: 1.29 to 4.23) and high comorbidity (HR: 2.84; 95% CI: 1.67 to 4.83), according to the Charlson Index, postoperative cardiovascular complications (HR: 3.85; 95% CI: 2.49 to 5.96), need for reintervention (HR: 5.31; 95% CI: 1.58 to 17.86) and belonging to the intervention group*. The adjusted HR for the IG was 0.61 (95% CI: 0.39 to 0.95).

4-Discussion

The use of GDHT guided by non-invasive haemodynamic monitoring in patients undergoing hip fracture surgery within an ERP, was associated with a reduction in intraoperative complications (haemodynamic instability, arrhythmias) and postoperative cardiovascular, respiratory and infectious complications, but not postoperative renal complications. This strategy was also associated with a shorter hospital stay and increased survival one year after surgery.

Preoperative chronic conditions and insufficient preoperative optimization in this patient profile, associated with intraoperative conditions such as bleeding and hypovolemia, predispose these elderly patients to hemodynamic instability or arrhythmias during surgery (Alecu et al. 2010); (Rocos et al. 2017). The occurrence of intraoperative complications may compromise the balance between tissue oxygen delivery and oxygen consumption, and increase the patient's susceptibility to postoperative complications (Merry and Mitchell 2018); (Beecham et al. 2020).

Our results showed a significant decrease in intraoperative haemodynamic instability episodes in patients in the IG, similarly to a recently published study (Davies et al. 2019). In addition, patients in the IG had fewer postoperative cardiovascular, respiratory and infectious complications. These results may be due to improvements in haemodynamic control of these patients as a result of GDHT guided by a non-invasive monitoring system implemented. One of its main objectives is to avoid intraoperative hypoperfusion (Brienza et al. 2019) which may have been reflected in fewer postoperative complications in IG.

A higher incidence of postoperative acute kidney injury (AKI) found in IG may be due to several reasons. First, patients in the IG have more risk factors for postoperative AKI, including age, female sex, hypertension and chronic kidney disease. (Meersch et al. 2017). Secondly, patients treated with GDHT received higher amounts of 0.9% saline. Hyperchloremic acidosis associated with saline infusion is detrimental to renal artery blood flow velocity and renal cortical tissue perfusion (Chowdhury et al. 2012). Third, the AKI definition itself. A single and transient, postoperative serum creatinine elevation above a very sensitive level, was considered a renal complication. An isolated elevation could neither be associated with kidney cell damage (Hahn 2015) nor be significant compared to baseline value. In patients with normal creatinine value at hospital admission, no

differences in the risk of suffering postoperative renal complications were observed between the groups. The limitations of AKI definition and the influence on mortality only by postoperative creatinine elevations associated with kidney cell damage, may explain a significant decrease in mortality one year after surgery, despite an increase in postoperative renal complications in IG.

The GDHT protocol applied in this study differs from that used in the most recent trials in this patient profile (Bartha et al. 2013; Davies et al. 2019; Moppett et al. 2015). The GDHT protocol used by Bartha and colleagues includes fluid resuscitation prior to anaesthetic induction, intraoperative use of vasoactive support if SAP declined by more than 30% from pre-anaesthesia values, and optimisation with fluids and dobutamine for stroke volume (SV) and DO_2 respectively. Colloid therapy to optimise SV was protocolised by Moppett and co-workers in their IG. Finally, Davies and colleagues applied a GDHT protocol based on SV optimisation by crystalloids and mean arterial pressure maintenance above 30% of baseline values with vasopressors.

Our IG shows a similar percentage of responders to the first fluid challenge as previously described (Bartha et al. 2013). This lower-than-expected percentage can be explained by the optimisation starting immediately after admission to hospital, according to the ERP applied in both patient cohorts. Total fluid used in our IG is comparable or slightly less than the amounts given in two previous studies' intervention groups: 1.078 (Bartha et al. 2013) and 850 ml (Davies et al. 2019) respectively and slightly higher than the volume given in another previous intervention group: 750 ml (Moppett et al. 2015). A lower use of vasopressors in our IG stands out, probably because of following a decision algorithm. The non-application of a haemodynamic algorithm may lead to an early use of vasopressors, even if it is not physiologically appropriate for the patient's condition.

No IG patients were treated intraoperatively with dobutamine, probably due to the establishment of an individualized CI goal and by the absence of intraoperative pathophysiological tributary situations. Fewer patients had been transfused in our IG. In addition to the use of less bleeding surgical techniques (Yu et al. 2015), patients in IG may suffered less haemodilution than patients in CG due to lower amount of fluids received (Ince 2015).

We found a reduction in hospital stay and a significant increased survival in IG patients throughout the first year after surgery. These findings can be explained by the significant reduction in intraoperative complications and postoperative cardiovascular, respiratory and infectious complications, and surgical reinterventions (Monk et al. 2015); (Roche et al. 2005). After adjusting for potential confounding variables, IG membership was a protective factor for one-year mortality.

The results of this study suggest that not only haemodynamic strategy we perform on our patients will influence their outcomes. The type of fluid used during major surgery may affect postoperative results (Heming et al. 2020). The results of the fluid infusion strategy used cannot be evaluated without considering the type of drug used.

Our study has some limitations. It was a single-centre, non-randomised design with a three-years gap between the two study groups. However, no changes were made between groups in the ERP, nor in the composition of the multidisciplinary team or in the care protocols during the study period. IG recruitment rate was lower than expected, probably because of the real emergency surgery status applied to hip fracture patients in this hospital since 2010. Patients with contraindications for haemodynamic monitoring, poor quality signal obtained or with preoperative psychomotor agitation that prevented hemodynamic monitoring were excluded only from the IG. However, our exclusion rate for these reasons (9%) is lower than previously reported (Davies et al. 2019), but we cannot

rule out that these excluded patients had worse clinical status on arrival in the operating theatre.

Uncontrolled before-and-after study provides less quality evidence than randomised controlled trials (RCT) (Sedgwick 2014). However, this design offers valuable insights into the potential benefits of GDHT protocols under real-life conditions, and can complement evidence from RCT (Saugel et al. 2019). Moreover, this is the largest sample size published to date evaluating the effect of GDHT guided by non-invasive haemodynamic monitoring during hip fracture surgery.

5-Conclusions

In patients undergoing hip fracture surgery, the use of a GDHT protocol guided by non-invasive hemodynamic monitoring was associated with a reduction in intraoperative complications and postoperative cardiovascular, respiratory and infectious, but not postoperative renal complications. This strategy was also associated with shorter hospital stay and higher survival one year after surgery.

6-List of abbreviations

- AKI – Acute Kidney Injury
- CG - Control group
- CI - Cardiac Index
- DO_2 - Oxygen Delivery
- ERP - Enhanced Recovery Pathway
- FB – Fluid Bolus
- GDHT - Goal-Directed Hemodynamic Therapy

- HR - Hazard Ratio
- IG - Intervention Group
- IQR – Interquartile Range
- MDRD – Modification of Diet in Renal Disease
- METS – Metabolic Equivalents
- PACU - Post-Anaesthetic Care Unit
- PRBC - Packed Red Blood Cells
- SAP - Systolic Arterial Pressure
- SpO_2 – Oxygen Saturation
- SV - Stroke Volume
- SVI - Indexed Stroke Volume
- VO_2 - Oxygen Consumption

7-Declarations

7.1. Ethics approval and consent to participate

This manuscript was written according to CONSORT statement. The study was approved by an independent Ethics Committee (Fundació Unio Catalana Hospitals, Chairperson: Dr. Miquel Nolla) on 27 January 2015 (CEIC 15/03). All patients signed an informed consent to participate. The study was conducted according to the Declaration of Helsinki and all local legal and regulatory requirements

7.2. Consent for publications

Not applicable

7.3. Availability of data and materials

The datasets used and/or analysed during this study are available from the corresponding author on reasonable request

7.4. Competing interest

Dr Lorente, Dr Jiménez, Dr Ripollés-Melchor and Dr Monge have received conference fees from Edwards Lifesciences.

Dr Lorente & Dr Ripollés-Melchor have received conference fees from Fresenius Kabi and bioMérieux.

Dr Ripollés-Melchor & Dr Monge have received conference fees from Dextera Medical

Dr Lorente has received conference fees from Vifor Pharma, Grifols and financial support for research obtained through Edwards Lifesciences Grant Portal. Economic research support from bioMérieux.

Dr Ripollés-Melchor has received conference fees from MSD

The rest of the authors declare no conflict of interest.

7.5. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

7.6. Authors' contributions

- JVL: Study design, patient recruitment, acquisition of data, review of perioperative complications in IG, analysis and interpretation of data, writing up of the paper and final approval of the version to be published.

- FR: Study design, patient recruitment, acquisition of data, review of perioperative complications in CG, analysis and interpretation of data and review of the paper's content.
- AA: Study design, analysis and interpretation of data and review of the paper's content.
- MB: patient recruitment, acquisition of data and review of the paper's content.
- JCP: patient recruitment, acquisition of data and review of the paper's content paper.
- JT: patient recruitment, acquisition of data and review of the paper's content.
- LC: patient recruitment, acquisition of data and review of the paper's content.
- PS: patient recruitment, acquisition of data and review of the paper's content.
- IP: patient recruitment, acquisition of data and review of the paper's content.
- CF: patient recruitment, acquisition of data and review of the paper's content.
- IJL: analysis and interpretation of data and review of the paper's content.
- JRM: analysis and interpretation of data and review of the paper's content.
- MIMG: analysis and interpretation of data and review of the paper's content.
- JB: Study design, analysis and interpretation of data and review of the paper's content.

All authors have approved the latest version of the manuscript and agree to be responsible for all aspects of the work ensuring that issues relating to the accuracy or completeness of any part of the work have been properly investigated and resolved.

7.7. Acknowledgements

We would like to acknowledge the contribution of Dr Omar El Boutrouki and Ms Mercé Castejón for their help in the development of the study.

9-Figure titles and legends

Figure 1. Flow chart of patients during recruitment and 12-month follow-up.

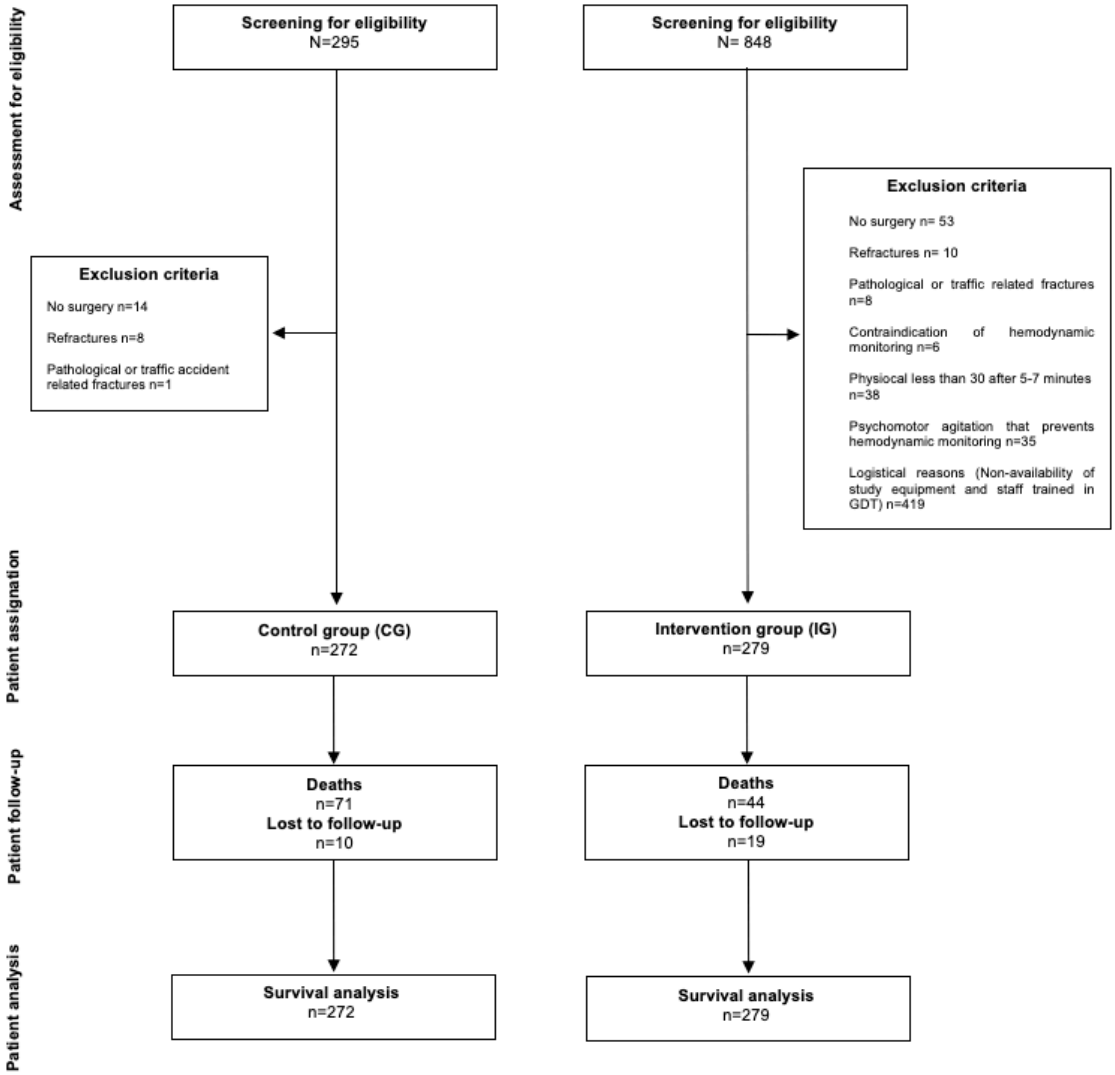
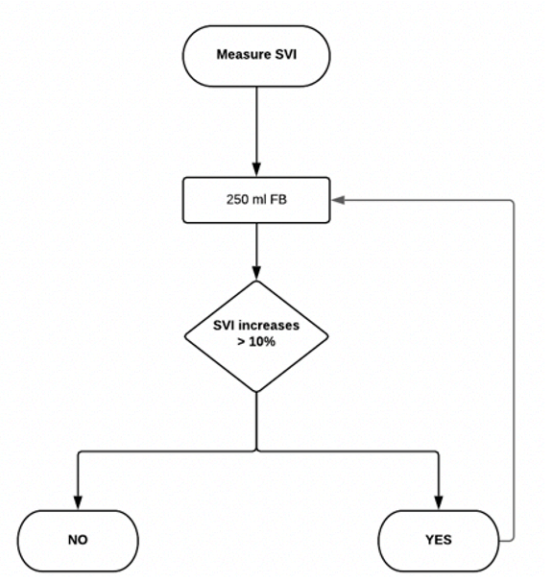
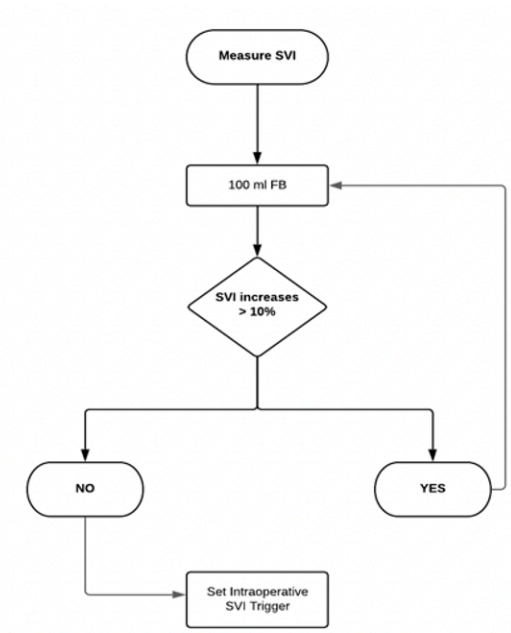


Figure 2. Algorithms for goal-directed haemodynamic therapy phases.

Phase 1: Preoperative resuscitation



Phase 2: Post-incision optimization



Phase 3: Maintenance during surgery

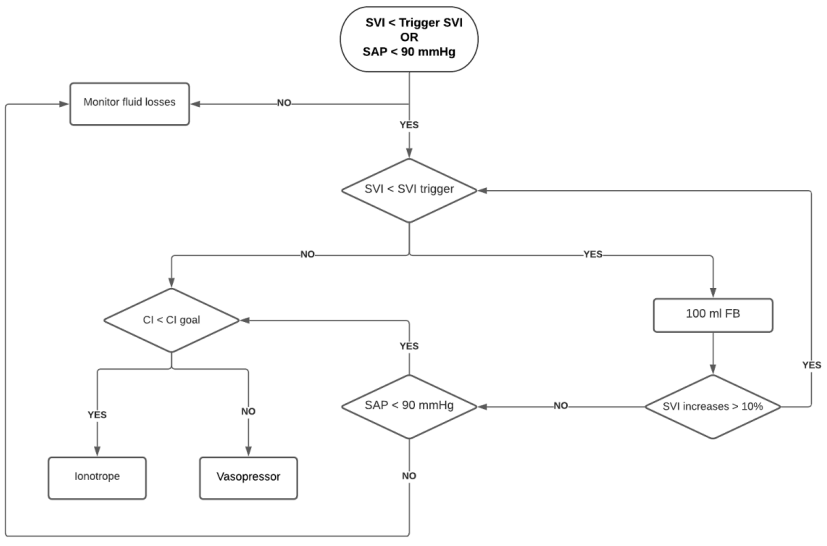
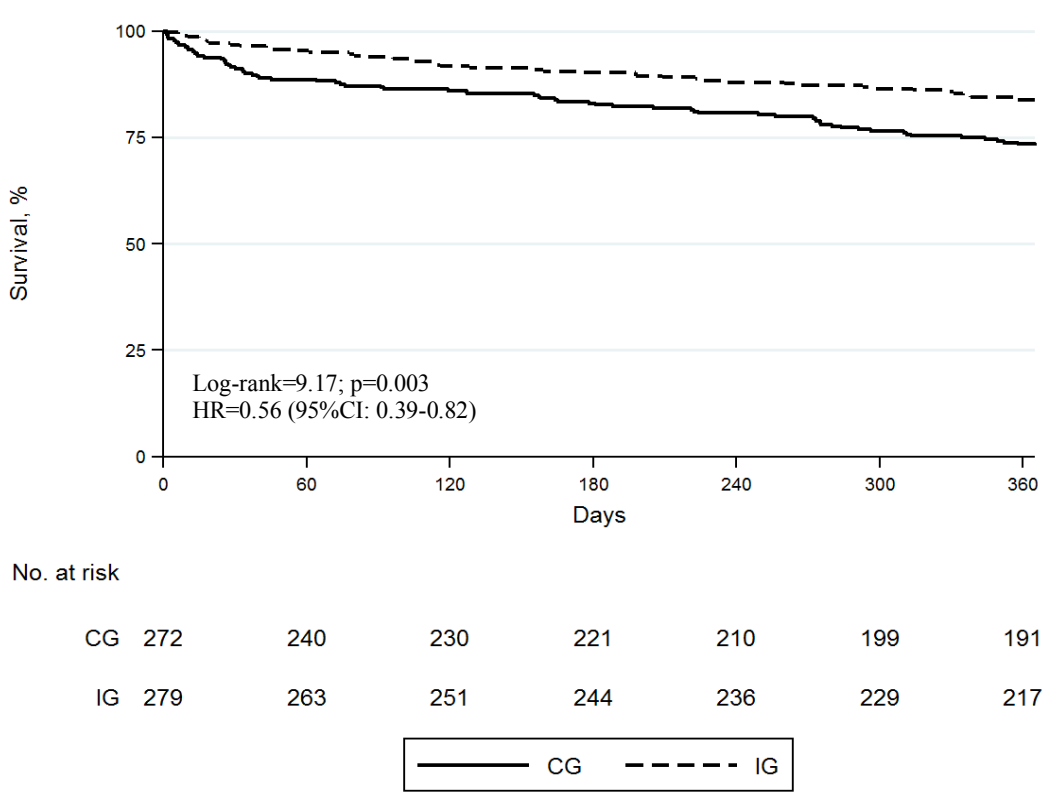


Figure 3. Kaplan-Meier survival curves according to group allocation. Crude hazard ratio for one-year survival



10-Tables

Table 1. Main interventions of Enhanced Recovery Pathway Unit for Hip Fracture patients.

Preoperative period

- Specialized hip fracture ward
- Internist support
- Assessment by anesthesiologist
- Nursing aids
- Intravenous Fluids
- Monitor oxygen saturation/8 h. Oxygen therapy when < 92% and maintenance until 48 h after surgery
- Pain control: avoiding opioids if possible
- Carbohydrate loading until 2 h before surgery.
- Protocol for patients who received antiplatelet drugs or oral anticoagulants on admission.[a]

- Prioritize surgery within 48 h on admission in patients with medical stable condition.

Intraoperative period

- Prevention of intraoperative hypotermia
- Intraoperative nausea and vomiting prophylaxis
- Prophylactic antibiotic 30 minutes before surgical incision [b]
- Avoid intrathecal opioids
- Performance of peripheral nerve blocks

Postoperative period

- Specialized hip fracture ward
- Internist support
- Nursing aids
- Postoperative fluids should be stopped when possible, in favour of early oral intake.
- Monitor oxygen saturation/8 h. Oxygen therapy when < 92% and maintenance until 48 h after surgery
- Optimal postoperative analgesia, preferably with intraoperative peripheral nerve blocks and NSAIDs
- Deep vein thrombosis prevention
- Early respiratory physiotherapy
- Early and standardized mobilization 24h after surgery.
- Early urinary catheter removal

Perioperative Interventions

- Gastric ulcer prophylaxis iv/24 h.
- To avoid using opioids and/or benzodiazepines.
- Screening and treatment when appropriate of urinary infection
- Bladder catheterisation only in case of incontinency or when needing to monitor renal and/or cardiac function.
- Treatment protocol for anaemia when haemoglobin was < 13 g/dl on admission. Transfusion was administered if haemoglobin level was < 8 g/dl and to patients with cardiorespiratory disease and/or haemodynamic instability when haemoglobin level was < 10 g/dl.

[a]-Surgery was postponed for 4 days in patients who, at admission, had been administered acetylsalicylic acid >100 mg, triflusal >300 mg, or clopidrogel/ticlopidine. Surgery was postponed in patients who were on OAC treatment at admission, until INR < 1.5.
[b] 2 g cefazolin in intramedullary nail surgery in 100 ml saline, or cefuroxime and teicoplanin in prosthesis surgery in a total of 200 ml saline)

Table 2. Baseline characteristics according to group allocation

	Control (CG) n=272	Intervention (IG) n=279
Age	84.9 ± 6.2	85.2 ± 7.4
65 to < 75 years	15 (5.5%)	30 (10.8%)
75 to < 85 years	125 (46.0%)	97 (34.8%)
≥ 85 years	132 (48.5%)	152 (54.5%)
Gender		
Male	84 (30.9%)	68 (24.4%)
Female	188 (69.1%)	211 (75.6%)
ASA		
I – II	85 (31.2%)	41 (14.7%)
III – IV	187 (68.8%)	238 (85.3%)
Charlson comorbidity index		
Absence de comorbidity (0-1)	125 (46.0%)	109 (39.1%)
Low comorbidity (2)	50 (18.4%)	57 (20.4%)
High comorbidity (3 or more)	97 (35.7%)	113 (40.5%)
Cardiovascular history		
Valvulopathy	21 (7.7%)	31 (11.1%)
Arrhythmia	73 (26.8%)	58 (20.8%)
Ischemic cardiopathy	17 (6.3%)	29 (10.4%)
Pulmonary thromboembolism (PTE)	1 (0.4%)	3 (1.1%)
Hypertension	177 (65.1%)	212 (76.0%)
Total number of drugs	6 (IQR 4 to 8)	7 (IQR 5 to 10)
≤ 4 drugs	89 (32.7%)	68 (24.4%)
> 4 drugs	183 (67.3%)	211 (75.6%)
Type of fracture		
Intra-capsular	121 (44.5%)	124 (44.4%)
Extra-capsular	151 (55.5%)	155 (55.6%)
Hemoglobin at admission		
Hemoglobin > 12 g/dl	159 (58.5%)	169 (60.6%)

Hemoglobin ≤ 12 g/dl	113 (41.5%)	110 (39.4%)
Creatinine at admission		
Creatinine ≤ 1.09 mg/dl	178 (65.7%)	175 (62.7%)
Creatinine > 1.09 mg/dl	93 (34.3%)	104 (37.3%)
Anesthesia		
General	28 (10.3%)	28 (10.0%)
Spinal	244 (89.7%)	251 (90.0%)
Type of implant		
Hip prosthesis	103 (37.9%)	102 (36.6%)
Dynamic hip screw	122 (44.9%)	57 (20.4%)
Intramedullary nail	43 (15.8%)	118 (42.3%)
Others	4 (1.5%)	2 (0.7%)
Surgical delay		
≤ 48 hours	150 (55.1)	191 (68.5)
> 48 hours	122 (44.9)	88 (31.5)
Surgery time (minutes)	80 (IQR 65 to 105)	90 (IQR 70 to 120)

Mean ± Standard deviation; n (%); median (IQR 25th percentile to 75th percentile).

Table 3. Main and secondary outcomes at one-year follow-up.

	Control (CG) n=272	Intervention (IG) n=279	p-value
Intraoperative complications			
Hemodynamic instability	102 (37.5%)	78 (28.0%)	0.017[a]
Nº episodes hemodynamic instability[1]	2 (IQR 1 to 4)	1 (IQR 1 to 2)	<0.001[b]
Arrhythmias	6 (2.2%)	2 (0.7%)	0.172[c]
Postoperative complications	123 (45.2%)	118 (42.3%)	0.489[a]
Cardiovascular	51 (18.8%)	20 (7.2%)	<0.001[a]
Major	12 (4.4%)	11 (3.9%)	0.783[a]
Myocardial infarction	1 (0.4%)	0 (0.0%)	0.494[c]
Cardiorespiratory arrest	3 (1.1%)	6 (2.2%)	0.505[c]
Acute pulmonary edema	8 (2.9%)	5 (1.8%)	0.374[a]
Pulmonary Thromboembolism	0 (0.0%)	0 (0.0%)	-
Cardiorespiratory arrest	0 (0.0%)	0 (0.0%)	-
Minor	40 (14.7%)	12 (4.3%)	<0.001[a]
Hemodynamic instability	34 (12.5%)	5 (1.8%)	<0.001[a]
Arrhythmias	4 (1.5%)	7 (2.5%)	0.384[a]
Others	2 (0.7%)	1 (0.4%)	0.620[c]
Respiratory	41 (15.1%)	10 (3.6%)	<0.001[a]
Hypoxia	17 (6.3%)	2 (0.7%)	<0.001[a]
Decompensation of Chronic Obstructive Pulmonary Disease	6 (2.2%)	1 (0.4%)	0.066[c]
Acute respiratory infection	16 (5.9%)	5 (1.8%)	0.012[a]
Others	3 (1.1%)	2 (0.7%)	0.682[c]
Renal	33 (12.1%)	94 (33.7%)	<0.001[a]
Infections	57 (21.0%)	11 (3.9%)	<0.001[a]
Surgical wound	8 (2.9%)	0 (0.0%)	0.003[c]
Urinary	47 (17.3%)	10 (3.6%)	<0.001[a]
Systemic	3 (1.1%)	2 (0.7%)	0.682[a]

	Control (CG) n=272	Intervention (IG) n=279	p-value
Secondary to spinal anesthesia			
Hematoma/infection/neurological lesion	0 (0.0%)	0 (0.0%)	-
Surgical re-intervention	6 (2.2%)	0 (0.0%)	0.014[c]
Length of stay (days)	11 (IQR 8 to 16)	8 (IQR 6 to 11)	<0.001[b]
Destination after discharge			0.327[a]
Convalescence	128 (49.8%)	142 (52.0%)	
Family home	81 (31.5%)	71 (26.0%)	
Residence	48 (18.7%)	60 (22.0%)	
Thirty-day readmission	29 (11.3%)	21 (7.7%)	0.157[a]
Survival			0.003[d]
1-month	91.2% (87.1% to 94.0%)	96.8% (93.9 to 98.3%)	
3-month	88.6% (84.2% to 91.8%)	95.3% (92.1 to 97.3%)	
6-month	83.0% (78.0% to 87.0%)	90.2% (86.0 to 93.2%)	
12-month	73.4% (67.7% to 78.3%)	83.8% (78.8 to 87.7%)	

Mean ± Standard deviation; n (%); median (range x to y) or median (IQR 25th percentile to 75th percentile).
[a] Pearson X^2; [b] Mann–Whitney U; [c] Fisher's exact test; [d] Log-rank test.
[1] In patients with hemodynamic instability

Table 4. Total fluid volumes, vasopressor doses and perioperative blood transfusion

	Control (CG) n=272		Intervention (IG) n=279		p-value
	n (%)	median (IQR)	n (%)	median (IQR)	
Fluid volumes					
Total fluids (ml)	272 (100%)	2600 (IQR 1700 to 2700)	279 (100%)	850 (IQR 750 to 1050)	0.001
Fluid creep -antibiotic prophylaxis- (ml)	272 (100%)	200 (IQR 200 to 200)	279 (100%)	200 (IQR 100 to 200)	0.001
Intraoperative fluids (ml)	272 (100%)	2500 (IQR 2000 to 2500)	279 (100%)	700 (IQR 550 to 900)	0.001
Crystalloids (ml)	253 (94.5%)	2000 (IQR 2000 to 2000)	278 (99.6%)	650 (IQR 550 to 850)	0.001
Saline (ml)	68 (25.0%)	1000 (IQR 1000 to 1000)	267 (95.7%)	650 (IQR 550 to 850)	0.001
Lactated Ringer (ml)	201 (73.9%)	1000 (IQR 1000 to 1000)	12 (4.3%)	1050 (IQR 850 to 1237)	0.889
Isofundin® (ml)	22 (8.1%)	500 (IQR 500 to 500)	-	-	-
Colloids (ml)	161 (59.2%)	500 (IQR 500 to 500)	25 (9.0%)	300 (IQR 200 to 500)	0.001
Voluven® (ml)	153 (56.3%)	500 (IQR 500 to 500)	25 (9.0%)	300 (IQR 200 to 500)	0.001
Gelaspan® (ml)	11 (4.0%)	500 (IQR 500 to500)	-	-	-
Vasopressor	108 (39.7%)		71 (25.5%)		<0.001
Ephedrine (mg)	108 (39.7%)	15 (IQR 10 to 30)	65 (23.3%)	10 (IQR 10 to 20)	0.002
Phenylephrine (mg)	-	-	11 (4.0%)	100 (IQR 50 to 150)	-
Noradrenaline (mg)	2 (0.7%)	3.5 (IQR 2 to 3.5)	-	-	-
Blood transfusion	200 (73.5%)	-	124 (44.4%)	-	<0.001
Number of PRBC[1]		2 (IQR 2 to 4)		2 (IQR 1 to 2)	<0.001
Fluid Challenge Responder	-	-	82 (29.4%)		-

Median (IQR 25th percentile to 75th percentile). PRBC: Packed Red Blood Cells. [1]About transfused patients.

11-Additional files

- Additional file 1. Intraoperative cardiac index goal groups.
- Additional file 2. Bivariant analysis. Prognostic factors of one-year mortality. Crude Hazard Ratio (HR) and statistical significance according to bivariate COX regression models.
- Additional file 3. Multivariant analysis. Independent prognostic factors for mortality. Adjusted HR for one-year survival.
- Additional file 4. Renal complications according creatinine at admission and group allocation

Additional file 1. Intraoperative cardiac index goal groups:

	Age (years)	65-74	75-85	> 85
Functional Capacity (METS)				
< 4 METS		2.4	2.2	2.2
Between 4-6 METS		2.6	2.4	2.2
> 6 METS		2.6	2.4	2.2

Intraoperative cardiac index goal groups according to age and METS

Cardiac index expressed in L/min/m2

Additional file 2. Bivariant analysis. Prognostic factors of one-year mortality. Raw hazard ratio (HR) and statistical significance according to bivariate COX regression models.

	No death n=436	Death n=115	p-value	crude HR	CI 95%
Age			<0.001[a]		
65 to < 75 years	44 (97.8%)	1 (2.2%)		1	
75 to < 85 years	189 (85.1%)	33 (14.9%)		7.25	0.99 to 53.04
≥85 years	203 (71.5%)	81 (28.5%)		14.85	2.07 to 106.7
	84.2 ± 6.8	88.1 ± 6.0	<0.001[b]	1.09	1.06 to 1.12
Gender			<0.001[a]		
Female	332 (83.2%)	67 (16.8%)		1	
Male	104 (68.4%)	48 (31.6%)		2.11	1.46 to 3.06
ASA			<0.001[a]		
I – II	118 (93.7%)	8 (6.3%)		1	
III-IV	318 (74.8%)	107 (25.2%)		4.47	2.18 to 9.17
Charlson comorbidity index			<0.001[a]		
Absence of comorbidity (0-1)	212 (90.6%)	22 (9.4%)		1	
Low comorbidity (2)	81 (75.7%)	26 (24.3%)		2.86	1.62 to 5.04
High comorbidity (3 or more)	143 (68.1%)	67 (31.9%)		3.87	2.39 to 6.26
Total number of drugs			<0.006[a]		
≤ 4 drugs	136 (86.6%)	21 (13.4%)		1	
> 4 drugs	300 (76.1%)	94 (23.9%)		1.84	1.15 to 2.96
Antiplatelet agents			0.607[a]		
No	272 (79.8%)	69 (20.2%)		1	
AAS100mg	99 (76.2%)	31 (23.8%)		1.19	0.78 to 1.82
AAS>100mg/Clopidogrel	65 (81.3%)	15 (18.8%)		0.90	0.52 to 1.58
Anticoagulants			0.095[a]		
No	404 (80.0%)	101 (20.0%)		1	
Yes	32 (69.6%)	14 (30.4%)		1.63	0.93 to 2.85
Type of fracture			0.811[a]		
Intra-articular	195 (79.6%)	50 (20.4%)			
Extra-articular	241 (78.8%)	65 (21.2%)		1.06	0.73 to 1.53
Haemoglobin at admission			<0.001[a]		
Hb>12 g/dl	276 (84.1%)	52 (15.9%)		1	
Hb ≤12 g/dl	160 (71.7%)	63 (28.3%)		1.93	1.34 to 2.79
Surgical delay			0.693[a]		
0 - 48 hours	268 (78.6%)	73 (21.4%)		1	
> 48 hours	168 (80.0%)	42 (20.0%)		0.92	0.63 to 1.35

	No death n=436	Death n=115	p-value	crude HR	CI 95%
Anaesthesia			0.914[a]		
Spinal	392 (79.2%)	103 (20.8%)		1	
General	44 (78.6%)	12 (21.4%)		1.05	0.58 to 1.91
Surgical technique			0.074[a]		
Hip prosthesis	165 (80.5%)	40 (19.5%)		1	
Dynamic hip screw	134 (74.9%)	45 (25.1%)		1.34	0.88 to 2.06
Intramedullary nail	134 (83.2%)	27 (16.8%)		0.87	0.54 to 1.42
Others	3 (50.0%)	3 (50.0%)		2.94	0.91 to 9.52
Blood transfusion			0.008[a]		
No	192 (84.6%)	35 (15.4%)		1	
Yes	244 (75.3%)	80 (24.7%)		1.71	1.15 to 2.55
Surgery time (minutes)	85 (IQR 65 to 115)	80 (IQR 60 to 111)	0.357[b]	1.00	0.99 to 1.00
Intraoperative complications					
Haemodynamic instability			0.011[a]		
No	305 (82.2%)	66 (17.8%)		1	
Yes	131 (72.8%)	49 (27.2%)		1.67	1.15 to 2.41
Arrhythmias			0.675[c]		
No	430 (79.2%)	113 (20.8%)		1	
Yes	6 (75.0%)	2 (25.0%)		1.45	0.36 to 5.86
Postoperative complications					
Cardiovascular			<0.001[a]		
No	403 (84.0%)	77 (16.0%)		1	
Yes	33 (46.5%)	38 (53.5%)		4.79	3.24 to 7.07
Major			<0.001[c]		
No	429 (81.3%)	99 (18.8%)		1	
Yes	7 (30.4%)	16 (69.6%)		6.68	3.93 to 11.34
Minor			<0.001[a]		
No	408 (81.8%)	91 (18.2%)		1	
Yes	28 (53.8%)	24 (46.2%)		3.24	2.07 to 5.09
Respiratory			<0.001[a]		
No	408 (81.6%)	92 (18.4%)		1	
Yes	28 (54.9%)	23 (45.1%)		3.07	1.95 to 4.86
Haematological			0.604 [a]		
No	416 (78.9%)	111 (21.1%)		1	
Yes	20 (83.3%)	4 (16.7%)		0.80	0.29 to 2.16
Renal			<0.001[a]		
No	352 (83.0%)	72 (17.0%)		1	

	No death n=436	Death n=115	p-value	crude HR	CI 95%
Yes	84 (66.1%)	43 (33.9%)		2.35	1.61 to 3.43
Infections			0.064[a]		
No	388 (80.3%)	95 (19.7%)		1	
Yes	48 (70.6%)	20 (29.4%)		1.61	0.99 to 2.61
Surgical reintervention			0.109[c]		
No	433 (79.4%)	112 (20.6%)		1	
Yes	3 (50.0%)	3 (50.0%)		3.26	1.04 to 10.28
Length of stay (days)	9 (IQR 7 to 13)	10 (IQR 8 to 17)	0.008[b]	1.02	1.00 to 1.03
Destination after discharge			<0.007[a]		
Family home	132 (86.8%)	20 (13.2%)		1	
Convalescence	226 (83.7%)	44 (16.3%)		1.24	0.73 to 2.11
Residence	78 (72.2%)	30 (27.8%)		2.24	1.27 to 3.94
Thirty-day readmission			0.006[a]		
No	402 (83.8%)	78 (16.3%)		1	
Yes	34 (68.0%)	16 (32.0%)		2.21	1.29 to 3.79
Group allocation			0.003[a]		
Control group	201 (73.9%)	71 (26.1%)		1	
Intervention group	235 (84.2%)	44 (15.8%)		0.56	0.39 to 0.82

n (%); median (IQR 25- percentile to 75- percentile).
[a]Pearson χ; [b] Mann–Whitney U; [c]Fisher's exact test.

Additional file 3. Multivariant analysis. Independent prognostic factors for mortality. Adjusted HR for one-year survival.

	Adjusted HR	95% CI	p-value
Age	1.09	1.05 to 1.12	<0.001
Gender			
Female	1		
Male	2.10	1.43 to 3.11	<0.001
ASA			
I-II	1		
III-IV	1.92	0.87 to 4.24	0.105
Charlson Index			
Absence of comorbidity (0-1)	1		
Low comorbidity (2)	2.33	1.29 to 4.23	0.005
High comorbidity (3 or more)	2.84	1.67 to 4.83	<0.001
Intraoperative haemodynamic instability			
No	1		
Yes	1.44	0.97 to 2.14	0.073
Postoperative cardiovascular complications			
No	1		
Yes	3.85	2.49 to 5.96	<0.001
Postoperative renal complications			
No	1		
Yes	1.47	0.96 to 2.25	0.075
Reintervention			
No	1		
Yes	5.31	1.58 to 17.86	0.007
Group allocation			
Control group (CG)	1		
Intervention group (IG)	0.61	0.39 to 0.95	0.029

Additional file 4. Renal complications according to creatinine at admission and group allocation.

	Control (CG)	Intervention (IG)	p-value
Creatinine at admission ≤ 1.09 mg/dl	n=178	n=175	
Renal Postoperative complications	11 (6.2%)	21 (12.0%)	0.057[a]
Creatinine at admission > 1.09 mg/dl	n=93	n=104	
Renal Postoperative complications	22 (23.7%)	73 (70.2%)	<0.001[a]

N (%); [a] χ^2 de Pearson

12-References

Alecu C, Cuignet-Royer E, Mertes PM, Salvi P, Vespignani H, Lambert M, et al. Pre-existing arterial stiffness can predict hypotension during induction of anaesthesia in the elderly. Br. J. Anaesth. [Internet]. British Journal of Anaesthesia. Published by Elsevier Ltd.; 2010;105(5):583–8. Available from: http://dx.doi.org/10.1093/bja/aeq231

Bartha E, Arfwedson C, Imnell A, Fernlund ME, Andersson LE, Kalman S. Randomized controlled trial of goal-directed haemodynamic treatment in patients with proximal femoral fracture. Br. J. Anaesth. 2013;110(4):545–53.

Beecham G, Cusack R, Sebastian Vencken. Hypotension during hip fracture surgery and postoperative morbidity. Ir. J. Med. Sci. Irish Journal of Medical Science; 2020;189(3):1087–96.

Brienza N, Biancofiore G, Cavaliere F, Corcione A, de Gasperi A, de Rosa RC, et al. Clinical guidelines for perioperative hemodynamic management of non cardiac surgical adult patients. Minerva Anestesiol. 2019;85(12):1315–33.

Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? Curr. Opin. Crit. Care. 2011;17(3):290–5.

Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann. Surg. 2012;256(1):18–24.

Cowan R, Lim JH, Ong T, Kumar A, Sahota O. The Challenges of Anaesthesia and Pain Relief in Hip Fracture Care. Drugs and Aging. Springer International Publishing; 2017;34(1):1–11.

Davies SJ, Yates DR, Wilson RJT, Murphy Z, Gibson A, Allgar V, et al. A randomised trial of non-invasive cardiac output monitoring to guide haemodynamic optimisation in high risk

patients undergoing urgent surgical repair of proximal femoral fractures (ClearNOF trial NCT02382185). Perioper. Med. Perioperative Medicine; 2019;9(30):1–11.

Giglio M, Manca F, Dalfino L, Brienza N. Perioperative hemodynamic goal-directed therapy and mortality: A systematic review and meta-analysis with meta-regression. Minerva Anestesiol. 2016;82(11):1199–213.

Griffiths R, Babu S, Dixon P, Freeman N, Hurford D, Kelleher E, et al. Guideline for the management of hip fractures 2020: Guideline by the Association of Anaesthetists. Anaesthesia. 2021;76(2):225–37.

Grocott MPW, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: A cochrane systematic review. Br. J. Anaesth. The Author(s); 2013;111(4):535–48.

Guinot PG, Bernard E, Defrancq F, Petiot S, Majoub Y, Dupont H, et al. Mini-fluid challenge predicts fluid responsiveness during spontaneous breathing under spinal anaesthesia: An observational study. Eur. J. Anaesthesiol. 2015;32(9):645–9.

Hahn RG. Renal injury during hip fracture surgery: an exploratory study. Anestezjol. Intens. Ter. 2015;47(4):284–90.

Heming N, Moine P, Coscas R, Annane D. Perioperative fluid management for major elective surgery. Br. J. Surg. 2020;107(2):e56–62.

Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit. Care [Internet]. BioMed Central Ltd; 2015;19(Suppl 3):S8. Available from: http://www.ccforum.com/content/19/S3/S8

Ishihara H. Kidney function after the intraoperative use of 6 % tetrastarches (HES 130/0.4 and 0.42). J. Anesth. 2014;28(2):249–56.

Jacob M, Chappell D, Hofmann-Kiefer K, Conzen P, Peter K, Rehm M. Determinants of insensible fluid loss. Perspiration, protein shift and endothelial glycocalyx. Anaesthesist.

2007;56(8):747–64.

Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery a review. JAMA Surg. 2017;152(3):292–8.

Lugo G, Arizpe D, Dominguez G RM et al. Relationship between oxygen consumption and oxigen delivery during anesthesia in high-risk surgical patients. Crit. Care Med. 1993;21(1):64–9.

Mallat J, Meddour M, Durville E, Lemyze M, Pepy F, Temime J, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. Br. J. Anaesth. 2015;115(3):449–56.

Marik PE. Fluid therapy in 2015 and beyond: The mini-fluid challenge and mini-fluid bolus approach. Br. J. Anaesth. 2015;115(3):347–9.

Meersch M, Schmidt C, Zarbock A. Perioperative Acute Kidney Injury: An Under-Recognized Problem. Anesth. Analg. 2017;125(4):1223–32.

Merry AF, Mitchell SJ. Complications of anaesthesia. Anaesthesia. 2018;73:7–11.

Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). Can. J. Anesth. 2015;62(2):158–68.

Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping STJ, Bentt DR, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology [Internet]. 2015 Aug;123(2):307–19. Available from: http://insights.ovid.com/crossref?an=00000542-201508000-00016

Montenij L, Waal E De, Frank M, Beest P Van, Wit A De, Kruitwagen C, et al. Influence of early goal-directed therapy using arterial waveform analysis on major complications after high-risk abdominal surgery : study protocol for a multicenter randomized controlled superiority trial. 2014;1–12.

Moppett IK, Rowlands M, Mannings A, Moran CG, Wiles MD, Van DeWalt G, et al. LiDCO-based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: A randomized trial and systematic review. Br. J. Anaesth. 2015;114(3):444–59.

Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: The mini-fluid challenge study. Anesthesiology. 2011;115(3):541–7.

Muñoz JL, Gabaldón T, Miranda E, Berrio DL, Ruiz-tovar J, Ronda JM, et al. Goal-Directed Fluid Therapy on Laparoscopic Sleeve Gastrectomy in Morbidly Obese Patients. Obes Surg. 2016;26(11):2648–53.

Reguant F, Arnau A, Lorente J V, Maestro L, Bosch J. Efficacy of a multidisciplinary approach on postoperative morbidity and mortality of elderly patients with hip fracture. J. Clin. Anesth. [Internet]. Elsevier; 2019;53(September 2018):11–9. Available from: https://doi.org/10.1016/j.jclinane.2018.09.029

Roche JJW, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: Prospective observational cohort study. Br. Med. J. 2005;331(7529):1374–6.

Rocos B, Whitehouse MR, Kelly MB. Resuscitation in hip fractures : a systematic review. Br. Med. J. 2017;7(e015906):1–6.

Saugel B, Cecconi M, Wagner JY, Reuter DA. Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. Br. J. Anaesth. [Internet]. The Author(s); 2015;114(4):562–75. Available from: http://dx.doi.org/10.1093/bja/aeu447

Saugel B, Joosten A, Scheeren TWL. Perioperative goal-directed therapy: what's the best study design to investigate its impact on patient outcome? J. Clin. Monit. Comput. [Internet]. Springer Netherlands; 2019;33(3):361–3. Available from:

http://dx.doi.org/10.1007/s10877-018-0196-2

Sedgwick P. Before and after study designs. BMJ. 2014;349(January):g5074.

Tassoudis V, Vretzakis G, Petsiti A, Stamatiou G, Bouzia K, Melekos M, et al. Impact of intraoperative hypotension on hospital stay in major abdominal surgery. J. Anesth. 2011;25(4):492–9.

Teboul JL, Saugel B, Cecconi M, De Backer D, Hofer CK, Monnet X, et al. Less invasive hemodynamic monitoring in critically ill patients. Intensive Care Med. Springer Berlin Heidelberg; 2016;42(9):1350–9.

Veronese N, Maggi S. Epidemiology and social costs of hip fracture. Injury [Internet]. Elsevier Ltd; 2018;49(8):1458–60. Available from: https://doi.org/10.1016/j.injury.2018.04.015

Wesseling, K H; de Wit, B; Van der Hoeven, A;Van Goudoever JSJ. Physiocal, calibrating finger vascular physiology for FInapres. Homeostasis. 1995;36(2–3):67–82.

Yu J, Zhang C, Li L, Kwong JSW, Xue L, Zeng X, et al. Internal fixation treatments for intertrochanteric fracture: A systematic review and meta-Analysis of randomized evidence. Sci. Rep. [Internet]. Nature Publishing Group; 2015;5(June):1–11. Available from: http://dx.doi.org/10.1038/srep18195

4.2. Artículo 2

INTRAOPERATIVE HAEMODYNAMIC OPTIMISATION USING THE HYPOTENSION PREDICTION INDEX AND ITS IMPACT ON TISSULAR PERFUSION: A PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

Juan Victor Lorente, Ignacio Jimenez, Javier Ripollés-Melchor, Alejandra Becerra, Wilbert Wesselink, Francesca Reguant, Irene Mojarro, Maria de los Angeles Fuentes, Ane Abad-Motos, Elizabeth Agudelo, Francisco Herrero-Machancoses, Paula Callejo, Joan Bosch, Manuel Ignacio Monge.

BMJ Open 2022; 12:e051728
Factor de Impacto 2022: 3.587
Categoría: General Medicine, Segundo Cuartil

Intraoperative hemodynamic optimization using the Hypotension Prediction Index and its impact on tissular perfusion. A protocol for a randomized controlled trial.

Lorente JV MD, [a,b,*], Jiménez I MD, PhD [c] , Ripollés-Melchor J MD [d] , Becerra AI MD, PhD [e] , Wesselink WA MD, PhD [f], Reguant F MD, PhD [g,b], Mojarro I MD [a] , Fuentes MA MD, PhD [c] , Abad-Motos A MD [d] , Agudelo E MD [e] , Machancoses FH MD, PhD [h] , Callejo P MD [i], Bosch J MD, PhD [b] , Monge García MI MD [j]

[a] Clinical Management Anesthesiology Unit, Resuscitation and Pain Therapy, Juan Ramón Jiménez Hospital, Huelva, Spain

[b] School of Medicine and Health Sciences, International University of Catalonia (UIC), Barcelona, Spain

[c] Clinical Management Anesthesiology Unit, Resuscitation and Pain Therapy, Virgen del Rocio Hospital, Sevilla, Spain

[d] Anesthesia and Critical Care Department, Infanta Leonor Hospital, Madrid, Spain

[e] Clinical Management Anesthesiology Unit, Resuscitation and Pain Therapy, Infanta Cristina University Hospital, Badajoz, Spain

[f] Edwards Lifesciences, Irvine, California, USA

[g] Department of Anaesthesiology. Althaia. Xarxa Assistencial Universitària de Manresa. C/ Dr. Joan Soler, 1-3, 08243 Manresa. Barcelona. Spain.

[h] Predepartamental Unit of Medicine, Science Health Faculty, Jaume I University, Castellón, Spain

[i] Clinical Research Unit. Fundación Pública Andaluza Progreso y Salud.

[j] Intensive Care Unit, Hospital Universitario SAS de Jerez, Jerez de la Frontera, Spain

[*] *Corresponding author*: Clinical Management Anaesthesiology Unit, Resuscitation and Pain Therapy, Juan Ramón Jiménez Hospital, Ronda Norte s/n, 21005, Huelva, Spain

E-mail address: juanvictor.lorente@gmail.com

Keywords: intraoperative hypotension; goal-directed haemodynamic therapy; machine learning; acute kidney injury; microcirculation monitoring

ABSTRACT:

Introduction: Intraoperative arterial hypotension is associated with poor postoperative outcomes. The Hypotension Prediction Index (HPI) developed using machine learning techniques, allows the prediction of arterial hypotension analyzing the arterial pressure waveform. The use of this index may reduce the duration and severity of intraoperative hypotension in adults undergoing non-cardiac surgery. This study aims to determine whether a treatment protocol based on the prevention of arterial hypotension using the HPI algorithm reduces the duration and severity of intraoperative hypotension compared with the recommended goal-directed fluid therapy strategy and may improve tissue oxygenation and organ perfusion.

Methods and analysis: We will conduct a multicenter, randomized, controlled trial (N=80) in high-risk surgical patients scheduled for elective major abdominal surgery. All participants will be randomly assigned to a control or intervention group. Hemodynamic management in the control group will be based on standard hemodynamic parameters. Hemodynamic management of patients in the intervention group will be based on functional hemodynamic parameters provided by the HemoSphere platform (Edwards Lifesciences Corp.), including dynamic arterial elastance, $dP/dt_{max,}$ and the Hypotension Prediction Index. Tissue oxygen saturation will be recorded non-invasively and continuously by using near-infrared spectroscopy technology. Biomarkers of acute kidney stress (cTIMP2 and IGFBP7) will be obtained before and after surgery. The primary outcome will be the intraoperative time-weighted average of a mean arterial pressure < 65mmHg.

Ethics and dissemination: Ethics Committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). Findings will be widely disseminated through peer-reviewed publications and conference presentations.

Trial registration: ClinicalTrials.gov, NCT04301102.

Strengths and limitations of this study.

- A multicenter randomized controlled trial to test whether an HPI-based therapeutical protocol reduces intraoperative hypotension and affects tissue oxygenation and organ perfusion in non-cardiac surgery.
- The primary outcome is the intraoperative time-weighted average of the mean arterial blood pressure below 65 mmHg (TWA-MAP<65) and other variables related to IOH. Secondary outcomes are intraoperative S_tO_2, as an indicator of tissue oxygenation, postoperative measurements of the TIMP-2 and IGFBP7 (AKIRisk), postoperative complications, length of hospital stay, and 30-day mortality.
- The study sample size was calculated based on the potential reduction in intraoperative hypotension, not the potential reduction in postoperative complications.
- Although the clinical teams performing the trial interventions will not be blinded to the patient inclusion group, they will not be aware of the perioperative StO_2 and AKIRisk variables. Research staff assessing clinical outcomes will not be aware of treatment group assignment.
- No one-year mortality follow-up of recruited patients is currently proposed.

Introduction

Intraoperative monitoring of usual hemodynamic parameters, such as heart rate or blood pressure, is insufficient to ensure adequate oxygen delivery (DO_2) to the tissues and prevent organ hypoperfusion [1]. Moreover, tissue hypoxia is a significant determinant of a surgical patient's outcome [2]. Hemodynamic strategies aimed to optimize DO_2 and prevent organ hypoperfusion, also known as goal-directed therapies (GDT), have been demonstrated to be superior to the traditional care of patients undergoing surgery. This perioperative hemodynamic optimization has been associated with a significant reduction in morbidity and mortality [3].

Moreover, arterial hypotension is a frequent phenomenon during the intraoperative period and has been related to the development of organ hypoperfusion and poor postoperative outcomes [4]. Both the duration and severity of arterial hypotension are significant determinants of the postoperative outcome [5]. Particularly, intraoperative hypotension (IOH) significantly increases acute kidney and myocardial injury [6].

The Hypotension Prediction Index (HPI) is a recently available index developed from machine learning that predicts the occurrence of arterial hypotension from the analysis of the arterial pressure waveform. The HPI value indicates the likelihood of an arterial hypotension event in the following 5-10 minutes [7]. The use of this index coupled with a proactive therapeutic attitude may reduce intraoperative hypotension in adults undergoing non-cardiac surgery patients [8] [9] [10]. However, not all studies that have used intraoperative HPI-guided therapy have successfully reduced the time and severity of IOH. Particularly, the pilot study by Maheshwari et al.[11] did not demonstrate a significant reduction in IOH using an HPI-guided therapeutical protocol. Furthermore, all these positive results came from single-center studies or retrospective analysis of available data, which reduces the external validity of their results.

Moreover, since tissue oxygenation depends not only on DO_2 but also on perfusion pressure, hemodynamic optimization should be targeted to achieve an adequate blood flow and arterial pressure that ensures normal organ function. We, therefore, hypothesize that an HPI-based therapeutic protocol will reduce the overall duration of intraoperative arterial hypotension and may improve tissue oxygenation and organ perfusion during non-cardiac surgery.

Methods and analysis

This manuscript was written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline (Additional file 1) on reporting of interventional trial protocols [12].

A multicentre, randomized controlled trial, with daily follow-up of patients until hospital discharge and mortality censured at 30 days after surgery, will be conducted. The study will be carried out at five different Spanish hospitals: Juan Ramón Jiménez University Hospital (Huelva), Virgen del Rocío University Hospital (Sevilla), Infanta Leonor University Hospital (Madrid), Hospital Universitario SAS de Jerez (Jerez de la Frontera) and Infanta Cristina University Hospital (Badajoz).

Enrolled patients will be at least 65 years old and/or American Society of Anesthesiologist (ASA) physical status III/IV, scheduled for elective major abdominal surgery (general surgery, urology, or gynecology, through laparoscopic or open approach), with general or combined anesthesia. Surgery will be considered to be major if the expected duration is > 2 h, or the estimated blood loss is > 15% of blood volume, or if the expected required transfusion is ≥ 2 packed red blood cells.

Exclusion criteria will be pregnancy, preoperative glomerular filtrate < 60 ml/min/1.73m^2 according to the CKD-EPI 2009 formula, persistent atrial fibrillation,

known cardiac shunts, right ventricular dysfunction, severe valvulopathy, kidney transplant recipient and refusal to participate in the study.

Study protocol

Researchers will screen all patients who present for elective, non-cardiac surgery. Patients will be contacted by the principal investigator (PI) of each hospital and informed if they are eligible. The patient's informed consent will be obtained the day before surgery. Patient demographics and comorbidities will be collected before randomization. Patients will be assigned by the local PI to the intraoperative HPI algorithm (intervention group) or a GDT algorithm (control group). We will use a computer-generated, variable block randomization method through age strata. Patients will not be aware of the group allocation. Although intraoperative personnel (anesthesiologists, surgeons…) will be not blinded to monitoring allocation, data-analysis will remain blinded.

All principal investigators and collaborators will receive specific training with the monitoring used for hemodynamic management.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is shown in Figure 1. All data will be entered using an electronic Clinical Report Form in Castor EDC, a Good-Clinical-Practice-compliant data management system [13].

Common perioperative measures

Before the induction and during surgery, all subjects will receive standard of care with a five-lead electrocardiogram, pulse oximetry, a peripheral intravenous line, and an indwelling radial arterial catheter.

All subjects will receive general or combined anaesthesia, neuraxial analgesia technique (epidural or intradural) will be performed according to the preference of the

anaesthesiologist before induction. For pragmatic reasons, the administration of the drugs used in the induction of anaesthesia and neuromuscular relaxants will be at the discretion of the anaesthesiologist. Bispectral-index monitoring (BIS; Medtronic, Dublin, Ireland) will be used to monitor the depth of anaesthesia. Sevoflurane will be used for hypnosis maintenance, with a BIS target range of 40-60. All patients will receive invasive and continuous arterial pressure monitoring with an indwelling radial arterial catheter connected to a FloTrac® sensor in the control group or an Acumen IQ® sensor in the intervention group (Edwards Lifesciences Corp., Irvine, CA, USA).

All subjects will receive standard measures to maintain oxygen saturation by pulse oximetry >94%, normothermia (>36ºC), and heart rate <100 beats/min. Ventilation with an inspired oxygen fraction of 60% will be mechanically controlled to maintain $PaCO_2$ between 4.7 and 6.0 kPa, with a positive end-expiratory pressure of 4-6 mmHg and a tidal volume of 8ml/kg. For maintenance fluid therapy, a balanced crystalloid (Isofundin®/Plasmalyte®) will be administered at 1-3 ml/kg/h for laparoscopic surgery and 5-7 ml/kg/h for open surgery. Flow optimization will be performed with hydroxyethyl starch (Voluven®)[14]. Packed red blood cells will be transfused if the haemoglobin level is < 8 g/dL [15]. The choice and dose of the vasopressor and ionotropic drugs will be determined by the anaesthesiologist in charge of the patient in both groups.

Tissue oxygen saturation (StO_2) will be non-invasively and continuously recorded every 2 seconds placing an adult sensor (ForeSight Elite® sensor, model FSESL, Edwards Lifesciences Corp., Irvine, CA, USA) over the brachioradial muscle by using near-infrared spectroscopy (NIRS) technology (ForeSight Elite® tissue oximetry system, Edwards Lifesciences Corp., Irvine, CA, USA). Details about this NIRS technology are provided elsewhere [16]. StO_2 values will be hidden from the main screen in both groups but

will be recorded internally into the HemoSphere system, so StO_2 values will not be available to clinicians and therefore cannot induce changes in patient management.

The hemodynamic optimization algorithm will begin 15 minutes after the start of the surgery, once the hemodynamic impact of anaesthesia and surgery have been stabilized. Meanwhile, the hemodynamic goal in both groups will be to achieve a mean arterial pressure (MAP) > 65 mmHg with the administration of boluses of vasopressors at the choice of the anaesthesiologist. In both groups, hemodynamic data will be recorded every 20 seconds in the HemoSphere system after starting the hemodynamic optimization protocols and downloaded after the surgery for offline analysis.

During the surgery, any procedure carried out with repercussions for the hemodynamic status of the patient will be marked and adequately labeled for further identification.

Biomarkers of acute kidney stress in the perioperative period will be measured by the PI and blinded for the rest of the researchers. Urinary [TIMP-2]-[IGFBP7] will be measured with the Astute140 Meter (BioMérieux). This device applies a sandwich immunoassay technique and converts the fluorescent signals from each of the two immunoassays (TIMP-2 and IGFBP7) contained within the Nephrocheck test cartridge into a single numerical risk result (AKIRisk). The result is calculated as the product of the measured concentrations of the two cell-cycle arrest biomarkers and can quantify the stress developed by kidney epithelial cells during surgery, identifying patients at risk of postoperative Acute Kidney Injury (AKI) [17] [18] [19].

The first urine sample will be collected when performing the bladder catheterization after induction. The first postoperative sample will be collected 4 hours after the patient's admission to the Intensive Care Unit for postoperative stay. If the value of this

sample is in the grey zone, between 0.3 and 2, a second postoperative sample will be collected 12 hours after the first one [20].

Arterial blood analyses will be performed after induction of anaesthesia, midway through the surgery, immediately after admission to the Intensive Care Unit, and daily from postoperative day 1 to day 5 inclusive.

Hemodynamic management

Control group

Hemodynamic management will be based on the hemodynamic parameters provided by the HemoSphere platform® with the FloTrac® sensor, including cardiac index (CI) and stroke volume variation (SVV). The hemodynamic optimization algorithm on this group is shown in Figure 2. If SVV increases above 13%, a fluid bolus of 250 ml of colloid will be performed. MAP will be maintained above 65 mmHg by a vasoconstrictor drug. An ionotropic agent will be added if the CI persists < 2.5 l/ml/m^2 after previous steps.

Intervention group

Hemodynamic management will be based on the hemodynamic parameters provided by the HemoSphere platform with the Acumen IQ sensor, including CI, SVV, and Acumen IQ specific parameters: maximum arterial pressure rise (dP/dt_{max}), dynamic arterial elastance (Ea_{dyn}), and HPI. The hemodynamic optimization algorithm on the intervention group is based on the three main mechanisms leading to arterial hypotension: hypovolemia, impaired contractility, and vasoplegia (Figure 3). When HPI rises above 85%, SVV will be checked. If SVV is < 13%, a vasoconstrictor will be administered if dP/dt_{max} value is > 400 mmHg·s, or an inotrope if dP/dt_{max} is < 400 mmHg·s. If SVV is

>13%, a 250 ml fluid bolus will be administered if the Ea_{dyn} value is > 1, or a vasoconstrictor if Ea_{dyn} < 1.

Study outcomes

Primary Outcomes

- Intraoperative time-weighted average of MAP < 65mmHg (TWA-MAP<65), calculated as the area between 65 mmHg threshold and the curve of the MAP measurements (AUC 65 mmHg) divided by the total continuous reading time [21]:

$$TWA - MAP < 65 = \frac{\sum_{i=1}^{k}(area_1<65)+(area_2<65+\cdots+area_k<65)}{Total\ time\ of\ measurements}$$

The advantage of using TWA-MAP instead of MAP is that the former combines the severity and duration of the hypotension considering the overall duration of the surgery.

- Other variables related to IOH: the number of intraoperative hypotension episodes (defined as an event of MAP < 65 mmHg of at least 1-minute duration) and the total time of hypotension per case.

Secondary Outcomes

The secondary outcomes include:

- Intraoperative StO_2, as an indicator of tissue oxygenation and wellness of the microcirculation. StO_2 will be non-invasively and continuously recorded in the brachioradial muscle in the arm opposite to the arterial line. We will calculate the

time-weighted average of all StO_2 measurement values, the time weighted averaged below an individual specific threshold obtained during the first minute of optimization and identifying the minimum StO_2, defined as the minimum value sustained at least for 5 min [22] [23].

- Postoperative measurements of the TIMP-2 and IGFBP7 (AKIRisk). We will compare the AKIRisk at baseline and the evolution among both groups.

At the end of the surgery, data regarding the total fluid therapy during surgery, the accumulated dose of opioids during the intraoperative period, accumulated dose of vasoactive agents during the intraoperative period, accumulated dose of ionotropic drugs during the intraoperative period, other drugs with a hemodynamic impact not included in previous groups, total intraoperative diuresis, and transfusion of total blood products during surgery, will be collected.

Secondary outcomes will also include postoperative complications in accordance with the European Perioperative Clinical Outcome (EPCO) definitions [24], length of hospital stay, and 30-day mortality. Postoperative follow-up of patients will be performed by a collaborating investigator from each centre, blinded for the randomization. For an overview of the outcome assessments see Figure 4

Sample Size and Data Analysis

The literature indicates that a cumulative hypotension time of more than 10 minutes during surgery is clinically relevant [25]. Given the novelty of the HPI parameter and the lack of publications during the design of this study, a pilot study in 31 patients undergoing major surgery was performed at the Virgen del Rocío Hospital. In this preliminary study, two groups were defined: a control group with invasive and continuous arterial pressure

monitoring but without the use of HPI; and an intervention group with invasive and continuous blood pressure monitoring, in which the anaesthesiologist also had access to the HPI value and the additional parameters during surgery. In both groups, the hemodynamic objective during the intraoperative period was to maintain the MAP above 65 mmHg. The results from this preliminary study revealed that in the control group (15 patients), 68.75% of the patients accumulated more than 10 minutes of hypotension (11 patients), while in the intervention group with HPI (16 patients), only 31.25% of the patients accumulated periods of a MAP < 65 mmHg more than 10 minutes (5 patients).

Based on this pilot study, to achieve a 90% power, and a significance level of 5%, 72 patients will be required (36 in each group). Assumed a drop-out rate of 10%, a total of 80 patients will be required (40 patients per group).

Statistical Analysis

The normality of data distribution was assessed by the D'Agostino-Pearson test and confirmed by inspection of a Q-Q Plot. The results are expressed as the mean ± standard deviation (SD) when normally distributed or the median (25^{th} to 75^{th} interquartile). Categorical data were given as frequencies with percentages.

Comparison of quantitative variables between control and intervention group will be performed with the Mann-Whitney U test or the independent *t* test, and the Chi-square test ($\chi 2$) for categorical variables. To establish a relationship between changes intraoperative hypotension management and tissue perfusion, a regression analysis will be performed between TWA-MAP and the perfusion indexes (StO_2 and AKIRisk).

A p value < 0.05 will be considered statistically significant. The statistical analyses will be performed with the SPSS software, version 23.0.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Discussion

Our goal is to determine whether a goal-directed algorithm based on the prevention of arterial hypotension using the HPI and the aid of the additional parameters, such as arterial dP/dt_{max} and Ea_{dyn}, reduces the duration and severity of intraoperative hypotension when compared with the recommended goal-directed fluid therapy. We also aim to determine whether this optimization of the systemic perfusion pressure influences intraoperative tissue perfusion and postoperative complications. To achieve this objective, we will include patients with a higher risk of intraoperative hypoperfusion (>65 years old and/or ASA III/IV).

Considering the significant impact of intraoperative arterial hypotension on mortality and morbidity, arterial pressure should be considered as a critical element. Therefore, maintaining blood pressure within a physiological range that ensures tissue perfusion should be considered not an option. Furthermore, the definition of blood pressure as a critical element, also implies a paradigm shift in the current treatment of intraoperative arterial hypotension from a reactive attitude to a proactive action based on predictors, such as HPI. If this proactive attitude associates with a better patient's outcome still needs to be proven clinically. Moreover, the proper correction of arterial hypotension also depends on the adequate identification of the pathophysiological mechanisms leading to low blood pressure and the choice of the optimal treatment [9]. Accordingly, the clinical benefit of an artificial parameter based on machine learning, such as HPI, should be analyzed coupled with the hemodynamic protocol that determines the best treatment according to

those physiological mechanisms involved in the development of arterial hypotension. Therefore, if this preemptive hemodynamic protocol affects tissue perfusion is also one of the goals of our study.

Ethics and dissemination

Ethics Committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). Written informed consent will be obtained from all included patients. Patients will be informed that they may decline to participate or withdraw from the study at any time.

Serious adverse effect of the product which, by its nature, incidence, intensity, or consequences has not been identified in the updated version of the risk analysis report.

The trial was registered in the ClinicalTrials.gov database on March 10th, 2020 (NCT04301102) by the main investigator (JVL).

Regardless of the outcomes, it is our intention to publish the results of this study in a peer-reviewed journal. Findings will also be presented at Spanish and international conferences.

Trial Status

Protocol version 1.0; March 2020. Recruitment started in November 2020, and it is expected to be finished on February 2022.

List of abbreviations

- **AKI**: Acute Kidney Injury
- **AKIRisk**: Acute Kidney Injury risk.
- **ASA:** The American Society of Anaesthesiologists (ASA) physical status classification system.
- **AUC**: Area Under the Curve.
- **aVR-MAP**: Average Real Variability of the Mean Arterial Pressure.
- **CKD-EPI:** Chronic Kidney Disease Epidemiology Collaboration.
- **Ea_{dyn}**: Dynamic Arterial elastance.
- **EPCO:** European Perioperative Clinical Outcome.
- **HPI:** Hypotension Prediction Index.
- **ICU:** Intensive Care Unit.
- **IGFBP-7**: Insulin Growth Factor Binding Protein 7.
- **IOH:** Intraoperative Hypotension
- **MAP**: Mean Arterial Pressure.
- **MINS**: Myocardial Injury after Non-cardiac Surgery.
- **NIRS**: Near Infrared Light Spectrophotometry.
- **StO_2**: Tissue Oxygen Saturation.
- **SV**: Stroke Volume.
- **TIMP-2**: Tissue Metalloproteinase Inhibitor 2.

- **TWA-MAP < 65***:* Time Weighted Average of Mean Arterial Pressure under 65 mmHg.
- **SVV**: Stroke Volume Variation.

Additional File: SPIRIT checklist

Funding

This study was supported by Edwards Lifesciences through a grant provided after presenting the study to a competitive international call via its Grant Portal (Grant Number: HCP-8200579)

The design of the study, the writing of this manuscript and the collection and interpretation of data are being carried out independently by the research team, without any intervention from the funding body.

Availability of data and materials

Not applicable

Patient consent for publication Not required.

Authors` contributions

Concept, study design and first draft of manuscript: JVL, IJ, JRM, FH, PC, MIMG**.**

Manuscript review and data collection: JVL, IJ, JRM, MIMG, AIB, IM, MAF, AAM, EA.

Editing and critical review: JVL, IJ, JRM, MIMG, WW, FH, PC, JB, FR.

Monitoring

The study has been classified by the Spanish Agency for Medicines and Healthcare Products as a "Non-observational study without medicines", being applicable to it the provisions of Law 14/2007, of July 3rd, on Biomedical Research. Therefore, not need to be monitored by a Data Monitoring Committee.

Competing interest

JVL: Edwards Lifesciences, Fresenius Kabi, Baxter, Vifor Pharma and bioMérieux conference fees, financial support for Edwards Lifesciences research obtained through the Grant Portal of the company. Economic research support from bioMérieux.

IJ: Edwards Lifesciences conference fees

JRM: Edwards Lifesciences, MSD, Fresenius Kabi and Dextera Medical conference fees

MIMG: Clinical consultant for Edwards Lifesciences and Dextera Medical.

WW: Employed by Edwards Lifesciences

The rest of the authors declare no conflict of interest.

References

1 Shoemaker WC. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. *Crit Care Med* 1988;**16**:1117–20.

2 Parker T, Brealey D, Dyson A, *et al.* Optimising organ perfusion in the high-risk surgical and critical care patient : a narrative review. *Br J Anaesth* 2019;**123**:170–6. doi:10.1016/j.bja.2019.03.027

3 Heming N, Moine P, Coscas R, *et al.* Perioperative fluid management for major elective surgery. Br. J. Surg. 2020;**107**:e56–62. doi:10.1002/bjs.11457

4 Ahuja S, Mascha EJ, Yang D, *et al.* Associations of Intraoperative Radial Arterial Systolic, Diastolic, Mean, and Pulse Pressures with Myocardial and Acute Kidney Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. *Anesthesiology* Published Online First: 25 November 2019. doi:10.1097/ALN.0000000000003048

5 Walsh M, Devereaux PJ, Garg AX, *et al.* Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery. *Anesthesiology* 2013;**119**:507–15. doi:10.1097/ALN.0b013e3182a10e26

6 Khanna AK, Maheshwari K, Mao G, *et al.* Association Between Mean Arterial Pressure and Acute Kidney Injury and a Composite of Myocardial Injury and Mortality in Postoperative Critically Ill Patients. *Crit Care Med* 2019;**47**:910–7. doi:10.1097/CCM.0000000000003763

7 Hatib F. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. *Perioper Med* 2018;**129**:1–12.

8 Marije Wijnberge, MD; Bart F. Geerts, MD, PhD, MSc, MBA; Liselotte Hol, MD; Nikki Lemmers, MD; Marijn P. Mulder, BSc; Patrick Berge, MD; Jimmy Schenk, MSc; Lotte E. Terwindt, MD; MarkusW. Hollmann, MD, PhD; Alexander P.

Vlaar, MD, PhD, MBA; Denise P. Veel P. Effect of a Machine Learning–Derived Early Warning System for Intraoperative Hypotension vs Standard Care on Depth and Duration of Intraoperative Hypotension During Elective Noncardiac Surgery The HYPE Randomized Clinical Trial. *JAMA* 2020;**323**:1052–60. doi:10.1001/jama.2020.0592

9 de Keijzer IN, Vos JJ, Scheeren TWL. Hypotension Prediction Index: from proof-of-concept to proof-of-feasibility. *J Clin Monit Comput* Published Online First: 23 January 2020. doi:10.1007/s10877-020-00465-3

10 Schneck E, Schulte D, Habig L, *et al.* Hypotension Prediction Index based protocolized haemodynamic management reduces the incidence and duration of intraoperative hypotension in primary total hip arthroplasty: a single centre feasibility randomised blinded prospective interventional trial. *J Clin Monit Comput* Published Online First: 2019. doi:10.1007/s10877-019-00433-6

11 Maheshwari K, Shimada T, Yang D, *et al.* Hypotension Prediction Index for Prevention of Hypotension during Moderate- To High-risk Noncardiac Surgery: A Pilot Randomized Trial. *Anesthesiology* 2020;:1214–22. doi:10.1097/ALN.0000000000003557

12 Chan AW, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**:1–42. doi:10.1136/bmj.e7586

13 EDC C. Castor Electronic Data Capture. 2019.https://castoredc.com

14 Chappell D, van der Linden P, Ripollés-Melchor J, *et al.* Safety and efficacy of tetrastarches in surgery and trauma: a systematic review and meta-analysis of randomised controlled trials. *Br J Anaesth* 2021;**127**:556–68. doi:10.1016/j.bja.2021.06.040

15 Kozek-Langenecker SA, Ahmed AB, Afshari A, *et al. Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology*. 2017. doi:10.1097/EJA.0000000000000630

16 Scheeren TWL, Schober P, Schwarte LA. Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): Background and current applications. *J Clin Monit Comput* 2012;**26**:279–87. doi:10.1007/s10877-012-9348-y

17 Kianoush Kashan, Ali Al-Khafaji, Thomas Ardiles, Antonio Artigas, Sean M Bagshaw,Max Bell,Azra Bihorac, Robert Birkhahn,Cynthia M Cely, Lakhmir S Chawla, Danielle L Davison,Thorsten Feldkamp,Lui G Forni, Michelle Ng Gong, Kyle J Gunnerson, Michael Haase, KZ and JAK. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 2013;**17**. doi:10.1186/cc12503.

18 Meersch M, Schmidt C, Hoffmeier A, *et al.* Prevention of cardiac surgery - associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers : the PrevAKI randomized controlled trial. *Intensive Care Med* 2017;**43**:1551–61. doi:10.1007/s00134-016-4670-3

19 Ivan Gocze. Biomarker-guided Intervention to Prevent Acute Kidney Injury The Prospective Randomized BigpAK Study. *Ann Surg* 2017;**267**:1–8. doi:10.1097/SLA.0000000000002485

20 Engelman DT, Crisafi C, Germain M, *et al.* Utilizing Urinary Biomarkers to Reduce Acute Kidney Injury Following Cardiac Surgery. *J Thorac Cardiovasc Surg* Published Online First: 2019. doi:10.1016/j.jtcvs.2019.10.034

21 Maheshwari K, Khanna S, Bajracharya GR, *et al.* A Randomized Trial of Continuous Noninvasive Blood Pressure Monitoring During Noncardiac Surgery. 2018;**127**:424–31. doi:10.1213/ANE.0000000000003482

22 Abdelmalak BB, Cata JP, Bonilla A, *et al.* Intraoperative tissue oxygenation and postoperative outcomes after major non-cardiac surgery: An observational study. *Br J Anaesth* 2013;**110**:241–9. doi:10.1093/bja/aes378

23 Spruit RJ, Schwarte LA, Hakenberg OW, *et al.* Association of intraoperative tissue oxygenation with suspected risk factors for tissue hypoxia. *J Clin Monit Comput* 2013;**27**:541–50. doi:10.1007/s10877-013-9460-7

24 Jammer I, Wickboldt N, Sander M, *et al.* Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine : European Perioperative Clinical Outcome (EPCO) definitions A statement from the ESA-ESICM joint taskforce on perioperative outcome meas. 2015;:88–105. doi:10.1097/EJA.0000000000000118

25 Wesselink EM, Kappen TH, Torn HM, *et al.* Intraoperative hypotension and the risk of postoperative adverse outcomes : a systematic review. *Br J Anaesth* 2018;**16**. doi:10.1016/j.bja.2018.04.036

Figures

Figure 1: Consort Flow diagram

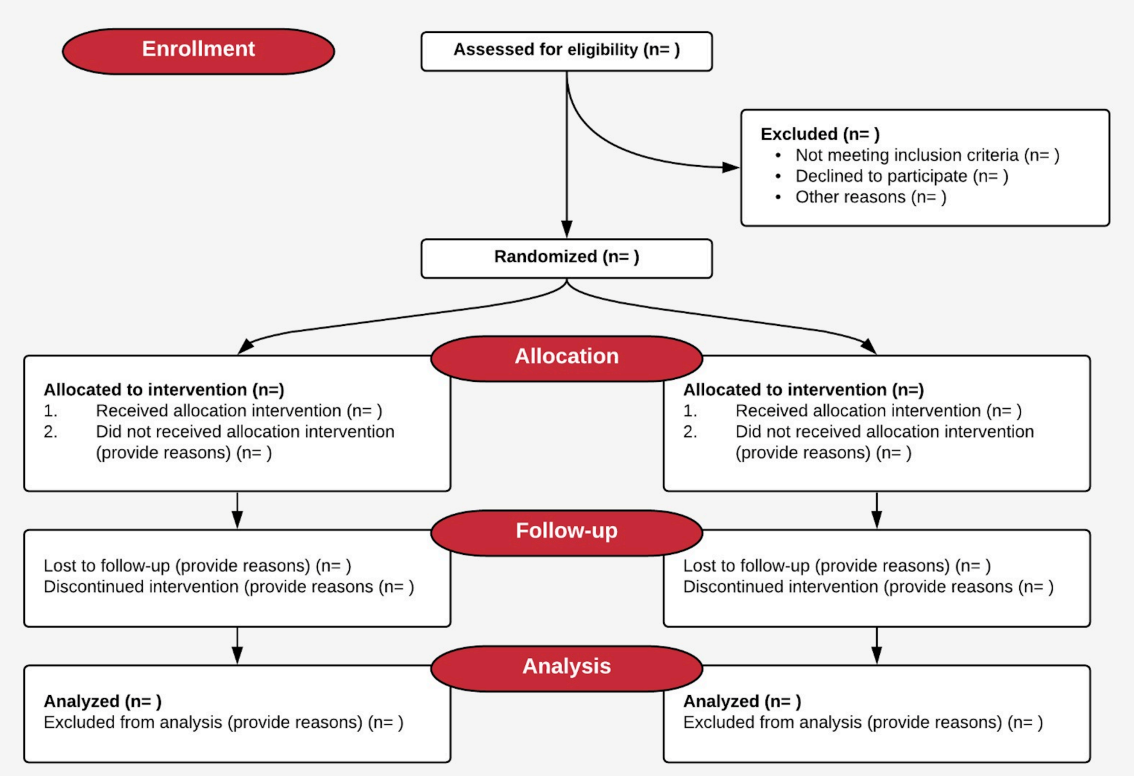


Figure 2: Control group hemodynamic optimization algorithm

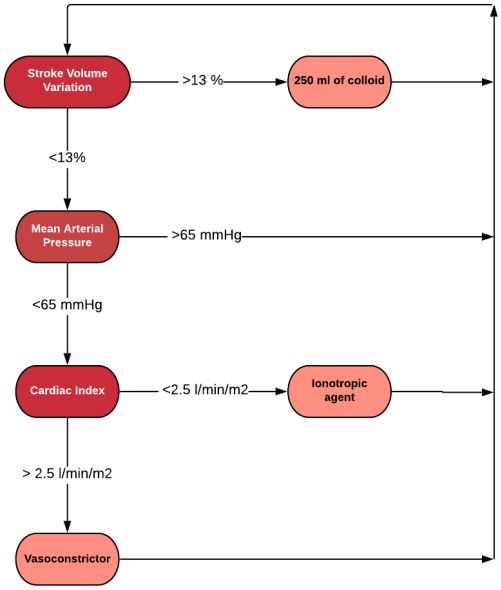


Figure 3: Intervention group hemodynamic optimization algorithm

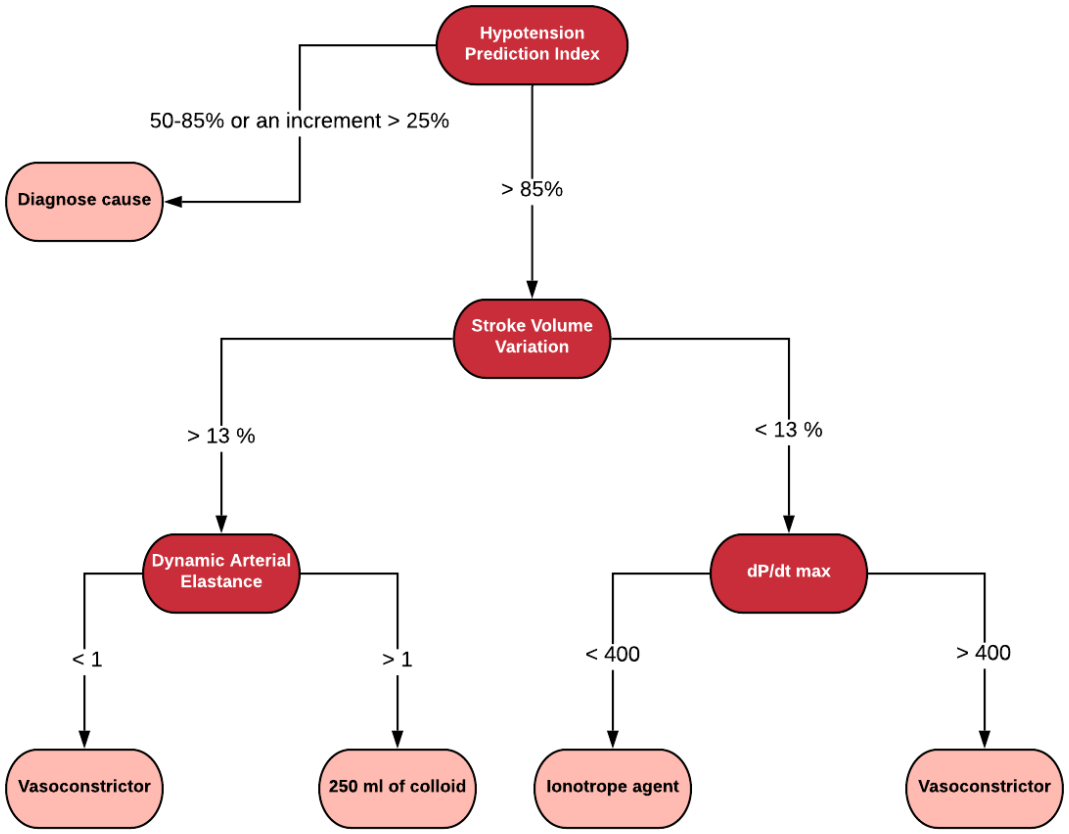


Figure 4: Schedule of enrolment, interventions and assessments

	STUDY PERIOD				
	Enrolment	Study Intervention			
TIMEPOINT**	***d_{-1}***	***Surgical day (d_0)***	***Daily follow-up (d_1-d_{hd})***	***Hospital discharge (d_{hd})***	***Follow-up (d_{30})***
ENROLMENT:					
Eligibility screen	X				
Written and oral project explanation	X				
Written Informed consent	X				
Allocation		X			
Patient demographic/comorbidities	X	X			
INTERVENTIONS:					
Control group		X			
Intervention group]		X			
ASSESSMENTS:					
Primary outcomes		X			
Secondary outcomes		X	X	X	X

Figure 4 Schedule of enrolment, interventions and assessments

6-DISCUSIÓN.

El objetivo de esta tesis doctoral es en primer lugar, la disminución de las complicaciones perioperatorias en los pacientes con fractura de cadera mediante la aplicación de un protocolo intraoperatorio de Terapia Dirigida por Objetivos y como consecuencia, una reducción de la estancia hospitalaria y en aumento en la supervivencia postoperatoria de este perfil de paciente. En segundo lugar, fruto de los avances tecnológicos recientes derivados de la aplicación de la inteligencia artificial al ámbito sanitario, evaluar si la incorporación de un parámetro predictivo a un protocolo de optimización hemodinámica intraoperatoria permite reducir de forma global la hipotensión intraoperatoria y lograr una mejor perfusión en los pacientes que se someten a una cirugía abdominal mayor electiva.

6.1. Discusión de las características sociodemográficas y clínicas de los pacientes incluidos.

Las características sociodemográficas de los pacientes afectos de fractura de cadera se encuentran en constante evolución (Condorhuamán-Alvarado et al., 2022). Existe una evolución demográfica del perfil de paciente con fractura de cadera, salvo en el sexo de los que la padecen, hacia una mayor prevalencia de los factores asociados con peores resultados postoperatorios en términos de complicaciones y mortalidad (Pallardo Rodil et al., 2020). Estas variaciones se observan incluso si comparamos los dos grupos de estudio pese a que menos de tres años los separan. Un mayor porcentaje de los pacientes del grupo intervención se encontraban en el grupo de edad de 85 años ó más, coincidiendo con los hallazgos reportados por Etxebarria-Foronda y colaboradores (Etxebarria-Foronda, 2015). También de forma similar, se observa un aumento del porcentaje de pacientes afectos, de sexo femenino.

El índice de comorbilidad de Charlson, aglutina la práctica totalidad de comorbilidad previa de tipo cardiovascular, respiratoria, renal entre otros. Tanto el porcentaje de pacientes con un índice de Charlson mayor o igual a 2, como el porcentaje de pacientes con consumo crónico de más de cuatro fármacos fue superior en el grupo intervención. Los pacientes del grupo intervención presentaban, además, un mayor riesgo anestésico-quirúrgico representado por la escala de la Sociedad Americana de Anestesiología (ASA).

Una mayor edad, un valor mayor en la escala ASA, un mayor índice de Charlson y la presencia de polifarmacia, se han asociado en estudios previos a un aumento de la morbimortalidad postoperatoria en el paciente afecto de fractura de cadera (Barceló et al., 2021).

En cuanto al tipo de fractura que presentaron los pacientes incluidos y los valores de hemoglobina al ingreso, no se observaron diferencias entre ambos grupos. Cabe destacar que casi un 60% de los pacientes incluidos en el estudio, presentaba anemia al ingreso, definida como una hemoglobina menor a 12 g/dL, pese a que ese valor de corte de hemoglobina elegido es subóptimo para poder enfrentarse a cualquier cirugía mayor, más aún, a una osteosíntesis de fractura de hueso largo (Gómez-Ramírez et al., 2019).

6.2. Discusión del tratamiento perioperatorio de los pacientes con fractura de cadera

El único cambio en la trayectoria clínica entre ambos grupos fue la implementación en el grupo intervención de un protocolo de optimización hemodinámica guiada por monitorización no invasiva.

La demora quirúrgica es un tema muy controvertido si valoramos de forma global la evidencia científica de la que disponemos actualmente (Saul et al., 2019). Pese a ello, las guías vigentes recomiendan la realización de la cirugía de osteosíntesis en las primeras 48 horas de ingreso hospitalario (Griffiths et al., 2021). Por este motivo, la priorización de la intervención en este periodo temporal fue un objetivo de la trayectoria clínica en ambos grupos de estudio. Observamos una menor demora quirúrgica en el grupo intervención que puede ser explicada por la evolución paulatina pero constante de la sensibilización de los profesionales con este objetivo desde su establecimiento.

A su llegada a quirófano un 29.4% de los pacientes fueron respondedores a la infusión de fluido. Este porcentaje es menor al observado por Bartha y colaboradores (Bartha et al., 2013) y por Agerskov y colaboradores (Agerskov et al., 2022). Este hallazgo puede deberse a la presencia de una mayor demora hasta la intervención en nuestro grupo de pacientes y al funcionamiento óptimo de la trayectoria clínica multidisciplinar, capaz de optimizar de forma preoperatoria a los pacientes con fractura de cadera.

La elección de la técnica anestésica en este grupo de pacientes de elevado riesgo quirúrgico es de gran complejidad. Clásicamente en diversas cohortes analizadas, la anestesia neuroaxial es la más utilizada pero no disponemos de evidencia que demuestre una superioridad de una técnica respecto a otra (Van Waesberghe et al., 2017). No observamos diferencias en este aspecto entre los dos grupos estudiados.

El protocolo de TDO aplicado en este estudio, difiere de los usados en los estudios más recientemente publicados en este perfil de paciente. El protocolo utilizado por Bartha y colaboradores incluyó la resucitación con fluidos antes de la inducción anestésica, la utilización intraoperatoria de soporte vasoactivo si la presión arterial sistólica descendía más de un 30% respecto a los valores que el paciente presentaba previos a la inducción anestésica y la optimización del volumen sistólico y el aporte de oxígeno con fluidos y dobutamina respectivamente (Bartha et al., 2013). En cambio, Moppett y colaboradores protocolizaron en su grupo intervención, la aplicación de coloides sintéticos para optimizar

el volumen sistólico, utilizando un protocolo basado únicamente en la optimización del flujo (Moppett et al., 2015). Finalmente, Davies y colaboradores aplicaron un protocolo basado en la optimización del volumen sistólico mediante cristaloides y en el mantenimiento con vasopresores de la presión arterial media por encima del 30% del valor basal preinducción anestésica de cada paciente (Davies et al., 2019).

Existen probablemente, tantos algoritmos propuestos para la realización de TDO intraoperatoria como estudios han evaluado su eficacia. Dos aspectos fundamentales son compartidos por los algoritmos cuya evaluación ha sido recientemente publicada. En primer lugar, dada su no equivalencia en el sistema cardiovascular, es fundamental la inclusión en el algoritmo de dos objetivos a mantener, uno de flujo como puede ser el volumen sistólico y uno de presión, como por ejemplo la presión arterial media, habitualmente un umbral absoluto, no relativo (Salmasi et al., 2017). En segundo lugar, pese al elevado número de algoritmos propuestos y testados, un porcentaje alto de ellos, poseen un fundamento fisiológico común. La práctica totalidad de los algoritmos detectan y tratan el estado de precarga-dependencia en el paciente y valoran la indicación de vasoactivos o fármacos ionotropos según el estado hemodinámico del paciente (Fellahi et al., 2021).

Como resultado de la aplicación de nuestro algoritmo durante el periodo intraoperatorio en pacientes de fractura de cadera, hemos utilizado una cantidad menor de fluidos en el grupo intervención con respecto al grupo control. Si comparamos el volumen de fluido infundido con el resto de estudios que aplican TDO al paciente con fractura de cadera, observamos como es similar o ligeramente menor que el usado por Davies y colaboradores (Davies et al., 2019) y por Bartha y colaboradores (Bartha et al., 2013) respectivamente, así como discretamente mayor a la cantidad de fluido utilizado por Moppett y colaboradores (Moppett et al., 2015). Destaca además un menor uso de vasoactivos en nuestro grupo intervención con respecto al grupo control, probablemente debido al seguimiento de un algoritmo de decisión. La no aplicación de un algoritmo hemodinámico puede derivar en una utilización precoz de vasoactivos, aunque no sea el tratamiento fisiológicamente apropiado para el paciente en ese momento concreto. Ningún paciente del grupo intervención fue tratado con dobutamina, probablemente por el establecimiento de un índice cardiaco objetivo individualizado y por la ausencia de situaciones clínicas tributarias de su utilización.

No se registraron cambios en el protocolo de transfusión del hospital y el porcentaje de pacientes con hemoglobina menor a 12 g/dL al ingreso hospitalario fue similar en ambos

grupos. Los resultados de nuestro estudio muestran un número menor de pacientes del grupo intervención que requirió transfusión de hemoderivados con respecto al grupo control. Esto podría explicarse por la utilización en el grupo intervención de técnicas quirúrgicas asociadas a un menor sangrado quirúrgico, como los clavos intramedulares (Smith et al., 2011). Además, los pacientes pertenecientes a este grupo, pudieron sufrir menor hemodilución que los pacientes del grupo control, debido a la menor cantidad de fluidos recibidos derivado de la utilización intraoperatoria de un protocolo de TDO (Heather, 1979).

6.3. Discusión de los resultados relativos a las complicaciones perioperatorias

La bibliografía existente relativa a las complicaciones intraoperatorias en el paciente con fractura de cadera es limitada. El foco se ha puesto clásicamente en las complicaciones postoperatorias, ya que éstas últimas son causantes directas de un aumento en la estancia hospitalaria y de la mortalidad asociada a la intervención (Blanco et al., 2021). Pese a ello, la presencia o desarrollo de complicaciones intraoperatorias se ha asociado a la aparición de complicaciones postoperatorias (Kinaci et al., 2016).

Las complicaciones intraoperatorias más destacadas son de tipo cardiovascular, tanto por su elevada prevalencia, como por las consecuencias derivadas de su aparición, pudiendo destacar la aparición de hipoperfusión sistémica, hipotensión o arritmias como las principales entidades. Fisiológicamente, existe entre ellas un punto de unión al ser causa y/o consecuencia de un desequilibrio entre el aporte y la demanda de oxígeno del paciente, condicionado en este entorno intraoperatorio habitualmente, por un gasto cardiaco insuficiente (Doherty & Buggy, 2012). Pero no solamente un flujo sanguíneo suficiente que permita alcanzar los requerimientos de oxigenación corporal total es necesario, también un valor de presión arterial capaz de conducir el flujo sanguíneo es imprescindible (Awad et al., 2022). Por ello, tanto la presión arterial como el flujo sanguíneo son considerados los determinantes esenciales de la perfusión orgánica y la presencia de valores inadecuados de cualquiera de estos dos pilares durante una intervención, se asocia al desarrollo de complicaciones postoperatorias (Heming et al., 2020).

Una arritmia es una alteración de la frecuencia y/o del ritmo cardiaco. Ambas alteraciones, pueden condicionar en determinadas situaciones la aparición de un gasto cardiaco insuficiente. Un aumento en la frecuencia cardiaca puede ser causada por un gasto cardiaco insuficiente e inicialmente condiciona un aumento de este, pero en determinadas situaciones y valores, puede ser deletéreo y asociar una caída del gasto cardiaco (Fu, 2015). La alteración del ritmo más prevalente en los pacientes con fractura de cadera es la fibrilación auricular y se asocia a la supresión de la contracción auricular y disminución del llenado ventricular, condicionando un gasto cardiaco menor (Abu-Assi et al., 2020).

En nuestro estudio, la implementación de un protocolo intraoperatorio de TDO se asoció a una disminución de las arritmias durante la intervención, probablemente debido a la

optimización de la precarga inmediatamente antes de la cirugía y de forma intraoperatoria. En el grupo intervención, también obtuvimos una reducción tanto del porcentaje de pacientes que sufrieron inestabilidad hemodinámica durante la cirugía, así como el número de episodios que estos presentaron. Estos hallazgos probablemente se deben a la mejora en el control hemodinámico de los pacientes como resultado de la implementación de un protocolo de TDO guiado por monitorización no invasiva.

Los pacientes del grupo intervención sufrieron de manera estadísticamente significativa, menos complicaciones postoperatorias cardiovasculares, respiratorias e infecciosas. Estos resultados podrían deberse a una disminución de la presencia de hipoperfusión intraoperatoria con respecto al grupo control, objetivo prioritario y crucial de los protocolos de TDO, que puede haberse reflejado en la aparición de un número menor de complicaciones postoperatorias (Kendrick et al., 2019).

Este hallazgo difiere de los obtenidos en los ensayos clínicos realizados previamente en los pacientes fractura de cadera. Únicamente en el ensayo realizado por Bartha y cols. y en el realizado por Davies y cols., las complicaciones postoperatorias fueron el resultado primario planificado. El primer estudio, tuvo que detenerse precozmente debido a una tasa de reclutamiento menor a la esperada, que condicionó una potencia estadística insuficiente para detectar diferencias en el resultado primario (Bartha et al., 2013). En el caso del segundo estudio, Davies y cols., obtuvieron una tendencia hacia la reducción de las complicaciones postoperatorias en el grupo intervención no estadísticamente significativa (Davies et al., 2019). El mayor tamaño muestral recogido en nuestro estudio y el protocolo de optimización hemodinámica usado pueden ser los causantes de estas diferencias en cuanto a los resultados obtenidos.

Destaca una mayor incidencia de insuficiencia renal postoperatoria en el grupo intervención que puede ser debida a diversas causas. En primer lugar, los pacientes del grupo intervención presentaban un mayor número de factores de riesgo para la aparición de insuficiencia renal postoperatoria que los pacientes del grupo control (Zorrilla-Vaca et al., 2021), al ser pacientes de una mayor edad, con una mayor proporción de pacientes de sexo femenino y con hipertensión como antecedente y finalmente, con una mayor proporción de insuficiencia renal crónica al ingreso. En segundo lugar, los pacientes del grupo intervención recibieron una mayor cantidad de solución salina al 0.9% que los pacientes del grupo control. Esta utilización, puede ser explicada al ser el único cristaloide

con presentaciones de 250 ml y 100 ml, volúmenes usados en el grupo de la TDO para la realización de los bolos de fluido.

Existe evidencia del efecto negativo de la infusion de solución salina al 0.9%. Tras la infusión de únicamente 2 litros de solución salina al 0.9%, aumenta de forma importante el contenido total de sodio en el organismo, produciéndose una ganancia de peso asociada a la formación de edema, que se ha asociado a la aparición de complicaciones postoperatorias (Lobo et al., 2002). Nuestro organismo, además, necesita al menos 48 horas para excretar de forma activa el exceso de sodio aportado, pero los cambios hormonales generados en el medio interno del paciente se mantienen presentes hasta incluso 9 días tras la infusión de solución salina al 0.9% con potencial repercusión clínica (Drummer et al., 1992).

Además, la infusión de únicamente dos litros de solución salina al 0.9%, genera acidosis hiperclorémica, que se ha asociado a una disminución de la velocidad del flujo de la arteria renal con disminución asociada de la perfusión cortical renal y disminución del filtrado glomerular por vasoconstricción de la arteria renal (Chowdhury et al., 2012). Estos cambios fisiológicos se reflejan en una mayor aparición de insuficiencia renal en los pacientes con un régimen liberal de cloro, tanto de origen médico como quirúrgico (Yunos et al., 2012).

Finalmente, la definición de la complicación postoperatoria tipo insuficiencia renal puede haber tenido también influencia en el aumento observado en el grupo intervención. Una elevación transitoria y única de la creatinina sérica por encima de un nivel muy sensible, fue considerado como aparición de esta complicación de tipo renal. Una elevación aislada de creatinina durante el postoperatorio de los pacientes con fractura de cadera no tuvo que deberse en muchos casos a la aparición de daño celular renal (Hahn, 2015), ni ser una elevación significativa comparado con el nivel basal de este parámetro al ingreso hospitalario. Las limitaciones de los criterios diagnósticos utilizados para la insuficiencia renal postoperatoria y la influencia en la mortalidad únicamente por las elevaciones de creatinina asociadas a daño celular renal, pueden explicar el descenso en la mortalidad postoperatoria pese al aumento en la insuficiencia renal postoperatoria en el grupo intervención.

6.4. Discusión de los resultados de estancia hospitalaria y mortalidad.

Un objetivo de este estudio fue la reducción de la estancia hospitalaria media de los pacientes de más de 65 años afectos de fractura de cadera. En el grupo intervención, la estancia hospitalaria fue significativa menor que en el grupo control. La importancia de este resultado es doble, por un lado, esta reducción de estancia hospitalaria permite una mejor accesibilidad de la población a un servicio de hospitalización y por otro, reduce los costes adicionales de tratamiento de esta patología tan prevalente (Pech-Ciau et al., 2021). Este hallazgo, puede ser debido a la reducción de las complicaciones postoperatorias de tipo cardiovascular, respiratorias e infecciosas en el grupo intervención, cuya aparición, se asocia en múltiples cohortes publicadas con un aumento de la estancia hospitalaria (Khan et al., 2006). Probablemente el aumento de las complicaciones de tipo renal en el grupo intervención no aumentó la estancia hospitalaria a expensas de los pacientes que las sufrieron ya que, el destino al alta de los pacientes de ambos grupos en más del 50% de los casos fue un recurso de convalecencia, en el que el seguimiento y tratamiento de un discreto empeoramiento de la función renal puede realizarse de forma óptima. El estudio realizado por Bartha y cols. evaluó una posible reducción de la estancia hospitalaria como objetivo secundario, no encontrando beneficios en el grupo en el que se aplicó un protocolo de TDO, probablemente derivado al tamaño muestral insuficiente, metodología usada y a la ausencia de una reducción estadísticamente significativa de las complicaciones postoperatorias en el grupo intervención (Bartha et al., 2013). Este segundo motivo, fue probablemente el que llevó a Moppett y cols. a no encontrar tampoco diferencia en la estancia hospitalaria entre sus grupos, pese a que esta variable fue configurada como resultado primario del estudio (Moppett et al., 2015).

La fractura de cadera se asocia a una elevada mortalidad postoperatoria. La máxima probabilidad de fallecer se produce en los primeros 6 meses tras la fractura y es entre 5 y 8 veces mayor al resto de población de similares características (Xu et al., 2019). Como resultados de nuestro estudio hemos obtenido una mayor supervivencia en el grupo intervención durante el año de seguimiento establecido posterior a la fractura. Además, debemos de tener en cuenta que las dos cohortes no son basalmente comparables, los pacientes del grupo intervención son más ancianos y poseen una comorbilidad previa mayor. En el

análisis multivariante, la pertenencia al grupo intervención fue identificado como un factor protector independiente de mortalidad al año y reducía el riesgo de morir en estos pacientes un 39% comparados con los pacientes del grupo intervención en cualquier momento del periodo de seguimiento. Únicamente el estudio llevado a cabo por Bartha y cols. evaluó la mortalidad postoperatoria, un año tras la intervención quirúrgica, no encontrando diferencias entre los grupos control e intervención (Bartha et al., 2016). Los datos advertidos en nuestro estudio difieren de éstos nuevamente, por la no reducción de complicaciones postoperatorias y el insuficiente tamaño muestral del estudio citado.

6.5. Limitaciones y valoración global.

Nuestro estudio no está exento de limitaciones. Fue un estudio unicéntrico, con un diseño no aleatorizado, con tres años de diferencia entre los dos grupos de estudio. Pese a ello, el único cambio introducido en la trayectoria clínica del paciente con fractura de cadera fue la implementación del protocolo de optimización hemodinámica mediante TDO. No se produjeron cambios en la composición del equipo multidisciplinar encargado de la atención a los pacientes con fractura de cadera ni en los protocolos asistenciales durante el periodo de reclutamiento. La tasa de reclutamiento en el grupo intervención fue discretamente menor a la esperada, derivada en parte, de la condición real de cirugía urgente aplicada a la cirugía de fractura de cadera desde el año 2010, interviniéndose en franjas horarias con problemas logísticos para la inclusión de pacientes en el estudio. Además, los pacientes con limitaciones para la monitorización hemodinámica avanzada no invasiva o con agitación psicomotora preoperatoria que impidió la aplicación del sistema, fueron excluidos únicamente del grupo intervención. Nuestra tasa de exclusión por estos motivos fue incluso menor a la reportada previamente en el estudio de Davies y cols., realizado con el mismo sistema de monitorización hemodinámica (Davies et al., 2019). No podemos descartar que estos pacientes excluidos tuvieran un estado clínico más deteriorado a su llegada a quirófano. Finalmente, la dificultad en la valoración clínica de la presencia de complicaciones postoperatorias neurológicas tipo delirium hicieron que en el diseño del estudio, pese a su importancia, el potencial beneficio de la aplicación de un protocolo de TDO sobre esta complicación, no fuera evaluado.

Los estudios antes-después aportan una evidencia de menor calidad que los ensayos clínicos (Sedgwick, 2014). Pese a ello, este tipo de diseños ofrece información importante acerca de los potenciales beneficios de la implementación de un protocolo de TDO en "condiciones reales", pudiendo así complementar la evidencia proveniente de los ensayos clínicos (Saugel et al., 2019). Este es el estudio con el mayor tamaño muestral hasta la fecha que ha evaluado el posible efecto de la implementación de un protocolo de TDO en los pacientes con fractura de cadera.

7-CONCLUSIONES

A. La implementación de un protocolo de terapia dirigida por objetivos reduce el porcentaje de pacientes con edad igual o superior a 65 años afectos de fractura de cadera que presentan inestabilidad hemodinámica como complicación intraoperatoria así como el número de episodios de inestabilidad hemodinámica por paciente.

B. La implementación de un protocolo de terapia dirigida por objetivos reduce el porcentaje de pacientes con edad igual o superior a 65 años afectos de fractura de cadera que presentan arritmias como complicación intraoperatoria,

C. La aplicación de un protocolo de terapia dirigida por objetivos reduce la aparición de complicaciones postoperatorias de tipo cardiocirculatorias, respiratorias e infecciosas. En nuestro estudio, hemos encontrado un aumento de las complicaciones postoperatorias de tipo renal

D. La estancia hospitalaria y la mortalidad al año de la intervención quirúrgica se reducen con la aplicación de un protocolo de terapia dirigida por objetivos.

8-BIBLIOGRAFÍA.

Abu-Assi, R., Campbell, J., Bacchi, S., Gill, T. K., George, D., & Chehade, M. (2020). Association between atrial fibrillation and hip fractures and the implications for hip fracture patients: A systematic review. *ANZ Journal of Surgery*, *90*(4), 448-453. https://doi.org/10.1111/ans.15460

Agerskov, M., Sørensen, H., Højlund, J., Secher, N. H., & Foss, N. B. (2022). Fluid-responsiveness, blood volume and perfusion in preoperative haemodynamic optimisation of hip fracture patients; a prospective observational study. *Acta Anaesthesiologica Scandinavica*, *66*(6), 660-673. https://doi.org/10.1111/aas.14070

Alexiou, K., Roushias, A., Varitimidis, S., & Malizos, K. (2018). Quality of life and psychological consequences in elderly patients after a hip fracture: A review. *Clinical Interventions in Aging*, *Volume 13*, 143-150. https://doi.org/10.2147/CIA.S150067

Arnau, A., Espaulella, J., Serrarols, M., Canudas, J., Formiga, F., & Ferrer, M. (2016). Risk factors for functional decline in a population aged 75 years and older without total dependence: A one-year follow-up. *Archives of Gerontology and Geriatrics*, *65*, 239-247. https://doi.org/10.1016/j.archger.2016.04.002

Awad, H., Alcodray, G., Raza, A., Boulos, R., Essandoh, M., Bhandary, S., & Dalton, R. (2022). Intraoperative Hypotension–Physiologic Basis and Future Directions. *Journal of Cardiothoracic and Vascular Anesthesia*, *36*(7), 2154-2163. https://doi.org/10.1053/j.jvca.2021.05.057

Azagra, R., López-Expósito, F., Martin-Sánchez, J. C., Aguyé, A., Moreno, N., Cooper, C., Díez-Pérez, A., & Dennison, E. M. (2014). Changing trends in the epidemiology of hip fracture in Spain. *Osteoporosis International*, *25*(4), 1267-1274. https://doi.org/10.1007/s00198-013-2586-0

Barceló, M., Torres, O. H., Mascaró, J., & Casademont, J. (2021). Hip fracture and mortality: Study of specific causes of death and risk factors. *Archives of Osteoporosis*, *16*(1), 15. https://doi.org/10.1007/s11657-020-00873-7

Bartha, E., Arfwedson, C., Imnell, A., Fernlund, M. E., Andersson, L. E., & Kalman, S. (2013). Randomized controlled trial of goal-directed haemodynamic treatment in patients with proximal femoral fracture. *British Journal of Anaesthesia*, *110*(4), 545-553. https://doi.org/10.1093/bja/aes468

Bartha, E., Arfwedson, C., Imnell, A., & Kalman, S. (2016). Towards individualized perioperative, goal-directed haemodynamic algorithms for patients of advanced age: Observations during a randomized controlled trial (NCT01141894). *British Journal of Anaesthesia*, *116*(4), 486-492. https://doi.org/10.1093/bja/aew025

Bartha, E., Davidson, T., Berg, H. E., & Kalman, S. (2019). A 1-year perspective on goal-directed therapy in elderly with hip fracture: Secondary outcomes. *Acta Anaesthesiologica Scandinavica*, *63*(5), 610-614. https://doi.org/10.1111/aas.13320

Beard, J. R., Officer, A., de Carvalho, I. A., Sadana, R., Pot, A. M., Michel, J.-P., Lloyd-Sherlock, P., Epping-Jordan, J. E., Peeters, G. M. E. E. (Geeske), Mahanani, W. R., Thiyagarajan, J. A., & Chatterji, S. (2016). The World report on ageing and health: A policy framework for healthy ageing. *The*

Lancet, *387*(10033), 2145-2154. https://doi.org/10.1016/S0140-6736(15)00516-4

Bellamy, M. C. (2006). Wet, dry or something else? *British Journal of Anaesthesia*, *97*(6), 755-757. https://doi.org/10.1093/bja/ael290

Bhandari, M., & Swiontkowski, M. (2017). Management of Acute Hip Fracture. *New England Journal of Medicine*, *377*(21), 2053-2062. https://doi.org/10.1056/NEJMcp1611090

Blanco, J. F., da Casa, C., Pablos-Hernández, C., González-Ramírez, A., Julián-Enríquez, J. M., & Díaz-Álvarez, A. (2021). 30-day mortality after hip fracture surgery: Influence of postoperative factors. *PLOS ONE*, *16*(2), e0246963. https://doi.org/10.1371/journal.pone.0246963

Borges, F. K., Bhandari, M., Guerra-Farfan, E., Patel, A., Sigamani, A., Umer, M., Tiboni, M. E., Villar-Casares, M. del M., Tandon, V., Tomas-Hernandez, J., Teixidor-Serra, J., Avram, V. R., Winemaker, M., Ramokgopa, M. T., Szczeklik, W., Landoni, G., Wang, C. Y., Begum, D., Neary, J. D., … Wright, J. (2020). Accelerated surgery versus standard care in hip fracture (HIP ATTACK): An international, randomised, controlled trial. *The Lancet*, *395*(10225), 698-708. https://doi.org/10.1016/S0140-6736(20)30058-1

Carpintero, P. (2014). Complications of hip fractures: A review. *World Journal of Orthopedics*, *5*(4), 402. https://doi.org/10.5312/wjo.v5.i4.402

Chong, M. A., Wang, Y., Berbenetz, N. M., & McConachie, I. (2018). Does goal-directed haemodynamic and fluid therapy improve peri-operative out-

comes?: A systematic review and meta-analysis. *European Journal of Anaesthesiology*, *35*(7), 469-483. https://doi.org/10.1097/EJA.0000000000000778

Chowdhury, A. H., Cox, E. F., Francis, S. T., & Lobo, D. N. (2012). A Randomized, Controlled, Double-Blind Crossover Study on the Effects of 2-L Infusions of 0.9% Saline and Plasma-Lyte® 148 on Renal Blood Flow Velocity and Renal Cortical Tissue Perfusion in Healthy Volunteers. *Annals of Surgery*, *256*(1), 18-24. https://doi.org/10.1097/SLA.0b013e318256be72

Condorhuamán-Alvarado, P. Y., Pareja-Sierra, T., Muñoz-Pascual, A., Sáez-López, P., Diez-Sebastián, J., Ojeda-Thies, C., Gutiérrez-Misis, A., Alarcón-Alarcón, T., Cassinello-Ogea, M. C., Pérez-Castrillón, J. L., Gómez-Campelo, P., Navarro-Castellanos, L., Otero-Puime, Á., González-Montalvo, J. I., & on behalf of the participants in the Spanish National Hip Fracture Registry. (2022). Improving hip fracture care in Spain: Evolution of quality indicators in the Spanish National Hip Fracture Registry. *Archives of Osteoporosis*, *17*(1), 54. https://doi.org/10.1007/s11657-022-01084-y

Davies, S. J., Yates, D. R., Wilson, R. J. T., Murphy, Z., Gibson, A., Allgar, V., & Collyer, T. (2019). A randomised trial of non-invasive cardiac output monitoring to guide haemodynamic optimisation in high risk patients undergoing urgent surgical repair of proximal femoral fractures (ClearNOF trial NCT02382185). *Perioperative Medicine*, *8*(1), 8. https://doi.org/10.1186/s13741-019-0119-x

Doherty, M., & Buggy, D. J. (2012). Intraoperative fluids: How much is too much? *British Journal of Anaesthesia*, *109*(1), 69-79. https://doi.org/10.1093/bja/aes171

Drummer, C., Gerzer, R., Heer, M., Molz, B., Bie, P., Schlossberger, M., Stadaeger, C., Rocker, L., Strollo, F., Heyduck, B., Bauer, K., Warberg, J., Baisch, F., Christensen, J., Konig, A., & Norsk, P. (1992). Effects of an acute saline infusion on fluid and electrolyte metabolism in humans. *American Journal of Physiology-Renal Physiology*, *262*(5), F744-F754. https://doi.org/10.1152/ajprenal.1992.262.5.F744

Edwards, M. R., Forbes, G., MacDonald, N., Berdunov, V., Mihaylova, B., Dias, P., Thomson, A., Grocott, M. P., Mythen, M. G., Gillies, M. A., Sander, M., Phan, T. D., Evered, L., Wijeysundera, D. N., McCluskey, S. A., Aldecoa, C., Ripollés-Melchor, J., Hofer, C. K., Abukhudair, H., … Pearse, R. M. (2019). Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) trial: Study protocol for a multicentre international trial of cardiac output-guided fluid therapy with low-dose inotrope infusion compared with usual care in patients undergoing major elective gastrointestinal surgery. *BMJ Open*, *9*(1), e023455. https://doi.org/10.1136/bmjopen-2018-023455

Etxebarria-Foronda, Í. (2015). Incidencia de la fractura de cadera en España. *Medicina Clínica*, *145*(11), 482-484. https://doi.org/10.1016/j.medcli.2015.04.009

Feldt, K. S., & Oh, H. L. (2000). Pain and Hip Fracture Outcomes for Older Adults: *Orthopaedic Nursing*, *19*(6), 35-44. https://doi.org/10.1097/00006416-200019060-00008

Fellahi, J.-L., Futier, E., Vaisse, C., Collange, O., Huet, O., Loriau, J., Gayat, E., Tavernier, B., Biais, M., Asehnoune, K., Cholley, B., & Longrois, D. (2021). Perioperative hemodynamic optimization: From guidelines to implementation—an experts' opinion paper. *Annals of Intensive Care*, *11*(1), 58. https://doi.org/10.1186/s13613-021-00845-1

for the Fragility Fracture Network (FFN) Rehabilitation Research Special Interest Group, Dyer, S. M., Crotty, M., Fairhall, N., Magaziner, J., Beaupre, L. A., Cameron, I. D., & Sherrington, C. (2016). A critical review of the long-term disability outcomes following hip fracture. *BMC Geriatrics*, *16*(1), 158. https://doi.org/10.1186/s12877-016-0332-0

Foss, N. B., & Kehlet, H. (2005). Mortality analysis in hip fracture patients: Implications for design of future outcome trials. *British Journal of Anaesthesia*, *94*(1), 24-29. https://doi.org/10.1093/bja/aei010

Foster, C., Shilton, T., Westerman, L., Varney, J., & Bull, F. (2018). World Health Organisation to develop global action plan to promote physical activity: Time for action. *British Journal of Sports Medicine*, *52*(8), 484-485. https://doi.org/10.1136/bjsports-2017-098070

Fu, D. (2015). Cardiac Arrhythmias: Diagnosis, Symptoms, and Treatments. *Cell Biochemistry and Biophysics*, *73*(2), 291-296. https://doi.org/10.1007/s12013-015-0626-4

Giglio, M., Manca, F., Dalfino, L., & Brienza, N. (2016). Perioperative hemodynamic goal-directed therapy and mortality: A systematic review and meta-analysis with meta-regression. *Minerva Anestesiologica*, *82*(11), 1199-1213.

Gómez-Ramírez, S., Bisbe, E., Shander, A., Spahn, D. R., & Muñoz, M. (2019). Management of Perioperative Iron Deficiency Anemia. *Acta Haematologica*, *142*(1), 21-29. https://doi.org/10.1159/000496965

Griffiths, R., Babu, S., Dixon, P., Freeman, N., Hurford, D., Kelleher, E., Moppett, I., Ray, D., Sahota, O., Shields, M., & White, S. (2021). Guideline for the management of hip fractures 2020: Guideline by the Association of Anaesthetists. *Anaesthesia*, *76*(2), 225-237. https://doi.org/10.1111/anae.15291

Guven, G., Hilty, M. P., & Ince, C. (2020). Microcirculation: Physiology, Pathophysiology, and Clinical Application. *Blood Purification*, *49*(1-2), 143-150. https://doi.org/10.1159/000503775

Guzon-Illescas, O., Perez Fernandez, E., Crespí Villarias, N., Quirós Donate, F. J., Peña, M., Alonso-Blas, C., García-Vadillo, A., & Mazzucchelli, R. (2019). Mortality after osteoporotic hip fracture: Incidence, trends, and associated factors. *Journal of Orthopaedic Surgery and Research*, *14*(1), 203. https://doi.org/10.1186/s13018-019-1226-6

Hahn, R. G. (2015). Renal injury during hip fracture surgery: An exploratory study. *Anestezjologia Intensywna Terapia*, *47*(4), 284-290. https://doi.org/10.5603/AIT.a2015.0029

Hardy, J. D. (1963). Tissue hypoxia in surgical practice. *The American Journal of Surgery*, *106*(3), 476-490. https://doi.org/10.1016/0002-9610(63)90134-X

Hatib, F., Jian, Z., Buddi, S., Lee, C., Settels, J., Sibert, K., Rinehart, J., & Cannesson, M. (2018). Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. *Anesthesiology*, *129*(4), 663-674. https://doi.org/10.1097/ALN.0000000000002300

Heather, B. P. (1979). HÆMODILUTION AND BLOOD-FLOW. *The Lancet*, *314*(8137), 309. https://doi.org/10.1016/S0140-6736(79)90326-X

Heming, N., Moine, P., Coscas, R., & Annane, D. (2020). Perioperative fluid management for major elective surgery. *British Journal of Surgery*, *107*(2), e56-e62. https://doi.org/10.1002/bjs.11457

Hoorn, E. J. (2017). Intravenous fluids: Balancing solutions. *Journal of Nephrology*, *30*(4), 485-492. https://doi.org/10.1007/s40620-016-0363-9

Jentzer, J. C., Coons, J. C., Link, C. B., & Schmidhofer, M. (2015). Pharmacotherapy Update on the Use of Vasopressors and Inotropes in the Intensive Care Unit. *Journal of Cardiovascular Pharmacology and Therapeutics*, *20*(3), 249-260. https://doi.org/10.1177/1074248414559838

Jessen, M. K., Vallentin, M. F., Holmberg, M. J., Bolther, M., Hansen, F. B., Holst, J. M., Magnussen, A., Hansen, N. S., Johannsen, C. M., Enevoldsen, J., Jensen, T. H., Roessler, L. L., Lind, P. C., Klitholm, M. P., Eggertsen, M. A., Caap, P., Boye, C., Dabrowski, K. M., Vormfenne, L., … Andersen, L. W. (2022). Goal-directed haemodynamic therapy during general anaesthesia for noncardiac surgery: A systematic review and meta-analysis.

British Journal of Anaesthesia, *128*(3), 416-433. https://doi.org/10.1016/j.bja.2021.10.046

Jiménez-Sánchez, M. D., Córcoles-Jiménez, M. P., del Egido-Fernández, M. Á., Villada-Munera, A., Candel-Parra, E., & Moreno-Moreno, M. (2011). Análisis de las caídas que producen fractura de cadera en ancianos. *Enfermería Clínica*, *21*(3), 143-150. https://doi.org/10.1016/j.enfcli.2011.02.004

Kampmeier, T. G., & Ertmer, C. (2020). Individualized Goal-Directed Therapy: The Challenge With the Fluids. *Anesthesia & Analgesia*, *130*(3), 596-598. https://doi.org/10.1213/ANE.0000000000004525

Kendrick, J., Kaye, A., Tong, Y., Belani, K., Urman, R., Hoffman, C., & Liu, H. (2019). Goal-directed fluid therapy in the perioperative setting. *Journal of Anaesthesiology Clinical Pharmacology*, *35*(5), 29. https://doi.org/10.4103/joacp.JOACP_26_18

Khan, N. A., Quan, H., Bugar, J. M., Lemaire, J. B., Brant, R., & Ghali, W. A. (2006). Association of postoperative complications with hospital costs and length of stay in a tertiary care center. *Journal of General Internal Medicine*, *21*(2), 177-180. https://doi.org/10.1007/s11606-006-0254-1

Kinaci, E., Sevinc, M. M., Bayrak, S., Erdoğan, E., Ozakay, A., & Sari, S. (2016). Is the classification of intraoperative complications (CLASSIC) related to postoperative course? *International Journal of Surgery*, *29*, 171-175. https://doi.org/10.1016/j.ijsu.2016.03.068

Labgaa, I., Joliat, G.-R., Grass, F., Jarrar, G., Halkic, N., Demartines, N., & Hübner, M. (2020). Impact of postoperative weight gain on complications after

liver surgery. *HPB*, *22*(5), 744-749. https://doi.org/10.1016/j.hpb.2019.09.015

Leach, R. M. (2002). The pulmonary physician in critical care 2: Oxygen delivery and consumption in the critically ill. *Thorax*, *57*(2), 170-177. https://doi.org/10.1136/thorax.57.2.170

Lewis, S. R., Butler, A. R., Brammar, A., Nicholson, A., & Smith, A. F. (2016). Perioperative fluid volume optimization following proximal femoral fracture. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD003004.pub4

Li, W., Hu, Z., Yuan, Y., Liu, J., & Li, K. (2022). Effect of hypotension prediction index in the prevention of intraoperative hypotension during noncardiac surgery: A systematic review. *Journal of Clinical Anesthesia*, *83*, 110981. https://doi.org/10.1016/j.jclinane.2022.110981

Lobo, D. N., Bostock, K. A., Neal, K. R., Perkins, A. C., Rowlands, B. J., & Allison, S. P. (2002). Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: A randomised controlled trial. *The Lancet*, *359*(9320), 1812-1818. https://doi.org/10.1016/S0140-6736(02)08711-1

Lugo, G., Arizpe, D., Dominguez, G., Ramirez, M., & Tamariz, O. (1993). Relationship between oxygen consumption and oxygen delivery during anesthesia in high-risk surgical patients: *Critical Care Medicine*, *21*(1), 64-69. https://doi.org/10.1097/00003246-199301000-00014

Lumb, P. D. (2016). William C. Shoemaker, M.D., MCCM. *Journal of Critical Care*, *33*, 1. https://doi.org/10.1016/j.jcrc.2016.03.012

Magder, S. (2018). The meaning of blood pressure. *Critical Care*, *22*(1), 257. https://doi.org/10.1186/s13054-018-2171-1

McLain, N., Parks, S., & Collins, M. J. (2021). Perioperative Goal-Directed Fluid Therapy: A Prime Component of Enhanced Recovery After Surgery. *AANA Journal*, *89*(4), 351-357.

McLaughlin, M. A., Orosz, G. M., Magaziner, J., Hannan, E. L., McGinn, T., Morrison, R. S., Hochman, T., Koval, K., Gilbert, M., & Siu, A. L. (2006). Preoperative status and risk of complications in patients with hip fracture. *Journal of General Internal Medicine*, *21*(3), 219-225. https://doi.org/10.1111/j.1525-1497.2006.00318.x

Meng, L. (2021). Heterogeneous impact of hypotension on organ perfusion and outcomes: A narrative review. *British Journal of Anaesthesia*, *127*(6), 845-861. https://doi.org/10.1016/j.bja.2021.06.048

Moppett, I. K., Rowlands, M., Mannings, A., Moran, C. G., & Wiles, M. D. (2015). LiDCO-based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: A randomized trial and systematic review. *British Journal of Anaesthesia*, *114*(3), 444-459. https://doi.org/10.1093/bja/aeu386

Pallardo Rodil, B., Gómez Pavón, J., & Menéndez Martínez, P. (2020). Mortalidad tras fractura de cadera: Modelos predictivos. *Medicina Clínica*, *154*(6), 221-231. https://doi.org/10.1016/j.medcli.2019.09.020

Pech-Ciau, B. A., Lima-Martínez, E. A., Espinosa-Cruz, G. A., Pacho-Aguilar, C. R., Huchim-Lara, O., & Alejos-Gómez, R. A. (2021). [Hip fracture in the

elderly: Epidemiology and costs of care]. *Acta Ortopedica Mexicana*, *35*(4), 341-347.

Pfeiffer, K., Kampe, K., Klenk, J., Rapp, K., Kohler, M., Albrecht, D., Büchele, G., Hautzinger, M., Taraldsen, K., & Becker, C. (2020). Effects of an intervention to reduce fear of falling and increase physical activity during hip and pelvic fracture rehabilitation. *Age and Ageing*, *49*(5), 771-778. https://doi.org/10.1093/ageing/afaa050

Registro Nacional de Fracturas de Cadera. (2021). *Informe anual 2020*. http://rnfc.es/wp-content/uploads/2022/03/Informe-RNFC-2020_digital.pdf

Reguant, F., Arnau, A., Lorente, J. V., Maestro, L., & Bosch, J. (2019). Efficacy of a multidisciplinary approach on postoperative morbidity and mortality of elderly patients with hip fracture. *Journal of Clinical Anesthesia*, *53*, 11-19. https://doi.org/10.1016/j.jclinane.2018.09.029

Ripollés-Melchor, J., Lorente, J. V., & Monge García, M. I. (2020). Manejo intraoperatorio de la hipertensión arterial en cirugía no cardiaca. *Revista Española de Anestesiología y Reanimación*, *67*, 14-19. https://doi.org/10.1016/j.redar.2020.01.004

Ruetzler, K., Khanna, A. K., & Sessler, D. I. (2020). Myocardial Injury After Noncardiac Surgery: Preoperative, Intraoperative, and Postoperative Aspects, Implications, and Directions. *Anesthesia & Analgesia*, *131*(1), 173-186. https://doi.org/10.1213/ANE.0000000000004567

Salmasi, V., Maheshwari, K., Yang, D., Mascha, E. J., Singh, A., Sessler, D. I., & Kurz, A. (2017). Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery. *Anesthesiology*, *126*(1), 47-65. https://doi.org/10.1097/ALN.0000000000001432

Saugel, B., Joosten, A., & Scheeren, T. W. L. (2019). Perioperative goal-directed therapy: What's the best study design to investigate its impact on patient outcome? *Journal of Clinical Monitoring and Computing*, *33*(3), 361-363. https://doi.org/10.1007/s10877-018-0196-2

Saul, D., Riekenberg, J., Ammon, J. C., Hoffmann, D. B., & Sehmisch, S. (2019). Hip Fractures: Therapy, Timing, and Complication Spectrum. *Orthopaedic Surgery*, *11*(6), 994-1002. https://doi.org/10.1111/os.12524

Scheeren, T. W. L., & Ramsay, M. A. E. (2019). New Developments in Hemodynamic Monitoring. *Journal of Cardiothoracic and Vascular Anesthesia*, *33*, S67-S72. https://doi.org/10.1053/j.jvca.2019.03.043

Sedgwick, P. (2014). Before and after study designs. *BMJ*, *349*(aug08 2), g5074-g5074. https://doi.org/10.1136/bmj.g5074

Sim, Y. E., Sim, S. D., Seng, C., Howe, T. S., Koh, S. B., & Abdullah, H. R. (2018). Preoperative Anemia, Functional Outcomes, and Quality of Life After Hip Fracture Surgery: Preoperative anemia and hip fracture repair. *Journal of the American Geriatrics Society*, *66*(8), 1524-1531. https://doi.org/10.1111/jgs.15428

Sioutas, G., & Tsoulfas, G. (2020). Frailty assessment and postoperative outcomes among patients undergoing general surgery. *The Surgeon*, *18*(6), e55-e66. https://doi.org/10.1016/j.surge.2020.04.004

Smith, G. H., Tsang, J., Molyneux, S. G., & White, T. O. (2011). The hidden blood loss after hip fracture. *Injury*, *42*(2), 133-135. https://doi.org/10.1016/j.injury.2010.02.015

Soysal, P., Stubbs, B., Lucato, P., Luchini, C., Solmi, M., Peluso, R., Sergi, G., Isik, A. T., Manzato, E., Maggi, S., Maggio, M., Prina, A. M., Cosco, T. D., Wu, Y.-T., & Veronese, N. (2016). Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing Research Reviews*, *31*, 1-8. https://doi.org/10.1016/j.arr.2016.08.006

Turégano, F. (2022). Focus on emergency general surgery. *European Journal of Trauma and Emergency Surgery*, *48*(1), 1-3. https://doi.org/10.1007/s00068-022-01877-3

Ungvari, Z., Tarantini, S., Donato, A. J., Galvan, V., & Csiszar, A. (2018). Mechanisms of Vascular Aging. *Circulation Research*, *123*(7), 849-867. https://doi.org/10.1161/CIRCRESAHA.118.311378

Van Waesberghe, J., Stevanovic, A., Rossaint, R., & Coburn, M. (2017). General vs. neuraxial anaesthesia in hip fracture patients: A systematic review and meta-analysis. *BMC Anesthesiology*, *17*(1), 87. https://doi.org/10.1186/s12871-017-0380-9

Veronese, N., & Maggi, S. (2018). Epidemiology and social costs of hip fracture. *Injury*, *49*(8), 1458-1460. https://doi.org/10.1016/j.injury.2018.04.015

Vincent, J.-L. (2008). Understanding cardiac output. *Critical Care*, *12*(4), 174. https://doi.org/10.1186/cc6975

Waldron, N. H., Miller, T. E., & Gan, T. J. (2014). Perioperative Goal-Directed Therapy. *Journal of Cardiothoracic and Vascular Anesthesia*, *28*(6), 1635-1641. https://doi.org/10.1053/j.jvca.2014.07.008

Wesselink, E. M., Kappen, T. H., Torn, H. M., Slooter, A. J. C., & van Klei, W. A. (2018). Intraoperative hypotension and the risk of postoperative adverse outcomes: A systematic review. *British Journal of Anaesthesia*, *121*(4), 706-721. https://doi.org/10.1016/j.bja.2018.04.036

Xu, B. Y., Yan, S., Low, L. L., Vasanwala, F. F., & Low, S. G. (2019). Predictors of poor functional outcomes and mortality in patients with hip fracture: A systematic review. *BMC Musculoskeletal Disorders*, *20*(1), 568. https://doi.org/10.1186/s12891-019-2950-0

Yaffe, K., Hoang, T. D., Byers, A. L., Barnes, D. E., & Friedl, K. E. (2014). Lifestyle and health-related risk factors and risk of cognitive aging among older veterans. *Alzheimer's & Dementia*, *10*(3S). https://doi.org/10.1016/j.jalz.2014.04.010

Yu, Q., Qi, J., & Wang, Y. (2020). Intraoperative hypotension and neurological outcomes. *Current Opinion in Anaesthesiology*, *33*(5), 646-650. https://doi.org/10.1097/ACO.0000000000000904

Yunos, N. M., Bellomo, R., Hegarty, C., Story, D., Ho, L., & Bailey, M. (2012). Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults. *JAMA*, *308*(15), 1566. https://doi.org/10.1001/jama.2012.13356

Zorrilla-Vaca, A., Mena, G. E., Ripolles-Melchor, J., Lorente, J. V., Ramirez-Rodriguez, J. J. M., & Grant, M. C. (2021). Risk factors for acute kidney injury in an enhanced recovery pathway for colorectal surgery. *Surgery Today*, *51*(4), 537-544. https://doi.org/10.1007/s00595-020-02107-2

9-ANEXOS

9.1. Anexo 1: Inscripción estudio "Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera" en ClinicalTrials.gov

ClinicalTrials.gov PRS DRAFT Receipt (Working Version)
Last Update: 12/22/2021 14:17

ClinicalTrials.gov ID: NCT02479321

Study Identification

Unique Protocol ID:	CEIC 15/03
Brief Title:	Goal Directed Hemodynamic Therapy Based on Noninvasive Monitoring in Patients With Hip Fracture
Official Title:	Efficacy of Goal Directed Hemodynamic Therapy Based on Noninvasive Monitoring to Reduce Perioperative Complications in Patients With Hip Fracture
Secondary IDs:	

Study Status

Record Verification:	December 2021
Overall Status:	Completed
Study Start:	June 2015 [Actual]
Primary Completion:	February 2018 [Actual]
Study Completion:	February 2019 [Actual]

Sponsor/Collaborators

Sponsor:	Juan-Víctor Lorente, MD, PhD
Responsible Party:	Sponsor-Investigator Investigator: Juan-Víctor Lorente, MD, PhD [jvíctor] Official Title: Medical Doctor Affiliation: Althaia Xarxa Assistencial Universitària de Manresa
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Unapproved/Uncleared Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: CEIC 15/03 Board Name: Comitè Ètic d'Investigació Clínica de la Fundació Unió Catalana d'Hospitals Board Affiliation: Ethics Commitee Phone: +34935529208 Email: vanessamasso@uch.cat

	Address: Bruc, 72, 1r. 08009 Barcelona
Data Monitoring:	No
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary:	Crude incidence rate in Spain of hip fracture in people over 65 years was 511 cases per 100,000 in 2002. About 30% of patients die in the first year. Cardiocirculatory complications during and after surgery partly explain this high morbidity and mortality. Most patients are frail and with multicomorbidity. Goal-Directed Hemodynamic Therapy (GDT) based on noninvasive continuous monitoring of blood pressure, heart rate, oxygen saturation, cardiac output, cardiac index, stroke volume and stroke volume index can reduce perioperative complications and improve survival. The objective of our study is to assess the efficacy of a goal-directed hemodynamic therapy in reducing perioperative complications. Patients and Methods: non-randomized intervention study with a historical control and 1-year follow-up. Patients older than 64 years with non-traumatic hip fracture requiring surgical intervention. In the control group standard care was performed based on non-invasive, intermittent arterial pressure measurement, obtained every 5 minutes, continuous heart rate, and oxygen saturation. In the intervention group GDT based on noninvasive monitoring will be performed. The main outcome will be the percentage of patients with perioperative complications. Secondary outcomes: LOS and survival at 12 months of surgery.
Detailed Description:	NOTE : Detailed Description has not been entered.

Conditions

Conditions:	Hip Fractures
Keywords:	Fluid therapy Aged Perioperative complications Survival Intraoperative Goal Directed Therapy

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	N/A
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	None (Open Label)
Allocation:	Non-Randomized
Enrollment:	568 [Actual]

Arms and Interventions

Arms	Assigned Interventions
No Intervention: Control group Hemodynamic optimization according to the standards of perioperative monitoring of our center. In the intraoperative period hemodynamic monitoring will be done by management of blood pressure, heart rate and oxygen saturation	
Experimental: GDT noninvasive monitoring group GDT based on noninvasive monitoring System ClearSight® and Platform EV Clinic 1000®	GDT based on noninvasive monitoring Before entering the operating room, hemodynamic optimization start by optimizing preload with Fluid Challenge according to evidence-based GDT protocols. Once stabilized the cardiovascular system after induction of anesthesia, hemodynamic optimization continue with Mini Fluid Challenge. In the intraoperative period, hemodynamic optimization is based on maintaining systolic blood pressure and stroke volume. A Mini Fluid Challenge is administered to patients who respond to volume or a vasoactive drug according cardiac index for non-responders. Other Names: • Intraoperative Goal-Directed Hemodynamic Therapy Device: System ClearSight® and Platform EV Clinic 1000® Hemodynamic control is held by non-invasive continuous monitoring techniques (system ClearSight® and Platform EV Clinic 1000®). Monitored variables: blood pressure, heart rate, oxygen saturation, cardiac output, cardiac index, stroke volume and stroke volume index.

Outcome Measures

Primary Outcome Measure:

1. Percentage of patients who developed intraoperative haemodynamic instability
   Intraoperative haemodynamic instability, defined as one measurement of SAP < 90 mmHg in the CG and for at least one minute in the IG and/or the need for a bolus of vasoconstrictor.

   [Time Frame: Intraoperative period]

Secondary Outcome Measure:

2. Intraoperative arrhythmias
   Electrocardiographic evidence of cardiac rhythm disturbance.

   [Time Frame: Intraoperative period]
3. Postoperative complications
   Major cardiovascular complications, minor cardiovascular complications, Respiratory, Renal, Infections, Surgical reintervention during hospital stay

   [Time Frame: Postoperative period]
4. Hospital stay
   Length of hospital stay (days)

   [Time Frame: Patients will be followed for the duration of hospital stay, an expected median of 11 days]

5. Survival
[Time Frame: One-year survival]

NOTE : Outcome Measure Description has not been entered.

Eligibility

Minimum Age:	65 Years
Maximum Age:	
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No
Criteria:	Inclusion Criteria:

- Hip fracture that require surgical treatment
- Agree to participate and sign informed consent

Exclusion Criteria:

- Pathological or traffic related fractures
- Anesthetic contraindication for surgery
- Refractures
- Contraindication for hemodynamic monitoring
- Physiocal less than 30 after 7 minutes
- Psychomotor agitation that prevents hemodynamic monitoring

Contacts/Locations

Central Contact Person:	Juan Víctor Lorente Olazábal, MD Telephone: 938742112 Email: jlorente@althaia.cat
Central Contact Backup:	Anna Arnau Bartés, MSc Telephone: 93 875 93 00 Ext. 3414 Email: aarnau@althaia.cat
Study Officials:	Joan Bosch Sabater, MD PhD Study Chair Althaia Xarxa Assistencial Universitària de Manresa Francesca Reguant Corominas, MD PhD Study Chair Althaia Xarxa Assistencial Universitària de Manresa
Locations:	**Spain** Althaia Xarxa Assistencial Universitària de Manresa Manresa, Barcelona, Spain, 08243 Contact: Juan Víctor Lorente Olazábal, MD +34938742121 jlorente@althaia.cat Contact: Anna Arnau Bartés, MSc +34938759300 Ext. 3414 aarnau@althaia.cat

IPDSharing

Plan to Share IPD:	

References

Citations:

Links:

Available IPD/Information:

9.2. Anexo 2: Hoja de información al paciente y consentimiento informado estudio "Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera"

ESTUDIO DE LA EFICACIA DE LA OPTIMIZACIÓN HEMODINÁMICA GUIADA POR MONITORIZACIÓN NO INVASIVA EN LAS COMPLICACIONES POSTOPERATORIAS DE LOS PACIENTES CON FRACTURA DE CADERA

Investigador principal: Dr. Juan Victor Lorente Olazábal

Por favor, lea atentamente esta hoja de información:

La Fundació Althaia, está realizando un estudio en el que se le invita a participar.

La Fractura de Cadera tiene una incidencia muy alta en personas mayores de 65 años, son pacientes que tienen una reserva fisiológica muy disminuida, sobre todo cardio-pulmonar, este hecho es un factor de riesgo mayor para desarrollar complicaciones tanto intraoperatorias como postoperatorias. La terapia hemodinámica dirigida por objetivos (TDPO) ha demostrado disminuir las complicaciones perioperatorias, así como la mortalidad al primer mes de la cirugía, especialmente en paciente de alto riesgo, como son casi la totalidad de afectos de Fractura de Cadera.

Algunas nuevas plataformas no invasivas permiten la obtención de parámetros hemodinámicos dinámicos para llevar a cabo esta TDPO

Por estos motivos, se ha diseñado este estudio con el objetivo de, utilizando esta monitorización no invasiva, intentar disminuir las complicaciones tanto intra, como postoperatorias en estos pacientes.

Es posible que de su participación en este estudio no obtenga un beneficio directo. Sin embargo, la evaluación de nuevos sistemas para mejorar el tratamiento de la fractura de cadera podría en un futuro facilitar la evolución en otros sujetos.

Su participación en el estudio consistirá en:

-Recibir durante la intervención quirúrgica y las ocho primeras horas tras la misma, de un método de monitorización no invasivo, que permitirá a su médico responsable conocer con más detalles su estado cardiovascular, para así, tomar decisiones de una forma más guiada, sobre el tratamiento idóneo para usted en ese momento.

-Una recogida de datos en la que se le pedirá que conteste a una serie de preguntas y test sobre sus antecedentes clínicos y su estado de salud tanto durante el alta, como al mes y a los 3, 6 y 12 meses después de la cirugía.

Debe saber que su participación es voluntaria, por lo que es necesario que antes de su inclusión en el estudio, haya otorgado por escrito su autorización mediante la firma de un consentimiento informado. Podrá retirarse del estudio o retirar su consentimiento para la utilización de sus datos cuando lo desee, sin tener que dar ninguna explicación al equipo de investigación y sin que ello suponga ninguna alteración en la relación con su médico.

Todos los datos que se recogen en el estudio, serán utilizados por los investigadores y el promotor de este estudio con la finalidad comentada anteriormente, serán tratados con total reserva y usted estará identificado mediante un número, no incluyéndose ningún dato que le identifique directamente.

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustarán a lo dispuesto en la Ley Orgánica de protección de datos de carácter personal 15/1999 de 13 de diciembre. De acuerdo a lo que establece la legislación mencionada, usted puede ejercer el derecho de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a su médico del estudio.

También es importante que sepa que este estudio ha sido sometido al criterio del Comité Ético de Investigación Clínica de la Fundació Unió, Unió Catalana d'Hospitals y cumple con toda la legislación vigente en España.

Si durante cualquier momento tiene alguna duda y quiere contactar con el médico responsable del estudio en este centro, Dr Juan Victor Lorente Olazábal, podrá hacerlo a través del siguiente número de teléfono 93.875.93.00-

Si está de acuerdo en participar en este estudio, por favor exprese su consentimiento rellenando el documento disponible a continuación.

FORMULARIO DE CONSENTIMIENTO INFORMADO ESCRITO

Yo, (nombre y apellidos) _____

He leído la hoja de información sobre: "Estudio de la eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera**".**

- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con el doctor.
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio:
    - Cuando quiera.
    - Sin tener que dar explicaciones.
    - Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio y para que mis datos puedan ser utilizados con fines de investigación.

Firma del paciente: Firma del investigador:

_____ _____

Fecha: _ _/_ _/_ _ (día/mes/año) Fecha: _ _/_ _/_ _ (día/mes/año)

9.3. Anexo 3: Aprobación Comité de Ética de la Investigación Clínica, estudio: "Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera"

FUNDACIÓ UNIÓ

INFORME DEL COMITÉ ÉTIC D'INVESTIGACIÓ CLÍNICA

Dr. Miquel Nolla, com a President del Comitè Ètic d'Investigació Clínica de la FUNDACIÓ UNIO CATALANA HOSPITALS

C E R T I F I C A:

Que aquest Comitè en la seva reunió del dimarts, 27 de gener, ha avaluat:

La proposta d'Althaia, Xarxa Assistencial Universitària de Manresa, per que es realitzi l'estudi que porta per títol: "Eficacia de la Optimización Hemodinámica guiada por monitorización no invasiva en las complicaciones perioperatorias de los pacientes con Fractura de Cadera." codi CEIC 15/03 i considera que:

Es compleixen els requisits necessaris d'idoneïtat del protocol en relació amb els objectius de l'estudi i que estan justificats els riscos i les molèsties previsibles per al subjecte.

La capacitat de l'investigador i els mitjans disponibles són apropiats per portar a terme l'estudi.

Són adequats tant el procediment per obtenir el consentiment informat com la compensació prevista per als subjectes per danys que es puguin derivar de la seva participació a l'estudi.

Que aquest comitè accepta que aquest estudi es digui a terme a Althaia, Xarxa Assistencial Universitària de Manresa, amb Juan Víctor Lorente Olazábal com investigador principal.

I que l'investigador principal no ha estat present en les deliberacions i aprovació d'aquest estudi.

En aquesta reunió s'han complert els requisits establerts en la legislació vigent – Orden SAS/347/2009, RD 223/22004. El CEIC tant en la seva composició, com en els PNT compleix amb les normes de BPC (CPMP/ICH/135/95).

FUNDACIÓ UNIÓ

MEMBRES DEL CEIC DE LA FUNDACIÓ UNIÓ CATALANA D'HOSPITALS

Dr. Miquel Nolla	President	Metge
Dra. Anna Altés	Secretari	Metge
Dra. Imma Guasch	Vocal	Metge
Dr. Ernesto Mònaco	Vocal	Metge
Dr. Jesús Montesinos	Vocal	Metge
Dr. Josep M Tormos	Vocal	Metge
Dra. Rosa Morros	Vocal	Farmacòloga Clínica
Dr. Jaume Trapé	Vocal	Farmacèutic
Dra. Imma Torre	Vocal	Farmacèutica
Dra. Concha Antolin	Vocal	Farmacèutica primària
Sra. Elisabet Juan	Vocal	Infermera
Sra. Laura Cedrón	Vocal	Infermera
Sra. Ana Barajas	Vocal	Psicòloga
Sra. Itziar Aliri	Vocal	Advocat
Sra. Anna Guijarro	Vocal	Filosofia
Sra. Vanessa Massó	Vocal	C. Empresarials

Barcelona, 5 de febrer de 2015

Dr. Miquel Nolla
President del CEIC

9.4. Anexo 4: Lorente JV, Reguant F, Arnau A, Borderas M, Prieto JC, Torrallardona J, Carrasco L, Solano P, Pérez I, Farré C, Jiménez I, Ripollés-Melchor J, Monge MI, Bosch J. Effect of goal-directed haemodynamic therapy guided by non-invasive monitoring on perioperative complications in elderly hip fracture patients within an enhanced recovery pathway. Perioper Med (Lond). 2022 Aug 10;11(1):46. doi: 10.1186/s13741-022-00277-w. PMID: 35945605; PMCID: PMC9364538.

Lorente *et al. Perioperative Medicine* (2022) 11:46
https://doi.org/10.1186/s13741-022-00277-w

Perioperative Medicine

RESEARCH Open Access

Effect of goal-directed haemodynamic therapy guided by non-invasive monitoring on perioperative complications in elderly hip fracture patients within an enhanced recovery pathway

Juan V. Lorente[1,2,3*], Francesca Reguant[2,4], Anna Arnau[5,6,2], Marcelo Borderas[4], Juan C. Prieto[4], Jordi Torrallardona[4], Laura Carrasco[4], Patricia Solano[4], Isabel Pérez[4], Carla Farré[4], Ignacio Jiménez[7,3], Javier Ripollés-Melchor[3,8], Manuel I. Monge[3,9] and Joan Bosch[2]

Abstract

Background: Goal-directed haemodynamic therapy (GDHT) has been shown to reduce morbidity and mortality in high-risk surgical patients. However, there is little evidence of its efficacy in patients undergoing hip fracture surgery. This study aims to evaluate the effect of GDHT guided by non-invasive haemodynamic monitoring on perioperative complications in patients undergoing hip fracture surgery.

Methods: Patients > 64 years undergoing hip fracture surgery within an enhanced recovery pathway (ERP) were enrolled in this single-centre, non-randomized, intervention study with a historical control group and 12-month follow-up. Exclusion criteria were patients with pathological fractures, traffic-related fractures and refractures. Control group (CG) patients received standard care treatment. Intervention group (IG) patients received a GDHT protocol based on achieving an optimal stroke volume, in addition to a systolic blood pressure > 90 mmHg and an individualized cardiac index. No changes were made between groups in the ERP during the study period. Primary outcome was percentage of patients who developed intraoperative haemodynamic instability. Secondary outcomes were intraoperative arrhythmias, postoperative complications (cardiovascular, respiratory, infectious and renal complications), administered fluids, vasopressor requirements, perioperative transfusion, length of hospital stay, readmission and 1-year survival.

Results: In total, 551 patients (CG=272; IG=279) were included. Intraoperative haemodynamic instability was lower in the IG (37.5% vs 28.0%; p=0.017). GDHT patients had fewer postoperative cardiovascular (18.8% vs 7.2%; $p < 0.001$), respiratory (15.1% vs 3.6%; $p<0.001$) and infectious complications (21% vs 3.9%; $p<0.001$) but not renal (12.1% vs 33.7%; $p<0.001$). IG patients had less vasopressor requirements (25.5% vs 39.7%; $p<0.001$) and received less fluids [2.600 ml (IQR 1700 to 2700) vs 850 ml (IQR 750 to 1050); $p=0.001$] than control group. Fewer patients required transfusion in GDHT group (73.5% vs 44.4%; $p<0.001$). For IG patients, median length of hospital stay was shorter [11 days (IQR 8 to 16) vs 8 days; (IQR 6 to 11) $p < 0.001$] and 1-year survival higher [73.4% (95%CI 67.7 to 78.3 vs 83.8% (95%CI 78.8 to 87.7) $p<0.003$].

*Correspondence: juanvictor.lorente@gmail.com

[1] Anaesthesia and Critical Care Department, Juan Ramón Jiménez Hospital, Ronda Norte s/n, 21590 Huelva, Spain
Full list of author information is available at the end of the article

Conclusions: The use of GDHT decreases intraoperative complications and postoperative cardiovascular, respiratory and infectious but not postoperative renal complications. This strategy was associated with a shorter hospital stay and increased 1-year survival.

Trial registration: ClinicalTrials.gov NCT02479321.

Keywords: Enhanced recovery after surgery, Enhanced recovery pathway, Fluid therapy, Goal-directed haemodynamic therapy, Hip fracture, Intraoperative complications, Mortality, postoperative complications

Background

Hip fracture represents an increasingly serious public health problem with a significant impact on life expectancy and economic burden (Veronese and Maggi 2018). Patients with hip fractures are at high risk of perioperative complications (Reguant et al. 2019) due to a limited cardiorespiratory reserve when facing the fracture and surgery-associated stress (Cowan et al. 2017). Moreover, postoperative complications related to hip fracture are a known independent risk factor for mortality (Griffiths et al. 2021).

Enhanced recovery pathways (ERP) comprise perioperative evidence-based care interventions designed to improve outcomes after surgery (Ljungqvist et al. 2017). Perioperative haemodynamic optimization is a key element of the ERP (Miller et al. 2015). The goal-directed haemodynamic therapy (GDHT) has been shown to reduce morbidity and mortality in high-risk surgical patients (Giglio et al. 2016). Nevertheless, in daily clinical practice, patients with hip fracture are usually intraoperatively monitored with routine haemodynamic parameters such as blood pressure and heart rate (Reguant et al. 2019). However, these standard physiological variables result insufficient for assessing an adequate balance between oxygen delivery (DO_2) and consumption (VO_2) (Lugo et al. 1993). This DO_2/VO_2 imbalance may eventually lead to intraoperative tissue hypoperfusion, facilitating the appearance of postoperative complications (Merry and Mitchell 2018).

Currently, there are monitoring platforms that provide advanced haemodynamic parameters to guide GDHT in a non-invasive way to avoid the complications of invasive techniques (Teboul et al. 2016).

The present study aimed to evaluate the effect of GDHT guided by non-invasive haemodynamic monitoring on perioperative complications in patients undergoing surgical hip fracture repair within an ERP.

Methods

This manuscript was written according to CONSORT statement. The study was approved by an independent Ethics Committee (Fundació Unio Catalana Hospitals) on 27 January 2015 (CEIC 15/03). All patients signed an informed consent to participate. The study was conducted according to the Declaration of Helsinki and all local legal and regulatory requirements. Trial registration: NCT02479321 (24/06/2015).

Study design

This is a single-centre, non-randomized, hospital-based intervention study with a historical control group (CG) and 12-month follow-up after hospital discharge.

Inclusion/exclusion criteria

Patients over 64 years with hip fracture within an ERP who underwent surgical treatment were included.

Exclusion criteria were as follows: patients with pathological fractures, traffic-related fractures and refractures; patients with known contraindication or limitations to advanced haemodynamic monitoring with ClearSight® system and EV1000 platform (Edwards Lifesciences, Irvine, USA) (Saugel et al. 2015); patients with Raynaud disease, with aortic valve prosthesis, proximal aortic aneurysm, known intra-cardiac shunts; moderate to severe mitral or aortic regurgitation; moderate to severe aortic or mitral stenosis; patients with poor-quality arterial waveform signal (see below) and patients with significant preoperative psychomotor agitation.

Conduct of the study

Perioperative management common to both groups

Both groups were treated during the perioperative period in a multidisciplinary ERP unit created in 2010 exclusively dedicated to patients undergoing hip fracture repair (Reguant et al. 2019).

This unit's objectives were to optimize patient health status before surgery, minimize preoperative stress, prevent and/or treat electrolyte imbalance, prevent and/or treat cardiovascular, respiratory, infectious and cognitive disorders, improve nutritional status and reduce surgical delay. The team comprised orthopaedic surgeons, anaesthesiologists, internists, a nurse case manager, a social worker, a physiotherapist and a nutritionist.

The main interventions of this multidisciplinary ERP unit for patients with hip fracture are shown in Table 1.

Table 1 Main interventions of enhanced recovery pathway unit for hip fracture patients

Preoperative period	Intraoperative period	Postoperative period
-Specialized hip fracture ward - Internist support - Assessment by anaesthesiologist - Nursing aids - Intravenous fluids - Monitor oxygen saturation/8 h. Oxygen therapy when < 92% and maintenance until 48 h after surgery - Pain control: avoiding opioids if possible - Carbohydrate loading until 2 h before surgery. - Protocol for patients who received antiplatelet drugs or oral anticoagulants on admission.[a] - Prioritize surgery within 48 h on admission in patients with medical stable condition.	- Prevention of intraoperative hypothermia - Intraoperative nausea and vomiting prophylaxis - Prophylactic antibiotic 30 min before surgical incision [b] - Avoid intrathecal opioids - Performance of peripheral nerve blocks	- Specialized hip fracture ward - Internist support - Nursing aids - Postoperative fluids should be stopped when possible, in favour of early oral intake. - Monitor oxygen saturation/8 h. Oxygen therapy when < 92% and maintenance until 48 h after surgery - Optimal postoperative analgesia, preferably with intraoperative peripheral nerve blocks and NSAIDs - Deep vein thrombosis prevention - Early respiratory physiotherapy - Early and standardized mobilization 24h after surgery. - Early urinary catheter removal
Perioperative interventions		
- Gastric ulcer prophylaxis iv/24 h. - To avoid using opioids and/or benzodiazepines. - Screening and treatment when appropriate of urinary infection - Bladder catheterisation only in case of incontinency or when needing to monitor renal and/or cardiac function. - Treatment protocol for anaemia when haemoglobin was < 13 g/dl on admission. Transfusion was administered if haemoglobin level was < 8 g/dl and to patients with cardiorespiratory disease and/or haemodynamic instability when haemoglobin level was < 10 g/dl.		

[a] Surgery was postponed for 4 days in patients who, at admission, had been administered acetylsalicylic acid >100 mg, triflusal >300 mg or clopidrogel/ticlopidine. Surgery was postponed in patients who were on OAC treatment at admission, until INR < 1.5

[b] 2 g cefazolin in intramedullary nail surgery in 100 ml saline, or cefuroxime and teicoplanin in prosthesis surgery (in a total of 200 ml saline)

Intraoperative period All subjects received standard of care with a 3-lead electrocardiogram, pulse oximetry and two peripheral intravenous lines. Patients in both groups received standard measures to maintain oxygen saturation by pulse oximetry >94% and heart rate <100 beats/min. Anaesthetic technique was at the discretion of the anaesthetist.

Post-anaesthetic care unit (PACU) After surgery, patients were treated in the PACU. The attendant physician determined discharge from this unit according to the local protocol.

Study arms

Control group Data from patients who underwent surgery for hip fracture between October 2010 and November 2011 with follow-up to December 2012 were used for the CG (Reguant et al. 2019).

Haemodynamic management was at the discretion of the attending anaesthetist, using fluid therapy with crystalloids (0.9% saline, lactated Ringer or Isofundin®), colloids (Voluven®, Gelaspan ®) and/or cardiovascular drugs (in bolus—ephedrine, or continuous infusion—noradrenaline, dobutamine).

Non-invasive, intermittent arterial pressure measurement was obtained at least every 5 min using a cuff (Dahtex Ohmeda-GE S/5 Aespire ®).

Intervention group Data from patients who underwent surgery for hip fracture between June 2015 and February 2018 with follow-up to March 2019 were used as the IG.

Pre- and intraoperative non-invasive haemodynamic monitoring was conducted using ClearSight® monitor (Edwards Lifesciences, Irvine, USA). This monitoring system is based on the volume clamp method to continuously measure arterial pressure and the Physiocal method that periodically recalibrates the system (Saugel et al. 2015). Baseline haemodynamic measurements were taken when the Physiocal value exceeded 30 (Wesseling et al. 1995). If a Physiocal value over 30 was not obtained after 7 min monitoring, the patient was excluded due to a poor-quality arterial waveform signal (Wesseling et al. 1995).

Haemodynamic optimisation was performed according to the following GDHT protocol.

GDHT protocol (Fig. 1)

Three groups of cardiac index (CI) goals were formed according to age and prior functional capacity expressed

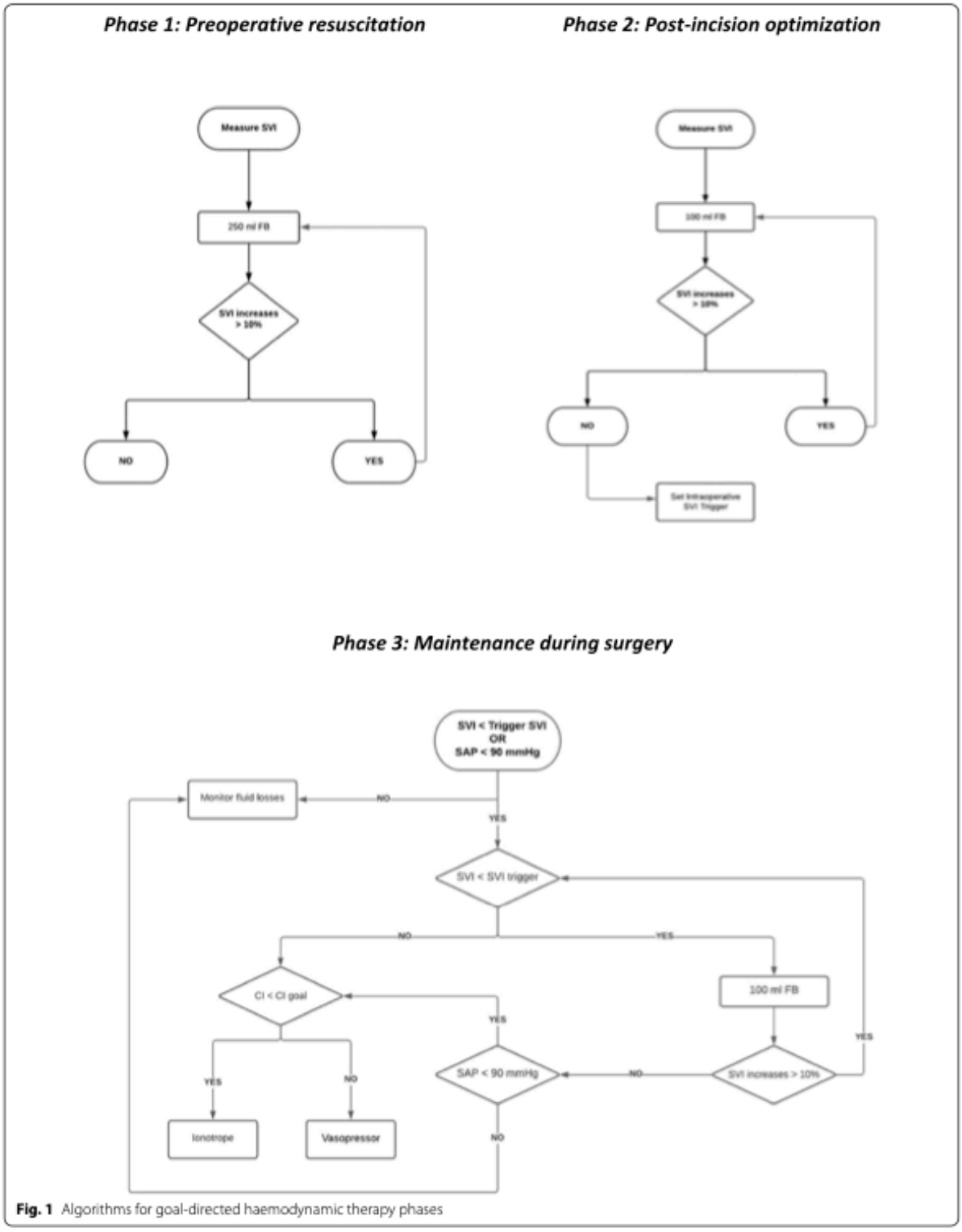


Fig. 1 Algorithms for goal-directed haemodynamic therapy phases

in metabolic equivalents (METS) (Montenij et al. 2014) Additional file 1.

Fluids were given based on a protocolized haemodynamic algorithm to achieve and maintain an adequate indexed stroke volume (SVI) using crystalloids (0.9% Saline, Lactated Ringer or Isofundin ®) or colloids (if preoperative glomerular filtration rate was above 60 mL/min using Modification of Diet in Renal Disease (MDRD) equation (Ishihara 2014)- Voluven ®, Gelaspan ®). Choice of fluid type was based on anaesthesiologist criteria.

If a fluid bolus (FB) was not indicated and/or the target perfusion pressure was not been achieved with its infusion, vasopressor was administered to maintain systolic arterial pressure (SAP) above 90 mmHg (in bolus—ephedrine, phenylephrine, or continuous infusion—noradrenaline) or continuous infusion of dobutamine was added to achieve in addition, the individualized CI goal.

Phase 1: Preoperative resuscitation

On arrival in the surgical area, patients received a FB of 250 ml of 5 min. If SVI increased by 10% or more (*First Fluid Bolus Responder*), the fluid bolus was repeated (Cecconi et al. 2011). Fluid boluses of 250 ml were repeated until the SVI failed to increase by 10%.

Once preoperative resuscitation was completed, prophylactic antibiotic was infused (Table 1). This fluid contribution covered the estimated insensible losses during surgery (Jacob et al. 2007).

Phase 2: Post-incision optimisation

Post-incision optimisation began 15 min after the surgical incision, if the haemodynamic stabilization was achieved (SAP and heart rate variation < 10% for 3 min); meanwhile, the haemodynamic priority was the maintenance of arterial pressure above goal set (Tassoudis et al. 2011).

Haemodynamic optimisation consisted of a 100-ml fluid bolus administered of less than 3 min (Guinot et al. 2015; Mallat et al. 2015; Marik 2015; Muller et al. 2011). If SVI rose >10%, the 100 ml fluid bolus was repeated. The trigger SVI during surgery was calculated by subtracting 10% from the SVI obtained from the last positive 100 ml fluid bolus (Muñoz et al. 2016).

Phase 3: Maintenance during surgery

If at least one of the following objectives, SVI>SVI trigger and /or SAP>90mmHg, were not achieved, SVI was analysed:

- If it was lower than the trigger SVI, a 100 ml FB was administered.
- If SVI was higher than trigger SVI, we look at the CI.
  - If its value was under goal level, dobutamine was added.
  - When CI was above goal level, a vasopressor was chosen.

After each therapy, we re-evaluated the achievement of SAP and SVI goals.

Measurements and data handling

Procedure

Intraoperative haemodynamic parameters (arterial pressure, heart rate, SpO_2 in CG and also CI and SVI in IG) were registered at 15-min intervals. Haemodynamic instability, between intervals, was registered as an event in the next record. Fluids and cardiovascular drugs used from the patient's arrival in the surgical area to their admission to the PACU were collected. In both groups, the evaluation of intraoperative complications was based on the intraoperative anaesthesia charts, whereas the postoperative complications were documented in the clinical course and hospital discharge report.

Post-discharge follow-up consisted of a structured telephone interview at 1, 3, 6 and 12 months after surgery. When the information could not directly be obtained from the patients (including deceased patients), the interview was done with next of kin or carer.

Assessment of outcomes

Primary outcome measures The primary outcome was the percentage of patients who developed intraoperative haemodynamic instability, defined as one measurement of SAP < 90 mmHg in the CG and for at least 1 min in the IG and/or the need for a bolus of vasoconstrictor.

Secondary outcome measures

- Intraoperative arrhythmias: defined as electrocardiographic evidence of cardiac rhythm disturbance.
- Postoperative complications, grouped as follows:
  - Major cardiovascular complications*: acute myocardial infarction, acute pulmonary oedema, ischemic stroke, pulmonary thromboembolism and cardiorespiratory arrest.*

- Minor cardiovascular complications: *haemodynamic instability*, defined as one measurement of SAP < 90 and *arrhythmias*.
- Respiratory: *hypoxia*, defined as oxygen saturation <92%. Other respiratory complications: *decompensation of chronic obstructive pulmonary disease*, *acute respiratory infection* (clinical and radiological diagnosis and antibiotic treatment) and others.
- Renal: presence of at least one of the following: *oligoanuria*, defined as urine output under 0.5ml/kg per hour, including absence of urine output. *Acute renal failure*, defined as an increase in urea > 50 mg/dl and creatinine levels > 1.09 mg/dl in any analysis during admission.
- Infections: *surgical wound (*infection within 30 days after surgery that involves only skin and subcutaneous tissue of the incision), *urinary* (positive urine culture causing patient's symptoms and which were not present on admission to hospital), *systemic* (fever >38 °C and positive blood antigen test with appropriate antimicrobial therapy instituted by a physician).
- Surgical reintervention during hospital stay.

– Total intraoperative volume and type of administered fluids, doses of cardiovascular drugs used, perioperative packed red blood cell transfusion, length of hospital stay, readmission within 30 days of surgery, and survival within 12 months after surgery.

Statistical analysis

Sample size

The rate of intraoperative haemodynamic instability described with standard of care was 37.5% (Reguant et al. 2019). We planned a relative risk reduction of 30% in IG.

To achieve a power of 80% using a bilateral χ^2 test for two independent samples with a level of significance of 0.05, 538 patients had to be included (269 patients in each group). With a potential dropout of 5%, 568 patients were included.

The percentage of patients who developed one or more postoperative complications in CG was 45.2%. A meta-analysis by Grocott and colleagues suggested a RR reduction of 0.68 for complications in patients undergoing major surgery (Grocott et al. 2013). A sample size of 568 patients, 284 in each group, would have 80% power to detect a reduction of at least 22% in the number of IG patients presenting one or more postoperative complications, using a bilateral χ^2 test for two independent samples.

Statistical analysis

Categorical variables were presented as absolute values and relative frequencies. Continuous variables are summarized as means and standard deviation for normal distribution and by the median and interquartile range (IQR) (25th to 75th percentiles) for non-normal distributions.

In the bivariate analysis, we used the Student's *t*-test or the non-parametric Mann–Whitney *U* test for continuous variables. We used the χ^2 test for categorical variables, and Fisher's exact test or bilateral exact *p*-values in contingency tables when the expected frequencies were less than five.

One-year survival Kaplan–Meier curves were constructed, and the log-rank test was used to compare them. Crude and adjusted hazard ratios and confidence intervals (CI 95%) were calculated using Cox proportional regression models. The proportionality of hazards was verified by examining Schoenfeld residual plots.

Outcomes were analysed on an intention-to-treat basis. The level of statistical significance was two-sided 5% ($p < 0.05$). The IBM SPSS Statistics v.26 (IBM Corporation®, Armonk, New York) and Stata v.14 (StataCorp LP®, College Station, Texas) programmes were used for statistical analysis.

Results

A total of 551 patients were recruited. Study flowchart is shown in Fig. 2. Table 2 shows the baseline characteristics of the 272 patients in CG and the 279 patients in IG.

Mean age was 84.9 years (69.1% female) in the CG and 85.2 years (75.6% female) in IG. Patients in the IG had a worse health status according to the criteria of ASA (III–IV 68.8% vs 85.3%; $p < 0.001$). A higher percentage of patients with intake of more than 4 drugs (67.4% vs 75.6%; $p=0.03$) was observed in the IG. No significant differences between groups were observed according to type of fracture; despite this, use of intramedullary nail increased in the IG (15.8% vs 42.3%; $p<0.001$). Surgical time was higher in the IG (80 min vs 90 min; $p<0.004$). There were no differences between anaesthesia techniques in two groups. Surgery was performed within 48 h of admission in 55.1% in the CG vs 68.5% of patients in the IG ($p=0.001$).

Primary outcome

Details of intraoperative complications are shown in Table 3. The number of patients with intraoperative haemodynamic instability was lower in IG (37.5% vs 28.0%; $p=0.017$). The median number of episodes of intraoperative haemodynamic instability in IG was lower than in the CG [2 (IQR 1 to 4) vs 1 (IQR 1 to 2), $p<0.001$].

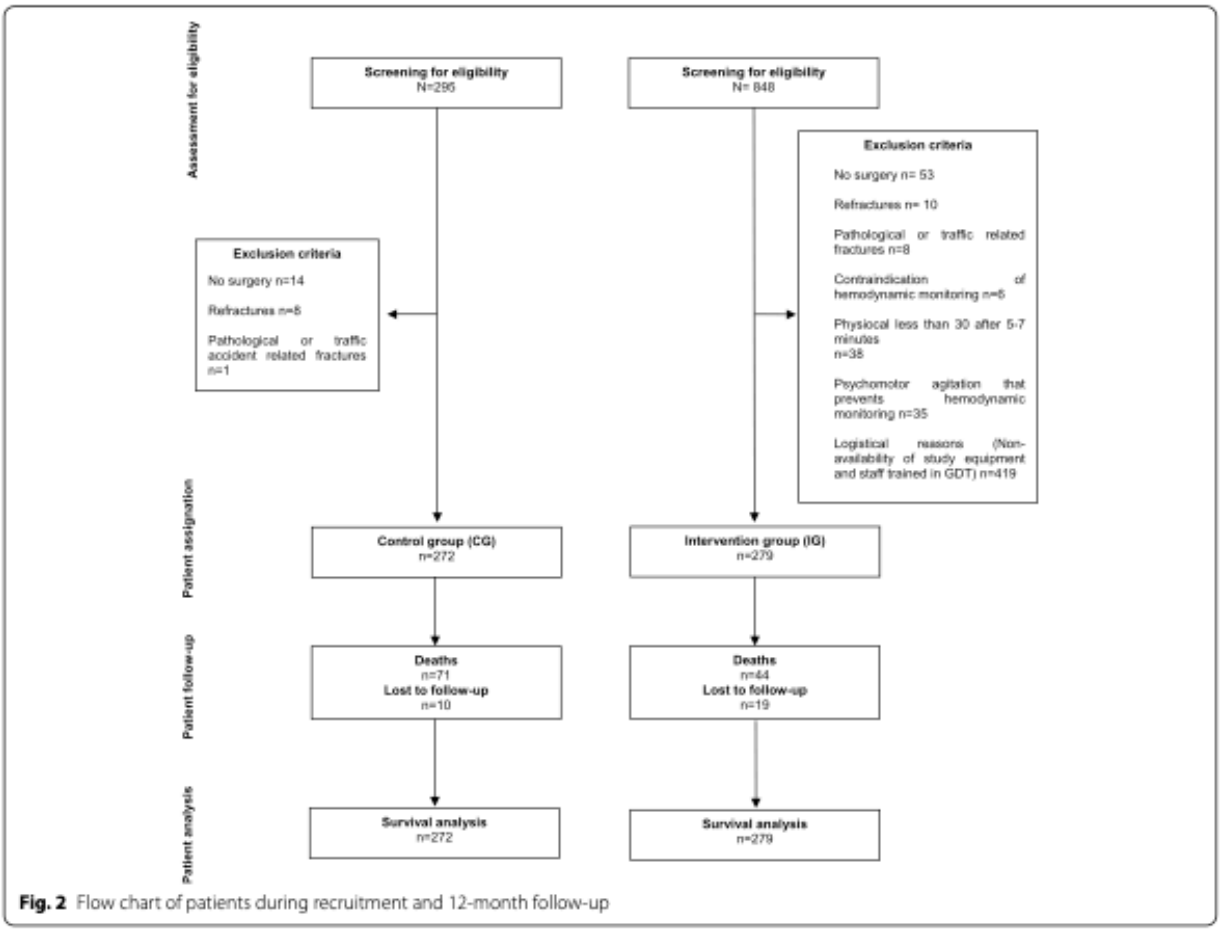


Fig. 2 Flow chart of patients during recruitment and 12-month follow-up

Secondary outcomes

Intraoperative arrhythmias

IG patients developed fewer arrhythmias than CG patients (2.2% vs 0.7%; p=0.172).

Postoperative complications

Postoperative complications are shown in Table 3. Postoperative complications rates were 42.3% in the IG versus 45.2% in CG (p=0.489). Patients in the IG had fewer cardiovascular complications (18.8% vs 7.2%; p< 0.001), fewer respiratory complications (15.1% vs 3.6%; p<0.001) and postoperative infections (21% vs 3.9%; p<0.001). However, IG patients had more renal complications (12.1% vs 33.7%; p<0.001). No differences in postoperative renal complications were observed between groups in patients with normal creatinine value at hospital admission. (Additional file 4).

Fluid volumes, vasopressor doses and perioperative transfusion

Details of fluid volumes and vasopressor doses in both groups are shown in Table 4.

29.4% of IG patients were responders to the first fluid bolus performed. Patients in the IG received less fluid [2.600 ml (IQR 1700 to 2700) vs 850 ml (IQR 750 to 1050); p=0.001] and vasopressors (39.7% vs 25.5%; p<0.001) than CG. Lactated Ringer's was the fluid most used during the intraoperative period in CG patients (73.9% vs 4.3%; p<0.001) while saline was chosen more often in the intraoperative period in IG (25% vs 95.7%; p=0.001). Fewer patients in IG received colloids than in CG (59.2% vs 9%; p<0.001).

Fewer patients required packed red blood cells (PRBC) transfusion in IG (73.5% vs 44.4%; p<0.001), with a lower median number of PRBC among transfused patients in IG [2 (IQR 2 to 4) vs 2 (IQR 1 to 2); p<0.001].

Table 2 Baseline characteristics according to group allocation

	Control (CG) *n*=272	Intervention (IG) *n*=279
Age	84.9 ± 6.2	85.2 ± 7.4
65 to < 75 years	15 (5.5%)	30 (10.8%)
75 to < 85 years	125 (46.0%)	97 (34.8%)
≥ 85 years	132 (48.5%)	152 (54.5%)
Gender		
Male	84 (30.9%)	68 (24.4%)
Female	188 (69.1%)	211 (75.6%)
ASA		
I–II	85 (31.2%)	41 (14.7%)
III–IV	187 (68.8%)	238 (85.3%)
Charlson comorbidity index		
Absence de comorbidity (0–1)	125 (46.0%)	109 (39.1%)
Low comorbidity (2)	50 (18.4%)	57 (20.4%)
High comorbidity (3 or more)	97 (35.7%)	113 (40.5%)
Cardiovascular history		
Valvulopathy	21 (7.7%)	31 (11.1%)
Arrhythmia	73 (26.8%)	58 (20.8%)
Ischemic cardiopathy	17 (6.3%)	29 (10.4%)
Pulmonary thromboembolism (PTE)	1 (0.4%)	3 (1.1%)
Hypertension	177 (65.1%)	212 (76.0%)
Total number of drugs	6 (IQR 4 to 8)	7 (IQR 5 to 10)
≤ 4 drugs	89 (32.7%)	68 (24.4%)
> 4 drugs	183 (67.3%)	211 (75.6%)
Type of fracture		
Intra-capsular	121 (44.5%)	124 (44.4%)
Extra-capsular	151 (55.5%)	155 (55.6%)
Haemoglobin at admission		
Haemoglobin > 12 g/dl	159 (58.5%)	169 (60.6%)
Haemoglobin ≤ 12 g/dl	113 (41.5%)	110 (39.4%)
Creatinine at admission		
Creatinine ≤ 1.09 mg/dl	178 (65.7%)	175 (62.7%)
Creatinine > 1.09 mg/dl	93 (34.3%)	104 (37.3%)
Anaesthesia		
General	28 (10.3%)	28 (10.0%)
Spinal	244 (89.7%)	251 (90.0%)
Type of implant		
Hip prosthesis	103 (37.9%)	102 (36.6%)
Dynamic hip screw	122 (44.9%)	57 (20.4%)
Intramedullary nail	43 (15.8%)	118 (42.3%)
Others	4 (1.5%)	2 (0.7%)
Surgical delay		
≤ 48 h	150 (55.1)	191 (68.5)
> 48 h	122 (44.9)	88 (31.5)
Surgery time (minutes)	80 (IQR 65 to 105)	90 (IQR 70 to 120)

Mean ± Standard deviation; *n* (%); median (IQR 25th percentile to 75th percentile)

Length of stay and survival within 12 months of surgery

The median length of stay was shorter for patients in the IG (median days: 11 vs 8; $p < 0.001$) (Table 3).

Demographic and clinical variables associated with 1-year mortality in the bivariate analysis appear in Additional file 2. Figure 3 shows the Kaplan–Meier survival curves for both groups. The likelihood of 1-year survival was higher in IG (log-rank test=9.17; $p = 0.003$) (see Fig. 3), with a crude HR of 0.56 (95% CI 0.39 to 0.82). Multivariate analysis (Additional file 3) showed that independent prognostic factors for 1-year survival were as follows: age (HR 1.09; 95% CI 1.05 to 1.12), male gender (HR 2.10; 95% CI 1.43 to 3.11), low (HR 2.33; 95% CI 1.29 to 4.23) and high comorbidity (HR 2.84; 95% CI 1.67 to 4.83), according to the Charlson Index, postoperative cardiovascular complications (HR 3.85; 95% CI 2.49 to 5.96), need for reintervention (HR 5.31; 95% CI 1.58 to 17.86) and belonging to the intervention group*. The adjusted HR for the IG was 0.61 (95% CI 0.39 to 0.95).

Discussion

The use of GDHT guided by non-invasive haemodynamic monitoring in patients undergoing hip fracture surgery within an ERP, was associated with a reduction in intraoperative complications (haemodynamic instability, arrhythmias) and postoperative cardiovascular, respiratory and infectious complications, but not postoperative renal complications. This strategy was also associated with a shorter hospital stay and increased survival 1 year after surgery.

Preoperative chronic conditions and insufficient preoperative optimization in this patient profile, associated with intraoperative conditions such as bleeding and hypovolemia, predispose these elderly patients to haemodynamic instability or arrhythmias during surgery (Alecu et al. 2010); (Rocos et al. 2017). The occurrence of intraoperative complications may compromise the balance between tissue oxygen delivery and oxygen consumption and increase the patient's susceptibility to postoperative complications (Merry and Mitchell 2018); (Beecham et al. 2020).

Our results showed a significant decrease in intraoperative haemodynamic instability episodes in patients in the IG, similarly to a recently published study (Davies et al. 2019). In addition, patients in the IG had fewer postoperative cardiovascular, respiratory and infectious complications. These results may be due to improvements in haemodynamic control of these patients as a result of GDHT guided by a non-invasive monitoring system implemented. One of its main objectives is to avoid

Table 3 Main and secondary outcomes at 1-year follow-up

	Control (CG) *n*=272	Intervention (IG) *n*=279	*p*-value
Intraoperative complications			
Hemodynamic instability	102 (37.5%)	78 (28.0%)	0.017[a]
No. of episodes of hemodynamic instability[e]	2 (IQR 1 to 4)	1 (IQR 1 to 2)	<0.001[b]
Arrhythmias	6 (2.2%)	2 (0.7%)	0.172[c]
Postoperative complications	123 (45.2%)	118 (42.3%)	0.489[a]
Cardiovascular	51 (18.8%)	20 (7.2%)	<0.001[a]
Major	12 (4.4%)	11 (3.9%)	0.783[a]
Myocardial infarction	1 (0.4%)	0 (0.0%)	0.494[c]
Cardiorespiratory arrest	3 (1.1%)	6 (2.2%)	0.505[c]
Acute pulmonary edema	8 (2.9%)	5 (1.8%)	0.374[a]
Pulmonary thromboembolism	0 (0.0%)	0 (0.0%)	-
Cardiorespiratory arrest	0 (0.0%)	0 (0.0%)	-
Minor	40 (14.7%)	12 (4.3%)	<0.001[a]
Haemodynamic instability	34 (12.5%)	5 (1.8%)	<0.001[a]
Arrhythmias	4 (1.5%)	7 (2.5%)	0.384[a]
Others	2 (0.7%)	1 (0.4%)	0.620[c]
Respiratory	41 (15.1%)	10 (3.6%)	<0.001[a]
Hypoxia	17 (6.3%)	2 (0.7%)	<0.001[a]
Decompensation of chronic obstructive pulmonary disease	6 (2.2%)	1 (0.4%)	0.066[c]
Acute respiratory infection	16 (5.9%)	5 (1.8%)	0.012[a]
Others	3 (1.1%)	2 (0.7%)	0.682[c]
Renal	33 (12.1%)	94 (33.7%)	<0.001[a]
Infections	57 (21.0%)	11 (3.9%)	<0.001[a]
Surgical wound	8 (2.9%)	0 (0.0%)	0.003[c]
Urinary	47 (17.3%)	10 (3.6%)	<0.001[a]
Systemic	3 (1.1%)	2 (0.7%)	0.682[a]
Secondary to spinal anaesthesia			
Hematoma/infection/neurological lesion	0 (0.0%)	0 (0.0%)	-
Surgical reintervention	6 (2.2%)	0 (0.0%)	0.014[c]
Length of stay (days)	11 (IQR 8 to 16)	8 (IQR 6 to 11)	<0.001[b]
Destination after discharge			0.327[a]
Convalescence	128 (49.8%)	142 (52.0%)	
Family home	81 (31.5%)	71 (26.0%)	
Residence	48 (18.7%)	60 (22.0%)	
Thirty-day readmission	29 (11.3%)	21 (7.7%)	0.157[a]
Survival			0.003[d]
1 month	91.2% (87.1 to 94.0%)	96.8% (93.9 to 98.3%)	
3 months	88.6% (84.2 to 91.8%)	95.3% (92.1 to 97.3%)	
6 months	83.0% (78.0 to 87.0%)	90.2% (86.0 to 93.2%)	
12 months	73.4% (67.7 to 78.3%)	83.8% (78.8 to 87.7%)	

Mean ± Standard deviation; *n* (%); median (range *x* to *y*) or median (IQR 25th percentile to 75th percentile)

[a] Pearson χ^2; [b] Mann–Whitney *U*; [c] Fisher's exact test; [d] Log-rank test

[e] In patients with haemodynamic instability

Table 4 Total fluid volumes, vasopressor doses and perioperative blood transfusion

	Control (CG) *n*=272		Intervention (IG) *n*=279		*p*-value
	n (%)	Median (IQR)	*n* (%)	Median (IQR)	
Fluid volumes					
Total fluids (ml)	272 (100%)	2600 (IQR 1700 to 2700)	279 (100%)	850 (IQR 750 to 1050)	0.001
Fluid creep -antibiotic prophylaxis- (ml)	272 (100%)	200 (IQR 200 to 200)	279 (100%)	200 (IQR 100 to 200)	0.001
Intraoperative fluids (ml)	272 (100%)	2500 (IQR 2000 to 2500)	279 (100%)	700 (IQR 550 to 900)	0.001
Crystalloids (ml)	253 (94.5%)	2000 (IQR 2000 to 2000)	278 (99.6%)	650 (IQR 550 to 850)	0.001
Saline (ml)	68 (25.0%)	1000 (IQR 1000 to 1000)	267 (95.7%)	650 (IQR 550 to 850)	0.001
Lactated Ringer (ml)	201 (73.9%)	1000 (IQR 1000 to 1000)	12 (4.3%)	1050 (IQR 850 to 1237)	0.889
Isofundin® (ml)	22 (8.1%)	500 (IQR 500 to 500)	-	-	-
Colloids (ml)	161 (59.2%)	500 (IQR 500 to 500)	25 (9.0%)	300 (IQR 200 to 500)	0.001
Voluven® (ml)	153 (56.3%)	500 (IQR 500 to 500)	25 (9.0%)	300 (IQR 200 to 500)	0.001
Gelaspan® (ml)	11 (4.0%)	500 (IQR 500 to500)	-	-	-
Vasopressor	108 (39.7%)		71 (25.5%)		<0.001
Ephedrine (mg)	108 (39.7%)	15 (IQR 10 to 30)	65 (23.3%)	10 (IQR 10 to 20)	0.002
Phenylephrine (mg)	-	-	11 (4.0%)	100 (IQR 50 to 150)	-
Noradrenaline (mg)	2 (0.7%)	3.5 (IQR 2 to 3.5)	-	-	-
Blood transfusion	200 (73.5%)	-	124 (44.4%)	-	<0.001
Number of PRBC[a]		2 (IQR 2 to 4)		2 (IQR 1 to 2)	<0.001
Fluid Challenge Responder	-	-	82 (29.4%)		-

Median (IQR 25th percentile to 75th percentile)

PRBC packed red blood cells

[a] About transfused patients

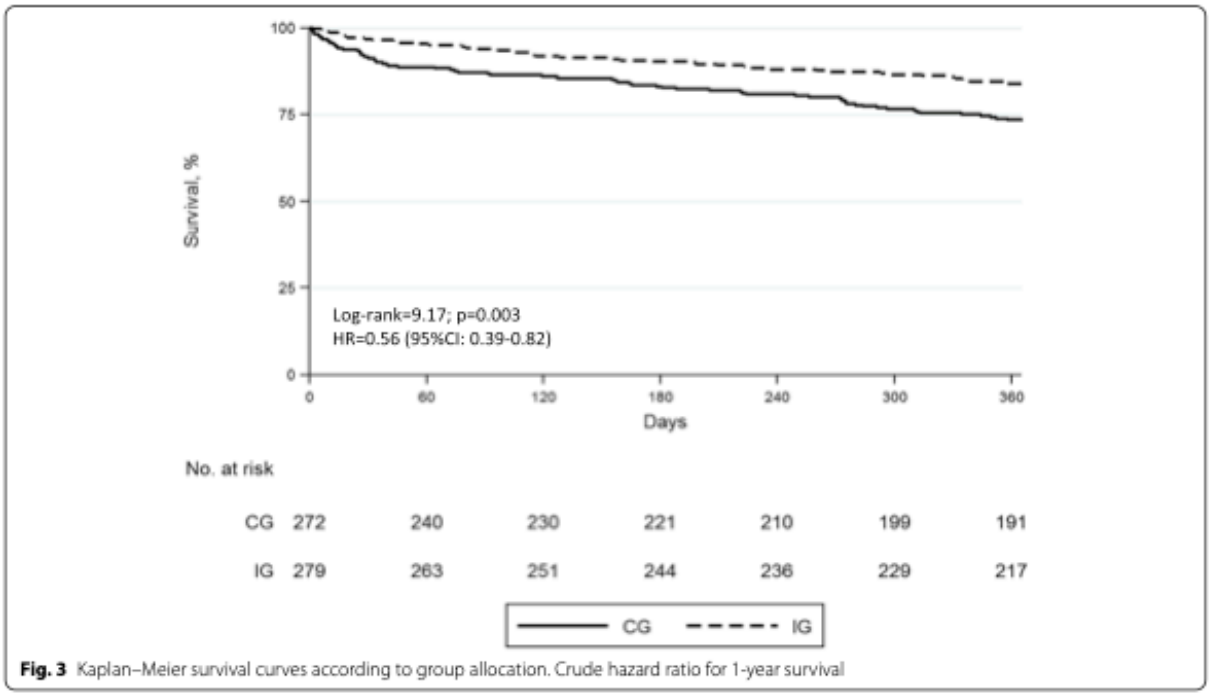


Fig. 3 Kaplan–Meier survival curves according to group allocation. Crude hazard ratio for 1-year survival

intraoperative hypoperfusion (Brienza et al. 2019) which may have been reflected in fewer postoperative complications in IG.

A higher incidence of postoperative acute kidney injury (AKI) found in IG may be due to several reasons. First, patients in the IG have more risk factors for postoperative AKI, including age, female sex, hypertension and chronic kidney disease. (Meersch et al. 2017). Secondly, patients treated with GDHT received higher amounts of 0.9% saline. Hyperchloremic acidosis associated with saline infusion is detrimental to renal artery blood flow velocity and renal cortical tissue perfusion (Chowdhury et al. 2012). Third, the AKI definition itself. A single and transient, postoperative serum creatinine elevation above a very sensitive level was considered a renal complication. An isolated elevation could neither be associated with kidney cell damage (Hahn 2015) nor be significant compared to baseline value. In patients with normal creatinine value at hospital admission, no differences in the risk of suffering postoperative renal complications were observed between the groups. The limitations of AKI definition and the influence on mortality only by postoperative creatinine elevations associated with kidney cell damage, may explain a significant decrease in mortality 1 year after surgery, despite an increase in postoperative renal complications in IG.

The GDHT protocol applied in this study differs from that used in the most recent trials in this patient profile (Bartha et al. 2013; Davies et al. 2019; Moppett et al. 2015). The GDHT protocol used by Bartha and colleagues includes fluid resuscitation prior to anaesthetic induction, intraoperative use of vasoactive support if SAP declined by more than 30% from pre-anaesthesia values, and optimisation with fluids and dobutamine for stroke volume (SV) and DO_2 respectively. Colloid therapy to optimize SV was protocolised by Moppett and co-workers in their IG. Finally, Davies and colleagues applied a GDHT protocol based on SV optimisation by crystalloids and mean arterial pressure maintenance above 30% of baseline values with vasopressors.

Our IG shows a similar percentage of responders to the first fluid challenge as previously described (Bartha et al. 2013). This lower-than-expected percentage can be explained by the optimisation starting immediately after admission to hospital, according to the ERP applied in both patient cohorts. Total fluid used in our IG is comparable or slightly less than the amounts given in two previous studies' intervention groups: 1.078 (Bartha et al. 2013) and 850 ml (Davies et al. 2019) respectively and slightly higher than the volume given in another previous intervention group: 750 ml (Moppett et al. 2015). A lower use of vasopressors in our IG stands out, probably because of following a decision algorithm. The non-application of a haemodynamic algorithm may lead to an early use of vasopressors, even if it is not physiologically appropriate for the patient's condition. No IG patients were treated intraoperatively with dobutamine, probably due to the establishment of an individualized CI goal and by the absence of intraoperative pathophysiological tributary situations. Fewer patients had been transfused in our IG. In addition to the use of less bleeding surgical techniques (Yu et al. 2015), patients in IG may suffered less haemodilution than patients in CG due to lower amount of fluids received (Ince 2015).

We found a reduction in hospital stay and a significant increased survival in IG patients throughout the first year after surgery. These findings can be explained by the significant reduction in intraoperative complications and postoperative cardiovascular, respiratory and infectious complications, and surgical reinterventions (Monk et al. 2015); (Roche et al. 2005). After adjusting for potential confounding variables, IG membership was a protective factor for 1-year mortality.

The results of this study suggest that not only haemodynamic strategy we perform on our patients will influence their outcomes, the type of fluid used during major surgery may also affect postoperative results (Heming et al. 2020). The results of the fluid infusion strategy used cannot be evaluated without considering the type of drug used.

Our study has some limitations. It was a single-centre, non-randomized design with a 3-year gap between the two study groups. However, no changes were made between groups in the ERP, nor in the composition of the multidisciplinary team or in the care protocols during the study period. IG recruitment rate was lower than expected, probably because of the real emergency surgery status applied to hip fracture patients in this hospital since 2010. Patients with contraindications for haemodynamic monitoring, with poor-quality signal obtained or with preoperative psychomotor agitation that prevented haemodynamic monitoring were excluded only from the IG. However, our exclusion rate for these reasons (9%) is lower than previously reported (Davies et al. 2019), but we cannot rule out that these excluded patients had worse clinical status on arrival in the operating theatre.

Uncontrolled before-and-after study provides less quality evidence than randomized controlled trials (RCT) (Sedgwick 2014). However, this design offers valuable insights into the potential benefits of GDHT protocols under real-life conditions and can complement evidence from RCT (Saugel et al. 2019). Moreover, this is the largest sample size published to date evaluating the effect of GDHT guided by non-invasive haemodynamic monitoring during hip fracture surgery.

Conclusions

In patients undergoing hip fracture surgery, the use of a GDHT protocol guided by non-invasive haemodynamic monitoring was associated with a reduction in intraoperative complications and postoperative cardiovascular, respiratory and infectious, but not postoperative renal complications. This strategy was also associated with shorter hospital stay and higher survival 1 year after surgery.

Abbreviations

AKI: Acute kidney injury; CG: Control group; CI: Cardiac Index; DO_2: Oxygen delivery; ERP: Enhanced recovery pathway; FB: Fluid bolus; GDHT: Goal-directed haemodynamic therapy; HR: Hazard ratio; IG: Intervention group; IQR: Interquartile range; MDRD: Modification of Diet in Renal Disease; METS: Metabolic equivalents; PACU: Post-anaesthetic care unit; PRBC: Packed red blood cells; SAP: Systolic arterial pressure; SpO_2: Oxygen saturation; SV: Stroke volume; SVI: Indexed stroke volume; VO_2: Oxygen consumption.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13741-022-00277-w.

Additional file 1.. Intraoperative cardiac index goal groups.

Additional file 2.. Bivariant analysis. Prognostic factors of 1-year mortality. Crude Hazard Ratio (HR) and statistical significance according to bivariate COX regression models.

Additional file 3.. Multivariant analysis. Independent prognostic factors for mortality. Adjusted HR for 1-year survival.

Additional file 4.. Renal complications according creatinine at admission and group allocation.

Acknowledgements

We would like to acknowledge the contribution of Dr Omar El Boutrouki and Ms Mercé Castejón for their help in the development of the study.

Authors' contributions

JVL: study design, patient recruitment, acquisition of data, review of perioperative complications in IG, analysis and interpretation of data, writing up of the paper and final approval of the version to be published. FR: study design, patient recruitment, acquisition of data, review of perioperative complications in CG, analysis and interpretation of data and review of the paper's content. AA: study design, analysis and interpretation of data and review of the paper's content. MB: patient recruitment, acquisition of data and review of the paper's content. JCP: patient recruitment, acquisition of data and review of the paper's content paper. JT: patient recruitment, acquisition of data and review of the paper's content. LC: patient recruitment, acquisition of data and review of the paper's content. PS: patient recruitment, acquisition of data and review of the paper's content. IP: patient recruitment, acquisition of data and review of the paper's content. CF: patient recruitment, acquisition of data and review of the paper's content. IJL: analysis and interpretation of data and review of the paper's content. JRM: analysis and interpretation of data and review of the paper's content. MIMG: analysis and interpretation of data and review of the paper's content. JB: study design, analysis and interpretation of data and review of the paper's content. All authors have approved the latest version of the manuscript and agree to be responsible for all aspects of the work ensuring that issues relating to the accuracy or completeness of any part of the work have been properly investigated and resolved.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Availability of data and materials

The datasets used and/or analysed during this study are available from the corresponding author on reasonable request

Declarations

Ethics approval and consent to participate

This manuscript was written according to CONSORT statement. The study was approved by an independent Ethics Committee (Fundació Unio Catalana Hospitals, Chairperson: Dr. Miquel Nolla) on 27 January 2015 (CEIC 15/03). All patients signed an informed consent to participate. The study was conducted according to the Declaration of Helsinki and all local legal and regulatory requirements.

Consent for publication

Not applicable.

Competing interests

Dr Lorente, Dr Jiménez, Dr Ripollés-Melchor and Dr Monge have received conference fees from Edwards Lifesciences.
Dr Lorente & Dr Ripollés-Melchor have received conference fees from Fresenius Kabi and bioMérieux.
Dr Ripollés-Melchor & Dr Monge have received conference fees from Dextera Medical.
Dr Lorente has received conference fees from Vifor Pharma, Grifols and financial support for research obtained through Edwards Lifesciences Grant Portal. Economic research support from bioMérieux.
Dr Ripollés-Melchor has received conference fees from MSD.
The rest of the authors declare that they have competing interests.

Author details

[1]Anaesthesia and Critical Care Department, Juan Ramón Jiménez Hospital, Ronda Norte s/n, 21590 Huelva, Spain. [2]School of Medicine and Health Sciences, International University of Catalonia (UIC), Barcelona, Spain. [3]Fluid Therapy and Hemodynamic Group of the Hemostasis, Transfusion Medicine and Fluid Therapy Section, Spanish Society of Anesthesia and Critical Care (SEDAR), Madrid, Spain. [4]Department of Anaesthesiology, Althaia Xarxa Assistencial Universitària, Manresa, Spain. [5]Central Catalonia Chronicity Research Group (C3RG), Research and Innovation Unit, Althaia Xarxa Assistencial Universitària, Manresa, Spain. [6]Centre d'Estudis Sanitaris i Socials, (CESS), Universitat de Vic–Universitat Central de Catalunya (UVIC-UCC), Vic, Spain. [7]Clinical Management Anesthesiology Unit, Resuscitation and Pain Therapy, Virgen del Rocio Hospital, Sevilla, Spain. [8]Anesthesia and Critical Care Department, Infanta Leonor Hospital, Madrid, Spain. [9]Intensive Care Unit, Hospital Universitario SAS, Jerez de la Frontera, Spain.

Received: 22 December 2021 Accepted: 13 July 2022
Published online: 10 August 2022

References

Alecu C, Cuignet-Royer E, Mertes PM, Salvi P, Vespignani H, Lambert M, et al. Pre-existing arterial stiffness can predict hypotension during induction of anaesthesia in the elderly. Br J Anaesth. 2010;105(5):583–8. Published by Elsevier Ltd. https://doi.org/10.1093/bja/aeq231.

Bartha E, Arfwedson C, Imnell A, Fernlund ME, Andersson LE, Kalman S. Randomized controlled trial of goal-directed haemodynamic treatment in patients with proximal femoral fracture. Br J Anaesth. 2013;110(4):545–53.

Beecham G, Cusack R, Vencken S. Hypotension during hip fracture surgery and postoperative morbidity. Ir J Med Sci Irish J Med Sci. 2020;189(3):1087–96.

Brienza N, Biancofiore G, Cavaliere F, Corcione A, de Gasperi A, de Rosa RC, et al. Clinical guidelines for perioperative hemodynamic management of non cardiac surgical adult patients. Minerva Anestesiol. 2019;85(12):1315–33.

Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? Curr Opin Crit Care. 2011;17(3):290–5.

Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline

and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012;256(1):18–24.
Cowan R, Lim JH, Ong T, Kumar A, Sahota O. The challenges of anaesthesia and pain relief in hip fracture care. Drugs Aging. 2017;34(1):1–11 Springer International Publishing.
Davies SJ, Yates DR, Wilson RJT, Murphy Z, Gibson A, Allgar V, et al. A randomised trial of non-invasive cardiac output monitoring to guide haemodynamic optimisation in high risk patients undergoing urgent surgical repair of proximal femoral fractures (ClearNOF trial NCT02382185). Perioper Med. 2019;9(30):1–11.
Giglio M, Manca F, Dalfino L, Brienza N. Perioperative hemodynamic goal-directed therapy and mortality: a systematic review and meta-analysis with meta-regression. Minerva Anestesiol. 2016;82(11):1199–213.
Griffiths R, Babu S, Dixon P, Freeman N, Hurford D, Kelleher E, et al. Guideline for the management of hip fractures 2020: Guideline by the Association of Anaesthetists. Anaesthesia. 2021;76(2):225–37.
Grocott MPW, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a cochrane systematic review. Br J Anaesth. 2013;111(4):535–48 The Author(s).
Guinot PG, Bernard E, Defrancq F, Petiot S, Majoub Y, Dupont H, et al. Mini-fluid challenge predicts fluid responsiveness during spontaneous breathing under spinal anaesthesia: an observational study. Eur J Anaesthesiol. 2015;32(9):645–9.
Hahn RG. Renal injury during hip fracture surgery: an exploratory study. Anestezjol Intens Ter. 2015;47(4):284–90.
Heming N, Moine P, Coscas R, Annane D. Perioperative fluid management for major elective surgery. Br J Surg. 2020;107(2):e56–62.
Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care. 2015;19(Suppl 3):S8 BioMed Central Ltd. Available from: http://www.ccforum.com/content/19/S3/S8.
Ishihara H. Kidney function after the intraoperative use of 6 % tetrastarches (HES 130/0.4 and 0.42). J Anesth. 2014;28(2):249–56.
Jacob M, Chappell D, Hofmann-Kiefer K, Conzen P, Peter K, Rehm M. Determinants of insensible fluid loss. Perspiration, protein shift and endothelial glycocalyx. Anaesthesist. 2007;56(8):747–64.
Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery a review. JAMA Surg. 2017;152(3):292–8.
Lugo G, Arizpe D, Dominguez GRM, et al. Relationship between oxygen consumption and oxigen delivery during anesthesia in high-risk surgical patients. Crit Care Med. 1993;21(1):64–9.
Mallat J, Meddour M, Durville E, Lemyze M, Pepy F, Temime J, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. Br J Anaesth. 2015;115(3):449–56.
Marik PE. Fluid therapy in 2015 and beyond: the mini-fluid challenge and mini-fluid bolus approach. Br J Anaesth. 2015;115(3):347–9.
Meersch M, Schmidt C, Zarbock A. Perioperative acute kidney injury: an under-recognized problem. Anesth Analg. 2017;125(4):1223–32.
Merry AF, Mitchell SJ. Complications of anaesthesia. Anaesthesia. 2018;73:7–11.
Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). Can J Anesth. 2015;62(2):158–68.
Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping STJ, Bentt DR, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. Anesthesiology. 2015;123(2):307–19 Available from: http://insights.ovid.com/crossref?an=00000542-201508000-00016.
Montenij L, De WE, Frank M, Van BP, De WA, Kruitwagen C, et al. Influence of early goal-directed therapy using arterial waveform analysis on major complications after high-risk abdominal surgery : study protocol for a multicenter randomized controlled superiority trial; 2014. p. 1–12.
Moppett IK, Rowlands M, Mannings A, Moran CG, Wiles MD, Van DeWalt G, et al. LiDCO-based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: a randomized trial and systematic review. Br J Anaesth. 2015;114(3):444–59.
Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: The mini-fluid challenge study. Anesthesiology. 2011;115(3):541–7.
Muñoz JL, Gabaldón T, Miranda E, Berrio DL, Ruiz-tovar J, Ronda JM, et al. Goal-Directed Fluid Therapy on Laparoscopic Sleeve Gastrectomy in Morbidly Obese Patients. Obes Surg. 2016;26(11):2648–53.
Reguant F, Arnau A, Lorente JV, Maestro L, Bosch J. Efficacy of a multidisciplinary approach on postoperative morbidity and mortality of elderly patients with hip fracture. J Clin Anesth. 2019;53(September 2018):11–9. Elsevier. https://doi.org/10.1016/j.jclinane.2018.09.029.
Roche JJW, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: Prospective observational cohort study. Br Med J. 2005;331(7529):1374–6.
Rocos B, Whitehouse MR, Kelly MB. Resuscitation in hip fractures : a systematic review. Br Med J. 2017;7(e015906):1–6.
Saugel B, Cecconi M, Wagner JY, Reuter DA. Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. Br J Anaesth. 2015;114(4):562–75. https://doi.org/10.1093/bja/aeu447.
Saugel B, Joosten A, Scheeren TWL. Perioperative goal-directed therapy: what's the best study design to investigate its impact on patient outcome? J Clin Monit Comput. 2019;33(3):361–3. Springer Netherlands. https://doi.org/10.1007/s10877-018-0196-2.
Sedgwick P. Before and after study designs. BMJ. 2014;349(January):g5074.
Tassoudis V, Vretzakis G, Petsiti A, Stamatiou G, Bouzia K, Melekos M, et al. Impact of intraoperative hypotension on hospital stay in major abdominal surgery. J Anesth. 2011;25(4):492–9.
Teboul JL, Saugel B, Cecconi M, De Backer D, Hofer CK, Monnet X, et al. Less invasive hemodynamic monitoring in critically ill patients. Intensive Care Med. 2016;42(9):1350–9 Springer Berlin Heidelberg.
Veronese N, Maggi S. Epidemiology and social costs of hip fracture. Injury. 2018;49(8):1458–60. Elsevier Ltd. https://doi.org/10.1016/j.injury.2018.04.015.
Wesseling KH, de Wit B, Van der Hoeven A, Van Goudoever JSJ. Physiocal, calibrating finger vascular physiology for Finapres. Homeostasis. 1995;36(2–3):67–82.
Yu J, Zhang C, Li L, Kwong JSW, Xue L, Zeng X, et al. Internal fixation treatments for intertrochanteric fracture: a systematic review and meta-Analysis of randomized evidence. Sci Rep. 2015;5(June):1–11. https://doi.org/10.1038/srep18195 Nature Publishing Group.

Publisher's Note

9.5. Anexo 5: Inscripción estudio "Manejo hemodinámico intraoperatorio mediante el índice de predicción de hipotensión (HPI) y su relación con la microcirculación. Detección del estrés renal agudo." en ClinicalTrials.gov

ClinicalTrials.gov PRS DRAFT Receipt (Working Version)
Last Update: 12/07/2022 15:05

ClinicalTrials.gov ID: NCT04301102

Study Identification

Unique Protocol ID:	v 1.0; March 2019
Brief Title:	The Predict H Trial NOTE : A title this short is probably not sufficiently descriptive.
Official Title:	Intraoperative Hemodynamic Optimization Using the Hypotension Prediction Index and Its Impact of Tissular Perfusion
Secondary IDs:	

Study Status

Record Verification:	December 2022
Overall Status:	Completed
Study Start:	November 1, 2020 [Actual]
Primary Completion:	February 28, 2022 [Actual]
Study Completion:	June 1, 2022 [Actual]

Sponsor/Collaborators

Sponsor:	Juan Victor Lorente
Responsible Party:	Sponsor-Investigator Investigator: Juan Victor Lorente [juan víctor] Official Title: Anesthesiologist Affiliation:
Collaborators:	Edwards Lifesciences

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 27 July 2020 Board Name: Comité de Etica de la Investigación Board Affiliation: Hospital Gregorio Marañón Phone: 959016000 Email: juanvictor.lorente@gmail.com Address:

	Calle Dr Esquerdo, 46 28007 Madrid
Data Monitoring:	No
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary:	The aim of the study is to determine whether a goal-directed algorithm based on the prevention of arterial hypotension using the Hypotension Prediction Index reduces the duration and severity of intraoperative hypotension when compared with the recommended standard therapy and if this intraoperative strategy affects tissue oxygenation and organ perfusion.
Detailed Description:	Background: Intraoperative arterial hypotension is associated with poor postoperative outcomes. The Hypotension Prediction Index developed from machine learning, predicts the occurrence of arterial hypotension from the analysis of the arterial pressure waveform. The use of this index can reduce the duration and severity of intraoperative hypotension in adults undergoing noncardiac surgery. Methods: We will conduct a multicenter, randomized, controlled trial (N=80) in high-risk surgical patients scheduled for elective major abdominal surgery. All participants will be randomly assigned to a control or intervention group. Hemodynamic management in the control group will be based on standard hemodynamic parameters. Hemodynamic management of patients in the intervention group will be based on functional hemodynamic parameters provided by Hemosphere platform (Edwards Lifesciences Ltd), including dynamic arterial elastance, dP/dtmax and the Hypotension Prediction Index. Tissue oxygen saturation will be non-invasively and continuously recorded by using near-infrared spectroscopy technology. Biomarkers of acute kidney stress (cTIMP2 and IGFBP7) will be obtained before and after surgery. The primary outcome will be intraoperative time-weighted average with a mean arterial pressure < 65mmHg. Discussion: The aim of the study is to determine whether a goal-directed algorithm based on the prevention of arterial hypotension using the Hypotension Prediction Index reduces the duration and severity of intraoperative hypotension when compared with the recommended standard therapy and if this intraoperative strategy affects tissue oxygenation and organ perfusion.

Conditions

Conditions:	Intraoperative Hypotension
Keywords:	goal directed hemodynamic therapy machine learning acute kidney injury

Study Design

Study Type:	Interventional
Primary Purpose:	Prevention
Study Phase:	N/A
Interventional Study Model:	Parallel Assignment

Number of Arms:	2
Masking:	Triple (Participant, Care Provider, Investigator)
Allocation:	Randomized
Enrollment:	80 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Experimental Hemodynamic management will be based on the functional hemodynamic parameters provided by Hemosphere platform with the Acumen IQ sensor, including cardiac output, stroke volume, SVV and Acumen IQ specific parameters: maximal arterial pressure rise (dP/dtmax), dynamic arterial elastance (Eadyn) and HPI As a pattern replacement of interstitial space, we will use balanced crystalloid (Isofundin®) at 1-3 ml / kg / h in case of laparoscopic surgery and 5 to 7 ml / kg / h in case of open surgery. The protocol of action on the intravascular space will be based on the maintenance of systolic volume with colloids (hydroxyethyl starch - Voluvén®).	Device: Hemosphere platform® together with the FloTrac Acumen IQ® sensor Clinical platform that, analyzing the pulse wave contour, obtained from the previously catheterized radial artery, is able to make available to the clinician both a continuous monitoring of blood pressure and advanced hemodynamic parameters that help patient management. It incorporates predictive parameters such as the hypotension prediction index and decision support parameters such as dynamic arterial elastance and maximum dP / dT. It also has the possibility of assessing regional oxygen saturation, measured by near-infrared light photoplethysmography, and the sensor can be applied in different locations (cerebral, muscular ...).
Control Hemodynamic management will be based on the functional hemodynamic parameters provided by the HemoSphere platform® with the FloTrac® sensor, including cardiac output (CO), stroke volume (SV), and stroke volume variation (SVV) As a pattern replacement of interstitial space, we use balanced crystalloid (Isofundin®) at 1-3 ml / kg / h in case of laparoscopic surgery and 5 to 7 ml / kg / h in case of open surgery. The protocol action for the intravascular space will be based on a recently published hemodynamic optimization algorithm (Heming N, Moine P, Coscas R, Annane D. Perioperative fluid management for major elective surgery. British Journal of Surgery. 2020;107:e56–62). The fluid used will be hydroxyethyl starch (Voluven®).	Device: Hemosphere platform® together with the FloTrac® sensor Clinical platform that, analyzing the pulse wave contour, obtained from the previously catheterized radial artery, is able to make available to the clinician both a continuous monitoring of blood pressure and advanced hemodynamic parameters that help patient management. It also has the possibility of assessing regional oxygen saturation, measured by near-infrared light photoplethysmography, and the sensor can be applied in different locations (cerebral, muscular ...).

Outcome Measures

Primary Outcome Measure:

1. TWA-MAP< 65 mmHg
   Area between 65 mmHg threshold and the curve of the MAP measurements divided by the total continuous reading time mmHg for a minimum duration of 1 minute (3 consecutive records from one minute to more between two consecutive falls).

   [Time Frame: Intraoperatively]
2. Number of intraoperative hypotension episodes
   defined as an event of MAP < 65 mmHg of at least 1-minute duration

[Time Frame: Intraoperatively]

3. Total time of hypotension per case
   Intraoperative Total time of hypotension (MAP < 65 mmHg)

   [Time Frame: Intraoperatively]

Secondary Outcome Measure:

4. StO2
   StO2 will be non-invasively and continuously recorded in the brachioradial muscle in the arm opposite to the arterial line. We calculated the time averaged StO2 per patient and identified the minimum StO2, defined as the minimum value sustained (+1%) over at least 5 min

   [Time Frame: Intraoperatively]

5. Acute kidney stress biomarkers
   Urine immunoassay, commercially known as Nephrocheck® (Biomerieux). The first sample (NC1) will be collected after anesthetic induction, when performing bladder catheterization. The first postoperative sample (NC2) will be collected during the first 4 hours after the patient is admitted to the UCI / REA for their postoperative stay. If the AKIRisk value in that first postoperative sample (NC2) is less than 0.3, no new Nephrocheck® determinations will be collected. If the AKIRisk value in the first postoperative sample (NC2) is greater than 2, no further Nephrocheck® determinations will be made. If the AKIRisk value in that first postoperative sample (NC2) is between 0.3 and 2, we will collect a second postoperative sample (NC3) at 12 hours of the first. No more Nephrocheck® determinations will be made.

   [Time Frame: NC1: after anestesic induction // NC2: First 4 hours after the patient is admitted to the UCI/REA // NC3: 12 hours after NC2.]

6. Postoperative complications
   The analysis of postoperative complications will be carried out in accordance with European EPCO recommendations.

   [Time Frame: Postoperatively]

7. Length of hospital stay
   [Time Frame: At 30 days]

8. Mortality
   [Time Frame: At 30 days]

9. Total fluid therapy during surgery
   Types and total amounts

   [Time Frame: Intraoperatively]

10. Accumulated dose of Fentanyl, remifentanyl and/or morphine.
    Accumulated dose during the intraoperative period

    [Time Frame: Intraoperatively]

11. Accumulated dose during the intraoperative period of vasoactive
    Specify by drugs used and method of infusion (bolus / continuous infusion pump)

    [Time Frame: Intraoperatively]

12. Accumulated dose during the intraoperative period of ionotopic drug
    In case of indication.

    [Time Frame: Intraoperatively]

13. Need and accumulated dose of drugs not included in previous groups
    Dexmedetomidine, esmolol or other drugs with hemodynamic impact

    [Time Frame: Intraoperatively]

14. Transfusion of total blood products during surgery
    [Time Frame: Intraoperatively]

NOTE : Outcome Measure Description has not been entered.

NOTE : Outcome Measure Description has not been entered.
NOTE : Outcome Measure Description has not been entered.

Eligibility

Minimum Age:	65 Years
Maximum Age:	
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No
Criteria:	Enrolled patients will be at least 65 years old and/or American Society of Anesthesiologist (ASA) physical status III/IV, scheduled for elective major abdominal surgery (general surgery, urology, or gynecology, through laparoscopic or open approach), with general or combined anesthesia. Surgery will be considered to be major if the expected duration is > 2 h, or the estimated blood loss is > 15% of blood volume, or if the expected required transfusion is ≥ 2 packed red blood cells. Exclusion criteria will be pregnancy, surgery performed only under regional anesthesia, preoperative glomerular filtrate < 60 ml/min/1.73m2 according to the CKD-EPI 2009 formula, persistent atrial fibrillation, known cardiac shunts or if the patient received a kidney transplant, and refusal of the patient to participate in the study. NOTE : Preferred format includes lists of inclusion and exclusion criteria.

Contacts/Locations

Central Contact Person:	Juan Víctor Lorente Olazábal Telephone: 695881448 Email: juanv.lorente.sspa@juntadeandalucia.com
Central Contact Backup:	
Study Officials:	NOTE : Study Official is required by the WHO and ICMJE.
Locations:	**Spain** Hospital Universitario Juan Ramón Jiménez Huelva, Spain, 21005 Contact: Juan Víctor Lorente 695881448 juanvictor.lorente@gmail.com Principal Investigator: Juan Víctor Lorente Olazábal, MD Hospital Universitario Virgen del Rocío Sevilla, Spain, 41013 Contact: Ignacio Jiménez López ignaciojl98s@gmail.com Principal Investigator: Ignacio Jiménez López, MD Hospital Universitario de Jerez de la Frontera Jerez De La Frontera, Cádiz, Spain, 11407 Contact: Manuel Ignacio Monge García ignaciomonge@gmail.com Principal Investigator: Manuel Ignacio Monge Garcia, MD Hospital Universitario Infanta Leonor Madrid, Spain, 28031 Contact: Javier Ripollés Melchor ripo542@gmail.com Principal Investigator: Javier Ripollés Melchor, MD

Hospital Universitario de Badajoz
Badajoz, Spain, 06080
Contact: Isabel Alejandra Becerra Cayetano isbeca@hotmail.com
Principal Investigator: Isabel Alejandra Becerra Cayetano, MD

IPDSharing

Plan to Share IPD: Yes

Data obtained through this study may be provided to qualified researchers with academic interest in sickle cell anemia. Data or samples shared will be coded, with no PHI included. Approval of the request and execution of all applicable agreements are prerequisites to the sharing of data with the requesting party.

Supporting Information:
Study Protocol
Statistical Analysis Plan (SAP)
Informed Consent Form (ICF)

Time Frame:
Data requests can be submitted starting 9 months after article publication and the data will be made accessible for up to 24 months. Extensions will be considered on a case-by-case basis

Access Criteria:
Access to trial IPD can be requested by qualified researchers engaging in independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). For more information or to submit a request, please contact juanvictor.lorente@gmail.com

URL:

References

Citations:

Links:

Available IPD/Information:

9.6. Anexo 6: Hoja de información al paciente y consentimiento informado estudio "Manejo hemodinámico intraoperatorio mediante el índice de predicción de hipotensión (HPI) y su relación con la microcirculación. Detección del estrés renal agudo."

HOJA INFORMACIÓN AL PACIENTE

(VERSIÓN 1.0, Febrero de 2019)

Nombre del Estudio: Manejo hemodinámico intraoperatorio usando el Índice de Predicción de Hipotensión y su relación con la microcirculación. Diagnóstico del estrés renal

Estimado paciente,

Usted ha sido invitado a participar en un estudio de investigación. Nos gustaría explicarle, por qué se está realizando este estudio y lo que implicará para usted. Por favor tómese el tiempo necesario para leer cuidadosamente la siguiente información y discutirla con otras personas, si lo desea. Por favor, pregúntenos si algo no está claro o si necesita más información. Tómese su tiempo para decidir si desea participar. Su participación es importante para obtener el conocimiento que necesitamos, pero antes de tomar una decisión debe:

- Leer este documento entero

- Entender la información que contiene el documento

- Hacer todas las preguntas que considere necesarias

- Consultar con su médico-persona de confianza - Tomar una decisión meditada

- Firmar el consentimiento informado, si finalmente desea participar.

Si decide participar se le entregará una copia de este documento y del consentimiento firmado. Por favor, consérvelos por si lo necesitara en un futuro.

¿Por qué se le pide participar?

Usted ha sido invitado a participar en este estudio, porque debe ser intervenido de forma programada y tiene indicación de Monitorización de la función cardiaca a partir de la medición de la Presión Arterial de forma directa a través de un catéter en una arterial del brazo (arteria radial). Este estudio pretende evaluar la utilidad de un nuevo parámetro que nos permite predecir cuándo va a sufrir usted un episodio de hipotensión y por lo tanto poder evitarlo. La hipotensión intraoperatoria se relaciona con la aparición de complicaciones en el periodo postoperatorio, por lo que es importante evitar su aparición. Para ello vamos a reclutar pacientes que deseen participar en varios centros de toda España.

¿Cuál es el propósito de este estudio?

Nuestro objetivo es llevar a cabo un estudio aleatorizado randomizado en el que los anestesiólogos responsables de los pacientes tomarán decisiones terapéuticas sobre las alteraciones de la función hemodinámica (la función de su corazón durante la intervención) con el objetivo de evitar que sufra usted un episodio de hipotensión y así conseguir la máxima estabilidad posible durante la operación. Para ello, utilizarán los monitores de función cardiaca que son habituales

durante las intervenciones como la que usted va a someterse. Si usted es asignado al grupo HPI, su monitor incluirá el parámetro que deseamos evaluar y que nos proporciona una indicación sobre la probabilidad de hipotensión. Si es asignado de forma aleatoria al grupo control, será usted monitorizado con las funciones habituales para su tipo de intervención, de modo que no será usted perjudicado de ninguna manera por el hecho de ser asignado a un grupo o a otro.

Con los datos obtenidos sobre la función cardiovascular durante la intervención, podremos saber si este indicador que predice la hipotensión nos ayuda a tomar mejores decisiones y con un margen de tiempo suficiente para disminuir el tiempo de hipotensión durante la operación y de esta manera que podamos tratar mejor a pacientes en el futuro y generar protocolos de actuación más apropiados.

Durante la intervención, de forma no invasiva y sin ocasionarle molestias, realizaremos una medición contínua de la oxigenación muscular. En el postoperatorio, realizaremos varios análisis para determinar si sus riñones están "en riesgo" de poder sufrir una caída en su función.

¿Qué tengo que hacer si decido participar?

Recuerde que su participación es voluntaria y si decide no participar esto no afectará a su asistencia o a su relación con sus médicos y sus equipos. Los investigadores recogerán datos derivados de la monitorización cardiovascular durante la operación así como datos clínicos recogidos durante la evaluación preanestésica. Siempre de forma que estos datos sean anónimos. Tratándose de un estudio que evalúa un elemento de ayuda a la toma de decisiones, no se realizará ninguna intervención adicional a las que se realizan de forma habitual en su centro. Tampoco se va a realizar ninguna prueba extraordinaria, y por supuesto, no se dejará de hacer ninguna prevista. Tampoco requiere que usted tenga que realizar más visitas al hospital, ni antes ni después de la intervención quirúrgica.

¿Tengo la obligación de participar?

No, su participación es completamente voluntaria. Si decide participar, por favor firme el formulario de consentimiento para demostrar que está de acuerdo en participar y guarde la copia que se le entregue junto con esta hoja de información. Si usted decide no participar en el estudio, su decisión no afectará de ninguna manera su tratamiento o a la atención que está recibiendo en estos momentos o que recibirá en el futuro.

¿Obtendré algún beneficio por participar?

Al tratarse de un estudio de investigación orientado a generar conocimiento No se espera que Vd. obtenga beneficio directo por participar ni va a recibir ninguna compensación económica por ello, si bien usted contribuirá al avance del conocimiento y al beneficio social.

¿Qué riesgos o inconvenientes tiene el participar?

Este es un estudio que analiza un parámetro predictivo basado en la información obtenida de monitorización estándar y habitual para su intervención quirúrgica, por lo tanto **su tratamiento no va a cambiar por participar en este estudio**. El tratamiento perioperatorio (antes, durante y después de su cirugía), se prescribirá según la práctica asistencial y sus necesidades como paciente y no se verá alterado por la inclusión en el estudio.

Riesgo para la confidencialidad

La información clínica obtenida en este proyecto será almacenada en una base de datos protegida por la legislación vigente, custodiada bajo la responsabilidad de los investigadores e instituciones responsables. Estos datos serán conservados para futuros estudios, a no ser que Vd. indique lo contrario. Por ello, los resultados de esta investigación se podrán difundir en revistas, bases de datos médicas y foros científicos. **Nunca** se desvelarán datos personales que pudieran identificarle. Los investigadores siempre tendrán el deber de proteger su privacidad y mantener toda su información de modo confidencial.

¿Cómo se protegerá la confidencialidad de mis datos?

El tratamiento, comunicación y cesión de sus datos se hará conforme a lo dispuesto por el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD). El responsable de la custodia de los códigos de identificación de las personas participantes en el estudio es **Dr. Juan Victor Lorente Olazábal**, investigador principal del estudio. Como participante, usted podrá ejercer su derecho de acceso, rectificación, cancelación y oposición contactando con cualquiera de los investigadores principales del proyecto en los teléfonos que se indican al final de este documento.

Además, también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio **(juanv.lorente.sspa@juntadaandalucia.es)** le recordamos que los datos no se pueden eliminar aunque deje de participar en el ensayo para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho

Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los

datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al/ a la ***Delegado de Protección de Datos del promotor Juan Victor Lorente (*****juanv.lorente.sspa@juntadaandalucia.es)**

Sólo el equipo investigador y sus colaboradores así como las autoridades sanitarias, que tienen deber de garantizar la confidencialidad, tendrán acceso a todos los datos recogidos por el estudio. En el caso de que alguna información sea transmitida a otros países, se realizará con un nivel de protección de los datos equivalente, como mínimo, al exigido por la normativa de nuestro país. Toda la información se mantendrá estrictamente confidencial y su nombre no aparecerá en ninguna publicación resultante de este estudio. Su historia médica será vista por los miembros autorizados del equipo de investigación del hospital, para que puedan recoger la información necesaria para el estudio. Se le asignará un número aleatorio y anónimo de participante en el estudio que no incluirá sus iniciales y fecha de nacimiento, y que será utilizado en los documentos que el equipo de investigación necesite rellenar. Toda la información referente a su persona será tratada como estrictamente confidencial y nada que pueda identificarle será revelado a terceras personas.

El personal médico y científico que lleva a cabo el estudio puede requerir examinar su historia médica para asegurar que el estudio se está ejecutando correctamente y que la información recogida en los formularios es la correcta. Su confidencialidad será protegida en todo momento.

El tratamiento, comunicación y cesión de los datos de carácter personal, se ajustará a lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal. Según la citada Ley, el consentimiento para el tratamiento de sus datos personales y para su cesión es revocable. Por lo tanto, en cualquier momento usted puede ejercer su derecho de acceso, rectificación, oposición y cancelación de sus datos dirigiéndose a: ***Juan Victor Lorente (*****juanv.lorente.sspa@juntadaandalucia.es)**Toda nueva publicación de trabajos de investigación que requiera hacer uso de datos estará sujeta a la aprobación del Comité Directivo del estudio y de un comité de ética independiente.

¿Qué sucederá si decido retirarme?

Si usted está participando en el estudio y decide retirarse, **puede hacerlo en cualquier momento y sin dar una explicación.** Su información médica también se eliminará de la base de datos del estudio.

¿Cómo puedo saber los resultados del estudio?

Usted tiene derecho a conocer los resultados del presente estudio, tanto los resultados generales como los derivados de sus datos específicos. También tiene derecho a no conocer dichos resultados si así lo desea. Por este motivo en el documento de consentimiento informado le preguntaremos qué opción prefiere. En caso de que desee conocer los resultados, el investigador le hará llegar los resultados. En ocasiones al realizar un proyecto de investigación se encuentran hallazgos inesperados que pueden ser relevantes para la salud del participante. En el caso de que esto ocurra nos pondremos en contacto con usted para que pueda acudir a su médico habitual.

Los resultados globales de este estudio serán remitidos a publicaciones médicas y científicas y presentados en reuniones del mismo ámbito para su difusión. Asimismo, algunos datos clínicos podrán difundirse entre la comunidad científica a través de bases de datos en internet, sin asociar ningún dato personal que pueda llevar a la identificación de los pacientes.

¿Puedo cambiar de opinión?

Tal como se ha señalado, su participación es totalmente voluntaria, puede decidir no participar o retirarse del estudio en cualquier momento sin tener que dar explicaciones y sin que esto repercuta en su atención sanitaria. Basta con que le manifieste su intención al investigador principal del estudio. Si usted desea retirarse del estudio se eliminarán los datos recogidos.

¿Qué pasa si me surge alguna duda durante mi participación?

En caso de duda o para cualquier consulta relacionada con su participación puede ponerse en contacto con el investigador responsable en su centro, o mediante correo electrónico en la dirección *juanv.lorente.sspa@juntadaandalucia.es*

¿Quién está organizando y financiando esta investigación?

Este estudio se está llevando a cabo por una red de médicos de toda España. Es un estudio nacional coordinado por el Dr. *Juan Victor Lorente* del A.H. Juan Ramón Jiménez de Huelva

¿Existen intereses económicos en este estudio?

Los investigadores no recibirán retribución específica por la dedicación al estudio (adicional a su salario habitual como investigadores o médicos). Vd. no será retribuido por participar. No existe posibilidad de que este estudio genere beneficios en forma de patentes.

¿Quién ha revisado este estudio?

Este estudio de investigación ha sido revisado por un grupo independiente de personas del Comité de Ética de Investigación Clínica (CEIC) de Andalucía, para proteger su seguridad, sus derechos, su bienestar y su dignidad. El Comité Autonómico de Ética de la Investigación de Andalucía ha revisado el estudio y ha dado la aprobación para realizarlo.

¿Qué debo hacer ahora?

Usted debe decidir si desea participar en este estudio. Por favor, piense acerca de lo que implica el estudio y hable con sus familiares. El médico investigador y la enfermera estará encantados de responder a cualquier pregunta que pueda tener. Cuando usted decida, por favor informe a su médico investigador o enfermera. Se le pedirá que firme un formulario de consentimiento y se le entregará una copia que debe mantener unida a esta hoja de información. Por favor conserve estos documentos. Si en cualquier momento tiene alguna pregunta sobre el estudio, puede contactar con los investigadores, cuyos datos de contacto se indican al final.

¿Quién me puede dar más información?

Para más información y aclaraciones no dude en contactar con: ***Juan Victor Lorente*** Anestesiología y Reanimación A.H. Juan Ramón Jiménez de Huelva

Nº de teléfono: 959 01 60 00

Email: **juanv.lorente.sspa@juntadaandalucia.es**.

Muchas gracias por considerar ayudarnos en nuestra investigación

DOCUMENTO DE CONSENTIMIENTO INFORMADO

Título del PROYECTO: Manejo hemodinámico intraoperatorio usando el Índice de Predicción de Hipotensión y su relación con la microcirculación. Diagnóstico del estrés renal

Yo,.....(nombre y apellidos del participante)

- He leído la hoja de información que se me ha entregado
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con:..... (nombre del investigador)

Comprendo que mi participación es voluntaria. Comprendo que puedo retirarme del estudio:

- cuando quiera
- sin tener que dar explicaciones
- sin que esto repercuta en mis cuidados médicos

Presto libremente mi conformidad para participar en el estudio.
Deseo ser informado sobre los resultados del estudio: **sí no** (marque lo que proceda)

Doy mi conformidad para que mis datos clínicos sean revisados por personal ajeno al centro, para los fines del estudio, y soy consciente de que este consentimiento es revocable.
He recibido una copia firmada de este Consentimiento Informado.

Firma del paciente

Nombre:

Fecha:

Firma del investigador

Nombre:

Fecha:

9.7. Anexo 7: Aprobación Comité de Ética de la Investigación Clínica, estudio: "Manejo hemodinámico intraoperatorio mediante el índice de predicción de hipotensión (HPI) y su relación con la microcirculación. Detección del estrés renal agudo."

Hospital General Universitario Gregorio Marañón
SaludMadrid
Comunidad de Madrid

DICTAMEN DEL COMITÉ de ÉTICA DE LA INVESTIGACIÓN con MEDICAMENTOS

D. Roberto Collado Borrell, Secretario Técnico del **COMITÉ de ÉTICA DE LA INVESTIGACIÓN con MEDICAMENTOS HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN**

CERTIFICA

Que se ha evaluado la propuesta del promotor referida al estudio:

Código ESTUDIO PREDICT H
TÍTULO: "Manejo hemodinámico intraoperatorio mediante el índice de predicción de hipotensión (HPI) y su relación con la microcirculación. Detección de estrés renal agudo"
Protocolo versión 1 de julio de 2020. **Hoja de Información al paciente y Consentimiento Informado** versión 05 de Agosto de 2020.
Promotor: Investigador

- El estudio se plantea siguiendo los requisitos legalmente establecidos, y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Es adecuado el procedimiento para obtener el consentimiento informado.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
- La capacidad del investigador y sus colaboradores, y las instalaciones y medios disponibles, tal y como ha sido informado, son apropiados para llevar a cabo el estudio.

Este CEIm actuando como comité evaluador, emite **dictamen favorable** y acepta que dicho estudio sea realizado en los centros siguientes por los investigadores principales que se relacionan a continuación:

Dr. Javier Ripollés Melchor / Hospital Universitario Infanta Leonor

Y HACE CONSTAR QUE:

1º En la reunión celebrada el día **27 de julio de 2020, acta 18/2020** se decidió emitir el informe correspondiente al estudio de referencia.
2º En dicha reunión se cumplieron los requisitos establecidos en la legislación vigente -Real Decreto 1090/2015 y Decreto 39/94 de la Comunidad de Madrid- para que la decisión del citado CEIm sea válida.
3º El CEIm, tanto en su composición, como en los PNT cumple con las normas de BPC (CPMP/ ICH/ 135/95)
4º La composición actual del CEIm es la siguiente:

D. FELIPE ATIENZA FERNÁNDEZ (Cardiología - Presidente)
D. ANDRÉS JESÚS MUÑOZ MARTÍN (Oncología Médica - Vicepresidente)
D. ROBERTO COLLADO BORRELL (Farmacia Hospitalaria – Secretario Técnico)
D. JUAN ANTONIO ANDUEZA LILLO (Medicina Interna)
Dª. MARÍA LUISA BAEZA OCHOA DE OCÁRIZ (Alergología)
Dª. PILAR AITANA CALVO FERRÁNDIZ (Farmacología Clínica)
Dª MARÍA DEL CARMEN DE LA CRUZ ARGUEDAS (Unidad de Apoyo a la Investigación)
D. RAFAEL CARRIÓN GALINDO (Oncología Médica)
D. VICENTE DE LAS PEÑAS GIL (Psicología Clínica)
D. JAVIER DE MIGUEL DÍEZ (Neumología)
Dª. PATRICIA FONT LÓPEZ (Hematología y Hemoterapia)
Dª. ISABEL GÓMEZ VALBUENA (Farmacia de Atención Primaria)
Dª. MARÍA DEL CARMEN HERAS ESCOBAR (Enfermería)
Dª. ANA MARÍA IGLESIAS MOHEDANO (Neurología)
D. LUIS ANDRÉS LÓPEZ FERNÁNDEZ (Biología)
Dª. ANA ESTHER LÓPEZ PÉREZ (Anestesiología y Reanimación)
D. ANTONIO MUIÑO MIGUEZ (Medicina Interna)
Dª. ANA MUR MUR (Farmacia Hospitalaria)
Dª. MARÍA LUISA NAVARRO GÓMEZ (Pediatría)
D. DIEGO RINCÓN RODRÍGUEZ (Aparato Digestivo)
D. CARLOS ROJAS-MARCOS ASENSI (Licenciado en Derecho)

Lo que firmo en Madrid, a 07 de septiembre de 2020

COLLADO BORRELL ROBERTO - 51459178J
Firmado digitalmente por COLLADO BORRELL ROBERTO - 51459178J
Fecha: 2020.09.07 11:23:00 +02'00'

Fdo.: Dr. Roberto Collado Borrell

C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, 28007 Madrid
ceim.hgugm@salud.madrid.org Tlf. 91 586 7007. Tlf de apoyo 91 426 9378

9.8. Anexo 8: Lorente JV, Jimenez I, Ripollés-Melchor J, Becerra A, Wesselink W, Reguant F, Mojarro I, Fuentes MLA, Abad-Motos A, Agudelo E, Herrero-Machancoses F, Callejo P, Bosch J, Monge MI. Intraoperative haemodynamic optimisation using the Hypotension Prediction Index and its impact on tissular perfusion: a protocol for a randomised controlled trial. The Predict H Trial. BMJ Open. 2022 Jun 2;12(6):e051728. doi: 10.1136/bmjopen-2021-051728. PMID: 35654467; PMCID: PMC9163532.

BMJ Open

Intraoperative haemodynamic optimisation using the Hypotension Prediction Index and its impact on tissular perfusion: a protocol for a randomised controlled trial

Juan Victor Lorente ,[1,2] Ignacio Jimenez,[3] Javier Ripollés-Melchor,[4] Alejandra Becerra,[5] Wilbert Wesselink,[6] Francesca Reguant,[2,7] Irene Mojarro,[1] Maria de los Angeles Fuentes,[3] Ane Abad-Motos,[4] Elizabeth Agudelo,[5] Francisco Herrero-Machancoses ,[8] Paula Callejo,[9] Joan Bosch,[2] Manuel Ignacio Monge[10]

To cite: Lorente JV, Jimenez I, Ripollés-Melchor J, *et al*. Intraoperative haemodynamic optimisation using the Hypotension Prediction Index and its impact on tissular perfusion: a protocol for a randomised controlled trial. *BMJ Open* 2022;**12**:e051728. doi:10.1136/bmjopen-2021-051728

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-051728).

Received 27 March 2021
Accepted 09 May 2022

For numbered affiliations see end of article.

Correspondence to
Dr Juan Victor Lorente; juanvictor.lorente@gmail.com

ABSTRACT

Introduction Intraoperative arterial hypotension is associated with poor postoperative outcomes. The Hypotension Prediction Index (HPI) developed using machine learning techniques, allows the prediction of arterial hypotension analysing the arterial pressure waveform. The use of this index may reduce the duration and severity of intraoperative hypotension in adults undergoing non-cardiac surgery. This study aims to determine whether a treatment protocol based on the prevention of arterial hypotension using the HPI algorithm reduces the duration and severity of intraoperative hypotension compared with the recommended goal-directed fluid therapy strategy and may improve tissue oxygenation and organ perfusion.

Methods and analysis We will conduct a multicentre, randomised, controlled trial (N=80) in high-risk surgical patients scheduled for elective major abdominal surgery. All participants will be randomly assigned to a control or intervention group. Haemodynamic management in the control group will be based on standard haemodynamic parameters. Haemodynamic management of patients in the intervention group will be based on functional haemodynamic parameters provided by the HemoSphere platform (Edwards Lifesciences), including dynamic arterial elastance, dP/dt_{max} and the HPI. Tissue oxygen saturation will be recorded non-invasively and continuously by using near-infrared spectroscopy technology. Biomarkers of acute kidney stress (cTIMP2 and IGFBP7) will be obtained before and after surgery. The primary outcome will be the intraoperative time-weighted average of a mean arterial pressure <65 mm Hg.

Ethics and dissemination Ethics committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). Findings will be widely disseminated through peer-reviewed publications and conference presentations.

Trial registration number NCT04301102.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A multicentre randomised controlled trial to test whether an Hypotension Prediction Index-based therapeutical protocol reduces intraoperative hypotension (IOH) and affects tissue oxygenation and organ perfusion in non-cardiac surgery.
⇒ The primary outcome is the intraoperative time-weighted average of the mean arterial blood pressure below 65 mm Hg (TWA- mean arterial pressure<65) and other variables related to IOH. Secondary outcomes are intraoperative S_tO_2, as an indicator of tissue oxygenation, postoperative measurements of the TIMP-2 and IGFBP7 (AKIRisk), postoperative complications, length of hospital stay and 30-day mortality.
⇒ The study sample size was calculated based on the potential reduction in IOH, not the potential reduction in postoperative complications.
⇒ Although the clinical teams performing the trial interventions will not be blinded to the patient inclusion group, they will not be aware of the perioperative StO_2 and AKIRisk variables. Research staff assessing clinical outcomes will not be aware of treatment group assignment.
⇒ No 1-year mortality follow-up of recruited patients is currently proposed.

INTRODUCTION

Intraoperative monitoring of usual haemodynamic parameters, such as heart rate or blood pressure, is insufficient to ensure adequate oxygen delivery (DO_2) to the tissues and prevent organ hypoperfusion.[1] Moreover, tissue hypoxia is a significant determinant of a surgical patient's outcome.[2] Haemodynamic strategies aimed to optimise DO_2 and prevent organ hypoperfusion, also known as

goal-directed therapies (GDT), have been demonstrated to be superior to the traditional care of patients undergoing surgery. This perioperative haemodynamic optimisation has been associated with a significant reduction in morbidity and mortality.[5]

Moreover, arterial hypotension is a frequent phenomenon during the intraoperative period and has been related to the development of organ hypoperfusion and poor postoperative outcomes.[4] Both the duration and severity of arterial hypotension are significant determinants of the postoperative outcome.[5] Particularly, intraoperative hypotension (IOH) significantly increases acute kidney and myocardial injury.[6]

The Hypotension Prediction Index (HPI) is a recently available index developed from machine learning that predicts the occurrence of arterial hypotension from the analysis of the arterial pressure waveform. The HPI value indicates the likelihood of an arterial hypotension event in the following 5–10 min.[7] The use of this index coupled with a proactive therapeutic attitude may reduce IOH in adults undergoing non-cardiac surgery patients.[8–10] However, not all studies that have used intraoperative HPI-guided therapy have successfully reduced the time and severity of IOH. Particularly, the pilot study by Maheshwari *et al*[11] did not demonstrate a significant reduction in IOH using an HPI-guided therapeutical protocol. Furthermore, all these positive results came from single-centre studies or retrospective analysis of available data, which reduces the external validity of their results.

Moreover, since tissue oxygenation depends not only on DO_2 but also on perfusion pressure, haemodynamic optimisation should be targeted to achieve an adequate blood flow and arterial pressure that ensures normal organ function. We, therefore, hypothesise that an HPI-based therapeutic protocol will reduce the overall duration of intraoperative arterial hypotension and may improve tissue oxygenation and organ perfusion during non-cardiac surgery.

METHODS AND ANALYSIS

This manuscript was written according to the Standard Protocol Items: Recommendations for Interventional Trials guideline (online supplemental file 1) on reporting of interventional trial protocols.[12]

A multicentre, randomised controlled trial, with daily follow-up of patients until hospital discharge and mortality censured at 30 days after surgery, will be conducted. The study will be carried out at five different Spanish hospitals: Juan Ramón Jiménez University Hospital (Huelva), Virgen del Rocío University Hospital (Sevilla), Infanta Leonor University Hospital (Madrid), Hospital Universitario SAS de Jerez (Jerez de la Frontera) and Infanta Cristina University Hospital (Badajoz).

Enrolled patients will be at least 65 years old and/or American Society of Anesthesiologist (ASA) physical status III/IV, scheduled for elective major abdominal surgery (general surgery, urology, or gynaecology, through laparoscopic or open approach), with general or combined anaesthesia. Surgery will be considered to be major if the expected duration is >2 hour, or the estimated blood loss is >15% of blood volume, or if the expected required transfusion is ≥2 packed red blood cells.

Exclusion criteria will be pregnancy, preoperative glomerular filtrate <60 mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 formula, persistent atrial fibrillation, known cardiac shunts, right ventricular dysfunction, severe valvulopathy, kidney transplant recipient and refusal to participate in the study.

Study protocol

Researchers will screen all patients who present for elective, non-cardiac surgery. Patients will be contacted by the principal investigator (PI) of each hospital and informed if they are eligible. The patient's informed consent will be obtained the day before surgery. Patient demographics and comorbidities will be collected before randomisation. Patients will be assigned by the local PI to the intraoperative HPI algorithm (intervention group) or a GDT algorithm (control group). We will use a computer-generated, variable block randomisation method through age strata. Patients will not be aware of the group allocation. Although intraoperative personnel (anaesthesiologists, surgeons…) will be not blinded to monitoring allocation, data-analysis will remain blinded.

All PIs and collaborators will receive specific training with the monitoring used for haemodynamic management.

A Consolidated Standards of Reporting Trials flow diagram of the study is shown in figure 1. All data will be entered using an electronic Clinical Report Form in Castor EDC, a Good Clinical Practice compliant data management system.[13]

Common perioperative measures

Before the induction and during surgery, all subjects will receive standard of care with a five-lead ECG, pulse oximetry, a peripheral intravenous line and an indwelling radial arterial catheter.

All subjects will receive general or combined anaesthesia, neuraxial analgesia technique (epidural or intradural) will be performed according to the preference of the anaesthesiologist before induction. For pragmatic reasons, the administration of the drugs used in the induction of anaesthesia and neuromuscular relaxants will be at the discretion of the anaesthesiologist. Bispectral-index monitoring (BIS; Medtronic, Dublin, Ireland) will be used to monitor the depth of anaesthesia. Sevoflurane will be used for hypnosis maintenance, with a BIS target range of 40–60. All patients will receive invasive and continuous arterial pressure monitoring with an indwelling radial arterial catheter connected to a FloTrac sensor in the control group or an Acumen IQ sensor in the intervention group (Edwards Lifesciences, Irvine, California, USA).

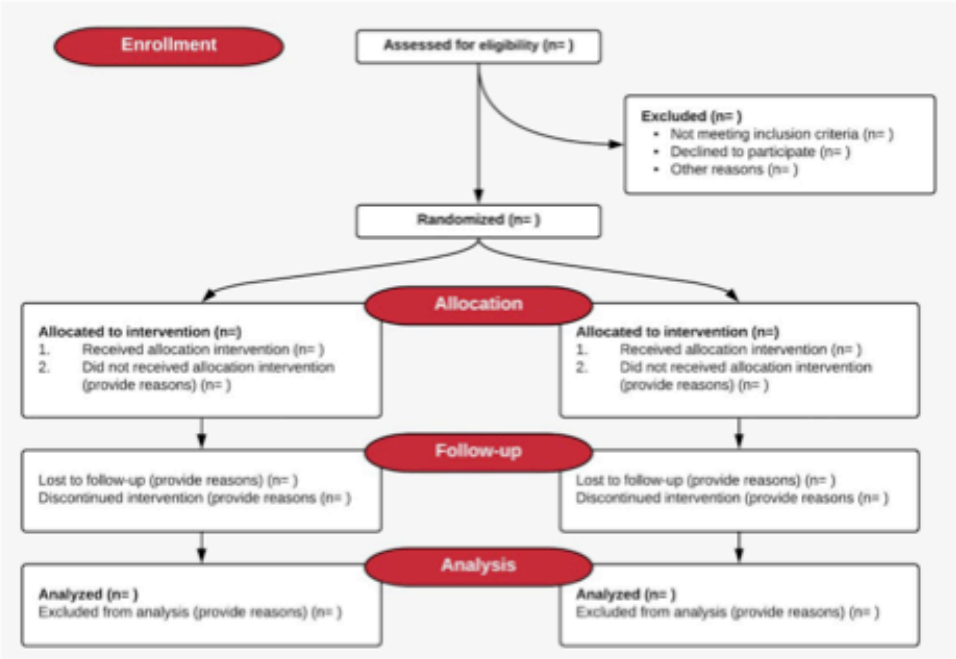


Figure 1 CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

All subjects will receive standard measures to maintain oxygen saturation by pulse oximetry >94%, normothermia (>36°C) and heart rate <100 beats/min. Ventilation with an inspired oxygen fraction of 60% will be mechanically controlled to maintain $PaCO_2$ between 4.7 and 6.0 kPa, with a positive end-expiratory pressure of 4–6 mm Hg and a tidal volume of 8 mL/kg. For maintenance fluid therapy, a balanced crystalloid (Isofundin/Plasmalyte) will be administered at 1–3 mL/kg/hour for laparoscopic surgery and 5–7 mL/kg/hour for open surgery. Flow optimisation will be performed with hydroxyethyl starch (Voluven).[14] Packed red blood cells will be transfused if the haemoglobin level is <80 g/L.[15] The choice and dose of the vasopressor and ionotropic drugs will be determined by the anaesthesiologist in charge of the patient in both groups.

Tissue oxygen saturation (StO_2) will be non-invasively and continuously recorded every 2 s placing an adult sensor (ForeSight Elite sensor, model FSESL, Edwards Lifesciences) over the brachioradial muscle by using near-infrared spectroscopy (NIRS) technology (ForeSight Elite tissue oximetry system, Edwards Lifesciences=). Details about this NIRS technology are provided elsewhere.[16] StO_2 values will be hidden from the main screen in both groups but will be recorded internally into the HemoSphere system, so StO_2 values will not be available to clinicians and therefore cannot induce changes in patient management.

The haemodynamic optimisation algorithm will begin 15 min after the start of the surgery, once the haemodynamic impact of anaesthesia and surgery have been stabilised. Meanwhile, the haemodynamic goal in both groups will be to achieve a mean arterial pressure (MAP) >65 mm Hg with the administration of boluses of vasopressors at the choice of the anaesthesiologist. In both groups, haemodynamic data will be recorded every 20 s in the HemoSphere system after starting the haemodynamic optimisation protocols and downloaded after the surgery for offline analysis.

During the surgery, any procedure carried out with repercussions for the haemodynamic status of the patient will be marked and adequately labelled for further identification.

Biomarkers of acute kidney stress in the perioperative period will be measured by the PI and blinded for the rest of the researchers. Urinary (TIMP-2)-(IGFBP7) will be measured with the Astute140 Meter (BioMérieux). This device applies a sandwich immunoassay technique and converts the fluorescent signals from each of the two immunoassays (TIMP-2 and IGFBP7) contained within the Nephrocheck test cartridge into a single numerical risk result (AKIRisk). The result is calculated as the product of the measured concentrations of the two cell-cycle arrest biomarkers and can quantify the stress developed by kidney epithelial cells during surgery, identifying patients at risk of postoperative acute kidney injury (AKI).[17–19]

The first urine sample will be collected when performing the bladder catheterisation after induction. The first postoperative sample will be collected 4 hours after the patient's admission to the Intensive Care Unit for postoperative stay. If the value of this sample is in the grey zone,

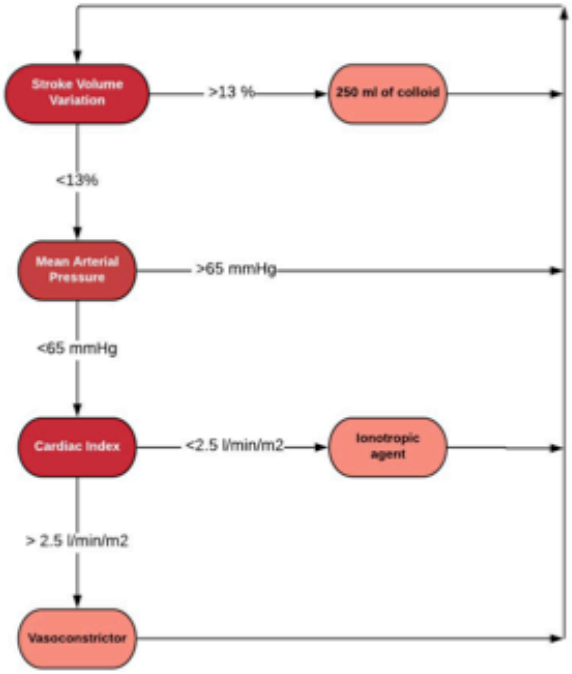


Figure 2 Control group haemodynamic optimisation algorithm.

between 0.3 and 2, a second postoperative sample will be collected 12 hours after the first one.[20]

Arterial blood analyses will be performed after induction of anaesthesia, midway through the surgery, immediately after admission to the intensive care unit, and daily from postoperative day 1–day 5 inclusive.

Haemodynamic management

Control group

Haemodynamic management will be based on the haemodynamic parameters provided by the HemoSphere platform with the FloTrac sensor, including cardiac index (CI) and stroke volume variation (SVV). The haemodynamic optimisation algorithm on this group is shown in figure 2. If SVV increases above 13%, a fluid bolus of 250 mL of colloid will be performed. MAP will be maintained above 65 mm Hg by a vasoconstrictor drug. An ionotropic agent will be added if the CI persists <2.5 l/mL/m^2 after previous steps.

Intervention group

Haemodynamic management will be based on the haemodynamic parameters provided by the HemoSphere platform with the Acumen IQ sensor, including CI, SVV and Acumen IQ specific parameters: maximum arterial pressure rise (dP/dt_{max}), dynamic arterial elastance (Ea_{dyn}) and HPI. The haemodynamic optimisation algorithm on the intervention group is based on the three main mechanisms leading to arterial hypotension: hypovolaemia, impaired contractility and vasoplegia (figure 3). When HPI rises above 85, SVV will be checked. If SVV is <13%,

Figure 3 Intervention group haemodynamic optimisation algorithm.

a vasoconstrictor will be administered if dP/dt_{max} value is >400 mm Hg·s, or an inotrope if dP/dt_{max} is <400 mm Hg·s. If SVV is >13%, a 250 mL fluid bolus will be administered if the Ea_{dyn} value is >1, or a vasoconstrictor if Ea_{dyn} <1.

Study outcomes

Primary outcomes

Intraoperative time-weighted average of MAP <65 mm Hg (TWA-MAP <65), calculated as the area between 65 mm Hg threshold and the curve of the MAP measurements (AUC 65 mm Hg) divided by the total continuous reading time:[21]

$$TWA-MAP<65=\frac{\sum_{i=1}^{k}\left(area_1\ 65\right)+\left(area_2\ 65+\ldots+area_k\ 65\right)}{Total\ time\ of\ measurements}$$

The advantage of using TWA-MAP instead of MAP is that the former combines the severity and duration of the hypotension considering the overall duration of the surgery.

Other variables related to IOH: the number of IOH episodes (defined as an event of MAP <65 mm Hg of at least 1 min duration) and the total time of hypotension per case.

Secondary outcomes

The secondary outcomes include:

- Intraoperative StO_2, as an indicator of tissue oxygenation and wellness of the microcirculation. StO_2 will be non-invasively and continuously recorded in the brachioradial muscle in the arm opposite to the arterial line. We will calculate the time-weighted average of all StO_2 measurement values, the time weighted averaged below an individual specific threshold obtained during the first minute of optimisation and identifying the minimum StO_2, defined as the minimum value sustained at least for 5 min.[22 23]
- Postoperative measurements of the TIMP-2 and IGFBP7 (AKIRisk). We will compare the AKIRisk at baseline and the evolution among both groups.

	STUDY PERIOD				
	Enrolment	Study Intervention			
TIMEPOINT**	d_{-1}	Surgical day (d_0)	Daily follow-up (d_1–d_{end})	Hospital discharge (d_{end})	Follow-up (d_{90})
ENROLMENT:					
Eligibility screen	X				
Written and oral project explanation	X				
Written informed consent	X				
Allocation		X			
Patient demographic/comorbidities	X	X			
INTERVENTIONS:					
Control group		X			
Intervention group)		X			
ASSESSMENTS:					
Primary outcomes		X			
Secondary outcomes		X	X	X	X

Figure 4 Schedule of enrolment, interventions and assessments. ** Specific timepoints listed

At the end of the surgery, data regarding the total fluid therapy during surgery, the accumulated dose of opioids during the intraoperative period, accumulated dose of vasoactive agents during the intraoperative period, accumulated dose of ionotropic drugs during the intraoperative period, other drugs with a haemodynamic impact not included in previous groups, total intraoperative diuresis, and transfusion of total blood products during surgery, will be collected.

Secondary outcomes will also include postoperative complications in accordance with the European Perioperative Clinical Outcome definitions,[24] length of hospital stay and 30-day mortality. Postoperative follow-up of patients will be performed by a collaborating investigator from each centre, blinded for the randomisation. For an overview of the outcome assessments, see figure 4.

Sample size and data analysis

The literature indicates that a cumulative hypotension time of more than 10 min during surgery is clinically relevant.[25] Given the novelty of the HPI parameter and the lack of publications during the design of this study, a pilot study in 31 patients undergoing major surgery was performed at the Virgen del Rocío Hospital. In this preliminary study, two groups were defined: a control group with invasive and continuous arterial pressure monitoring but without the use of HPI; and an intervention group with invasive and continuous blood pressure monitoring, in which the anaesthesiologist also had access to the HPI value and the additional parameters during surgery. In both groups, the haemodynamic objective during the intraoperative period was to maintain the MAP above 65 mm Hg. The results from this preliminary study revealed that in the control group (15 patients), 68.75% of the patients accumulated more than 10 min of hypotension (11 patients), while in the intervention group with HPI (16 patients), only 31.25% of the patients accumulated periods of a MAP <65 mm Hg more than 10 min (5 patients).

Based on this pilot study, to achieve a 90% power, and a significance level of 5%, 72 patients will be required (36 in each group). Assumed a drop-out rate of 10%, a total of 80 patients will be required (40 patients per group).

Statistical analysis

The normality of data distribution was assessed by the D'Agostino-Pearson test and confirmed by inspection of a Q-Q Plot. The results are expressed as the mean±SD when normally distributed or the median (25th–75th IQR). Categorical data were given as frequencies with percentages.

Comparison of quantitative variables between control and intervention group will be performed with the Mann-Whitney U test or the independent *t* test, and the χ^2 test for categorical variables. To establish a relationship between changes IOH management and tissue perfusion, a regression analysis will be performed between TWA-MAP and the perfusion indexes (StO_2 and AKIRisk).

A $p<0.05$ will be considered statistically significant. The statistical analyses will be performed with the SPSS software, V.23.0.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

Our goal is to determine whether a goal-directed algorithm based on the prevention of arterial hypotension using the HPI and the aid of the additional parameters, such as arterial dP/dt_{max} and Ea_{dyn}, reduces the duration and severity of IOH when compared with the recommended goal-directed fluid therapy. We also aim to determine whether this optimisation of the systemic perfusion pressure influences intraoperative tissue perfusion and postoperative complications. To achieve this objective, we will include patients with a higher risk of IOH (>65 years old and/or ASA III/IV).

Considering the significant impact of intraoperative arterial hypotension on mortality and morbidity, arterial pressure should be considered as a critical element. Therefore, maintaining blood pressure within a physiological range that ensures tissue perfusion should be considered not an option. Furthermore, the definition of blood pressure as a critical element, also implies a paradigm shift in the current treatment of intraoperative arterial hypotension from a reactive attitude to a proactive action based on predictors, such as HPI. If this proactive attitude associates with a better patient's outcome still needs to be proven clinically. Moreover, the proper correction of arterial hypotension also depends on the adequate identification of the pathophysiological mechanisms leading to low

blood pressure and the choice of the optimal treatment.[9] Accordingly, the clinical benefit of an artificial parameter based on machine learning, such as HPI, should be analysed coupled with the haemodynamic protocol that determines the best treatment according to those physiological mechanisms involved in the development of arterial hypotension. Therefore, if this preemptive haemodynamic protocol affects tissue perfusion is also one of the main goals of our study.

ETHICS AND DISSEMINATION

Ethics Committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). Written informed consent will be obtained from all included patients. Patients will be informed that they may decline to participate or withdraw from the study at any time.

Serious adverse effect of the product which, by its nature, incidence, intensity or consequences has not been identified in the updated version of the risk analysis report.

Regardless of the outcomes, it is our intention to publish the results of this study in a peer-reviewed journal. Findings will also be presented at Spanish and international conferences.

Trial status

Protocol V.1.0; March 2020. Recruitment started in November 2020, and it is expected to be finished on February 2022.

Author affiliations
[1]Anesthesia and Critical Care, Hospital Juan Ramon Jimenez, Huelva, Spain
[2]School of Medicine and Health Science, Universitat Internacional de Catalunya, Barcelona, Spain
[3]Anesthesia and Critical Care, Virgen del Rocio University Hospital, Sevilla, Spain
[4]Anesthesia and Critical Care, Infanta Leonor University Hospital, Madrid, Spain
[5]Anesthesia and Critical Care, Complejo Hospitalario Universitario de Badajoz, Badajoz, Spain
[6]Edwards Lifesciences Corp, Irvine, California, USA
[7]Anesthesia, Fundacio Althaia de Manresa, Manresa, Spain
[8]Predepartamental Unit of Medicine, Science Health Faculty, Universitat Jaume I, Castello de la Plana, Spain
[9]Fundación Progreso y Salud, Sevilla, Spain
[10]Intensive Care Unit, Hospital Universitario de Jerez de la Frontera, Jerez de la Frontera, Spain

Twitter Juan Victor Lorente @jv_lorente, Ignacio Jimenez @ignatiusjl and Francisco Herrero-Machancoses @Machancoses78

Contributors Concept, study design and first draft of manuscript: JVL, IJ, JR-M, FH-M, PC and MIM. Manuscript review and data collection: JVL, IJ, JR-M, MIM, AB, IM, MdlAF, AA-M and EA. Editing and critical review: JVL, IJ, JR-M, MIM, WW, FH-M, PC, JB and FR.

Funding This study was supported by Edwards Lifesciences through a grant provided after presenting the study to a competitive international call via its Grant Portal (Grant Number: HCP-8200579).

Disclaimer The design of the study, the writing of this manuscript and the collection and interpretation of data are being carried out independently by the research team, without any intervention from the funding body.

Competing interests JVL: Edwards Lifesciences, Fresenius Kabi, Baxter, Vifor Pharma and bioMérieux conference fees, financial support for Edwards Lifesciences research obtained through the Grant Portal of the company. Economic research support from bioMérieux. IJ: Edwards Lifesciences conference fees. JR-M: Edwards Lifesciences, MSD, Fresenius Kabi and Dextera Medical conference fees. MIM: Clinical consultant for Edwards Lifesciences and Dextera Medical. WW: Employed by Edwards Lifesciences. The rest of the authors declare no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Juan Victor Lorente http://orcid.org/0000-0002-3158-7014
Francisco Herrero-Machancoses http://orcid.org/0000-0003-0280-5972

REFERENCES

1 Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. *Crit Care Med* 1988;16:1117–20.
2 Parker T, Brealey D, Dyson A, *et al*. Optimising organ perfusion in the high-risk surgical and critical care patient: a narrative review. *Br J Anaesth* 2019;123:170–6.
3 Heming N, Moine P, Coscas R, *et al*. Perioperative fluid management for major elective surgery. *Br J Surg* 2020;107:e56–62.
4 Ahuja S, Mascha EJ, Yang D, *et al*. Associations of intraoperative radial arterial systolic, diastolic, mean, and pulse pressures with myocardial and acute kidney injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology* 2020;132:291–306.
5 Walsh M, Devereaux PJ, Garg AX, *et al*. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013;119:507–15.
6 Khanna AK, Maheshwari K, Mao G, *et al*. Association between mean arterial pressure and acute kidney injury and a composite of myocardial injury and mortality in postoperative critically ill patients: a retrospective cohort analysis. *Crit Care Med* 2019;47:910–7.
7 Hatib F, Jian Z, Buddi S, *et al*. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. *Anesthesiology* 2018;129:663–74.
8 Wijnberge M, Geerts BF, Hol L, *et al*. Effect of a machine Learning-Derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: the hype randomized clinical trial. *JAMA* 2020;323:1052–60.
9 de Keijzer IN, Vos JJ, Scheeren TWL. Hypotension prediction index: from proof-of-concept to proof-of-feasibility. *J Clin Monit Comput* 2020;34:1135–8.
10 Schneck E, Schulte D, Habig L, *et al*. Hypotension prediction index based protocolized haemodynamic management reduces the incidence and duration of intraoperative hypotension in primary total hip arthroplasty: a single centre feasibility randomised blinded prospective interventional trial. *J Clin Monit Comput* 2020;34:1149-1158.
11 Maheshwari K, Shimada T, Yang D, *et al*. Hypotension prediction index for prevention of hypotension during moderate- to high-risk noncardiac surgery. *Anesthesiology* 2020;133:1214–22.
12 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586–42.

13 EDC C. Castor electronic data capture., 2019. Available: https://castoredc.com
14 Chappell D, van der Linden P, Ripollés-Melchor J, *et al*. Safety and efficacy of tetrastarches in surgery and trauma: a systematic review and meta-analysis of randomised controlled trials. *Br J Anaesth* 2021;127:556–68.
15 Kozek-Langenecker SA, Ahmed AB, Afshari A. *Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology*. , 2017: 34, 332–95.
16 Scheeren TWL, Schober P, Schwarte LA. Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. *J Clin Monit Comput* 2012;26:279–87.
17 Kashani K, Al-Khafaji A, Ardiles T, *et al*. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 2013;17:R25.
18 Meersch M, Schmidt C, Hoffmeier A, *et al*. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med* 2017;43:1551–61.
19 Gocze I. Biomarker-Guided intervention to prevent acute kidney injury the prospective randomized BigpAK study. *Ann Surg* 2017;267:1–8.
20 Engelman DT, Crisafi C, Germain M. Utilizing urinary biomarkers to reduce acute kidney injury following cardiac surgery. *J Thorac Cardiovasc Surg* 2020.
21 Maheshwari K, Khanna S, Bajracharya GR, *et al*. A randomized trial of continuous noninvasive blood pressure monitoring during noncardiac surgery. *Anesthesia & Analgesia* 2018;127:424–31.
22 Abdelmalak BB, Cata JP, Bonilla A, *et al*. Intraoperative tissue oxygenation and postoperative outcomes after major non-cardiac surgery: an observational study. *Br J Anaesth* 2013;110:241–9.
23 Spruit RJ, Schwarte LA, Hakenberg OW, *et al*. Association of intraoperative tissue oxygenation with suspected risk factors for tissue hypoxia. *J Clin Monit Comput* 2013;27:541–50.
24 Jammer I, Wickboldt N, Sander M, *et al*. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European perioperative clinical outcome (EPCO) definitions: a statement from the ESA-ESICM joint Taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015;32:88–105.
25 Wesselink EM, Kappen TH, Torn HM, *et al*. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018;121:706–21.

9.9. Anexo 9: Research Grant. The Predict H Trial. ClinicalTrials.gov: NCT04301102

Agreement Between Fundación Pública Andaluza Progreso y Salud, Fundación Andaluza Beturia para la Investigación en Salud and Edwards Lifesciences LLC

Sevilla and Huelva, December 9, 2019

BY AND BETWEEN

Of the first part, Mr. Gonzalo Balbontín Casillas, with identity card (NIF) No. 28.733.391-C, for and on behalf of the **Fundación Pública Andaluza Progreso y Salud** ("Sponsor"), with VAT (CIF) No. G-41825811, domiciled in Seville (Spain), at Avenida Américo Vespucio 15, Edificio S-2, in his capacity as the managing director and legal representative of the aforementioned Centre, pursuant to powers of attorney conferred by its Trust on 17 July 2019 and certified under a public deed by the notary José Javier Muñoz Layos on 3 September 2019, under order number 2325 of notary Alberto Moreno Ferreiro´s protocol.

Of the second part, Mrs. María Victoria Alonso, with identity card (NIF) No. 16.259.841-Z, for and on behalf of the **Fundación Andaluza Beturia para la Investigación en Salud** (managing body of the Hospital), with VAT (CIF) No. G-21395132, domiciled in Huelva (Spain), Hospital Universitario Juan Ramón Jiménez, Avda. Ronda Norte s/n, in her capacity as the managing director and legal representative of the aforementioned Centre, pursuant to powers of attorney conferred by its Trust and certified under a public deed by the notary D. Miguel Ferre Molto on 28 January 2010, under order number 147 of his protocol.

Edwards Lifesciences LLC (Sponsor of the Study), with US Federal Tax ID Number: 36-4345053, having its registered office at One Edwards Way, Irvine, California 92614 USA, represented by Mrs. Katie Szyman ("Edwards")

Finally, for the purposes of assuring cognizance and acceptance of the content of this document, Mr. Juan Víctor Lorente Olazábal, with identity card (NIF) No 48.617.677-R, **as investigator***,* who shall assume the scientific responsibility for the activities pursuant to this Agreement, domiciled for these purposes in Huelva (Spain), Hospital Universitario Juan Ramón Jiménez, Avda. Ronda Norte s/n.

Called hereinafter individually "the Party" and/or collectively "the Parties".

The appearing parties declare that they fulfil the necessary conditions to enter into this Agreement and hereby make the following

RECITALS

A. Sponsor wish to develop undertake a clinic study entitled: "Intraoperative Hemodynamic Management using HPI and its Relationship with Microcirculation and Detection of acute kidney damage: The pReDict Trial.", conducted by Dr. Juan Víctor Lorente Olazábal, attached to the Anaesthesiology, Reanimation and Pain Medicine Service at Hospital Universitario Juan Ramón Jiménez, from Huelva, whose managing entity is Fundación Andaluza Beturia para la Investigación en Salud.

B. The Fundación Pública Andaluza Progreso y Salud (FPS), a public-sector entity attached to the Andalusian Regional Ministry of Health and Families, is structured around three areas of activity related to services for the Andalusian public social and healthcare system: research support and management, development of information and communication technology, and training and assessment of professional technical skills. In the field of health-related RDI, the FPS is the central entity for research support and management in the Andalusian public-health system ("SSPA"). It is responsible for the effective fostering of health research and innovation in the region. Within the SSPA, biomedical research is organised in such a way as to confer upon the FPS the role of acting as a facilitator, providing support and unifying services for research centres and groups at every stage of the scientific process. The FPS acts as an in-house instrumental resource and technical service for the regional health ministry and agencies and other subsidiary instrumental entities, under the terms set out in their respective articles of association.

C. FPS shall act as Sponsor, according to applicable law.

D. The Study shall be conducted in Hospital Universitario Juan Ramón Jiménez, from Huelva (Spain), according to the contents of the Protocol.

E. Dr. Juan Víctor Lorente Olazábal is a medical doctor as defined in national law, which is recognised in Spain as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.

F. The Fundación Andaluza Beturia Para La Investigación En Salud is a non-profit organisation, with its own legal personality and full legal capacity and the capacity to act, constituted on a permanent basis and for an indefinite period of time. Its aim is to develop three lines of service activity in the province of Huelva: promotion, support and management of quality biomedical research, as well as the promotion and development of innovations in health technologies, information and communications, and support for training to develop the technical skills of professionals. Likewise, FABIS, is the beneficiary entity and responsible for the management of the funds of the three lines of activity of services, previously described, of the centers and public health institutions of the province of Huelva, among which is the Hospital Universitario Juan Ramón Jiménez de Huelva, according to a collaboration agreement signed on February 7, 2012 with the Andalusian Health Service (SAS).

G. Edwards Lifesciences LLC (Edwards) is the global leader in patient-focused medical innovations for structural heart disease, as well as critical care and surgical monitoring. Driven by a passion to help patients, the company collaborates with the world's leading clinicians and researchers to address unmet healthcare needs, working to improve patient outcomes and enhance lives. This company has agreed to provide funding for the conduct of the Research.

And therefore they agree to formalize this Agreement according to the following:

CLAUSES

FIRST.- OBJECT

The Object of this Agreement is to regulate the terms by the parties in conduct of the Clinical Study "Intraoperative Hemodynamic Management using HPI and its Relationship with Microcirculation and Detection of acute kidney damage: The pReDict Trial." (the Research),

SECOND.- CONDUCT OF THE STUDY

The research program which is contemplated by this Agreement is set forth in the Research Plan attached as Exhibit A. This Research Plan sets forth the research tasks and objectives to be performed by the sponsor, managing entity and coordinating investigator, the amount of funding to be provided by Edwards. The Research Organization will conduct the Research in accordance with the Research Plan of Exhibit A.

The Research will be conducted, with the support of the Fundación Andaluza Progreso y Salud as Sponsor, under the direction of Dr. Juan Victor Lorente Olazabal, investigator and staff of the hospital ("Coordinating Investigator")

In addition, three other hospital sites and their corresponding Investigators will participate in the research en Spain. They are as follows: Hospital Virgen del Rocío, Sevilla (Dr. Ignacio Jiménez López), Hospital Universitario de Jerez de la Frontera (Dr. Manuel Ignacio Monge García), Hospital Infanta Leonor, Madrid (Dr. Javier Ripollés Melchor).

Sponsor shall comply with all requirements and obligations of research sponsors in accordance with applicable laws, regulations and guidance, including but not limited to requirements relating to record keeping, informed consent, patient privacy, and the reporting of the Research and its results. Sponsor will obtain approval for the Research from an appropriate ethics committee (EC) where required. Edwards shall have the right to terminate, after prior written notice with appropriate remedy period, its support for the Research in the event that Sponsor is unable or unwilling to fulfill obligations set forth above.

THIRD.- OBLIGATIONS

A) Sponsor:

1. Manage authorization for Conducting the Research.
2. Conduct the Research.

B) Managing entity:

1. Carry out the economic and administrative management of the Research, in accordance with the Collaboration Agreement signed between the Andalusian Health Service and the managing foundations of the research, development and innovation of the Andalusian Public Health System

C) Coordinating investigator:

1. Ensuring that the clinic study is carried out correctly.
2. Respect the confidentiality of the information related to the study and guarantee the anonymity of participants.

D) Edwards:

1. Provide financial contribution as set forth in Sec. FOURTH

FOURTH.- FINANCIAL PROVISIONS

Edwards shall provide a research grant to the Managing Entity in the amount totaling €50,944 ("Contribution"), which will be paid in installments as set forth in the budget included in Exhibit D attached hereto, within thirty (30) days upon receipt by Edwards of the invoice justifying the payment and any required reports as set forth in article 5 of this Agreement. All amounts as described in Exhibit D include all applicable taxes and overheads. No additional payment shall be made by Edwards. Edwards shall monitor, audit and reconcile all payments that are made to the managing Entity, and shall be entitled to prompt refund of any overpayments or erroneous payments. The amounts received in connection with this Agreement are used solely in the collective interest of Mananging in compliance with its objectives and the applicable statutory limitations. Such amounts are not subject to, or motivated by the granting by Sponsor for healthcare professionals or students, of any direct or indirect benefits whether in kind or in cash, prohibited pursuant to national or international laws and regulations. Compensation shall not be considered as the consideration of the commitment of prescription, use or influence to the prescription of Edwards' products. Investigator will not receive any sum or any in-kind advantage directly from Edwards or indirectly through Sponsor in connection with the performance of this Agreement.

FIFTH.- RESEARCH DATA

Sponsor shall have all rights to data and results of the Research ("Research Data"), except as may be limited by the terms of this Agreement. Edwards has the right to a copy of the Research Data in a timely manner after Research completion, and must be afforded an opportunity to utilize the Research Data after publication or with Sponsor's consent, which shall not be unreasonably withheld, except that any use or disclosure of Data, as defined in the EU and/or local Data Protection regulation will be subject to the authorization provided by the Research subject in the informed consent or other authorization document.

SIXTH.- ACCESS TO RECORDS

Sponsor agrees to maintain and preserve the documents, original records and Research Data that result from the Research and agrees to provide Edwards reasonable access to such records, in accordance with applicable laws, and regulations, during the term of this Agreement, and for a period of five (5) years thereafter. Similarly, Sponsor shall maintain all written reports provided to Edwards and all related documentation which describes the progress of the Research.

SEVENTH.- RESEARCH MAINTENANCE

Sponsor shall submit, to Edwards a written report describing, results and description of the progress of the Research, as well as of the inventions that could be developed within the research, after the validation by Andalucian Technology Transfer Office as a standard procedure in the Andalusian public health system. The final written report must be summarizing the results and findings of the Research and providing the analysis and conclusions.

EIGTH.- EDWARDS MATERIAL

Edwards shall provide to Sponsor products and equipment, as set forth respectively in Exhibit B and Exhibit C, for use in performance of the Research ("Edwards Material"). Edwards will retain title to all Edwards Material provided to Sponsor. Sponsor shall not distribute or release Edwards Material to any person or entity other than Investigator and his/her laboratory personnel working on the Research, without the prior written permission of Edwards. Sponsor shall not use any of Edwards Material except in performance of the Research, and shall not analyze or have analyzed any of Edwards Material, in whole or in part. Sponsor shall not modify or attempt to improve any of Edwards Material.

Upon the end of the Research or early termination of this Agreement (whichever of these events is the first to occur), any remaining Edwards Material shall be returned to Edwards by Sponsor.

NINTH.- CONFIDENTIAL INFORMATION

The parties do not anticipate that the conduct of the Research shall require Edwards to disclose any confidential or proprietary information to Sponsor and/or Investigator. In the event that such disclosure becomes necessary, Sponsor will keep confidential, and not use, except in connection with the performance of the Research hereunder, any information which is provided to Sponsor by Edwards and/or developed by Sponsor while performing the Research, including without limitation any information which relates to the Research, or any information which Sponsor may acquire with respect to Edwards' business, or any information relating to Edwards' products, manufacturing processes, customers, product pricing, technical know-how, and business practices.

The obligations of confidentiality and for non-use of such information shall survive the termination of this Agreement unless or until:
a) such information is publicly known or shall become publicly known through no fault of Sponsor, or
b) such information was already in Sponsor's possession, as evidenced by written documentation prior to the disclosure of such information to Sponsor, or
c) such information shall be subsequently disclosed to Sponsor on a non-confidential basis by a third party who is not under any obligation of confidentiality. Specific information which has been disclosed to Sponsor by Edwards, or developed by Sponsor during the course of performing under this Agreement, must not be deemed to be available to the public or in Sponsor's prior possession merely because it was embraced by more general information available to the public or in the prior possession of Sponsor.
d) is required to be disclosed by any law, competent jurisdiction or court or government regulation, act or order.

Edwards may disclose information regarding the terms of this Agreement and any payment made hereunder if required by any federal, state or local law, rule or regulation, and Edwards may also publish such information on its website or in any other public manner to permit Edwards to provide the public with full disclosure of its financial arrangements with healthcare professionals.

TENTH.- PUBLICATIONS

Sponsor shall have the right to publish Research Data or other findings relating to the Research subject to the following conditions:

a. Sponsor shall submit to Edwards any and all drafts of such publications, including without limitation or restriction, any abstract, manuscript, or press releases at least three (3) months prior to the submission of such publication to any third party.
b. Edwards will have the right to exclude from such publication Edwards' confidential information pursuant to article 9.

c. Edwards will have thirty (30) days from receipt of such publication to advise Sponsor as to whether such publication discloses inventions intellectual property for which Edwards desires to seek patent or copyright protection.
d. Sponsor shall delay the submission of such publication, including the submission of any abstract for such publication for a period of up to ninety (90) days to permit Edwards to prepare and file patent or copyright applications. If additional time is required to properly file a patent or copyright application Sponsor shall, upon Edwards' request, extend this time for an additional thirty (30) days.
e. Edwards' support of the Research shall be acknowledged in any publication relating to the Research.

ELEVENTH.- PATENTS AND INVENTIONS

Edwards shall retain any and all right, title and interest in any intellectual property owned by or licensed to Edwards which existed prior to the date of this Agreement ("Pre-existing Edwards IP"). Edwards shall retain any and all right, title and interest in any intellectual property which is conceived or reduced to practice at any time solely by Edwards' employees or Edwards' consultants other than Sponsor ("Separate Edwards IP").

Sponsor shall have all right, title and interest in any intellectual property conceived solely by Sponsor as a result of the Research, insofar as such Sponsor's intellectual property is not already owned by Edwards. Edwards shall have no obligation to provide information, funding, or other assistance to Sponsor in support of any patent application, patent prosecution or enforcement effort undertaken by Sponsor, as long as Edwards is not co-owner of the object of protection.. For clarity, Sponsor has no right, title or interest in, nor license to, any Edwards' intellectual property, including Pre-existing Edwards IP, Separate Edwards IP and any intellectual property acquired by or licensed to Edwards from a third-party.

TWELFTH.- DURATION OF THE AGREEMENT AND EARLY TERMINATION

This Agreement will commence on the Effective Date and shall terminate on September 15, 2021, unless terminated earlier as provided herein. This Agreement, and Edwards' research grant, may be terminated by any party hereto upon the following timetables, if any of the following conditions have occurred:

a. Mutual agreement.
b. Immediately by either party, upon emergence of any adverse reaction or side effect with any device/product employed in the Research which is of such magnitude or incidence that in the opinion of Investigator or EC it supports termination; or
c. Immediately by either party, if a party hereto fails to comply with the terms of the Agreement, has been provided with written notice of breach, and has failed to cure such breach within ten (10) days after receipt of said written notice of breach; or
d. By Edwards on ten (10) days' written notice, if Sponsor is unwilling or unable to continue to serve as the sponsor of the Research; or
e. Not obtaining authorization of the competent Ethics Committee.

Within thirty (30) days after the effective date of termination, Sponsor will return to Edwards any unused funds or other Research supplies provided by Edwards. Except for a breach by Sponsor, Edwards shall be responsible for funding work completed and non-cancellable expenses incurred through the date of termination in accordance with Exhibit A.

THIRTEENTH.- PRIVACY AND DATA PROTECTION

The Parties agree that each will comply with their respective obligations as required under applicable privacy and data protection laws, in Spain Regulation (EU) 2016/679, of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and Organic Law 3/2018, of 5 December, on personal data:

a) Personal data will be processed and used for treatment with purpose related to managment of the Agreement and contact, if necessary, for appropiated relationship of the parties, and will be stored for the period necessary for implementing the obligations under the Agreement.

b) Legal basis for processing is the execution of the Agreement, without whose signature the purpose described in the previous paragraph could not be fulfilled.

c) Personal data will not be disclosed, except in cases indicated by law.

d) Controller are Fundación Pública Andaluza Progreso y Salud, domiciled at Avda. Américo Vespucio, 15, edificio S-2, Sevilla (Spain), Fundación Andaluza Beturia para la Investigación en Salud domiciled at Hospital Universitario Juan Ramón Jiménez, Avda. Ronda Norte s/n, Huelva (Spain), and Edwards, domiciled at One Edwards Way, Irvine, California 92614 USA.

e) You could contact to data protección officer: dpd.csalud@juntadeandalucia.es (on behalf of the sponsor) and dpd@grupoiwi.com (on Behalf of managing entity)

f) You have the right to acces, rectification, or ensure of personal data or restriction of processing, or portability, sending a letter, with a copy of your Identity card, to Fundación Pública Andaluza Progreso y Salud, Avda. Américo Vespucio, 15, Edificio S-2, 41092 Sevilla; o by e-mail to lopd.fps@juntadeandalucia.es, to Fundación Andaluza Beturia para la Investigación en Salud; Hospital Universitario Juan Ramón Jiménez, Avda. Ronda Norte s/n, Huelva or by e-mail to rgpd@fabis.org or to Edwards, One Edwards Way, Irvine, California 92614 USA, or by e-mail to investor_relations@edwards.com.

FOURTEENTH.- NOTICES

A) Notices to the Sponsor shall be addressed as follows:

Attn. Marta Reboredo Ares

Fundación Pública Andaluza Progreso y Salud

Av. Americo Vespucio, núm 15. Edif S-2. Sevilla. 41092. Spain

Email: marta.reboredo@juntadeandalucia.es

B) Notices to the Managind Body shall be addressed to:

Attn. M. Victoria Alonso Martínez

Fundación Andaluza Beturia para la Investigación en Salud

Hospital Universitario Juan Ramón Jiménez, Avda. Ronda Norte s/n. 21005 Huelva. Spain

E-mail: gerencia@fabis.org

C) Notices to Investigator shall be addressed to:

Attn. Mr. Juan Víctor Lorente Olazábal

Hospital Universitario Juan Ramón Jiménez, Avda. Ronda Norte s/n. 21005 Huelva. Spain

Email: juanvictor.lorente@gmail.com

The foregoing addresses and addressees may be changed by giving notice thereof in writing.

FIFTEENTH.- AMENDMENTS

Any change or amendment that take place after the signature of this Agreement will have to be made in writing and with the agreement of the Parties and shall be appended to the same.

The cancellation or amendment of one or more clauses shall not alter the validity of the remainder of the Agreement, the terms and conditions of which shall remain in effect, provided that the affected clause is separate from the rest and not of such importance that without it the Agreement would not have been entered into.

SIXTEENTH.- INDEPENDENT CONTRACTOR

In the performance of the Research, Sponsor shall be an independent contractor and, as such, shall not be entitled to any benefits applicable to employees of Edwards. Sponsor and Edwards shall not become, nor be regarded as, partners or as agents for the other and neither shall make any undertaking, or incur any liability, on behalf of the other. Sponsor acknowledges that Sponsor is and remains fully responsible for all aspects of the Research.

SEVENTEENTH.- EXCLUSIVITY OF RESEARCH

Sponsor, and in particular Investigator, shall not during the term of this Agreement perform any research similar to the Research for any other entity, nor assist any other entity, in pursuing any work related to the field of the Research without the written approval of Edwards.

EIGHTEENTH.- INDEMNIFICATION

The Research is not sponsored by Edwards and is being conducted independent of Edwards' oversight of Research activities. Edwards will bear no liability for the conduct or outcome of the Research. Sponsor shall indemnify, defend, and hold harmless Edwards and its affiliates, officers, employees, agents, and representatives from and against any and all liabilities, claims, damages, actions or suits (including attorneys' fees and court costs, regardless of outcome) arising out of, or in connection with, the Research. Sponsor shall maintain sufficient insurance coverage or a program of self-insurance to protect against liability under this provision.

NINETEENTH.- PUBLICITY

No party will, without the prior written consent of the other party, use in advertising, publicity, or otherwise, the name, trademark, logo, symbol, or other image of the other party or that party's employee or agent, except as set forth herein. Edwards may accurately describe Sponsor's role in Edwards' reports to regulatory agencies. Additionally, notwithstanding anything herein to the contrary, Sponsor shall have the right to post Edwards' name, the Research name, and the Research period, on FPS's publicly accessible lists of research conducted at Sponsor and as may be required in submissions to funding agencies.

TWENTIETH.- COMPLAINT

A "Complaint" means a written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of an Edwards' product after it is released for distribution. In the event that the Research involves, in any way, an Edwards' products and in the case of a Complaint, Sponsor must inform Edwards about the event by forwarding all Complaint information to the Edwards complaint handling function (complaints_eu@edwards.com; FAX number: +34 96 305 37 07) without delay, but no later than within 4 days from awareness. In case of a Complaint involving a death or public health threat, Complaint information shall be forwarded within 2 working days from awareness.

TWENTY-FIRST.- GENERAL PROVISIONS

1. The parties declare that they are aware of and undertake to comply with the Spanish legislation on corrupt practices and/or against the interests of the Public Administration, which, without limitation, consists of articles 419 to 427 bis relating to bribery, articles 428 to 431 relating to the traffic of influences, and articles 432 to 435 relating to embezzlement, articles 436 to 438 relating to fraud and unlawful exactions, articles 439 to 444 relating to negotiations and activities prohibited to public servants, and article 445 bis relating to corruption offences in international transactions, all of them of the Criminal Code, and any other related regulation that may be applicable. In addition, Edwards declares that it is aware of and agrees to comply with the corrupt practices act in the alien of the United States - Foreign Corrupt Practices Act (FCPA) and UK Bribery Act.

2. This Agreement, including its exhibits, constitutes and contains the entire agreement and final understanding between the parties concerning the Research and all other subject matters addressed herein or pertaining to the subject matter hereof. This Agreement supersedes and replaces all prior negotiations and all prior or contemporaneous representations, promises or agreements, proposed or otherwise made between the parties, whether written or oral, concerning the Research and all other subject matters addressed therein or pertaining thereto.

3. This Agreement may only be extended, renewed or otherwise amended by the written consent of the parties hereto or as otherwise provided in this Agreement. No party hereto may assign, cede or transfer any of its rights or obligations under this Agreement without the written consent of the other parties; provided, however, Edwards may assign this Agreement in whole or in part to any entity that purchases all or substantially all of its assets or equity or to any affiliate or subsidiary, informing to the Sponsor, who has the right to cancel this Agreement.

4. No waiver of any term, provision or condition of this Agreement whether by conduct or otherwise in any one or more instances shall be deemed to be or construed as a further or continuing waiver of any such term, provision or condition, or of any other term, provision or condition of this Agreement.

5. This Agreement shall be governed by and construed and enforced in accordance with the laws of Spain without reference to its choice of law rules. Any and all disputes, controversies, or differences between the Parties arising out of or in connection with this Agreement shall be settled by the competent court subject to the exclusive jurisdiction of Huelva, Spain.

IN WITNESS WHEREOF, the parties have indicated their acceptance of the terms of this Agreement by the signatures set forth below on the dates indicated. Each individual signing for a corporate entity hereby personally warrants his or her legal authority to bind that entity.

Fundación Pública Andaluza Progreso y Salud (Sponsor)

Signature: BALBONTIN CASILLAS GONZALO - 28733391C

Firmado digitalmente por BALBONTIN CASILLAS GONZALO - 28733391C
Nombre de reconocimiento (DN): c=ES, serialNumber=IDCES-28733391C, givenName=GONZALO, sn=BALBONTIN CASILLAS, cn=BALBONTIN CASILLAS GONZALO - 28733391C
Fecha: 2019.12.11 14:58:48 +01'00'

Name: Gonzalo Balbontín Casillas

Title: Managing Director

Date: _____

Fundación Andaluza Beturia para la Investigación en Salud (Managing Entity)

Signature 16259841Z MARIA VICTORIA ALONSO (R: G21395132)

Firmado digitalmente por 16259841Z MARIA VICTORIA ALONSO (R: G21395132)
Fecha: 2019.12.09 20:20:49 +01'00'

Name: Mª Victoria Alonso Martínez

Title: Managing Director

Date: _____

Edwards Lifesciences LLC

Signature: DocuSigned by: 87383C223CBC4F8...

Name: Katie Szyman

Title: Legal Representative Edwards

Date: 1/21/2020

READ AND ACKNOWLEDGED:

Investigator

Signature: LORENTE OLAZABAL JUAN VICTOR - 48617677R

Firmado digitalmente por LORENTE OLAZABAL JUAN VICTOR - 48617677R
Fecha: 2019.12.09 17:20:59 Z

Juan Victor Lorente Olazábal

Date: _____

Exhibit A
Research Plan

Study Synopsis/Scientific Research Grant Proposal

Date of submission: 11.03.2019
ID Grant Portal: CC-I19-022

Project title	Intraoperative Hemodynamic Management using Hypotension Prediction Index (HPI) and its Relationship with Microcirculation. Detection of acute kidney damage. The pReDict H Trial
Principal Investigator	Juan Victor Lorente Olazábal, Dr. Medical Staff
Investigator(s)	Dr. Juan Víctor Lorente Olazábal, Dr. Ignacio Jiménez López, Dr. Javier Ripollés-Melchor, Dr. Manuel Ignacio Monge García
Institution	Hospital Juan Ramón Jiménez. Huelva, Anesthesiology, Critical Care and Pain Management, Huelva,
Background	The achievement of a balance between oxygen supply and demand is a shared objective for anaesthesiology, intensive care, and emergency medicine specialties. For this purpose, maintaining "classically" monitored parameters within a correct range during surgical intervention has been demonstrated to be insufficient, and, moreover, is inexact when predicting patient clinical results such as perioperative complications and hospital stay duration [1] Goldman and Caldera indicated that intraoperative hemodynamic instability contributes to the occurrence of cardiovascular complications and produces an increase in postoperative mortality, with intraoperative management being the most effective means of avoiding this problem [2]. In this regard, hypovolaemia and non-detected global hypoperfusion during the perioperative period —whilst not associated with hypotension and/or tachycardia — predispose the patient to the occurrence of postoperative complications, which determine long-term survival after surgery [3]. Intraoperative hypotension is related to adverse postoperative outcomes in terms of acute kidney injury (AKI) and myocardial injury in non-cardiac surgery (MINCS) according to the intraoperative hypotension accumulated time. [2]. The harmful effects of hypotension depend on several dimensions, which include, in addition to blood pressure value in itself, time and its severity, which must be taken into consideration. [4]. A large number of patients, particularly those of high risk, could benefit from hemodynamic optimization by means of fluid therapy, blood derivatives, and/or the use of vasoactive/ionotropic drugs to ensure correct perfusion, thereby preserving organ function. Moreover, Sessler has demonstrated that intraoperative hypotension is related to an increased hospital stay as the accumulated time (not necessarily consecutive) of hypotension increases, which becomes significant when that time exceeds 30 minutes [5]. According to the study reported by Sessler, among the adverse outcomes regarding hemodynamic instability, there is a significant increase in mortality 30 days from the 60 minutes of accumulated hypotension time in the intervention. [5]. When adjusting for preoperative risk factors, the probability of mortality according to instability was observed to be significantly higher in the group that

suffered from intraoperative hypotension in comparison with the reference group [6].

With respect to the previously mentioned inaccuracy of the "classical" static hemodynamic parameters (such as blood pressure) for detecting tissue hypoperfusion, it is necessary to have a tool that is able to detect the latter with accuracy and precocity, thus limiting the incidence of organic dysfunction in these patients. [7]. In this regard, SvO2, SvcO2 and Lactate are useful measurement tools for assessing the presence of hypoperfusion in patients that present various pathological processes, since they reveal circulatory deficiencies in an effective way [8]. These three parameters have been shown to have a relationship with postoperative complications and outcomes in patients presenting septic and/or surgical processes, particularly in cardiac and high-risk surgery [7], with lactate being the less invasive parameter.

Other variables, such as those related to blood flow, obtained from various minimally invasive clinical platforms allow for obtaining advanced, continuous, and validated hemodynamic parameters, as opposed to more invasive reference methods. For example, the pulse wave obtained from the radial artery and the analysis of its contour show several morphologic characteristics, the shape and temporal evolution of which are related to the cardiovascular system function in terms of variables such as cardiac contractility, aortic compliance, and vascular tone. Pulse wave contour analysis is a technique for extracting complex characteristics of blood pressure wave, which enables us to calculate functional parameters such as systolic volume (SV), SV variation (SVV), pulse pressure variation (PPV), pressure elevation speed in the Left Ventricle (dP /dt), and Dynamic Arterial Elastance (EaDyn), allowing us to gain more in-depth knowledge regarding the patient's cardiovascular function. These parameters enable us to individualise the treatment of our patient during the perioperative period, with the use of perioperative goal directed therapy (PGDT) as an alternative to classic perioperative fluid therapies, which has been shown to reduce postoperative complications in surgery, particularly when the surgery is high risk [9].

Recent studies suggest that the early stages of hemodynamic instability are characterised by changes in the different physiological variables, which reflect a decline in compensatory mechanisms, leaving a detectable "print" in the blood pressure [10][11]. This means that dynamic changes of the Blood Pressure Wave could signal an imminent hemodynamic event. Adequate management of this information by the clinician would help to prevent an event whilst significantly reducing intraoperative hypotension accumulated time. With this aim in mind, a new hemodynamic monitoring device has been launched to the market, which incorporates a new probabilistic parameter known as the Hypotension Predictive Index (HPI). The HPI would indicate, in percentage terms, the risk that a hemodynamic event occurs, as defined by an average blood pressure of less than 65 mmHg for more than a minute [11]. This indicator is the result of the analysis and integration of various hemodynamic variables, estimated following systemic blood pressure curve analysis obtained from a radial arterial line of the

patient by means of the sensor Flotrac® (Edwards Lifesciences Ltd).
Due to all the above, we can confirm that early detection of alterations in the oxygenation of regional tissue may be of considerable interest, because we could avoid the worsening of global perfusion whilst treating this early alteration. To this aim, microcirculation has also been established as a clinical event that precedes the alteration of static hemodynamic parameters, and even global perfusion analytic variables (SvcO2, lactate, etc.), at least in septic patients [12]. In this patient profile, given the dissociation between the existing microcirculation and macrohemodynamics, it has been demonstrated that microcirculation alteration is prognostic, that is to say, septic patients admitted to hospital with altered microcirculation have higher mortality. [13].
Due to its simplicity and non-invasiveness, one of the most widely used methods to measure microcirculation is regional oxygen saturation (StO2), measured by near infrared light spectroscopy (NIRS)[14]. The brachioradialis muscle is one of the recommended places, as it is easily accessible in most of the patients and during most types of surgery; moreover, measurements in brachioradialis muscle are minimally affected by obesity, age, gender, edema, skin color, or hypothermia [15].
It should also be noted that, patients with ASA III, ASA IV and / or older than 65 years of age, have more risk of altered StO during the perioperative period [12].
Finally, it should be highlighted that the absence of a balance between oxygen supply and demand during the intraoperative period — whilst it is only represented by microcirculation alteration — may cause postoperative organic damage, with the being one of the first affected organs [16]. Acute Kidney Injury (AKI) is an independent death risk factor with general mortality rates of 25%, reaching 50% in an IUC adult environment. Moreover, patients with AKI have a higher probability of developing significant morbidity [17].
With regard to the treatment of acute kidney damage, Expert Societies recent recommendations include early detection, even before the occurrence of organ dysfunction. For this purpose, the measurement of kidney damage by biomarkers is recommended (including its alteration) within the AKI definition. In terms of the need to resolve the inaccuracy of using high creatinine levels to define renal failure, and to detect and treat kidney damage before it evolves to dysfunction, the emergence of kidney biomarkers offers a promising way forward. Since kidney damage is caused before creatinine levels increase, there are multiple factors that could have an impact on its value. Therefore, experts agree that creatinine is insufficient for assessing postoperative kidney damage caused by a major surgical intervention [16]. For this purpose, tissue inhibitor of metalloproteinases-2 and IGFBP7 were the two more promising biomarkers in the DISCOVERY study, both of which were validated in the SAPPHIRE study demonstrating a combined Area under Curve (AUC) of 0.80 for AKI prediction in a heterogeneous population. The subgroup analysis indicated that these markers were highly correlated both in septic patients and postsurgical patients (AUC 0.85) [18]. An additional validation study known as TOPAZ was able to demonstrate that a cut-off point of 0.3 mg / ml2 /

1000 of AKIRisk [(TIMP2 x IGFBP7)/1000, (ng/ml)2/1000] was capable of successfully identifying patients with an imminent risk of AKI with AUC of 0.82.

Therefore, and as the objective of this study, our aim was to assess the relationship between a non-physiological parameter obtained from Machine Learning (HPI) and physiological parameters such as StO and the Integration of the tissue inhibitor of metalloproteinase 2 (TIMP-2) and the binding protein of the insulin-like growth factor 7 (IGFBP-7), as indicators of microcirculation and the presence of renal damage respectively. The integration of this non-physiological factor (HPI) in everyday clinical practice could help to achieve significant advancements in surgical patient care, thus improving postoperative prognosis.

References:

1. Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy: Review article. Acta Anaesthesiol Scand. 2007.

2. Goldman L, Caldera DL. Risks of general anesthesia and elective operation in the hypertensive patient. Anesthesiology. 1979;50:285–92. http://www.ncbi.nlm.nih.gov/pubmed/434530.

3. Marik PE, Varon J. Perioperative hypertension: a review of current and emerging therapeutic agents,. J Clin Anesth. 2009;21:220–9. doi:10.1016/j.jclinane.2008.09.003.

4. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KGM, Kalkman CJ. Incidence of Intraoperative Hypotension as a Function of the Chosen Definition. Anesthesiology. 2007;107:213–20. doi:10.1097/01.anes.0000270724.40897.8e.

5. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, et al. Hospital Stay and Mortality Are Increased in Patients Having a "Triple Low" of Low Blood Pressure, Low Bispectral Index, and Low Minimum Alveolar Concentration of Volatile Anesthesia. Anesthesiology. 2012;116:1195–203. doi:10.1097/ALN.0b013e31825683dc.

6. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping STJ, Bentt DR, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology. 2015;123:307–19. doi:10.1097/ALN.0000000000000756.

7. Allen M. Lactate and acid base as a hemodynamic monitor and markers of cellular perfusion. Pediatr Crit Care Med. 2011;12:S43–9. doi:10.1097/PCC.0b013e3182211aed.

8. Litton E, Silbert B, Ho KM. Clinical predictors of a low central venous oxygen saturation after major surgery: a prospective prevalence study. Anaesth Intensive Care. 2015;43:59–65. http://www.ncbi.nlm.nih.gov/pubmed/25579290

9. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014.

10. Pinsky MR, Dubrawski A. Gleaning Knowledge from Data in the Intensive Care Unit. Am J Respir Crit Care Med. 2014;190:606–10.

doi:10.1164/rccm.201404-0716CP.
11. Hatib F, Jian Z, Buddi S, Lee C, Settels J, Sibert K, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. Anesthesiology. 2018;129:663–74. doi:10.1097/ALN.0000000000002300.
12. van Beest PA, Vos JJ, Poterman M, Kalmar AF, Scheeren TW. Tissue oxygenation as a target for goal-directed therapy in high-risk surgery: a pilot study. BMC Anesthesiol. 2014.
13. Rodriguez A, Lisboa T, Martín-Loeches I, Díaz E, Trefler S, Restrepo MI, et al. Mortality and Regional Oxygen Saturation Index in Septic Shock Patients: A Pilot Study. J Trauma. 2011;70:1145–52.
14. Scheeren TWL, Schober P, Schwarte LA. Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. J Clin Monit Comput. 2012;26:279–87. doi:10.1007/s10877-012-9348-y.
15. Rodríguez A, Claverias L, Marín J, Magret M, Rosich S, Bodí M, et al. Regional oxygen saturation index (rSO2) in brachioradialis and deltoid muscle. Correlation and prognosis in patients with respiratory sepsis. Med Intensiva. 2015;39:68–75.
16. Griffin BR, Gist KM, Faubel S. Current Status of Novel Biomarkers for the Diagnosis of Acute Kidney Injury: A Historical Perspective. J Intensive Care Med. 2019;:088506661882453. doi:10.1177/0885066618824531.
17. Koyner JL, Garg AX, Coca SG, Sint K, Thiessen-Philbrook H, Patel UD, et al. Biomarkers Predict Progression of Acute Kidney Injury after Cardiac Surgery. J Am Soc Nephrol. 2012;23:905–14. doi:10.1681/ASN.2011090907.
18. Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, DeMuth GE, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med. 201419. Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, Casans-Francés R, Balik A, Artacho JP, et al. Effect of goal-directed haemodynamic therapy on postoperative complications in low–moderate risk surgical patients: a multicentre randomised controlled trial (FEDORA trial). Br J Anaesth. 2018;120:734–44. doi:10.1016/j.bja.2017.12.018.
20. Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine : European Perioperative Clinical Outcome (EPCO) definitions A statement from the ESA-ESICM joint taskforce on perioperative outcome measures. 2015;:88–105.
21. van Beest PA, Scheeren TWL. Tissue oxygen saturation as a goal, but when and where should we measure it? J Clin Monit Comput. 2013;27:211–3.

Hypothesis	-The use of the Hypotension Predictive Index (HPI), as part of Functional Hemodynamic Monitoring (FHM), will improve microcirculation in surgical patients during the intraoperative period. H0: The difference between p1 proportions (microcirculation improvement with HPI) and p2 (microcirculation improvement without HPI) is lower than the 10% cut-off -The use of the hypotension predictive Index for decreasing hypotension total time (MAP under 65 mmHg) as part of Functional Hemodynamic

	Monitoring (FHM) will improve microcirculation status in surgical patients during the intraoperative period in comparison with conventional FHM. -The use of the Hypotension Predictive Index for decreasing hypotension total time (MAP under 65mmHg) as part of Functional Hemodynamic Monitoring (FHM) is capable of improving kidney injury risk measured in perioperative surgical patients in comparison with conventional FHM.
Objective	General Objective: -To establish the relationship between a non-physiological parameter obtained by Machine Learning (FHM) and two physiological parameters such as StO2 and AKIRisk [Integration of tissue inhibitor of metalloproteinase 2 (TIMP-2) and the binding protein of the insulin-like growth factor 7 (IGFBP-7)], as an indicator of microcirculation and the presence of renal damage associated with surgery. The integration of this non- physiological factor (HPI) in everyday clinical practice will lead to improvements in the indicated physiological parameters. Specific Objectives: - To assess the use of the Hypotension Predictive Index (HPI) as part of Functional Hemodynamic Monitoring (FHM), in the improvement of microcirculation in surgical patients during the intraoperative period. - To assess the use of the Hypotension Predictive Index as part of the Functional Hemodynamic Monitoring (FHM) for reducing the risk of kidney damage associated with major surgical interventions. - To assess the possible association between the occurrence of altered microcirculation measured by NIRS during the intraoperative period and the occurrence of perioperative kidney damage. - To assess the use of the hypotension predictive index as part of the Functional Hemodynamic Monitoring (FHM) in the reduction of postoperative complications in major surgical interventions. - To assess a possible association between the occurrence of altered microcirculation measured by NIRS during the intraoperative period and the occurrence of postoperative complications, establishing cut-off points of StO2 levels associated with the occurrence of these complications. - To assess the use of the Hypotension Predictive Index as part of the Functional Hemodynamic Monitoring (FHM) for decreasing the length of the hospital stay associated with major surgery. - To assess the use of the Hypotension Predictive Index as part of the Functional Hemodynamic Monitoring (FHM) for improving survival 30 days after a major surgical intervention.
Method	Study Design: A non-observational study will be conducted, making use of a controlled, randomised, multicentre design, with daily follow-up of the patients until hospital discharge, with mortality assessed after 30 days (Classification AEMPS). Sponsor: Fundación FABIS (FABIS Foundation). Participant Centres: Juan Ramón Jiménez A.H. Huelva (coordinator Centre). Vírgen del Rocío Hospital. Sevilla. University Hospital of Jerez. Infanta Leonor Hospital (Madrid)

Study Protocol: All individuals in both groups will receive balanced general anaesthesia with the use of intravenous anaesthetics and muscle relaxants. Due to pragmatic reasons, administration will be at the discretion of the anaesthesiologist. The Neuraxial analgesia technique will be performed (spinal or intradural) according to the preference of the anaesthesiologist before induction.
Bispectral index monitoring was used (BIS; Medtronic, Dublin, Ireland) with objective range of BIS of 40-60, maintained with Sevofluorane. Basic anaesthetic monitoring was employed, with three cardiac electrodes, oximetry pulse, at least one intravenous peripheral catheter, and in the case of needing several, we will try to group them in a single upper extremity to avoid the possible (albeit minimal) influence of fluid infusion below body temperature in microcirculation monitoring. Continuous blood pressure monitoring will be achieved by arterial line canalisation. Standard measures will be used to maintain oxygen saturation, by pulse oximetry with 94% minimum, normothermia, and cardiac frequency <100 heartbeats per minute. Mechanical ventilation will be maintained with inspired FiO2 of 60% to maintain PaCO2 between 4.7 and 6.0 kPa, with PEEP of 4-6 mm Hg and current volume of 6/8 ml kg. In both groups, red cell concentrates will be transfused according to the transfusion protocol of each centre. The treatment for patients who take antiplatelet agent drugs (AAP) or oral anticoagulation (OAC) will be established according to the Clinical Practice Guides of the Sociedad Española de Anestesiología y Reanimación – SEDAR (Anaesthesiology and Resuscitation Spanish Society) and the agreed current protocol in each centre.
In both groups, we will monitor microcirculation in the brachioradialis muscle during surgery with NIRS, with the collaborating anaesthesiologist responsible for the patient during surgery being blind to this value.
We will measure kidney damage biomarkers in perioperative period, by the PI, with the clinician responsible for the patient during the postoperative period being blind to this value.
All of the patients will undergo follow-up during the hospital stay and there will be revision of postoperative complications in survivors until hospital discharge

Control Group: Hemodynamic management will be based on the functional hemodynamic parameters provided by the hemodynamic monitor (sensor FloTrac® and Hemosphere platform®, Edwards Lifesciencies S.L. Appendix 3) and will be focused on the prevention of arterial hypotension and treatment defined by a MAP under 65 mmHg.
The anaesthesiologist must assess the most appropriate moment and type of intervention, based on basic anaesthetic monitoring, advanced hemodynamic parameters (Cardiac Output, Cardiac Index, Systolic Volume, and Systolic Volume Variation) and the perception of hemodynamic risk derived from this analysis, in order to avoid the event of defined hypotension and/or minimise hypotension accumulated time during the intraoperative period. The collaborating anaesthesiologist responsible for

	the patient during the intraoperative period will be blind to the Hypotension Predictive Index (HPI) and dP / dt functional parameters and Dynamic Arterial Elastance (EaDyn) Ethical Aspects: The study requires the approval of the corresponding Comité Ético de Investigación Clínica – CEIC (Clinical Research Ethics Committee) of all the participating centres. All procedures will be carried out in compliance with the ethical criteria of the responsible committee of local human experimentation (Law 14/2007 modification: June, 2nd. 2011 and the Helsinki Declaration of 1975, amended in 1983). The study will not include or reveal the names of the patients, their initials, or the numbers to which they have been assigned in the hospitals. An information sheet will be used to provide the patient with information related to the study objectives, the methodology used, and data confidentiality. If the individual agrees to participate in the study they will be asked to sign the informed consent. Limitations -There are different areas where StO2 can be measured, with the brachioradialis muscle being a frequently used location due to the excellent correlation between sensor measurement depth and muscle depth in this site, and, moreover, this site is one of the areas where the StO2 value is affected by the action of fewer mechanisms [10]. However, in spite of these advantages, recent studies have revealed that, for example, StO2 measurement in masseter can be very promising [21], and the comparison between these two measurement points and HPI application could be the subject of study in future projects. -To measure microcirculation, we do not intend to carry out the Vascular Occlusion Test (VOT), in spite of the fact that it could provide us with information about tissue de- oxygenation and re-oxygenation kinetics. Instead, we will attempt to obtain data using the simplest possible measurement, collecting information in a continuous way in order to prioritise application to daily clinical practice. -Despite the importance of the immediate postoperative period in surgical patient outcomes, we intend to focus our efforts on intraoperative management. One of the possible initiatives following this study could be to extend our work to postoperative management, even more so in patients with detected AKIRisk > 0.3, in an attempt to avoid kidney dysfunction.
Study Design	Interventional Multi-center Randomized
Inclusion and exclusion criteria	Inclusion criteria: Patients of either gender under general / combined anaesthesia; more than 65 years of age and/or physical status ASA III or IV; major elective surgery; abdominal surgery; neurosurgical, urological, gynaecological or orthopaedic by laparoscopy or open approach. Surgery

	was considered major if it met at least one of the following criteria: estimated duration > 2 h, estimated blood loss > 15% of blood volume, or transfusion requirements of at least two red cells concentrates [19]. Exclusion criteria: Patients only under regional anaesthesia; patients under 65 years of age and/or physical status ASA I or II;, Urgent or emergency surgery, or any patient that did not express consent.
Number of patients	80
Number of centers	4
Name of centers	Juan Ramón Jiménez A.H. Huelva (coordinator Centre). Vírgen del Rocío Hospital. Sevilla. University Hospital of Jerez. Infanta Leonor Hospital (Madrid)
Intervention	
Devices to be used	Hemosphere platform, FloTrac sensor, FloTrac Acumen IQ sensor, Noninvasive Tissue regional oximeter sensor. NephroCheck Test
Primary endpoint	Primary Variables * Minimally invasive and related hemodynamic monitoring variables: In both groups, we will obtain hemodynamic data (invasive AT, cardiac output, cardiac index, systolic volume, systolic volume variation, HPI, dP/dtmax, Eadyn) every 20 seconds, using the Hemosphere platform download (Edwards Lifesciencies SL). During the intervention, we will record on the clinical platform any intervention carried out that has an impact at the hemodynamic level in the patient, including: spinal bolus, fluid charge (type and quantity), bolus and / or continuous perfusion (CP) of vasoactive drugs, ionotropic CP and blood hemoderivative transfusion. We will record data for the total fluid therapy indicated during surgery, specifying the drug and its dose. *Perioperative blood analytics: Data from 3 arterial blood analyses (following anaesthetic induction, halfway through surgery, and immediately after admission in the anaesthesia ICU). We will measure levels of haemoglobin, lactate, pH, and base excess. During the postoperative period, we will carry out a daily morning blood analysis from Day 1 until Day 5 inclusively, measuring: haemoglobin, urea, and creatinine, along with the parameters chosen by the clinician responsible for the patient. *StO2 microcirculation monitoring: During intervention, using the mentioned NIRS technique, we will record StO2 in a non-invasive, continuous way, in the brachioradialis muscle. We will obtain this value every 2 seconds during the intraoperative period by the clinical platform download used for its measurement (Hemosphere -Edwards Lifesciencies SL). If we find an Arterio-Venous Fistula for dialysis, StO2 measurements will be taken on the contralateral side. *Kidney damage variables: TIMP2-IGFBP7. Urine immunoassay, commercially known as Nephrocheck® (Orto Clinical Diagnostics). The first sample (NC1) will be collected following induction of the anaesthetic, when performing vesical catheterisation. The first postoperative sample (NC2) will

	be collected during the first 4 hours after patient admission in the ICU/REA for their postoperative stay. If AKI Risk value in the first postoperative sample (NC2), is below 0.3, we will not collect new measurements of Nephrocheck®. If AKI Risk value in the first postoperative sample (NC2) is over 2, we will not take any further measurements of Nephrocheck®. If the AKI Risk value in the first postoperative sample (NC2) is between 0.3 and 2, we will collect a postoperative sample (NC3) 12 hours after the first sample. We will not take any further measurements of Nephrocheck® *Postoperative variables, postoperative complications, hospital stay duration, and mortality after 30 days: Presence of postoperative treatment with: diuretics, IECAs, ARA-II, beta-blockers, AINEs and other postoperative nephrotoxics, as well as daily fluid therapy. The analysis of postoperative complications will be conducted according to the European recommendations EPCO [20]. We will, in addition, monitor the presence of postoperative hyperglycemia, defined as glucose level in blood ≥150 mg / dl> 3 h in the first 72 h after surgery. In both groups, we will collect data regarding hospital stay duration and mortality after 30 days.
Secondary endpoint(s)	Secondary Variables: Case Number, HC/NUHSA no, admission date, surgery date, age, gender, hospital discharge date. Presence of preoperative treatment with: diuretics, IECAs, ARA-II, beta blockers and AINEs. ASA, American College of Surgeons (ACS) NSQIP in PDF from the web of ACS. Type of anaesthesia used in the intervention, surgical technique, and timing of surgery.
Study duration	13.01.2020 - 13.01.2021
Follow-up	Baseline After procedure At discharge 1 month
Justification of sample size	Sample Size: To achieve a power of 90% to reject H0, the difference between proportions (p1 and p2) is lower than the cut-off limit, on the basis of a Normal asymptotic test for unilateral proportions for two independent samples, with a level of statistical significance of 1%, and assuming, according to the pilot study performed in Virgen del Rocío Hospital (currently collaborating with them in this and other studies), that the Reference group proportion (control, without HPI) is 68.75% (n = 11), intervention group proportion (with HPI) is 31.25% (n = 5), and that both groups include the same number of individuals, with a 2% limit of Non-Inferiority making it necessary to include 36 patients in each group, that is, a total 72 patients in the study. Assuming a drop-out rate of 10%, it will be necessary to recruit 40 patients per group, that is, a total of 80 patients in the study. With the aim of maintaining randomisation, the assignment of individuals to each one of the groups will be carried out by Excel software and function =RANDOM.BETWEEN(1;2) for a range of 100 cells. This function randomly returns a whole number between 1 and 2, which will allow for establishing

	the assignment order of the individuals to the groups according to their appearance on the theatre lists.
Study timelines	First Patient In: 01.03.2020 Last Patient In: 01.12.2020 Last Patient Out: 01.01.2021 (Revision of last patient mortality one month after surgery)
Ethical committee/ IRB approval	No, will be submitted
Publication outcomes	First, we will prepare the research protocol, to publish it, probably in BMC Anesthesiology, given the novelty of the technology used. After obtaining the results and their analyse, we will prepare manuscritps to publish them at least in three journals placed in Q1 of Anaesthesia and Intensive Care. We will transmit the knowledge and data obtained in congresses of national and international scope (SEDAR, ESA,...)
Total budget requested	230 €
Budget breakdown	1-Execution expenses 1.1. Promoter 1.2. Insurance RC 1.3. External monitoring 1.4. Intraoperative Hemodynamic Monitoring Budget FUNGIBLES: -Sensor FloTrac Acumen IQ® intervention group: 40 ud +10 ud pilot Phase: 50 sensors x 400€: 24.200€ (VAT incl.) -Sensor StO2 control and intervention groups: 80 ud+20 ud pilot Phase: 100 sensors x 220€: 26.620€ (VAT incl.) MONITORS: -Monitor Hemosphere®: 4 centres x 26.500€/unit: 128.260 € (VAT incl.). SOFTWARE AND TECHNICAL SERVICE: -Predictive Software: 14.520€ + tissue oximetry Software: 14.520€ + Technical Service 4 centres, 3 years: 29.040€ Total: 58.080€ (VAT incl.) software and technical service. 1.5. Perioperative kidney injury risk detection Budget FUNGIBLES: -Test Nephrocheck® control + intervention group: 80 patients Minimum 2 measurements/patient: 160 test. Maximum 3 measurements/patient: 240 + pilot phase. Total 250 test: 10 boxes 10 boxes x 1.500 €/box 25 test: 15.000 € (VAT excluded) 18.150€ (VAT included)

	MONITORS: -Monitor: 4 centres x 3.000€/unit: 12.000€ (VAT excl.). As the company finances a monitor: 9.000€ for 3 monitors (VAT excluded) 10.890 € (VAT included) TECHNICAL SERVICE/CALIBRATION: Each month a calibration is necessary during data collection: 12 months of data collection x 4 centres: 2.400€ (VAT excluded), 2.904 € (VAT included) 2- Production expenses and scientific disclosure -Translations for 3 scientific publications in JCR journals placed in Q1 of Anaesthesia and Intensive Care: 2.000€ -Travel costs, expenses, and registration for conferences and scientific meetings (both national and international) Sociedad Española de Anestesia (SEDAR) Conference during the second year and the third year, a national conference (Congreso sección española de Sociedad Europea de Anestesia Regional-ESRA) and another international conference (European Society of Anaesthesia-ESA): 3.000€
Additional comment	

Exhibit B
Products

1. As set forth in art. 8 of this Agreement, Edwards shall provide Research Organization with the products listed below. For purposes of this Agreement, the "Products" shall be defined as the following:

Product	Quantity
Acumen IQ sensors	50
FloTrac sensors	50

2. The Products will be hand delivered or shipped to Institution. Upon completion or termination of the Study, Institution agrees to return to Edwards any unused Products.

Exhibit C
Equipment

1. As set forth in art. 8 of this Agreement, Edwards shall provide Research Organization with Equipment. For purposes of this Agreement, the "Equipment" shall be defined as the following:

Equipment	Quantity
Hemosphere	4
Roll Stands	4

Exhibit D
Support Milestones & Budget

1. Total Funding: €50,944 (on the achievement by Institution of the milestones outlined below). Milestone payments shall occur after Edwards' receipt of Institution's written notification that Institution has achieved the following milestones:

Milestone	Percentage of Payment (%)	Payment (£)
Milestone 1: Contract Execution	10%	€5,094.40
Milestone 2: Ethics Committee Submission and Approval	15%	€7,641.60
Milestone 3: Enroll 50% of the total patients (40)	25%	€12,736.00
Milestone 4: Enroll 100% of the total patients (40)	25%	€12,736.00
Milestone 5: Clinical study manuscript submission to journal	25%	€12,736.00
Total	**100%**	**€50,944.00**