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AVANCES EN LA PATOGENIA Y EL DIAGNÓSTICO DE LA ANGIODISPLASIA GASTROINTESTINAL

Memoria para optar al Grado de Doctor en Medicina y Cirugía

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A mi familia

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1. INTRODUCCIÓN

ANGIODISPLASIA GASTROINTESTINAL

1.1 INTRODUCCIÓN

Las lesiones vasculares del tracto digestivo se reconocen cada vez con mayor frecuencia como una causa importante de hemorragia digestiva recurrente. El reconocimiento de la importancia de estas lesiones como causa de hemorragia digestiva ha sido consecuencia del desarrollo y la implementación de las exploraciones endoscópicas y la arteriografía selectiva que permiten su identificación.

Las lesiones vasculares del tracto digestivo se clasifican en base a criterios anatomopatológicos, como el tamaño, el tipo de vaso afectado y el grosor de su pared. Estas lesiones pueden ser solitarias o múltiples y pueden ser lesiones aisladas o primarias del tracto digestivo, o bien pueden formar parte de un síndrome o presentarse en el contexto de una enfermedad sistémica. Las lesiones vasculares primarias del tracto digestivo incluyen malformaciones arteriovenosas congénitas, angiodisplasias, la lesión de Dieulafoy, hemangiomas, y flebectasias. Algunas enfermedades o síndromes que presentan lesiones vasculares digestivas incluyen la enfermedad de Rendu-Osler, el síndrome de Turner, la enfermedad de Von Willebrand, el síndrome del nevus azul y las enfermedades del tejido conectivo que afectan a los vasos sanguíneos como el pseudoxantoma elástico y el síndrome de Ehlers-Danlos. Enfermedades sistémicas asociadas a lesiones vasculares del tracto digestivo incluyen la hipertensión portal, la insuficiencia renal crónica, vasculitis (CREST) y la enteritis por radiación (1).

1.2 CONCEPTO

La angiodisplasia es la lesión vascular más común del tracto digestivo y probablemente la causa más frecuente de hemorragia digestiva baja en pacientes de edad avanzada.

Aunque la utilización de distintos términos como "angiomas", "malformaciones arteriovenosas" o "telangiectasias" para definir a una misma lesión creo una gran confusión en el manejo clínico de estos pacientes, lo cierto es que la angiodisplasia gastrointestinal es una entidad clinicopatológica bien diferenciada que se caracteriza por acúmulos de vasos dilatados de pared delgada constituida por endotelio y una delgada capa de musculo liso (2).

Sin embargo es importante destacar que en la actualidad se desconoce si las angiodisplasia hemorrágica presenta características biológicas distintivas de las angiodisplasias clínicamente asintomáticas.

1.3 EPIDEMIOLOGÍA

Esta entidad se presenta más comunmente en pacientes de edad superior a 50 años y afecta por igual a ambos sexos. La mayoría de los pacientes presentan enfermedades asociadas. Se ha señalado que es más frecuente en pacientes con estenosis aórtica, insuficiencia renal, cirrosis hepática, enfermedad de Von Willebrand o enfermedades pulmonares, pero no se ha demostrado que exista una asociación entre la angiodisplasia y algunas de estas enfermedades (3). En un análisis retrospectivo llevado a cabo en nuestro centro, estudiamos las características clínicas de 33 pacientes diagnosticados de

hemorragia digestiva por angiodisplasia. El 89 % de los pacientes tenían enfermedades asociadas, siendo la cardiopatía valvular la enfermedad más frecuente (79%), seguido de hepatopatía crónica 30%, insuficiencia renal crónica 22%, y un 36% tenían otras enfermedades asociadas (4).

La prevalencia de la angiodisplasia de colon no es totalmente conocida, ya que estas lesiones pueden ser asintomáticas y su diagnóstico puede ser un hallazgo casual en una exploración practicada por otros motivos. En un estudio de más de 900 pacientes asintomáticos de edad superior a 50 años en los que se realizó una fibrocolonoscopia hasta ciego para el screening de cáncer de colon, su incidencia fue del 0.83% (5). Asimismo, estas lesiones pueden ser demostradas mediante angiografía o colonoscopia, hasta en un 3% de los pacientes en los que estas exploraciones se realizan por indicaciones distintas a la hemorragia (6,7). Sin embargo, el diagnóstico de angiodisplasia se establece generalmente tras la presentación de hemorragia digestiva .

1.4 MANIFESTACIONES CLÍNICAS

La hemorragia digestiva es la única manifestación clínica de esta entidad. La severidad de la hemorragia es muy variable pero suele presentarse con pérdidas ocultas crónicas o hemorragia aguda recurrente, mientras que la hemorragia masiva ocurre en menos del 15% de los casos. Aunque la historia natural de la angiodisplasia de colon no es totalmente conocida, tras un primer episodio de hemorragia se presentarán recidivas hemorrágicas hasta en un 50% de los pacientes a los 3 años de seguimiento (8). Los factores que contribuyen a la tendencia hemorrágica de estas lesiones no han sido

totalmente establecidos. Indudablemente, el tratamiento anticoagulante que reciben estos pacientes por las enfermedades asociadas puede contribuir a su tendencia hemorrágica recurrente. También se han implicado trastornos de la coagulación como alteración en la adhesión y en la agregación plaquetaria (9), y enfermedad de Von Willebrand (10). Asimismo, evidencias indirectas basada en la eficacia del tratamiento antifibrinolítico sugieren que existe un aumento de la actividad fibrinolítica en estas lesiones (11). Sin embargo un estudio sistemático de la coagulación no se ha practicado en estos pacientes.

1.5 ANATOMÍA PATOLÓGICA

La identificación histológica de estas lesiones mediante las técnicas de rutina es difícil (12), pero la mayoría pueden ser demostradas fácilmente mediante técnicas como la inyección vascular con goma de silicona y aclaramiento del especimen. Mediante esta técnica se ha demostrado que las lesiones son generalmente múltiples, miden entre 1 mm y 1 cm de diámetro y se localizan predominantemente en colon derecho. Microscópicamente las angiodisplasias consisten en acúmulos de vasos dilatados de pared delgada constituida por endotelio y una delgada capa de musculo liso (2). Estructuralmente los vasos ectáticos son venas, vénulas y capilares. El hallazgo más precoz es la dilatación de las venas submucosas, mientras que en las lesiones más avanzadas se identifican acúmulos de vasos dilatados también en la mucosa.

1.6 ETIOLOGIA Y PATOGENIA

La etiopatogenia de la angiodisplasia digestiva no es totalmente conocida. Estudios morfológicos han sugerido que las angiodisplasias son lesiones adquiridas con la edad debido a la obstrucción intermitente del drenaje de las venas submucosas durante las contracciones peristálticas del intestino (13). Su elevada prevalencia en el colon derecho se ha atribuido al mayor diámetro y a la mayor presión en la pared de este segmento del colon comparado con otros segmentos. Otros autores también han sugerido que podrían ser consecuencia de la hipoxemia crónica en la microcirculación colónica como resultado de las enfermedades cardiacas, pulmonares o vasculares asociadas que conduciría la dilatación y proliferación vascular (14). Estudios recientes indican que la angiogénesis participa en el aumento de la vascularización que caracteriza distintas condiciones asociadas a hipoxemia y/o isquemia tisular. Esta vasoproliferación patológica es el resultado de un desequilibrio entre factores angiogénicos y antiangiogénicos (15). Entre los factores angiogénicos identificados, el factor de crecimiento endotelial vascular (VEGF) y el factor de crecimiento fibroblástico básico (bFGF) son potentes mitógenos para las celulas endoteliales, íntimamente relacionados con la angiogénesis normal y patológica. De hecho, el VEGF es el mediador principal de la angiogénesis inducida por la hipoxia. En tejidos adultos, la expresión de este factor y sus receptores esta marcadamente aumentada en areas de vasoproliferación activa como la observada en la isquemia miocárdica y la hipertensión pulmonar (16,17).

1.7 DIAGNÓSTICO

La hemorragia por estas lesiones consituye frecuentemente un problema diagnóstico. Las exploraciones endoscópicas y la angiografía selectiva del tronco celiaco y de las arterias mesentéricas son técnicas de utilidad para el diagnóstico de la angiodisplasia. Las exploraciones radiológicas con bario no estan indicadas porque no pueden demostrar estas lesiones y interferirían con la realización posterior de exploraciones endoscópicas o angiográficas (18).

1.7.1 Endoscopia

La fibrocolonoscopia (FCS) tiene una sensibilidad del 80% y es la exploración inicial de elección para el diagnóstico de la hemorragia digestiva baja no masiva (7). Esta exploración puede identificar la mayoría de las lesiones, y detectará la presencia de otras lesiones concomitantes potencialmente sangrantes (divertículos, pólipos, etc.) que presentan un elevado número de pacientes.

El aspecto endoscópico es variable pero la mayoría de las lesiones son muy caracteristicas de color rojo, planas o ligeramente sobreelevadas, de 2 a 10 mm de tamaño y que en un elevado porcentaje de casos son múltiples (19).

Sin embargo exploraciones repetidas en ocasiones no consiguen la visualización de estas lesiones hasta en el 32% de las lesiones. En estas situaciones, debe considerarse la posibilidad de que estas lesiones se localizen en el intestino delgado, lo que ocurre hasta en un 11% de los pacientes. Esta posibilidad puede evaluarse mediante ileoscopia o enteroscopia con los nuevos enteroscopios con los que es posible conseguir una

intubación intestinal distal, que permiten establecer el diagnóstico en un elevado porcentaje de casos (20).

Finalmente, la enteroscopia intraoperatoria se reserva para los pacientes con hemorragia masiva o recurrente grave en los que las otras técnicas diagnósticas no han sido concluyentes, aunque esta exploración quirúrgica es especialmente recomendable en los pacientes de edad inferior a 50 años, en los que los tumores de intestino delgado o el divertículo de Meckel son más probables (21,22).

1.7.2 Arteriografía mesentérica.

La arteriografía selectiva mesentérica es una técnica complementaria a la fibrocolonoscopia cuando esta no es diagnóstica o bien puede ser la primera exploración, con o sin gammagrafía con hematies marcados previa, en pacientes con hemorragia masiva que impide la correcta exploración del colon (23). En esta situación, la elección entre estas exploraciones es una decisión clínica que dependerá de la disponibilidad en cada centro. Las caracteristicas angiográficas de la angiodisplasia son un relleno venoso precoz que es la opacificación de una vena durante la fase arterial, el ovillo vascular en la fase arterial y retraso en el vaciamiento venoso (24). Esta exploración radiológica demostrará extravasación de contraste cuando la hemorragia tiene un débito superior a 0.5 ml por minuto y puede localizar el origen de la hemorragia en el 50% al 72% de los pacientes con hemorragia masiva, pero este porcentaje se reduce a menos del 50% cuando la hemorragia es de bajo débito o ha cesado (8). Otra ventaja importante si esta exploración es positiva, es la posibilidad de tratamiento hemostático mediante la perfusión de vasopresina o

embolización con Gelfoam o la embolización de un marcador metálico que facilitará su localización operatoria (23).

La arteriografía selectiva esta también indicada en la hemorragia no masiva cuando la endoscopia y la enteroscopia son negativas. Sin embargo no es una técnica ampliamente disponible y complicaciones importantes como insuficiencia renal aguda, disección arterial y colitis isquémica ocurren hasta el 9% de los pacientes (25). Hay por tanto una necesidad clara de una técnica menos invasiva, más segura y altamente sensible para el diagnóstico de la angiodisplasia.

Más recientemente la tomografía computerizada (TAC) se ha implantado como una técnica mínimamente invasivo en la visualización del árbol vascular (26). De hecho el TAC helicoidal y el angioTAC son tan útiles como la arteriografía convencional en la evaluación de la aorta abdominal y de su ramas (27). Sin embargo la exactitud del angioTAC en la visualización de vasos de pequeño calibre no está establecido.

1.8 TRATAMIENTO

Las opciones terapéuticas disponibles incluyen la resección quirúrgica del segmento afectado, la intervención hemostática endoscópica, el tratamiento angiográfico y el tratamiento farmacológico.

1.8.1 Tratamiento quirúrgico

Las medidas de soporte y la resección quirúrgica del segmento intestinal afectado era el tratamiento habitual de estos pacientes. Sin embargo, en la mayoría de los casos es posible controlar la hemorragia mediante tratamiento no quirúrgico, evitando la elevada mortalidad del tratamiento quirúrgico de urgencia, que se reserva para los pacientes con hemorragia masiva o con hemorragia persistente en los que ha fracasado otras intervenciones terapéuticas (28).

1.8.2 Tratamiento endoscópico

Distintas técnicas hemostáticas endoscópicas han sido utilizadas para el tratamiento de estas lesiones. Desde 1976, diversos autores han comunicado la eficacia de la electrocoagulación monopolar (29,30), electrocoagulación bipolar (31,32), escleroterapia (33-36), láser Nd-YAG (37-41), y más recientemente la electrocoagulación con argon-beam (42,43,38) y las bandas elásticas (44-46) para el tratamiento de estas lesiones. Sin embargo, no existe ningún estudio randomizado, controlado que haya comparado la eficacia de las diferentes técnicas endoscópicas en el tratamiento de estas lesiones. No obstante, una revisión completa de toda la experiencia publicada no permite destacar una técnica sobre otra.

1.8.2.1 Electrocoagulación monopolar (Hot biopsy forceps)

La electrocoagulación monopolar (Hot biopsy forceps) fue la primera técnica utilizada en el tratamiento de estas lesiones. Presenta la ventaja de que permite simultaneamente obtener biopsia de las lesiones y coagularlas (29). Con este dispositivo se controló la hemorragia en el 47-81% de los pacientes, pero presentó una alta tasa de resangrado (19-53%) y que llegaban al 53% a los 3 años de seguimiento (19,8). Los principales inconvenientes de esta técnica es la perforación, con una incidencia del 3%, que es más frecuente cuando las lesiones tratadas se localizan en el colon derecho (30).

1.8.2.2 Electrocoagulación bipolar

La electrocoagulación bipolar o BICAP ha sido junto con la monopolar los métodos inicialmente más frecuentemente utilizados en el tratamiento de estas lesiones (31). Esta circunstancia es el resultado de su alta eficacia hemostática (85%), un bajo coste y a un riesgo descendido de perforación colónica (32).

1.8.2.3 Inyección de sustancias esclerosantes

La inyección de sustancias esclerosantes (etanolamina, tetradecil sulfato sódico, epinefrina más polidocanol) en el tratamiento de estas lesiones se ha limitado a series cortas de pacientes (33-35). A pesar de ser una técnica sencilla, barata, y disponible, su uso no se ha generalizado, debido a la imposibilidad del abordaje tangencial de las lesiones y a que puede ser una técnica tediosa en especial si las lesiones son múltiples. Otros

inconvenientes incluyen el resangrado de la lesión, la úlcera postratamiento, y la posibilidad de que la inyección profunda de esclerosante penetre en la cavidad peritoneal (36).

1.8.2.4 El láser de Nd-YAG

El láser de Nd-YAG (neodimio-itrio-aluminio-garnet) ha sido el láser más frecuentemente utilizado en el tratamiento de las angiodisplasia. Con esta técnica se controla el sangrado inicial en 71-87% de los pacientes. Sin embargo la hemorragia recidiva hasta en el 43% de las lesiones, lo cual es debido la aparición de nuevas lesiones, o de lesiones concomitantes no diagnosticadas, o lesiones parcialmente tratadas (37-40). La recidiva hemorrágica es más común en pacientes con edad superior a los 75 años, en aquellos con trastornos de la coagulación, o en individuos con lesiones difusas (37,40). La morbilidad del láser Nd-YAG afecta entre un 4 y un 10% de los pacientes. La hemorragía en 2º tiempo ocurre aproximadademente a la semana del tratamiento endoscópico, coincidiendo con la caida del tejido necrosado inducido por el láser (41). Asimismo el riesgo de perforación del colon ocurre en el 2.4% de los pacientes. Sin embargo, esta cifra probablemente infraestime el riesgo global pues la mayoría de de estos estudios incluyen numerosos pacientes con angiodisplasia del tracto digestivo superior, donde el riesgo de perforación es inferior debido a las características anatómicas de la zona tratada (el grosor de la pared del colon es 50% inferior que la del estómago) (37).

1.8.2.5 El láser de argón

El láser de argón emite luz con una longitud de onda entre 488-514 nm que es bien absorbida por la hemoglobina, ello le confiere la ventaja de una menor penetración y un menor daño tisular (42). Estudios experimentales sobre modelos de úlceras demuestran una menor capacidad de penetración frente al láser Nd-YAG, heater-probe y BICAP (43) .Cello y colaboradores (38) trataron 38 pacientes con hemorragia por angiodisplasia (70% en colon) produciendo solo una perforación y consiguieron una reducción significativa de los requerimientos trasfusionales a los 6 meses tras el tratamiento.

1.8.2.6 Coagulación con argon-beam (argón-plasma)

El tratamiento con argon-beam o coagulación con argón plasma es un método de electrocoagulación tisular sin contacto que resulta de la aplicación al tejido de energía producida por la ionización del gas argón. El gas es introducido a traves de un tubo flexible de teflon, el cual poseen en su punta un electrodo de tungsteno. Este electrodo de tungsteno al recibir una señal eléctrica de alta frecuencia, ioniza el gas argón el cual conduce la energía y la transmite a los tejidos sin contacto. Debido a la salida divergente del gas, permite una aplicación de la coagulación tanto axial, como lateral. La capacidad de coagulación tisular de este dispositivo, de 2 a 3 mm de profundidad, depende del flujo del gas emitido (1 a 4 litros) como del voltaje aplicado (5000 V/mm) (44). Este método fue utilizado inicialmente en cirugía abierta y posteriormente en el tratamiento paliativo de tumores digestivos (45). Posteriormente esta técnica se introdujo para el tratamiento en diversas patología que incluyen el adenoma velloso, el divertículo de Zenker, la hemostasia tras polipectomía y también la angiodisplasia (46) Al igual que en las otras técnicas

endoscópicas descritas no hay estudios controlados que compare esta técnica con otras modalidades terapeúticas. Estudios preliminares muestran como esta técnica tiene la capacidad de destrucción tisular de la lesión vascular y presenta como complicaciones más importante la perforación. Las ventajas de esta técnica sobre los láseres convencionales se basa en la menor capacidad de penetración tisular, disminuyendo el riesgo de perforación, su movilidad, fácil manejo y en un coste económico significativamente menor.

1.8.2.7 Ligadura con bandas elásticas

El tratamiento con ligadura con bandas elásticas, es otra alternativa en la terapeútica endoscópica de estas lesiones. Este tratamiento consiste en la aspiración de la lesión y del tejido adyacente mediante succión endoscópica y la liberación de una banda elástica provocando un seudopólipo que se libera por necrosis tisular. Si bien el uso de esta técnica está bien establecido en el tratamiento de la varices esofágicas (47), su utilización en el tratamientos de otras causas de sangrado digestivo es más reciente. Esta terapeútica endoscópica tiene como ventaja su simplicidad, bajo coste, fácil manejo, y como principal inconveniente la generación de una úlcera tras caida del seudopólipo (48,49). La experiencia con esta técnica se limita a series cortas de pacientes donde ha demostrado su eficacia y seguridad. Será necesario su comparación con otras modalidades endoscópicas para establecer el papel de esta técnica endoscópica en el tratamiento de la angiodisplasia.

En resumen, distintas técnicas endoscópicas han demostrado su eficacia hemostática en la hemorragia aguda por angiodisplasia gastrointestinal. Sin embargo, no se han

realizado estudios comparativos que demuestren la superioridad de ninguna de ellas.

Este tratamiento hemostático endoscópico es eficaz cuando las lesiones son accesibles y localizadas. Sin embargo, incluso en estas condiciones, el porcentaje de recidivas a los 3 años alcanza el 50% (30). Por tanto, la influencia del tratamiento endoscópico en la evolución natural de la hemorragia por angiodisplasia no ha sido aún totalmente definida.

1.8.3 Tratamiento Angiográfico

El tratamiento angiográfico también puede conseguir la hemostasia en la hemorragia por estas lesiones. La perfusión de vasopresina o la embolización transcateter con Gelfoam han sido los tratamientos más frecuentemente utilizados (50,51). La perfusión intrarterial de vasopresina consigue el cese de la hemorragia en el 80 % de los casos. La perfusión endovenosa parece ser menos eficaz que la intrarterial en la hemorragia de colon derecho o intestino delgado. Sus principales inconvenientes son el riesgo de este tratamiento en pacientes de edad avanzada y el elevado porcentaje de recidivas al suprimir la perfusión (23). Asimismo, la embolización es una técnica eficaz pero existe un elevado riesgo de infarto colónico.

1.8.4 Tratamiento Farmacológico

1.8.4.1 Tratamiento Hormonal

El tratamiento hormonal con una combinación de estrógenos-progestágenos ha sido el tratamiento farmacológico más utilizado. El empleo de estos fármacos se utilizó inicialmente en pacientes con Rendu-Osler-Weber basado en la observación de una disminución de los episodios hemorrágicos observados durante los periodos de embarazo y su incremento durante la menopausia (52).

El mecanismo de acción del tratamiento hormonal sobre estas lesiones no es bien conocido. Así se ha propuesto que actuarían.:

1. Manteniendo o restaurando la integridad de pared vascular (53).
2. Induciendo cambios en el flujo sanguíneo esplácnico: aumentando el éstasis en la microcirculación mesentérica (54).
3. Efectos sobre coagulación:
   - Aumentan la síntesis del factor de von Willebrand y de otros factores de coagulación (55).
   - Reduciendo el tiempo de sangría en pacientes con insuficiencia renal (56,57).

La eficacia del tratamiento médico con la asociación de estrógenos y progestágenos ha sido observada en casos aislados y en series no controladas. Disponemos en la actualidad de 2 estudios controlados que han evaluado la eficacia del tratamiento hormonal en la hemorragia digestiva por angiodisplasia. En un primer estudio Van Cutsem y colaboradores (58) randomizaron 10 pacientes con hemorragia digestiva por angiodisplasia gastrointestinal a recibir tratamiento hormonal o placebo durante 6 meses al cabo de los

cuales estos grupos se cruzaban. Durante el tratamiento
90% pacientes del grupo placebo requirieron trasfusiones frente a 10% paciente del grupo del tratamiento hormonal. Asimismo los requerimientos trasfusionales descendieron de 10 U/paciente a 1 U/paciente durante el ensayo clínico, sin registrarse efectos adversos importantes. Estos resultados sugirieron que el tratamiento hormonal podría ser beneficioso en el tratamiento de esta entidad. Sin embargo posteriormente Lewis y colaboradores (59) compararon en un estudio de cohortes el efecto de combinación de estrógenos y progestágenos en 30 pacientes y los compararon con 34 pacientes sin medicación que sirvieron de grupo control. El 50% de los pacientes en tratamiento hormonal cesó la hemorragia y esta respuesta fue similar a la observada en el grupo placebo (44%). Asimismo no hubo diferencias significativas en los requerimientos trasfusionales entre ambos grupos. Estos datos sugerían que el tratamiento hormonal era ineficaz en el tratamiento de la hemorragia digestiva por angiodisplasia. Sin embargo hay que reseñar una elevada tasa de abandono precoz de la medicación por el alto porcentaje de efectos adversos. En un estudio retrospectivo llevado a cabo en nuestro centro (4), analizamos 33 pacientes con hemorragia digestiva por angiodisplasia gastrointestinal durante el periodo comprendido entre enero 1986 y Diciembre 1993. De estas 33 angiodisplasias, 15 eran localizadas y recibieron tratamiento endoscópico y/o quirúrgico, las 18 restantes recibieron un tratamiento hormonal con una combinación de linestrenol y mestranol. Durante el tratamiento sólo 1 paciente tuvo que abandonar la medicación por trombosis venosa profunda al mes del inicio, los 17 restantes recibieron tratamiento hormonal durante una media de 22 ± 4 meses. Durante el tratamiento 13 de 17 pacientes (76%) no resentaron recidiva de la hemorragia. El tratamiento hormonal consiguió la

disminución del número de episodios hemorrágicos así como la disminución de los requerimientos trasfusionales. En conclusión nuestro estudio sugería que el tratamiento combinado con estrógenos y progestágenos previene la recidiva hemorrágica por angiodisplasia. Estos resultados, apoyaron la necesidad de realizar estudios prospectivos, controlados con mayor número de pacientes y con un seguimiento prolongado para evaluar la eficacia del tratamiento hormonal en la hemorragia digestiva por angiodisplasia.

1.8.4.2 Otros tratamientos farmacológicos

Otros tratamientos farmacológicos utilizados incluyen los beta-bloqueantes (60), el danazol (61-63), la desmopresina (63,64), los antifibrinolíticos (65,66,11) y los análogos de la somatostatina, si bien la experiencia con estos fármacos es limitada a pequeñas series de pacientes.

El octreótido, un análogo sintético de la somatostatina, es tras el tratamiento hormonal el fármaco más empleado en el tratamiento de la hemorragia digestiva por angiodisplasia. Su utilización se ha basado en su acción vasoconstrictora esplácnica, que es mediada por la inhibición de péptidos vasodilatadores, la cual induce una marcada reducción del flujo sanguíneo portal y mesentérico (67-69). Más recientemente, se ha descrito su capacidad antiangiogénica in vitro, aunque su posible contribución en la eficacia hemostática de este fármaco no ha sido estudiada (70,71). Los resultados de estudios preliminares: casos aislados (72,73) y series no controladas con escaso número de pacientes (74-76) indican que este tratamiento consigue el cese de hemorragia con disminución de requerimientos trasfusionales así como la recuperación de las cifras de

hemoglobina. Las dosis utilizadas son 50–100 μg/12h y la eficacia de este tratamiento se ha observado un periodo de seguimiento de hasta 4 años. El principales inconveniente de esta medicación es la necesidad de su administración parenteral. El empleo de análogos de acción más prolongada que requieren una dosificación menos frecuente podría sin embargo, minimizar este inconveniente.

2. HIPÓTESIS

Las hipótesis planteadas en los trabajos que conforman la presente Tesis Doctoral son los siguientes:

Estudio 1: **Increased expression of angiogenic factors in human colonic angiodysplasia.**

El aumento en la expresión de los factores angiogénicos en la angiodisplasia de colon proporcionará evidencia del papel relevante de la angiogénesis en la patogenia de estas lesiones vasculares.

Estudio 2: **Accuracy of helical computed tomographic angiography for the diagnosis of colonic angiodysplasia.**

El angioTAC es una herramienta útil en el diagnóstico de la angiodisplasia de colon.

Estudio 3: **Increased plasma fibrinolytic activity in bleeding gastrointestinal angiodysplasia.**

Los pacientes con angiodisplasia gastrointestinal presentan trastornos específicos de la coagulación que contribuyen a la hemorragia digestiva por estas lesiones vasculares.

Estudio 4: **A multicenter, randomized, controlled, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia.**

El tratamiento hormonal con una combinación oral de estrógenos y progestágenos es eficaz en la prevención de la recidiva hemorrágica por la angiodisplasia gastrointestinal.

3. OBJETIVOS

Los objetivos planteados en los trabajos que configuran la presente Tesis Doctoral son los siguientes:

Estudio 1: **Increased expression of angiogenic factors in human colonic angiodysplasia.**

Examinar la expresión y distribución de los factores angiogénicos, factor de crecimiento endotelial vascular (VEGF) y el factor de crecimiento fibroblástico básico (bFGF), así como de los receptores celulares del VEGF, flt-1 y KDR, en especímenes de colon de pacientes con angiodisplasia de colon y su comparación con su expresión en especímenes humanos de colon normal y de cáncer de colon.

Estudio 2: **Accuracy of helical computed tomographic angiography for the diagnosis of colonic angiodysplasia.**

Investigar si el angioTAC contribuye al diagnóstico de la angiodisplasia de colon humana.

Estudio 3: **Increased plasma fibrinolytic activity in bleeding gastrointestinal angiodysplasia.**

3.1 Investigar si la hemorragia digestiva por angiodisplasia esta asociado a un trastorno específico de la coagulación incluyendo la enfermedad de Von Willlebrand, hiperfibrinolisis plasmática, o alguna alteración en la activación de la coagulación por la vía extrínseca.

3.2 Estudiar si algún factor específico de la coagulación es un marcador predictivo de la tendencia hemorrágica de estas lesiones.

Estudio 4: **A multicenter, randomized, controlled, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia.**

Investigar la eficacia a largo plazo del tratamiento hormonal con una asociación de estrógenos y progestágenos en la prevención de la recidiva de la hemorragia por angiodisplasia gastrointestinal.

4. PUBLICACIONES

4.1 ESTUDIO 1

Increased expression of angiogenic factors in human colonic angiodysplasia. **Am J Gastroenterol 1999**;94: 1070-1076.

AUTORES: Junquera F, Saperas E, Torres I, Vidal T, Malagelada J-R.

4.2 ESTUDIO 2

Accuracy of helical computed tomographic angiography for the diagnosis of colonic angiodysplasia. **Gastroenterology 2000;**119:293-299.

AUTORES: Junquera F, Quiroga S, Saperas E, Pérez-Lafuente M, Videla S, Alvarez-Castells A, Armengol JR, Malagelada J-R.

4.3 ESTUDIO 3

Increased plasma fibrinolytic activity in bleeding gastrointestinal angiodysplasia**.** Remitida para evaluación a **Gastroenterology.**

AUTORES: Junquera F, Saperas E, Anglés A, Monasterio J, Malagelada J-R.

4.4 ESTUDIO 4

A multicenter, randomized, controlled, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia. Remitida para evaluación a **The New England Journal of Medicine.**

AUTORES: Junquera F, Feu F, Papo M, Videla S, Saperas E, Piqué JM, Malagelada J-R.

ESTUDIO 1:

Increased expression of angiogenic factors in human colonic angiodysplasia.

Reproducido de: American Journal of Gastroenterology 1999;94:1070-1076.

ESTUDIO 2:

Accuracy of helical computed tomographic angiography for the diagnosis of colonic angiodysplasia.

Reproducido de: Gastroenterology 2000;119:293-299.

ALIMENTARY TRACT

Accuracy of Helical Computed Tomographic Angiography for the Diagnosis of Colonic Angiodysplasia

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See editorial on page 581.

Background & Aims: **The diagnosis of colonic angiodysplasia is often challenging and relies on endoscopy or catheter angiography. We investigated whether computed tomographic angiography (CTA) contributes to the diagnosis of colonic angiodysplasia.** ***Methods:*** **Twenty-eight patients with suspected bleeding from colonic angiodysplasia were prospectively evaluated. Gastrointestinal bleeding was investigated by colonoscopy plus visceral angiography and by CTA. The level of agreement between CTA and the former procedures was determined.** ***Results:*** **CTA images of diagnostic quality were obtained in 26 patients. Eighteen patients were diagnosed with colonic angiodysplasia by colonoscopy plus visceral angiography, and 14 by CTA ($\kappa = 0.68$; $P < 0.001$). Sensitivity, specificity, and positive predictive values of CTA for detection of colonic angiodysplasia were 70%, 100%, and 100%, respectively. CTA signs including accumulation of vessels in the colonic wall, early filling vein, and supplying enlarged artery were present in 55%, 50%, and 22% of cases, respectively. None of these signs were present in the 8 patients with obscure gastrointestinal bleeding and negative diagnostic investigation of the digestive tract.** ***Conclusions:*** **CTA is a sensitive, specific, well-tolerated, and minimally invasive tool for the diagnosis of colonic angiodysplasia.**

Angiodysplasia (AGD) has been increasingly recognized as a major cause of gastrointestinal bleeding. These vascular lesions are the most common cause of obscure hemorrhage, accounting for up to 50% of such cases.[1] Currently, imaging assessment of gastrointestinal vascular lesions relies on invasive procedures such as endoscopy or catheter angiography. Endoscopic imaging is usually the initial investigation of these patients, although even repeated examination may fail to show vascular lesions in up to 32% of cases.[2,3] Angiography is an alternative to colonoscopy when the latter fails to show the source of bleeding, or may be the first diagnostic study in patients with massive bleeding.[4] Nevertheless, it is not widely available and significant complications of this procedure such as acute renal failure, arterial dissection, and ischemic colitis develop in up to 9% of patients.[5]

Recently, computed tomography (CT) has gained acceptance as a minimally invasive technique for imaging of the vascular system.[6] Helical CT and computed tomographic angiography (CTA) have been shown to be as useful as conventional angiography for the assessment of the abdominal aorta and its branches.[7] However, the accuracy of CTA in the visualization of small vessels has not been fully established. We conducted a prospective study to investigate whether helical CTA contributes to the diagnosis of human colonic AGD.

Patients and Methods

From January 1998 to February 1999, 30 consecutive patients with lower gastrointestinal hemorrhage and clinical suspicion of bleeding from colonic AGD participated in the study. Clinical suspicion of AGD, as first diagnosis, was established according to the following criteria: (1) patients older than 50 with acute or chronic recurrent bleeding and/or (2) unexplained chronic anemia with a positive fecal occult test result. Exclusion criteria included chronic liver disease, portal hypertension, and hereditary hemorrhagic telangiectasia.

Abbreviations used in this paper: AGD, angiodysplasia; C+A, colonoscopy plus angiography; CT, computed tomography; CTA, computed tomographic angiography; κ, kappa index; MIP, maximum intensity projection; P, probabilities; SSD, shadow surface display; STS-MIP, sliding thin slab maximum intensity projection.

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Study Design

This unicenter prospective study was held at a university general hospital of 700 beds that serves an area of about 500,000 people, geographically and socioeconomically distributed in the north and northwest of Barcelona, Spain. Gastrointestinal bleeding was first investigated by esophagogastroduodenoscopy and colonoscopy. When both procedures were negative, all patients were subjected to conventional visceral angiography, which was always performed during their hospital stay for the bleeding episode. Afterwards, all included patients underwent CTA after obtaining written informed consent. Patients underwent a small bowel barium study and ultrasonography as complementary studies.

Esophagogastroduodenoscopy and complete colonoscopy to the cecum were performed in all patients, with the use of a videoendoscope in the endoscopy unit by an experienced endoscopist. To avoid the influence of opiates on the endoscopic appearance of AGD,[8] propofol was the only treatment used during colonoscopy. Selective angiography of visceral trunks (celiac axis, superior and inferior mesenteric artery) was performed by a skilled angiographist using the Seldinger technique. Conventional angiography was performed when the patient was hemodynamically stable after either fluid resuscitation, blood transfusion, or both. AGD is defined endoscopically as a single or multiple 2–5-mm flat bright red spot, with a round uniform or slightly irregular margins. It may also appear as a raised and reddened area with a distinctly irregular margin, when larger than 5 mm.[9] Endoscopic criteria to define bleeding from AGD were as follows: active bleeding from AGD or presence of ulcerated AGD and blood in the digestive tract, or presence of AGD and blood in the digestive tract without any other potential source of gastrointestinal bleeding. Angiographic criteria to diagnose AGD were a densely opacified, slowly emptying, dilated tortuous vein; a vascular tuft; and/or an early filling vein.[10] Interpretation of the arteriographic images was performed independently by 2 observers without prior knowledge of the results of previous diagnostic procedures.

Helical CTA

All scans were obtained with a helical CT using the dual-slice spiral technique (Elscint CT Twin Plus II; Haifa, Israel). Nonionic contrast material (350 mg I/mL; total volume, 100 mL) was administered via an antecubital vein at a flow rate of 3 mL/s. Water was used as a negative contrast material to distend the stomach and duodenum, because it improves visualization of the gastrointestinal wall during bolus injection of contrast material and does not interfere with imaging of the vascular system. In all cases, helical CT scanning was performed during the arterial phase, 25 seconds after the start of contrast material infusion. Scanning included the volume of interest, i.e., right hemicolon, under the following conditions: slice width, 3.2–6.5 mm; pitch ratio, 1; and reconstruction at 2.5–5-mm intervals, depending on the length of the study. The duration of the helical sequence ranged from 25 to 35 seconds, because the maximum tolerated breath hold usually lasts 30–35 seconds. In all cases, sliding thin slab maximum intensity projection (STS-MIP) of the region of interest was used because this technique allows overlap of a selected number of axial sections in a single image, retaining the highest attenuated structures. Therefore, smaller blood vessels are visualized on a 1–1.5-cm rendered section that would otherwise be lost to partial volume averaging on a section acquired at a 1–1.5-cm thickness.[11,12] In several cases, maximum intensity projection (MIP) and shadow surface display (SSD) reconstructions were performed by a radiologist on a workstation, always after accurate analysis of the axial images. Interpretation of the images was performed independently by 2 observers (S.Q. and M.P.), who were blinded to the results of the previous diagnostic procedures (colonoscopy plus angiography [C+A]). The CT scans were reviewed for accumulation of ectatic vessels within the colonic wall; early filling vein, which is the presence of a single vein in the arterial phase when no other veins are seen; and enlarged arteries of the target area.

Statistical Analysis

Complete data collection was recorded on a database program (Microsoft Access 97 for Windows, Redmont, CA). Data analysis was performed using a statistical software package (Sigmastat for Windows version 1.0; Jandel Corp., San Rafael, CA).

The diagnostic accuracy of CTA in the detection of AGD was assessed by calculating the following probabilities (P):

$$\text{Sensitivity} = P(CTA^{+}/C{+}A^{+});$$

$$\text{Specificity} = P(CTA^{-}/C{+}A^{-});$$

$$\text{Predictive Value of Positive Result} = P(C{+}A^{+}/CTA^{+});$$

$$\text{Predictive Value of Negative Result} = P(C{+}A^{-}/CTA^{-}).$$

Because there is no definitive gold standard diagnostic test for AGD, a combination of 2 usual diagnostic techniques, C+A, was used as a reference standard. These values were for colonoscopy: sensitivity, 68%–80%; specificity, 90%; predictive value of a positive result, 90%[2]; for angiography: sensitivity, 50%–72%[13,14]; specificity, 100%[15]; and predictive value of a positive result, 100%.[16] Therefore, the above mentioned sensitivity, specificity, and predictive values are in fact probabilities calculated by comparison of a new diagnostic test, CTA, with the usual diagnostic test. They are actually "relative" sensitivity, specificity, and predictive values. The predictive values have been calculated directly from the observed data, assuming that prevalence [P ($C{+}A^{+}$)] = 69.2% of our study is representative of a population that meets the inclusion and the exclusion criteria.

The degree of agreement between C+A and CTA was analyzed using the kappa index (κ). κ is a measurement of the

degree of nonrandom concordance between observers or between measurements of the same variable. κ values are between 0 and 1, 0 representing absence of concordance and 1 complete concordance.[17] κ values between 0.6 and 0.8 are considered as substantial strength of agreement, and κ values of >0.8 as almost perfect strength of agreement.[18] This index was also used to analyze the interobserver agreement in angiography examination and CTA. We also examined agreement between recognition of signs of AGD by angiographic examination and CTA in patients in whom these vascular lesions had been previously diagnosed by conventional angiography. *P* values of <0.05 were considered statistically significant.

Results

Patients Characteristics

We evaluated 30 patients referred to our institution with gastrointestinal bleeding and clinical suspicion of colonic AGD over a 14-month period. Two patients were excluded: 1 patient with diagnosis of hereditary hemorrhagic telangiectasia, and the other patient refused to participate in the study. Twenty-eight patients met the inclusion criteria and were eligible for entry to the study. Colonic AGD was diagnosed in 20 patients (13 men and 7 women; mean age: 71 ± 8 years; age range, 58–81 years) on the basis of endoscopic or angiographic examinations. All these patients had acute recurrent or chronic gastrointestinal bleeding and the following associated diseases: cardiac disease (67%) including ischemic heart disease (18%) and cardiac valvular disease (49%) (50% with aortic stenosis, 30% with mitral stenosis, 10% with aortic insufficiency, and 10% with double aortic lesion); cerebral vascular insufficiency (35%); chronic renal failure (23.5%); chronic obstructive pulmonary disease (29%); diabetes mellitus (5%); and arterial hypertension (35%). One patient had von Willebrand's disease, and 3 patients associated deep vein thrombosis. Three patients were receiving antiplatelet agents and 6 patients anticoagulant drugs, and 1 patient described prior intake of a nonsteroidal anti-inflammatory drug. The number of total bleeding episodes per year was 2 ± 1.4, and the mean transfusion requirements were 3.4 ± 3.8 red pack cells units. Patients were followed up during a period of 1–14 months, with a mean follow-up of 7.2 ± 4.4 months.

Eight patients (6 men and 2 women; mean age: 67 ± 9 years; age range, 53–79 years) with clinical suspicion of AGD and no diagnosis after endoscopy, angiography, and complementary studies were similarly studied as a disease control group. All these patients had episodes of acute recurrent or chronic gastrointestinal bleeding, and had the following associated diseases: cardiac disease (62.5%) including ischemic heart disease (40%) and cardiac valvular disease (40%); cerebral vascular insufficiency (12.5%); chronic renal failure (12.5%); chronic obstructive pulmonary disease (25%); diabetes mellitus (25%); arterial hypertension (37.5%); and deep vein thrombosis (12.5%).

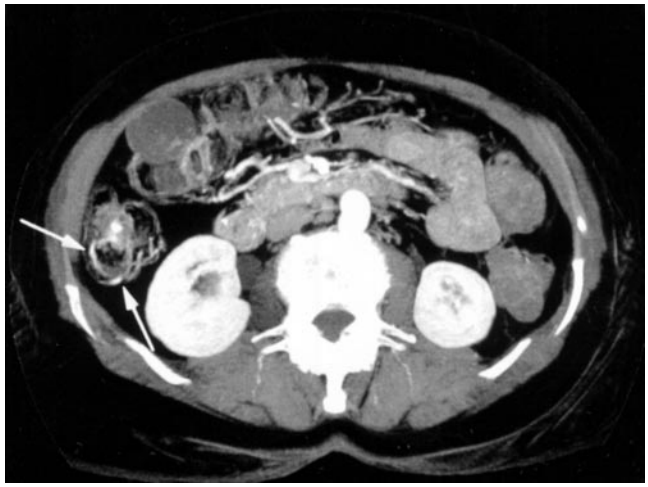

Figure 1. Colonic AGD. STS-MIP image (I5 mm thick) shows dilated vessels within the cecal wall (*arrows*) corresponding to colonic AGD.

CT Angiographic Examination

CT angiographic studies of diagnostic quality were obtained in 26 of 28 patients (applicability, 93%). Good quality CT images could not be obtained in 2 patients with colonic AGD, one diagnosed by colonoscopy and the other by conventional angiography, because they were unable to hold their breath longer than 15 seconds. This study describes the findings in 26 patients (18 patients with colonic AGD and 8 controls) with complete diagnostic information. Overall, CTA established the diagnosis of colonic AGD in 14 of 18 AGD patients, showing a sensitivity of 78%, which is reduced to 70% considering the 2 patients nonevaluable by CT. Accumulation of ectatic, dilated vessels in the wall of the right colon was observed in 10 of 18 (55%) patients with colonic AGD (Figures 1 and 2). In addition, CTA showed an early filling vein in 9 of 18 (50%; Figure 3) and an enlarged ileocolic artery in 4 of 18 (22%) patients with colonic AGD (Figure 4). By contrast, no signs of AGD were found in any control patient studied by CTA. CTA also diagnosed 5 of 8 colonic AGD cases previously detected by colonoscopy (sensitivity, 62.5%). Likewise, CTA was able to localize colonic AGD in 9 patients (50%) not diagnosed by colonoscopy. In fact, CTA scans detected 9 of 10 colonic AGD cases that were previously diagnosed by conventional angiography (sensitivity, 90%). The results of the diagnostic procedures and the diagnostic value of CTA in the diagnosis of colonic AGD are summarized in Table 1.

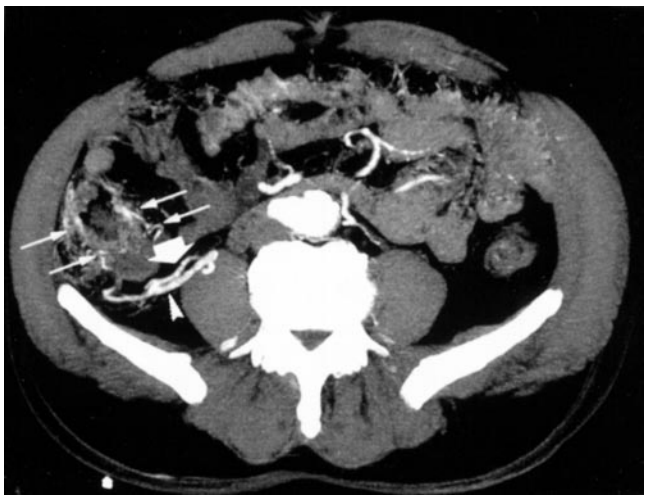

Figure 2. STS-MIP image (l5 mm thick) shows multiple dilated vessels within the right colonic wall (*arrows*), diagnostic of AGD. Note also early filling of ileocolic vein (*arrowhead*), simultaneous to the artery (*thick arrow*).

Eighteen patients received a diagnosis of colonic AGD by C+A, and 14 by CTA, showing a good degree of agreement between both techniques ($\kappa = 0.68$; $P < 0.001$). Complete concordance between observers was observed in the arteriographic and CT angiographic analysis of images. Likewise, a substantial degree of agreement was found between direct angiographic signs of colonic AGD between CTA and conventional angiography ($\kappa = 0.61$; $P < 0.001$).

No complications occurred after CTA. By contrast, 1 patient experienced acute renal failure after conventional visceral angiography.

Discussion

The results of this study indicate that helical CTA is a useful tool for the diagnosis of bleeding colonic AGD. In our opinion, CTA is valuable because of its noninvasiveness and comparative accuracy with the other 2 chief diagnostic procedures. CTA enabled us to visualize colonic AGD in 14 of 26 (54%) studied patients. CTA could show colonic AGD in 14 of 18 (73%) AGD patients previously detected by C+A. Likewise, CTA was able to diagnose 62.5% of AGD diagnosed by colonoscopy, but more importantly, diagnosed 50% of cases not visualized by colonoscopy. Moreover, this procedure detected 90% of cases diagnosed by conventional angiography.

CTA, an exciting application of helical CT technology, has achieved an essential role in the evaluation of many vascular lesions, such as aortic dissection, aneurysms of abdominal aorta, pulmonary arteriovenous malformations, and carotid artery and renal artery stenoses, all of which previously required conventional angiography.[19–24] The ability of CTA to show these common vascular lesions relates to the optimal vascular enhancement provided by the fast and continuous scanning of helical CT that allows image acquisition during the phase of higher concentration of intravascular contrast.[6,25] However, the major improvement of CT is the recent implementation of many postprocessing techniques, such as multiplanar reformatting, SSD, MIP, 3-dimensional perspectives of surface, and volume rendering.[26] More recently, STS-MIP technique has improved the ability of CT to display the morphology of small pulmonary blood vessels.[11,12] These studies have shown that STS-MIP reconstructions computed directly

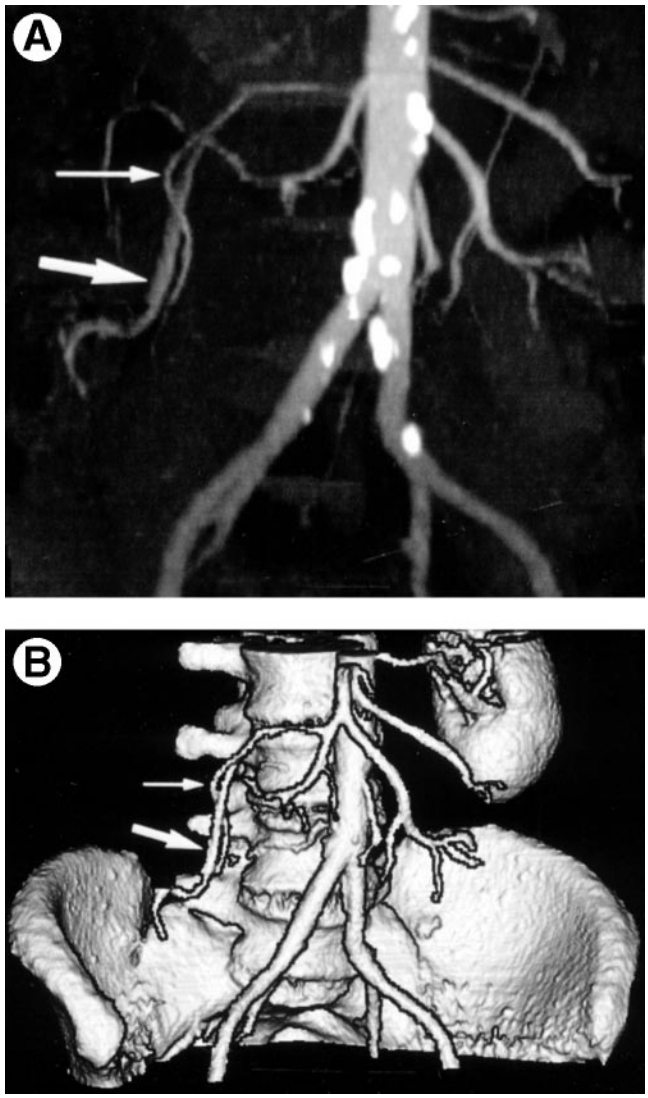

Figure 3. Early filling of ileocolic vein in right colonic AGD. (*A*) MIP reconstruction shows early filling of ileocolic vein (*thick arrow*), simultaneous to the artery (*thin arrow*). (*B*) SSD reconstruction of the same case showing identical findings (*thick arrow,* ileocolic vein; *thin arrow,* ileocolic artery).

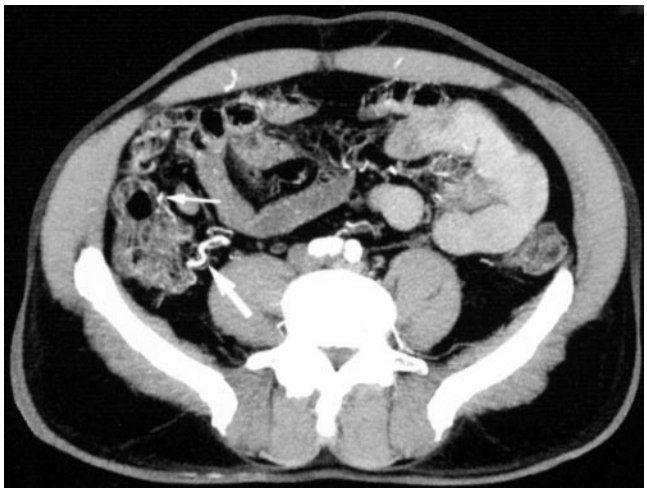

Figure 4. Enlarged ileocolic artery in right colonic AGD. STS-MIP image (I5 mm thick) shows an enlarged ileocolic artery (*thick arrow*) and a dilated vessel within the colonic wall (*thin arrow*).

from the transaxial sections enable visualization of much longer vessel courses than a single section. Thus, in the present study, we observed that CTA was able to diagnose some cases of colonic AGD not visualized by colonoscopy (9 of 18, 50%). This latter technique is a sensitive tool (68%–80%) in the diagnosis of colonic AGD, but it is limited by hemorrhage, which can blunt small lesions, hypovolemia,[27] and opiate drugs.[8] Likewise, minor endoscopic trauma, i.e., suction artifact during colonoscopy, may cause confounding images.[1] In our prospective study, colonoscopy had a lower sensitivity yield (9 of 20, 45%) than in previous retrospective series. The fact that this procedure was performed during active bleeding may account for the difference in sensitivity with prior studies.

On the other hand, CTA localized colonic AGD in 90% of cases diagnosed previously by angiography. Therefore, in this unselected series of elderly patients with bleeding colonic AGD, helical CTA could have made unnecessary an invasive angiographic procedure in most cases. Also, CTA is well tolerated and widely available. Additional advantages of this technique include a diminished risk of renal failure related to the scarce volume of contrast to be injected intravenously vs. conventional angiography, and avoidance of local angiographic complications such as femoral hematoma or arterial dissection.

In a previous study, Ettore et al., using a protocol consisting of helical CT of the abdomen after catheter angiography, proved this technique to be useful in the lesion-specific diagnosis of gastrointestinal bleeding of obscure origin, including AGD.[28] Although this combined technique is faster than conventional angiography, its major disadvantage relates to the not negligible morbidity and even mortality inherent to angiography.

The availability of a noninvasive CT as an alternative to angiography merits additional consideration, because conventional angiography is performed on elderly patients with recurrent bleeding who often have significant associated diseases (aortic stenosis, ischemic heart disease, and chronic renal failure). This implies numerous hospitalizations, which frequently entail repeated diagnostic procedures until diagnosis is confirmed, a deep impact in patient's quality of life, and a high socioeconomic cost. CTA is well tolerated, safer, and cheaper than conventional angiography, and its wide application may result in a reduction in staff time[29] and in radiation exposure of both patients and staff.[30] Another advantage of CTA includes its simplicity, applicability (93% of patients in our study), and speed. CTA also provides important additional information ruling out colonic carcinoma or colitis,[31] possibly avoiding false-positive cases of angiography when increased vascularity of colonic cancer mimics AGD.[32] Therefore, CTA should be considered in the evaluation of lower gastrointestinal bleeding, when colonoscopy fails to establish the diagnosis, avoiding invasive catheter angiography.

Although the prevalence of colonic AGD in the general asymptomatic population is not entirely known, and its natural history remains to be fully established, these common vascular lesions frequently do not bleed.[2,13,33] Therefore, incidental identification of colonic AGD by CTA performed for whatever reason in patients without gastrointestinal bleeding does not mandate further evaluation or therapy.[34]

A major limitation of CTA could be that it only allows dynamic examination of selected areas. However, this drawback is minimized because AGD is found in the cecum or right colon in 80%–100% of cases,[35,36] this site being the source of 70% of cases of massive bleeding in

Table 1. Results of the Diagnostic Procedures and Diagnostic Value of CTA in the Diagnosis of Colonic AGD

		C+A	
	Diagnosis	+	−
CTA	+	14	0
	−	4	8
	Nonevaluable	2	0

	Patients with complete information (n = 26)	All patients (n = 28)
Sensitivity	78%	70%
Specificity	100%	100%
Predictive value of positive result	100%	100%
Predictive value of negative result	67%	57%

the elderly.[14] Another limitation of this technique is its inability to demonstrate active bleeding and distinguish between bleeding and nonbleeding AGD. In fact, it has been shown that detection of active bleeding from AGD by CT requires direct injection of contrast directly into the mesenteric artery,[28] indicating that the rate of bleeding necessary to be detected by CTA is similar to that of conventional angiography. In clinical practice, active bleeding from gastrointestinal AGD can be shown by catheter angiography or colonoscopy only between 6% and 20% of cases.[1,10] Finally, the lack of therapeutic capability of CTA is a limitation that would require the use of endoscopic hemostatic methods or other hemostatic techniques, if necessary.

In conclusion, our results show the ability of CTA to accurately display the aberrant morphology of these common vascular lesions, providing a reliable diagnosis. This examination is safe, noninvasive, well tolerated, and widely available. It can be an appropriate diagnostic alternative in the study of gastrointestinal bleeding when endoscopy fails to establish the diagnosis, avoiding invasive catheter angiography. This development extends the diagnostic potential of helical CTA to the point that it may become the technique of choice for primary diagnosis of obscure gastrointestinal bleeding. However, prospective comparative studies with other intestinal imaging modalities are required to establish the definitive role of CTA in the evaluation of vascular lesions of the gut.

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Boas the Founder of Gastroenterology

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Izmar Isidor Boas (1858–1938) was born in the town of Exin in the Prussian province of Posen, the son of an impoverished merchant. All of the family's meager resources were mustered to support the education of Izmar who exhibited a phenomenal memory and a talent for languages early on. At the University of Berlin, he became a protégé of Carl Ewald (1845–1915), then transferred to the university at Halle where he took his M.D. degree in 1881. He returned to Berlin, renewed his contact with Ewald, and joined in investigation of techniques of gastric analysis. Boas then established his own clinic, the first devoted solely to the study and treatment of digestive disorders, an innovation that provoked animosity among those who insisted that gastroenterology remain subsumed to the broader field of internal medicine. Undeterred, Boas in 1895 founded the first journal of gastroenterology, now known by the title *Digestion*. In 1901 he advocated detection of fecal occult blood by means of guaiic test. That same year, he was elected an honorary member of the AGA. Meanwhile, his textbooks on diseases of the stomach and intestine gained worldwide acclaim. In 1933, he fled persecution in Nazi Germany and settled, destitute, in Austria. Three days after the infamous *Anschluss*, at age 80, he committed suicide.

—Contributed by WILLIAM S. HAUBRICH, M.D.
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ESTUDIO 3:

Increased plasma fibrinolytic activity in bleeding gastrointestinal angiodysplasia.

Abstract

Background: Gastrointestinal angiodysplasia is a major cause of recurrent bleeding. Haemostatic abnormalities have been implicated in the haemorrhage from these common vascular lesions but their precise contribution remains to be established. Our aim was to investigate whether bleeding angiodysplasia is associated with any specific coagulation disorder.

Methods: Clinical features and blood samples were prospectively obtained from 21 patients with bleeding gastrointestinal angiodysplasia 3 months after the last episode of haemorrhage. Plasma levels of von Willebrand factor (vWf), D-dimer (D-D), plasminogen activator inhibitor type 1 (PAI-1), tissue-plasminogen activator (t-PA) activity, tissue factor pathway inhibitor (TFPI) and activated factor VII (FVIIa-rTF) were measured. A group of 14 patients with bleeding duodenal ulcer were similarly studied as controls.

Findings: Mean plasma vWf levels were higher in angiodysplasia patients (208 ± 12 %) than in controls (143 ± 11 %)($p<0.05$). D-D levels (661 ± 80 ng/mL) and t-PA activity levels (2.04 ± 0.14 IU/mL) were also higher than in controls: 395 ± 99 ng/mL and 1.6 ± 0.1 IU/mL, respectively ($p<0.05$), whereas levels of PAI-1, FVIIa-rTF and TFPI were similar in both groups. However, PAI-1 levels (31.5 ± 11 ng/mL) were lower in high-bleeding-rate angiodysplasia than in low-bleeding-rate angiodysplasia PAI-1 (47 ± 14 ng/mL)($p<0.05$). In a multivariate regression analysis, the plasma level of PAI-1 was a predictor of haemorrhage from angiodysplasia ($p<0.05$).

Interpretation: Increased plasma fibrinolytic activity may contribute to bleeding from angiodysplasia. Low plasma PAI-1 levels constitute a risk factor for bleeding tendency in patients with angiodysplasia.

Introduction

Angiodysplasia is a major cause of recurrent gastrointestinal bleeding, particularly in the elderly. These vascular lesions are usually multiple and most commonly found in the cecum and ascending colon. Histologically they consist of an accumulation of ectatic, thin-walled blood vessels in the mucosa and submucosa (1). Why angiodysplastic lesions bleed is unknown, but several abnormalities of haemostasis including platelet dysfunction (2), as well as von Willebrand´s disease (3,4), appear to precipitate bleeding in some patients. Furthermore, the reported efficacy of antifibrinolytic therapy in some patients with persistent bleeding suggests that an underlying hyperfibrinolysis may induce or facilitate profuse haemorrhage from these lesions (5,6). Despite such tantalising evidence, a systematic investigation of the coagulation profile in angiodysplasia-associated gut haemorrhage has not been previously undertaken. Therefore, in the present study we examined whether von Willebrand's disease, hyperfibrinolysis or defective clotting activation via the extrinsic pathway are associated with bleeding gastrointestinal angiodysplasia. We also investigated whether a specific coagulation variable is a predictive marker for the bleeding tendency of these lesions.

Methods

Between January 1996 and February 1997, 25 consecutive patients with bleeding gastrointestinal angiodysplasia admitted to the Department of Gastroenterology of Vall d'Hebron Universitary General Hospital were studied. All patients were diagnosed with bleeding from gastrointestinal angiodysplasia on the basis of either endoscopic or angiographic examination. Angiodysplasia is defined endoscopically as a single or multiple 2-5 mm flat bright red spots, with round uniform or slightly irregular margins. It may also appear as raised and reddened areas with a distinctly irregular margin when larger than 5 mm (7). Specific criteria for inclusion in the study on the basis of endoscopy were as follows: active bleeding from angiodysplasia or presence of ulcerated angiodysplasia and blood in the digestive tract or presence of angiodysplasia and blood in the digestive tract with no other potential source of gastrointestinal bleeding. Specific for inclusion in the study on the basis of angiographic criteria were as follows: a densely opacified, slowly emptying, dilated tortuous vein; a vascular tuft; and/or an early filling vein (8). As controls, a group of patients with recurrent bleeding from duodenal peptic ulcer were similarly studied, and served as controls. Diagnosis of bleeding from peptic duodenal ulcer was established according to endoscopic criteria: active bleeding from ulcer crater, or stigmata of recent haemorrhage (visible vessel or adherent clot) overlying the duodenal ulcer base, or presence of duodenal ulcer and absence of another potential source of gastrointestinal bleeding. Moreover, control patients had to fulfil the following criteria: a) be older than 50 and b) have one or more of the following characteristics: history of cardiac valvular disease, ischaemic vascular disease, cerebral vascular insufficiency, or chronic renal failure. The latter

criteria were required to approximate as far as possible to the clinical and demographic characteristics of the angiodysplasia group. Exclusion criteria included chronic liver disease, previous intake of anticoagulant drugs, hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease) and age under 50.

Blood Sampling

Blood samples were obtained following an identical procedure from angiodysplasia (target) and peptic ulcer (control) groups of patients, three months after the last episode of haemorrhage. Blood samples were collected between 9 and 11 a.m. after overnight fasting, with the patient at rest in the supine position and after relaxing for 15 previous minutes and without smoking, to preclude any possible influence of circadian rhythm, food intake, exercise, postural changes and smoking on coagulation parameters. Venopuncture was always performed by the same technicians, with minimal stasis, discharging the first cubic centimeter of blood. Nine volumes of blood were added to 1 volume of sodium citrate 0.129M (vacutainer system, Becton Dickinson, France) in tubes, or to 1 volume of strong acidic citrate (for PAI-1 antigen and t-PA activity) in Stabilyte tubes (Biopool, Umea, Sweden). Tubes were centrifuged during the first hour after extraction at 1800 g for 15 minutes (25', in case of t-PA and PAI-1) at 4 ºC and plasma was aliquoted and stored at -40ºC until assayed.

Laboratory determinations

A) von Willebrand factor (vWf)

Plasma levels of von Willebrand factor (vWf) antigen were measured in tubes containing sodium citrate 0.129M (Becton Dickinson, France) by ELISA using the

Asserachrom vWF kit (Diagnostica Stago, Asnieres, France). This is an enzyme-linked-immunoassay based on a "sandwich principle" that detects vWf antigen. Samples were diluted at 1/200 to visualise the results obtained in a calibration curve supplied by the provider. Optic density was measured at 492 nm, which is directly proportional to vWf plasma levels (%). The intraassay coefficient of variability was 4.53%; normal range: 42-188 %.

B) Markers of Fibrinolysis

D-dimer (D-D). Plasma levels of D-dimer (D-D) were measured in tubes containing sodium citrate 0.129M (Becton Dickinson, France) by ELISA using the Fibrinostika FbDP Kit (Organon Teknika, Boxtel, The Netherlands). This is an immunoassay for the quantitative measurement of fibrin(ogen) degradation products in human plasma. It is based on a "sandwich principle" which, in a second step, specifically detects the fibrin degradation products (FbDP; D-dimer). Plasma levels of (FbDP; D dimer) (ng/mL) are proportional to the optic density obtained. The intraassay coefficient of variability was 8%; normal range: 220-430 ng/mL.

Tissue plasminogen activator (t-PA) activity. t-PA activity was determined in strong acidic citrate in Stabilyte tubes (Biopool, Umea, Sweden) using the Coaset t-PA functional assay (Chromogenix, Mölndal, Sweden). This is a specific test that measures tissue-plasminogen activator (t-PA) activity in human plasma. t-PA activity is quantified by determining the amidolytic activity exerted on the chromogenic substrate S-2251. The optic density at 405 nm is proportional to t-PA plasma activity levels (IU/mL). The intraassay coefficient of variability was 4%; normal range: 0.45-1.29 IU/mL.

Plasminogen activator inhibitor type 1 (PAI-1) antigen. PAI-1 antigen was measured in strong acidic citrate in Stabilyte tubes (Biopool, Umea, Sweden) by ELISA using the Tintelize PAI-1 kit (Biopool, Umea, Sweden) that detects active, latent PAI-1 and t-PA /PAI-1 and the uPA/PAI-1 complex. Plasma samples were diluted at 1/3 and optic density was measured at 492 nm, which is proportional to PAI plasma levels (ng/mL). The intraassay coefficient of variability was 7%; normal range: 0-37 ng/mL.

C) Markers of Clotting Activation Via the Extrinsic Pathway

Activated factor VII (FVIIa-rTF). Activated factor VII (FVIIa-rTF) plasma levels were measured in tubes containing sodium citrate 0,129M (Becton Dickinson, France) by ELISA using the Coagulative Staclot FVIIa-rTF assay (Diagnostica Stago, Asnieres, France). This clotting assay specifically quantifies human plasma levels of activated factor VII (mU/mL) which are inversely proportional to the clotting time (sec.). The intraassay coefficient of variability was 7%; normal range: 9-152 mU/mL.

Tissue factor pathway inhibitor (TFPI). Tissue factor pathway inhibitor (TFPI) was determined in tubes containing sodium citrate 0,129M (Becton Dickinson, France) by ELISA using the Inmubind total TFPI Kit (American Diagnostica Inc, Greenwich, USA) that detects TFPI and the complexes with tissue factor and factor VIIa (TF/VIIa/TFPI). The binary complex with Factor Xa (TFPI/Xa) and the quaternary complex with tissue factor, Factor VIIa and Factor Xa active (TF/VIIa/TFPI/Xa) are also detected but with slightly lower sensitivity. Plasma samples were diluted at 1/21 and the optic density was measured at 450 nm, which is proportional to TFPI plasma levels (ng/mL). The intraassay coefficient of variability was 3%; normal range: 40-80 ng/mL.

The investigators analysing the clinical outcomes were unaware of the results of vWf, D-dimer, t-PA, PAI-1, FVIIa-RTF and TFPI.

Follow-up

After baseline evaluation of clinical and laboratory variables, patients were followed periodically every three months or whenever necessary for a new bleeding episode or when symptoms raised clinical suspicion of haemorrhage. The following data were recorded at each visit: clinical evidence of acute or chronic bleeding, complete physical examination, biochemical and haematological profile including ferrum, ferritin, transferrin and transferrin saturation**;** and faecal occult test. The number of bleeding episodes/year was considered an endpoint of the study.

Ethical aspects

The protocol was approved by the Vall d'Hebron Hospital Ethics Committee, and informed consent was obtained from all patients enrolled in the study.

Statistical analysis Statistical analysis was performed with the Sigmastat software package (Sigmastat for Windows version 1.0). Data are presented as mean ± SD. Differences between groups were evaluated with X^2 test or Fisher's exact test for qualitative variables and Student´s t-test for quantitative variables following a normal distribution, or by Mann-Whitney rank sum test for those who failed the normality test.

Multivariate regression analysis was performed to investigate the prognostic value of the study variables (age, sex, associated cardiovascular diseases, vWf, D-D, t-PA, PAI-1, FVIIA-RTF, and TFPI) on the number of episodes of bleeding/ year during follow-up.

The level of statistical significance, p, was set at a value of 0.05.

RESULTS

Patients

A total of 25 patients fulfilled the criteria stated in Methods for having bleeding gastrointestinal angiodysplasia and entered the study. However, 4 of these 25 patients with angiodysplasia were subsequently excluded from the study for the following reasons: two were diagnosed with Rendu-Osler-Weber disease, one had chronic liver disease and another was 46 years old. Thus, 21 patients (10M/11F; mean age: 71 ± 2; age range: 58-90 yr.) with gastrointestinal bleeding were finally subjected to data analysis.

Angiodysplasia was diffuse (defined as present in more than one location and/or more than 3 lesions in the same organ) in 62% and isolated in 38% of our patients. Angiodysplasic lesions were located in the colon in 12 patients (57%), in the stomach in 2 (9.5%) and in distal ileum in 1 (5%). Combined gastric, duodenal and/or colonic lesions occurred in the remaining 6 patients (28.5%): joint gastric and colonic lesions in 1, gastric and duodenal in 2, duodenal and colonic in 2 and jejunal and ileal angiodysplasia in 1. All patients had associated diseases (heart disease 67%; cerebral vascular insufficiency 14%; ischaemic chronic limb disease 23%; chronic renal failure 14%; diabetes mellitus 14%, arterial hypertension 19%). Three patients were receiving antiplatelet drugs at the time of entry. In 6 patients bleeding was arrested by endoscopic electrocoagulation, 7 patients were administered an oral oestrogen-progestagen combination, and 8 patients received oral iron as required. All patients included in the study were prospectively followed up for a period of 23 ± 13 months (10-44 months) after inclusion to assess bleeding events. The number of total bleeding episodes/year was 3 ± 1.9 and mean transfusion requirements were 6 ± 5 red pack cell units.

A highly selected group of fourteen patients with previous bleeding from duodenal ulcer (10M/4F; mean age: 68 ± 2; age range: 59-79 yr.) diagnosed by endoscopy were also studied and as controls. They presented the following associated diseases: heart disease 70%; cerebral vascular insufficiency 21%; ischaemic chronic limb disease 35%; diabetes mellitus 21% and arterial hypertension 28%.

2. Coagulation profile

In patients with angiodysplasia, plasma levels of vWf (208 ± 12 %) were higher than in peptic ulcer controls (143 ± 11 %) ($p<0.05$) (Figure 1). Mean plasma levels of D-D (661 ± 80 ng/mL) and t-PA (2.04 ± 0.14 IU/mL) were higher in angiodysplasia than in controls: D-D (395 ± 99 ng/mL), t-PA (1.6 ± 0.1 IU/mL) ($p<0.05$), whereas mean levels of PAI-1 were similar in both groups: angiodysplasia (41 ± 14 ng/mL), controls (38 ± 12 ng/mL) (Figure 2). Mean plasma levels of FVIIa-rTF (62 ± 7 mU/mL) and TFPI (69.5 ± 2.9 ng/mL) in patients with angiodysplasia were similar to controls FVIIa-rTF (50 ± 9 mU/mL) and TFPI (69.5 ± 2.6 ng/mL).

Multivariate regression analysis showed plasma levels of PAI-1 to be the only independent predictor of haemorrhage in patients with angiodysplasia ($p<0.05$). To illustrate this finding we compared patients with frequent bleeding episodes "high-bleeding-rate angiodysplasia" (defined as >2 episodes/year) with those with infrequent bleeding episodes "low-bleeding-rate angiodysplasia" (≤ 2 episodes/year) and observed that PAI-1 levels (31.5 ± 11 ng/mL) were significantly lower in angiodysplasic patients with high bleeding rate than in those with low bleeding rate PAI-1 (47 ± 14 ng/mL). Establishing a PAI-1 cut-off plasma level of 40 ng/mL, only 1out of 8 patients (12.5%) with higher PAI-1 levels presented with more

than 2 bleeding episodes/year whereas the remaining patients with PAI-1 plasma levels above 40 ng/mL (7/8; 87.5%) presented with ≤ 2 episodes/year.

By contrast, no relevant differences in age, sex, associated cardiovascular diseases, vWf, D-D, t-PA, FVIIa-rTF and TFPI were detected between high and low-bleeding-rate angiodysplasia (Table 1).

DISCUSSION

The results of the present study show characteristic and intriguing changes in the coagulation profile of patients with bleeding gastrointestinal angiodysplasia. As assessed by the elevated plasma levels of D-dimer and t-PA activity, these patients present increased plasma fibrinolytic activity. Furthermore, low plasma levels of PAI-1 appear to constitute a risk factor for recurrent bleeding tendency in patients with angiodysplasia.

Various haemostatic disorders, in particular von Willebrand's disease, have been implicated in the bleeding tendency of these common vascular lesions (3,4). However, von Willebrand's disease was not diagnosed in any of the elderly patients included in the present series, in agreement with another previous prospective study of 22 consecutive patients (9). In fact, in our study, mean plasma vWf levels in patients with bleeding angiodysplasia were higher than in patients with bleeding duodenal ulcer, a finding possibly related to the severe associated ischaemic disease present in most of the patients with bleeding angiodysplasia, as has been the case in previous studies (10). In fact, increased plasma levels of vWf, a reliable marker of endothelial lesion, have been shown to be associated with thromboembolic stroke, coronary heart disease and peripheral ischaemic arterial disease (11). Moreover, such ischaemic processes elicit the expression and secretion of angiogenic factors (12) which, in turn, may stimulate the synthesis of vWf from endothelial cells (13).

Indirect evidence based on the efficacy of antifibrinolytic therapy in patients with gastrointestinal bleeding from angiodysplasia (5,6) suggests that an underlying hyperfibrinolysis may contribute to the haemorrhage from such vascular lesions. As assessed by elevated plasma levels of D-dimer, and t-PA activity, we now show that plasma fibrinolytic activity is indeed increased in patients with bleeding gastrointestinal

angiodysplasia. Plasma hyperfibrinolysis is a feature of diverse conditions associated with recurrent bleeding including hereditary haemorrhagic telangiectasia (14), prostatic carcinoma (15), liver cirrhosis (16), and orthotopic liver transplantation. Hyperfibrinolysis probably motivates or predisposes to haemorrhage since it reduces platelet adhesion and platelet aggregation via degradation of vWf and fibrin platelet receptors (glycoprotein I and IIb-IIIa) (17), thus provoking clot lysis by inducing platelet disaggregation and haemostatic plug disruption (18). Furthermore, clotting activation may be delayed due to consumption clotting factors and inhibition of fibrin polymerization (19). Hyperfibrinolysis can also favour episodes of haemorrhage by activation of enzymes with metalloproteinase activity, which can degrade vessel walls. The extracellular matrix of blood vessels, richly endowed with plasminogen and zymogens including collagenase, stromelysin, and ellastase, exhibits metalloproteinase activity when activated by plasmin and vascular endothelial growth factor (VEGF) (20,21).

All the above mechanisms could be involved in angiodysplasic bleeding, but the precise origin of the hyperfibrinolytic status in angiodysplasia remains unknown. A possible mechanism may have been uncovered by our recent finding of increased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in the endothelium of human colonic angiodysplasia (22), since both angiogenic factors have been shown to stimulate the synthesis and secretion of t-PA and its natural inhibitor, PAI-1 (23).

Although mean plasma levels of PAI-1 in patients with gastrointestinal angiodysplasia were similar to those of controls, PAI-1 levels were significantly lower in

patients with angiodysplasia associated with high bleeding rates in comparison to those

with a low bleeding rate ($p<0.05$). Under normal conditions, functional fibrinolytic activity of t-PA is counterbalanced by its natural inhibitor PAI-1. Thus, our findings are consistent with the hypothesis that a high bleeding tendency in angiodysplasia relates to the inability of low levels of PAI-1 to fully complex the increased t-PA activity.

At this point we can only speculate as to the cause of the lower PAI-1 plasma levels in the subgroup of angiodysplasic patients with high bleeding rates. However, since PAI-1 like vWf, is synthesised by endothelial cells (24), the association of low levels of PAI-1 and increased levels of vWf in patients with angiodysplasia could represent endothelial cell damage. In fact, our results bear some analogy to those reported in diabetic retinopathy, an angiogenic-dependent process, which is also associated with increased fibrinolytic activity, low PAI-1 plasma levels, elevated levels of Von Willebrand factor (24) and increased ocular levels of VEGF (25). Alternatively, reduced PAI-1 levels could be due to diminished synthesis. Shatos et al (26) have shown that t-PA and other plasminogen activators lead to a diminished elaboration of PAI-1 by endothelial cells in a specific manner. This effect is mediated at a level of transcription or in stabilisation of mRNA, and is not influenced by either plasmin or the catalytic site of t-PA (26). This blockade of PAI-1 synthesis in the endothelium exposed to t-PA may render the vessels susceptible to injury and hence haemorrhage into the gut (26). In fact, several studies support the contention that hyperfibrinolysis favours bleeding in cases of vascular injury (27,19). Endothelial vulnerability to proteolytic injury is compounded by established endothelial

damage, a relevant factor since atherosclerotic vascular disease is often associated with angiodysplasia.

Koh et al (28) have also shown that short-term treatment with oral conjugated estrogen, alone or combined with progestagen therapy, reduces PAI-1 levels by approximately 50% and increases plasma levels of D-dimer and t-PA activity in postmenopausal women. However, in our study we detected no differences in any of these parameters between treated or untreated patients with an oral oestrogen-progestagen combination. The presence of male patients in our series and the differences in time of treatment may explain the discrepancy with Koh's study. Furthermore, clotting activation via the extrinsic pathway does not appear to play a role in the recurrent bleeding from gastrointestinal angiodysplasia, since plasma levels of FVIIa-RTF and TFPI were similar in both groups.

In conclusion, as assessed by elevated plasma levels of vWf, D-dimer and t-PA activity, we have shown that patients with bleeding gut angiodysplasia have increased plasma fibrinolytic activity that may contribute to haemorrhage from these common vascular lesions. These findings provide a mechanism for the beneficial effect obtained with antifibrinolytic therapy. A key finding of the present study is the potential value of plasma PAI-1 levels to predict the bleeding risk associated with gastrointestinal angiodysplasia, particularly the light of the finding that other variables such as D-dimer and t-PA, previously associated with gastrointestinal bleeding, were unrelated (29,30). Thus, identification of a subgroup of angiodysplasic patients associated with a high risk of recurrent bleeding may aid the selection of patients for aggressive therapy.

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Table 1. Demographic, clinical and coagulation parameters in gastrointestinal angiodysplasia.

	GASTROINTESTINAL ANGIODYSPLASIA		
	High bleeding rate (>2/yr) n = 5	**Low bleeding rate (≤2/yr) n = 16**	**P**
Age (yrs.)	70 ± 2	68 ± 3	ns
Sex (M/F)	3 / 2	7 / 9	ns
Cardiovascular diseases:	78%	81%	ns
vW (%)	226 ± 14	201 ± 20	ns
D-dimer (ng/mL)	668 ± 91	692 ± 112	ns
t- PA (IU/mL)	1.9 ± 0.3	1.7 ± 0.2	ns
F VIIa-RTF (mU/mL)	42 ± 10	70 ± 8	ns
TFPI (ng/mL)	71 ± 3	70 ± 4	ns
PAI-1	31.5 ± 11	47 ± 14	**p=0.037***

* From multivariate regression analysis.

Legends

Figure 1. Mean plasma vWf levels were higher in the angiodysplasia group than in controls ($p<0.05$).

Figure 2. Mean plasma levels of D-dimer (D-D) and tissue plasminogen activator (t-PA) activity were higher in patients with angiodysplasia than in controls ($p<0.05$) whereas levels of plasminogen activator inhibitor type 1 (PAI-1) were similar in both groups.

Figure 1

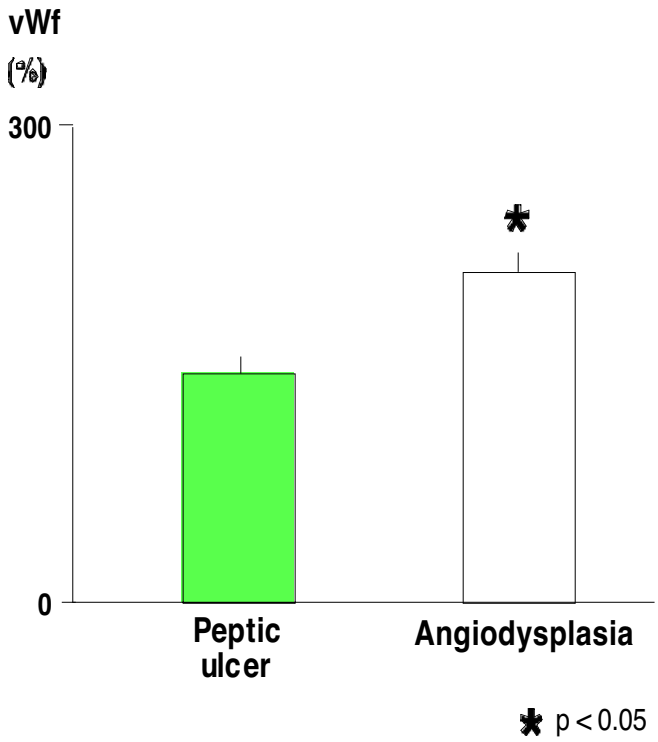
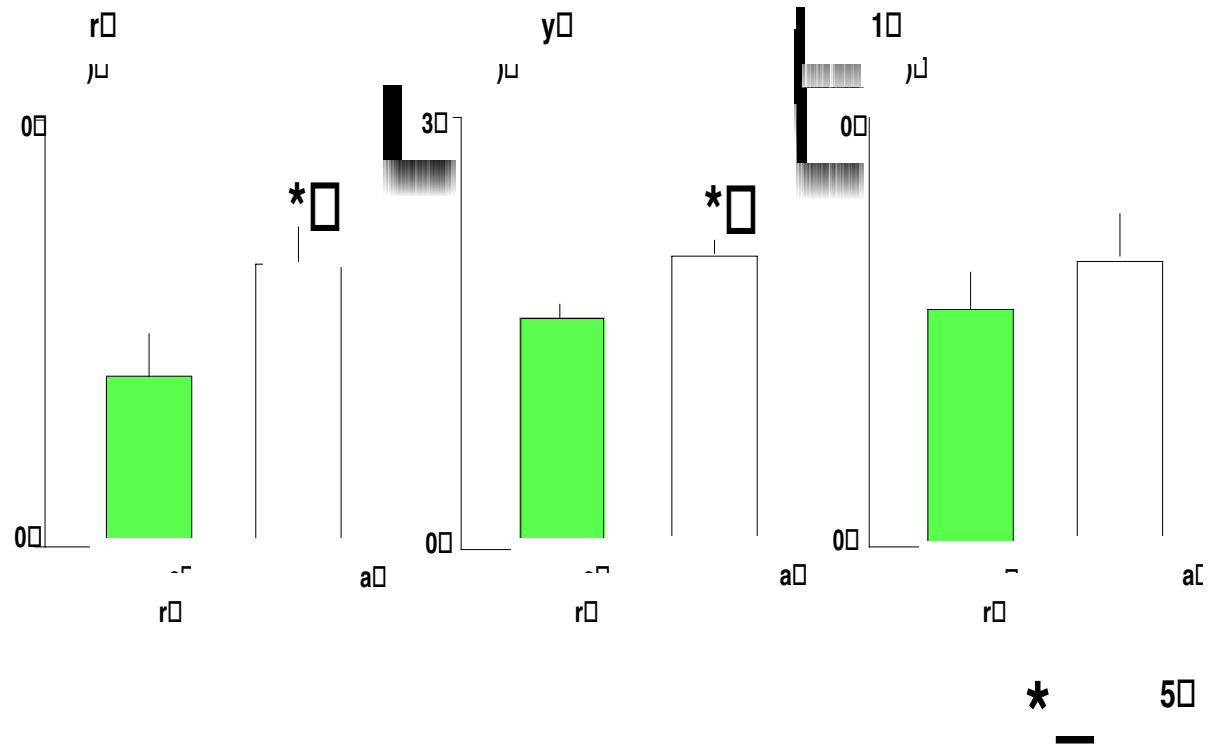


Figure 2



ESTUDIO 4:

A multicenter, randomized, controlled, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia.

Summary

Background: The efficacy of hormonal therapy for recurrent bleeding from gastrointestinal angiodysplasia remains uncertain. The aim of the present study was to investigate the efficacy of long-term estrogen-progestagen therapy in the prevention of rebleeding from gastrointestinal angiodysplasia.

Methods: Seventy-two non-cirrhotic patients bleeding from gastrointestinal angiodysplasia confirmed by endoscopy or angiography were randomized to receive in double-blind conditions treatment with ethinylestradiol (0.01 mg) plus norethisterone (2mg) (1tab./day), or placebo (1 tab./day) for a minimum period of 1 year (range: 1-2 years).

Results: Four patients could not be assessed since they did not attend the first follow-up visit. Failure of treatment occurred in 13 of 33 (39%) patients in the treatment group and in 16 of 35 (45%) patients in the placebo group (p=NS). No significant differences between groups were found according to number of bleeding episodes (0.7 ± 1.0 vs. 0.9 ± 1.5) and transfusional requirements (0.9 ± 1.9 vs. 0.7 ± 1.5 units). The actuarial probability of remaining free of rebleeding at 1 and 2 years of follow-up was 69% and 50% for the treatment group and 55% and 36% for the placebo group (log-rank test, p=0.649). Treatment received was not an independent predictor for rebleeding prevention in the multivariate regression analysis. Two patients in the treatment group and 1 in the placebo group suffered severe adverse events. There were no differences in mortality between the treatment and placebo groups (0 vs. 1 patient, respectively).

Conclusions: Continuous estrogen-progestagen treatment is not useful in the prevention of rebleeding from gastrointestinal angiodysplasia.

INTRODUCTION

Recurrent bleeding from acquired gastrointestinal angiodysplasia in the elderly often represents a therapeutic challenge (1). Surgical or endoscopic therapy have proven useful to arrest bleeding from angiodysplasia, but a high risk of rebleeding has been noticed after both procedures (2-5). Failure of these treatments has been attributed to the difficulty in identifying or treating all lesions, which are diffuse in nature and sometimes inaccessible (6). In such cases, medical therapy with a combination of estrogen-progestagen is considered. The evaluation of hormonal therapy efficacy for the prevention of rebleeding from gastrointestinal angiodysplasia has yielded conflicting results. Several case reports (7-9), uncontrolled studies (10-12) and one randomized clinical trial including a limited number of patients and short follow-up (13), have suggested that this hormonal therapy may be useful in the prevention of recurrent bleeding from gastrointestinal angiodysplasia. In contrast, Lewis et al. (14) found no beneficial effect in a more extensive series of patients in a nonrandomized, unblinded cohort designed study. Thus, we conducted a double-blind randomized clinical trial in non-cirrhotic patients to investigate the efficacy of long-term estrogen-progestagen therapy in the prevention of recurrent bleeding from gastrointestinal angiodysplasia. Cirrhotic patients were not considered since the development of vascular lesions of the gut in patients with portal hypertension, despite a similar endoscopic appearance, involves distinct pathogenic mechanisms (15).

PATIENTS AND METHODS

Three major geographically and socioeconomically comparable teaching hospitals distributed in the center, and northwest of Barcelona and in Tarragona (Spain) participated in this study. The protocol was approved by the hospital ethics committee of each participating center, and by the Spanish health authorities. Written informed consent was obtained from all patients (or their legally representative, when required) enrolled in the study. This study was not sponsored by any external financial sources including pharmaceutical funding, except government research agencies (Fondo de Investigaciones Sanitarias del Ministerio de Sanidad de España).

Study population

From January 1997 to December 1998, consecutive non-cirrhotic patients admitted with acute or chronic gastrointestinal bleeding from angiodysplasia confirmed by endoscopy or angiography , were eligible to enter the study. Angiodysplasia was defined at endoscopy as single or multiple 2-5 mm flat bright red spots, with a round uniform or slightly irregular margins or lesions appearing as raised and reddened areas with a distinctly irregular margin, when larger than 5 mm (16). Endoscopic criteria to define bleeding from angiodysplasia were: active bleeding from angiodysplasia or the presence of angiodysplasia and blood in the digestive tract with no other potential source of GI bleeding. Angiographic criteria to diagnose angiodysplasia were a densely opacified, slowly-emptying, dilated tortuous vein; a vascular tuft; and/or an early filling vein (17). In all patients, extensive diagnostic work-up including X-ray series and helical computed tomographic scans were performed to rule out other potential sources of bleeding. Patients presenting with chronic gastrointestinal bleeding were included

when hematocrit was below 30%, ferritin plasma evels below normal range, and repeated positive fecal occult blood

test documented. Exclusion criteria included: gynecologic neoplasms, thromboembolic disease, severe diseases with short life expectancy, hyperlipoproteinemia associated with other cardiovascular risk factors, sickle cell anemia, chronic intake of anticoagulant drugs, rifampicin and anticonvulsant drugs (interacting with estrogen and progestagen), age under 18, pregnancy and refusal to enter the study.

Randomization and Treatment

Patients who fulfilled inclusion criteria were stratified in two groups according to angiodysplasia location: gastroduodenal (group A) and colonic or diffuse (group B). Each patient was then randomly assigned to receive in a double-blind manner either ethinylestradiol (0.01 mg) plus norethisterone (2mg) (1 tab/24h p.o.) or placebo (1 tab/24h p.o.). Randomization was carried out independently for each participating center in blocks of 4 patients. In patients enrolled with acute bleeding, randomization was performed when the patient was hemodynamically stable and bleeding had stopped. Tablets of ethinylestradiol plus norethisterone and placebo, which were not distinguishable and had the same organoleptic characteristics, were packed, labeled (protocol code) and kindly donated by Schering España, Barcelona.

Patients stayed in hospital for at least one week and, after discharge, were followed as outpatients at 1 month after the bleeding episode. Thereafter, they were followed periodically every three months or whenever necessary if further hemorrhage developed. The following data were recorded at each visit: investigation of acute or chronic bleeding, physical examination,

biochemical and hematological profile, including serum iron, ferritin, transferrin and transferrin saturation, and fecal occult blood test. Possible side effects, with special attention to cardiovascular events such as increased arterial pressure, thromboarterial or thromboembolic disease, gastrointestinal effects including nausea and vomits, urogenital effects such as metrorrhagia, worsening of endometriosis and testicular atrophia, gynecomastia, and central nervous system symptoms such as headache were carefully evaluated throughout the study. In addition, prior to inclusion and annually thereafter women underwent gynecologic examination, mammography and transvaginal ultrasonography to rule out any possible complication from medication.

Treatment compliance was assessed through anamnesis and counting of the tablets. Patients were followed for a minimum period of 1 year (mean follow-up: 412 ± 255 days; range 1-3 years).

The primary endpoint was failure of treatment defined as any episode of acute gastrointestinal bleeding, or chronic gastrointestinal bleeding with positive fecal occult blood test and ferropenic anemia with hematocrit below 26% or hematocrit below 30% despite continuous iron therapy for 6 months. Secondary endpoints were the number of bleeding episodes, transfusional requirements and iron requirements per year, and adverse events and mortality during the study period. Blood transfusion was indicated when hematocrit fell below 26% or hemoglobin levels were below 8.5gr. Iron therapy was given when hematocrit was between 26% and 30%. End of treatment was considered in the following cases: end of study without incident, failure of treatment, major adverse events, or death. Whenever failure of treatment occurred, endoscopic or surgical treatment was indicated to arrest bleeding.

Statistical analysis

Sample size

Calculation of sample size was based on the expected reduction in rebleeding episodes. Assuming that the accumulated risk of rebleeding from angiodysplasia is 60% after two years (18), a total of 78 patients was considered necessary to show an absolute reduction of 30%, with a one-sided alpha error of 0.05 and a beta error of 0.2.

Statistical comparisons

Continuous data are summarized as mean ± standard deviation. Statistical analysis was carried out according to the 'intention-to-treat' analysis. Differences between groups were evaluated by the X^2 test or Fisher's exact test for qualitative variables and Student's t-test for quantitative variables following a normal distribution, or by the Mann-Whitney rank sum test for those who failed the normality test. The 95% confidence intervals were calculated. A p value less than 0.05 was considered statistically significant. The actuarial percentage of patients free of rebleeding from angiodysplasia was calculated by Kaplan-Meier curves and the differences assessed by the Mantel-Haenzel log-rank test.

Multivariate logistic regression analysis was performed to determine which of the following factors would predict rebleeding: age, sex, number of bleeding episodes prior to study entry, cardiac disease, chronic renal failure, cerebrovascular insufficiency, ischemic peripheral arterial disease, treatment with antiplatelet agents and non-steroidal antiinflammatory drugs (NSAIDs), and treatment received (estrogen-progestagen or placebo) during the trial.

Statistical analysis was performed using SAS software, version 6.12, and Sigmastat 2.0 by an external biostatistician group unaware of the treatments administered (triple-blind).

RESULTS

During the study period, 123 patients were eligible for the study at the three participating centers. Fifty-one patients were excluded from the study prior to randomization: 11 for previous intake of estrogen-progestagen treatment, 11 for ongoing treatment with anticoagulant drugs, 3 for a history of deep vein thrombosis, 9 because they underwent immediate right hemicolectomy or arterial embolization on account of massive bleeding, 14 owing to severe associated disease with short life expectancy and 3 because they refused to enter the protocol. Thus, a total of 72 patients were randomized: 34 receiving estrogen-progestagen treatment and 38 placebo. Three patients from the placebo group and one from the estrogen-progestagen group could not be assessed because they did not attend the first follow-up visit and were not included in the final analysis.

At entry both groups were similar regarding age, gender distribution, previous history of bleeding (including number of acute and chronic episodes, transfusional requirements and iron therapy received), presentation of GI bleeding and associated diseases (Table 1). Hematological and biochemical profiles of patients, including hematocrit, mean corpuscular volume, platelets, glucose, urea, creatinine (obtained in the Emergency Room), as well as serum iron, ferritin and transferrin (obtained in patients presenting with chronic gastrointestinal bleeding) and transfusional requirements prior to inclusion were similar in both groups (Table 1). No differences were observed between groups regarding number, location, or diagnostic procedures used to locate angiodysplasia.

Most patients complied with the study protocol and only two patients, one from each group had irregular compliance with protocol medication, defined as medication intake lower than 80% of prescribed tablets. Failure of treatment occurred in 13 of 33 (39%) patients in the

treatment group and in 16 of 35 (46%) in the placebo group (p=NS). The number of bleeding episodes per year was similar in both groups (0.7 ± 1.05 and 0.9 ± 1.5 in treatment and placebo groups, respectively). Similarly no difference was observed in mean transfusions requirements per year (0.9 ± 1.9 vs 0.7 ± 1.5 packed red cells) and iron requirements (197 ± 272 vs 166 ± 267 units). Moreover, no significant differences were found in the response to treatment according to acute (31% vs 38.5% failures in treatment and placebo groups, respectively) or chronic (47% vs 66%) bleeding presentation (Table 2). Distribution of the lesions along the gastrointestinal tract did not influence response to treatment, since failure of treatment in gastroduodenal angiodysplasia occurred in 50% of patients of the treatment group and 57% of the placebo group (p=NS), whereas in colonic and diffuse angiodysplasia failure occurred in 37% of the treatment group and 43% of the placebo group (p=NS).

The actuarial probability of remaining free of rebleeding at 1 and 2 years of follow-up was 69% (CI: 50%-87%) and 50% (CI: 20%-73%) for the treatment group and 55% (CI: 36%-74%) and 36% (CI: 14%-58%) for the placebo group (log-rank test, p= 0. 649) (Figure 1).

Multivariate regression analysis showed the number of bleeding episodes prior to inclusion in the study, but not treatment received during the trial, to be an independent significant predictor of rebleeding (OR:1.71;CI:1.12-2.62)(p=0.013). Chronic renal failure (p=0.094) showed a pronounced trend as a predictive factor, although it did not reach statistical significance. These results were later confirmed by bivariate regression analysis adjusted by treatment in which chronic renal failure (p= 0.033) (OR: 10.5; CI: 1.2-90.8) and, again, previous number of bleeding episodes (p= 0.024) (OR: 1.52; CI: 1.05-2.18) were predictors of rebleeding.

Adverse events

Adverse events occurring during the study period are described in detail in Table 3. The total number of patients who presented adverse events was higher in the treatment group (45%) than in the placebo group (14%) (p=0.007). Metrorrhagia was the commonest adverse event in the treatment group (5 of 17 females, 29%), but was absent in the placebo group (0 of 16 females, 0%)(p=0.044). Major complications were similar in both groups: one patient developed thromboembolic pulmonary disease and another had an episode of stroke in the treatment group, whereas one patient had a thromboembolic pulmonary episode in the placebo group (p=NS). One patient in the placebo group died from ischemic stroke, whereas no deaths occurred in the treatment group during the study period.

DISCUSSION

The results of the present study indicate that oral estrogen-progestagen therapy is not superior to placebo for prevention of rebleeding from gastrointestinal angiodysplasia. Further GI bleeding occurred in 46% of patients on placebo and in 39% of patients treated with the estrogen-progestagen combination. Similarly, hormonal therapy was unable to reduce either transfusional or iron therapy requirements. In addition, multivariate regression analysis ruled out estrogen-progestagen therapy as a predictive factor of rebleeding prevention. Our findings agree with those of a previous cohort study (14), in which prevention of rebleeding from GI angiodysplasia in patients treated with hormonal therapy was similar to that of placebo. In contrast, a number of case reports (7-9) and retrospective uncontrolled studies (10-12) have previously suggested that hormonal therapy effectively prevents recurrent bleeding from angiodysplasia. Our results also contrast with the beneficial effect of hormonal therapy reported by Van Cutsem et al. in a cross-over study (13). However, the variability in natural history of bleeding GI angiodysplasia (6,18,19) and several methodologic problems in all these previous studies, such as selection criteria, the limited number of patients evaluated and short follow-up may have precluded accurate assessment of hormonal therapy efficacy. In fact, in the study by Van Cutsem et al. (13), 50% of the patients included had Rendu-Osler-Weber disease. The pathogenesis of vascular lesions present in Rendu-Osler-Weber disease differs from that of acquired angiodysplasia of the elderly (20), and patients with the former entity might respond differently to estrogen-progestagen therapy (21). Therefore, we have studied a homogeneous group of highly- selected elderly patients with acquired angiodysplasia. Cirrhotic patients were not considered in our study because different

histomorphometric characteristics (22) and distinct pathogenic mechanisms (17) have been reported in the development of vascular lesions of the gut in these patients

Similarly, although the natural history of bleeding from GI angiodysplasia remains to be fully established, it is generally accepted that hemorrhage from AGD is usually intermittent with remissions and recurrences, and very variable non-bleeding periods (6,18,19). This variability in the natural history of bleeding GI angiodysplasia makes difficult to evaluate the efficacy of any treatment in uncontrolled trials or when follow-up is too short.

Another difference with the Van Cutsem et al. study relates to the doses of hormones employed. These authors suggested that the effect of hormonal therapy on prevention of rebleeding from GI angiodysplasia was dose-dependent (23). However, in the present study we observed no beneficial effect, although we used doses double those in the Van Cutsem et al. study.

The use of estrogen-progestagen for the prevention of rebleeding from GI angiodysplasia was supported by earlier clinical and experimental evidence. Previous studies showed that hormonal therapy reduced gastric hyperemia in animal models of portal hypertension (24) or uremia (25), two conditions in which gastrointestinal vascular lesions are common. Other actions of estrogen-progestagen, such as shortening of the bleeding time observed in patients with chronic renal failure (26,27), might also contribute to a hemostatic effect. However, other observations do not support the use of such therapy for the prevention of rebleeding. In fact, Koh et al. recently showed that, in postmenopausal women, short-term therapy with a combination of estrogen and progestagen increases plasma fibrinolytic activity, as shown by elevated plasma levels of D-dimer and tissue plasminogen activator (t-PA) activity (28). Plasma hyperfibrinolysis has been demonstrated in various conditions associated with

recurrent bleeding, including hereditary hemorrhagic telangiectasia (29), prostate cancer (30), liver cirrhosis (31) and bleeding gastrointestinal angiodysplasia (32). In this latter study we showed not only increased plasma levels of D-dimer and t-PA activity, but also that plasma levels of PAI-1, the natural inhibitor of t-PA, were significantly lower in patients with angiodysplasia associated with high frequent bleeding than in those with infrequent bleeding episodes. These findings suggest that a high bleeding tendency in angiodysplasia relates to the inability of low levels of PAI-1 to fully complex the increased t-PA activity.

A major drawback of long-term hormonal therapy with a combination of estrogen-progestagen relates to its many potential adverse events, particularly relevant in the elderly. In our study, the number of patients affected by adverse events was significantly higher in the hormone group (44%). However, adverse events were mainly mild, with metrorrhagia being the commonest, and hormonal treatment was in general well-tolerated. Our findings agree with those of the largest randomized placebo-controlled trial to date (33) that indicates that the effects of estrogen and progestagen on the cardiovascular system are neutral or slightly beneficial. Careful evaluation of these background studies suggests that the short and long-term risks of oral contraceptives on lipids, blood pressure, clotting factors, risk of venous thrombosis, myocardial infarction and stroke reported in the seventies (34) were related to the higher doses used at that time (35).

Our results also provide new insights into the natural history of bleeding gastrointestinal angiodysplasia. Previous retrospective studies (18,19) indicate that hemorrhage is usually intermittent with recurrences in up to 50% of patients within 3 years after the first bleeding episode. In our study the actuarial probability of remaining free of rebleeding after 2 years of follow-up was 55% (CI: 36%-74%) for the treatment group and 36% (CI: 14%-58%)

for the placebo group (log-rank test, p=0.649). In addition, we have now shown that previous number of acute and chronic bleeding episodes and chronic renal failure were found to be predictive factors of further bleeding in the multivariate or bivariate regression analyses. Seven of 8 (87.5%) patients with chronic renal failure presented new bleeding episodes during follow-up, a proportion significantly higher than that observed in patients without renal failure (24/60=40%; p= 0.019). This high rate of rebleeding, previously reported in uremic patients with angiodysplasia (36,37), has been related to platelet dysfunction, use of heparin during hemodialysis and ingestion of aspirin (38). Although rebleeding was also independent of the treatment received in uremic patients, the small number of patients included with this condition precludes drawing a definitive conclusion regarding the possible benefit of estrogen-progestagen therapy in bleeding angiodysplasia in uremia.

In conclusion, hormonal therapy with a combination of estrogen and progestagen is not useful in the prevention of rebleeding from gastrointestinal angiodysplasia. Identification of predictive factors of rebleeding such as a previous history of bleeding and chronic renal failure may help to improve the clinical management of these patients. Further research on other pharmacological alternatives is required for patients with persistent or recurrent bleeding after endoscopic or surgical therapy.

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Figure Legends

Figure 1. Actuarial probability of remaining free of rebleeding in both groups of treatment.

Table 1 . Demographic data

	Placebo group n=38		Treatment group n=34		Statistical analysis
Age		71 ± 11		68 ± 12	ns
Sex (M/F)		20/18		17/17	ns
Acute GI bleeding	28/38	73.7%	17/34	50%	ns
Chronic GI bleeding	10/38	26.3%	17/34	50%	
Hypovolemic shock		3		2	ns*
Number of patients with previous bleeding	24/38	63%	24/34	70.5%	ns
Associated diseases					
Cardiac disease	21/38	55.2%	18/34	52.9%	ns
Chronic renal failure	5/38	13.1%	3/34	8.8%	ns
Coagulopathies	1/38	2.6%	1/34	2.94%	ns
Cerebral vascular insufficiency	6/38	15.7%	6/34	17.6%	ns
Ischemic peripheral arterial disease	7/38	18.4%	1/34	2.94%	ns
Anticoagulant drugs	1/38	2.6%	1/34	2.94%	ns
Antiaggregants	4/38	10.5%	3/34	8.8%	ns
NSAIDs†	11/38	28.9%	5/34	14.7%	ns
Hematologic and iron profile					
Hematocrit (%)		27 ± 5.1		26 ± 7.4	ns
Mean corpuscular volume (fL)		82 ± 9		80 ± 13.2	ns
Platelets (number/μL)		252315 ± 80245		265062 ±107631	ns
Serum iron (μg/dL)‡		19.6 ± 3.5		31 ± 21.7	ns
Transferrin (μg/dL)‡		276 ± 203		347 ± 605	ns

Ferritin (ng/mL)‡	6.6 ± 3.6	13.9 ±10	ns
Transfusional requirements (red pack cells) §	1.76 ± 1.5	1.82 ± 2.15	ns

* Mann-Whitney rank sum test. † NSAID= non-steroidal antiinflammatory drugs. ‡ Analyzed in patients with chronic gastrointestinal bleeding. § before randomization.

Table 2. Therapeutic efficacy of both treatments

	Placebo group		Treatment group		Statistical analysis
Acute and chronic GI bleeding	n=35		n=33		
failure of treatment	16/35	46%	13 /33	39%	ns
Acute GI bleeding	n=26		n=16		
failure of treatment	10/26	38%	5/16	31%	ns
Chronic GI bleeding	n=9		n=17		
failure of treatment	6/9	66%	8/17	47%	ns
Number of bleeding episodes	0.9 ± 1.49		0.7 ± 1.02		ns
Transfusional requirements (red pack cells)	0.7 ± 1.49		0.9 ± 1.9		ns
Iron Units (total)*	166 ± 267		197 ± 272		ns
Major adverse events	1		2		ns
Mortality	1		0		ns
Gastroduodenal AGD†	n=7		n=6		
failure of treatment	4/7	57%	3/6	50%	ns
Colonic AGD†	n=28		n=27		
failure of treatment	12/28	43%	10/27	37%	ns

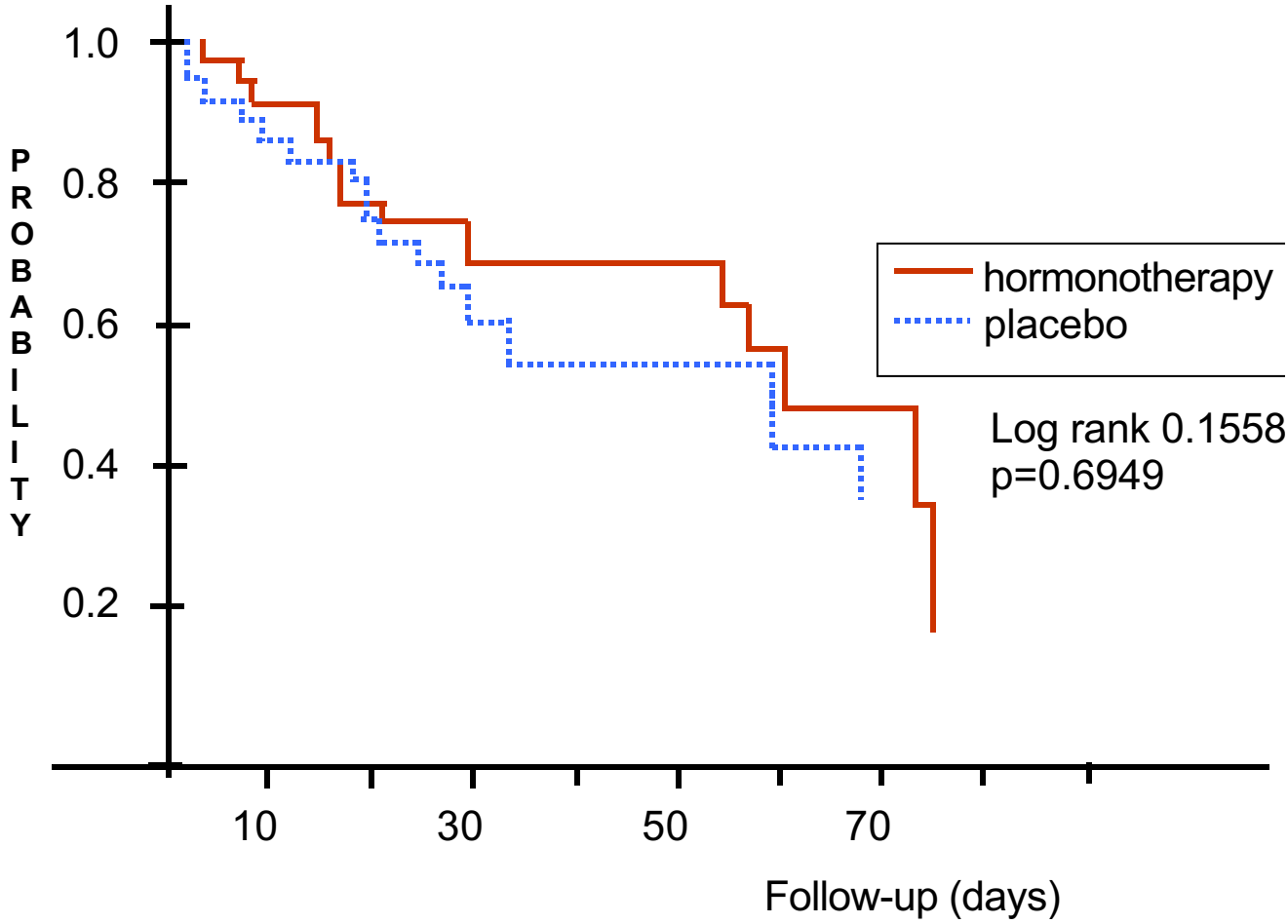
* Iron Units =1 iron unit corresponds to 1 tablet of iron of 525 mg. † AGD=angiodysplasia.

Table 3. Adverse events during the protocol

ADVERSE EVENTS	Placebo group n=35		Treatment group n=33		Statistical analysis
Number of patients	**5/35**	**14%**	**15/33**	**45%**	**p=0.007**
Metrorrhagia	**0/16***	**0%**	**5/17***	**29%**	**p=0.044**
Gynecomastia		0	2/33	6%	ns
Headache	2/35	5.7%	2/33	6%	ns
Dizziness		0	3/33	9%	ns
Pruritus	2/35	5.7%		0	ns
Paresthesia	1/35	2.8%		0	ns
Sleepiness		0	1/33	3%	ns
Capillary angioma	1/35	2.8%	1/33	3%	ns
Hypercholesterolemia	1/35	2.8%	3/33	8.8%	ns
Cholestasis	1/35	2.8%	1/33	3%	ns
Major complications	1/35	2.8%	2/33	6%	ns
Stroke	1/35	2.8%	1/33	3%	ns
Pulmonary embolism		0	1/33	3%	ns

* Calculated in female patients.

Figure 1. Actuarial probability of remaining free of rebleeding in both groups of treatment.



5. DISCUSIÓN

Estudio 1: Increased expression of angiogenic factors in human colonic angiodysplasia.

Los resultados del primer estudio sugieren que la angiogenesis está implicada en la patogénesis de la angiodisplasia de colon humana. Nuestros datos inmunohistoquímicos muestran que estas lesiones vasculares contienen altos niveles de moléculas angiogénicas. Una fuerte inmunoreactividad vascular para el VEGF y el bFGF fue detectada en el 89% y en el 39% de especímenes de los pacientes con angiodisplasia de colon, respectivamente, mientras que una inmunotinción muy limitada se detectó en los vasos sanguíneos del colon normal humano. El fuerte marcaje endotelial para el VEGF observado en vasos sanguíneos angiodisplásicos es similar al reportado previamente en la vascularización aumentada de varios tumores humanos (77-83), de la sinovial inflamada de los pacientes con artritis reumatoide (84), y en malformaciones arteriovenosas cerebrales (85). Nuestro argumento se apoya además en el hallazgo del presente estudio de que el patrón de tinción vascular del VEGF en la angiodisplasia de colon se parece al del cáncer de colon. Asimismo el patrón de tinción vascular para el VEGF y el bFGF observado en la angiodisplasia de colon mimetiza al de los hemangiomas en fase proliferativa (79). Por el contrario,en este último estudio, el patrón de tinción de varios tipos de presumiblemente malformaciones vasculares congénitas, en lactantes y niños era similar al observado a los hemangiomas en fase involutiva (79). Por lo tanto, nuestros hallazgos sugieren que la angiodisplasia de colon del anciano consiste en vasos sanguíneos que proliferan activamente posiblemente bajo el estímulo de factores angiogénicos locales.

En este estudio también detectamos altos niveles del receptor del VEGF, flt-1 pero no del KDR, en el borde endotelial de arterias y venas anómalas, en el 44% de la angiodisplasias de colon humana y en el 12.5% de los especímenes de cáncer de colon. Aunque la contribución biológica de estos dos receptores no es bien conocida, el KDR parece ser el receptor más importante para la trasducción de la actividad mitogénica del VEGF (86). Sin embargo, evidencias recientes indican el flt-1 es el principal receptor en respuesta a la hipoxia (87). El hecho que el receptor del VEGF, el KDR, no se apreciara en vasos sanguíneos angiodisplásicos o tumorales fue inesperado. Brown et al. (77) demostraron anteriormente que los RNA mensajeros que codifican ambos receptores del VEGF estaban significativamente sobreexpresados en las células endoteliales de los vasos sanguíneos del cáncer de colon comparadas con las células endoteliales alejadas del tumor. Por otra parte, en el único estudio inmunohistoquímico hasta la fecha, una tinción positiva para el KDR fue detectada en menos de un tercio de cáncer de colon metastásicos (88). Así, es plausible que nuestros hallazgos puedan estar relacionados con la baja sensibilidad de la inmunohistoquímica para detectar la expresión de la proteína KDR en archivos de tejidos parafinados.

La razón y la fuente celular responsable de los niveles aumentados de moléculas angiogénicas en la angiodisplasia de colon humana es desconocida. El bFGF ha sido localizado en muchos tipos de células normales del colon, incluyendo células endoteliales (89, 90). Asimismo, el VEGF se expresa abundantemente en células tumorales y varios tipos de células normales, tales como células epiteliales, fibroblastos, y células musculares lisas (77, 78, 80, 81, 84, 85). Aunque estudios previos de hibridación in situ no revelaron la expresión del VEGF en células endoteliales (84), más recientemente técnicas de Northern blot y reacción de la polimerasa en

cadena (PCR) han confirmado que copias de RNAm del VEGF se expresan también en cultivos de células endoteliales de varios tejidos, incluyendo células endoteliales del colon humano (92-94). Estos hallazgos indican que la célula endotelial es también una posible fuente de VEGF y por tanto, que los VEGFs actuando de forma paracrina y autocrina pueden participar en la proliferación de células endoteliales.

Concretamente el VEGF es el principal mediador de la angiogénesis inducida por la hipoxia (90,95). En respuesta a condiciones hipóxicas, varias lineas celulares normales regulan al alza intensamente la expresión génica y la proteína del factor de crecimiento endotelial vascular. Además, el VEGF estimula la proliferación in vitro de las células endoteliales microvasculares del colon humana, indicando que este lecho vascular quiescente es capaz de adaptarse a señales angiogénicas (96). Estos hallazgos, junto con la revascularización aumentada de tejidos isquémicos inducida por la administración local o sistémica del VEGF o del bFGF (97,98) sugieren que altos niveles de moléculas angiogénicas en la angiodisplasia humana pueden señalizar la remodelación vascular que restaure un flujo sanguíneo comprometido, en un intento de proteger los tejidos de la isquemia.

En conclusión, un aumento en la expresión de factores angiogénicos en la angiodisplasia de colon humana probablemente juege un papel en la biología de estas frecuentes malformaciones vasculares. Además, el VEGF también ejerce otras acciones directamente sobre las células endoteliales, como la producción de factor tisular o activadores del plasminógeno (99), que pueden incrementar la actividad fibrinolítica local, y contribuir por tanto a su característica tendencia hemorrágica mostrada por estas malformaciones vasculares. Elucidar los mecanismos implicados en el aumento en la expresión de factores angiogénicos puede aumentar nuestra

compresión de la patogénesis de la angiodisplasia de colon humana y, lo que es más importante, proporcionar un lugar potencial de intervención terapeútica para prevenir el sangrado.

Estudio 2: **Accuracy of Computed Tomographic Angiography for the diagnosis of colonic angiodysplasia.**

Los resultados del presente estudio indican que el angioTAC es una herramienta útil en el diagnóstico de la hemorragia digestiva por angiodisplasia de colon. En nuestra opinión, la importancia del angioTAC radica en el hecho de que no es invasiva y que posee una fiabilidad diagnóstica comparable con los otros 2 principales procedimientos diagnósticos. El angioTAC nos ha permitido la visualización de la angiodisplasia en 14 de los 26 pacientes estudiados (56%). El angioTAC pudo demostrar la angiodisplasia de colon en 14 de los 18 (73%) pacientes con angiodisplasia que habán sido detectadas previamente por colonoscopia más arteriografía. Asimismo, el angioTAC pudo diagnosticar el 62.5% de las angiodisplasias diagnosticadas por colonoscopia, pero lo que es más importante, diagnosticó un 50% de las angiodisplasias no visualizadas por colonoscopia. Además este procedimiento detectó el 90% de los casos diagnosticados por arteriografía convencional.

El angioTAC, una aplicación excelente de la tecnología del TAC helicoidal, ocupa actualmente un lugar relevante en la evaluación de muchas lesiones vasculares tales como, la disección aórtica, el aneurisma de la aorta abdominal, las malformaciones arteriovenosas pulmonares, las estenosis de la arteria carótida y de la arteria renal, que antes requerían de la arteriografía convencional para su diagnóstico (100-105). La capacidad del angioTAC para demostrar estas lesiones vasculares radica en que consigue un realce máximo de las estructuras vasculares como consecuencia de los cortes rápidos y continuos del TAC helicoidal, que permite la adquisición de las imágenes en la fase de máxima concentración intravascular del contraste (106,107). Sin embargo, los mayores avances del TAC han venido por la reciente implementación de las técnicas de postprocesamiento como el multiplanar reformatting, shaded

surface display (SSD), proyección de máxima intensidad (MIP), 3D perspectives of surface, y volume rendering (108). Más recientemente la técnica STS-MIP (sliding thin slab maximum intensity projection) ha mejorado la habilidad del TAC para mostrar la morfología de los vasos sanguíneos de pequeños tamaño. Al igual que en estudios previos pulmonares donde el STS-MIP se utilizó para realzar el arbol vascular (109,110), las reconstrucciones del STS-MIP nos ha permitido una visualización de trayectos vasculares más largos que en cortes simples del TAC mediante el procesamiento rápido, directo y sin necesidad de intervención externa, de los datos procedentes de los cortes transaxiales. Así en el presente estudio pudimos observar que el angioTAC no es sólamente capaz de detectar la angiodisplasia de colon, sino que diagnostica algunos casos (9 de 18, 50%) no visualizados por colonoscopia. Ésta última técnica es una herramienta sensible (60-80%) en el diagnóstico de la angiodisplasia de colon, pero está limitado por la hemorragia, que puede ocultar pequeñas lesiones, la hipovolemia (36), y por las fármacos opiáceos (111). Asimismo pequeños traumas del endoscopio como las marcas de succión durante la colonoscopia pueden crear imágenes equívocas (30). En este estudio prospectivo, la colonoscopia tuvo menor sensibilidad (50%) que en estudios retrospectivos anteriores. Ello puede ser debido a que este procedimiento se realizara durante la fase de sangrado activo, pudiendo ser la hemorragia, como se ha comentado antes, responsable de la discrepancia en la sensibilidad con los estudios previos.

Por otra parte el angioTAC localizó la angiodisplasia de colon en el 90% de los casos diagnosticados previamente por angiografía. Por lo tanto en esta serie no seleccionada de pacientes ancianos con hemorragia digestiva por angiodisplasia de colon, un angioTAC podría haber obviado un arteriografía invasiva en la mayoría de los casos. Además el angioTAC es bien tolerado y es un procedimiento disponible en la mayoría de los centros hospitalarios. Otras

ventajas adicionales de esta técnica incluyen: un riesgo disminuido de fallo renal, que se relaciona con la menor cantidad de contraste que se inyecta endovenosamente en comparación con la arteriografía, y por otra parte, evita las complicaciones locales de la arteriografía tales como el hematoma femoral o la disección arterial.

En un estudio previo, Ettore et al. utilizando un protocolo que consistía en la realización de TAC helicoidal del abdomen tras una arteriografía convencional, conseguía localizar diferentes causa del sangrado digestivo oculto incluyendo la angiodisplasia (112). Aunque esta técnica combinada es más rápida que la arteriografía convencional, presenta como inconveniente más importante la no despreciable morbimortalidad inherente a la arteriografía.

La disponibilidad de un angioTAC no invasivo, como procedimiento diagnóstico alternativo a la arteriografía merece una consideración especial, ya que la arteriografía convencional es una prueba invasiva, que se realiza en personas ancianos que han tenido episodios repetidos de sangrado digestivo y que a menudo presentan importantes enfermedades asociadas (estenosis aórtica, enfermedad coronaria, insuficiencia renal crónica etc). Todo ello implica numerosas hospitalizaciones, que frecuentemente conllevan repetición de pruebas diagnósticas hasta la confirmación diagnóstica, un fuerte impacto en la calidad de vida de estos pacientes, y un alto coste socioeconómico. El angioTAC es bien tolerado, más seguro y más barato que la arteriografía convencional, y su amplia aplicación consigue una reducción del tiempo utilizado por el personal sanitario (113) y una reducción de las radiación tanto del paciente como del personal sanitario (114). Otras ventajas del angioTAC incluyen su simplicidad, su aplicabilidad (93% de los pacientes en nuestro estudio) y su rapidez. Además el angioTAC proporciona una importante información adicional descartando el cáncer de colon o colitis (115), evitando posiblemente los falsos positivos de la angiografía en los casos en los que la

hipervascularización del cáncer de colon mimetiza la angiodisplasia (116). Por tanto el angioTAC puede ser una alternativa diagnóstica apropiada en la evaluación de la hemorragia digestiva baja cuando la endoscopia no consigue establecer el diagnóstico, evitando una arteriografía invasiva.

Aunque la prevalencia así como la historia natural de la angiodisplasia de colon en la población general no se conoce con exactitud, estas lesiones vasculares frecuentemente no sangran (7,28,14). Por tanto, la localización incidental de angiodisplasia de colon por angioTAC por otros motivos distintos de la hemorragia no requiere ninguna maniobra diagnóstica o terapeútica adicional (5).

El principal inconveniente del angioTAC podría estar relacionado con el hecho de que sólo permite la exploración dinámica de areas seleccionadas. Sin embargo este inconveniente es minimizado por el hecho que la angiodisplasia se localiza en el ciego o colon derecho en el 80-100% de los casos (3, 117), siendo esta última localización el origen del 70% de los casos de hemorragia masiva en el anciano (118). Otra limitación de esta técnica es su incapacidad para demostrar sangrado activo y distinguir entre angiodisplasia sangrante y no sangrante. Ello es debido a que la detección de hemorragia por angiodisplasia mediante el angioTAC requiere la inyección directa de contraste directamente en la arteria mesentérica (112), lo que indica que el flujo sanguíneo que se necesita para detectarse por angioTAC es similar al de la angiografía convencional. De hecho en la práctica clínica, la detección de hemorragia activa por angiodisplasia sólo se demuestra entre el 6% y el 20% de los casos por colonoscopia o arteriografía (30,24). Finalmente el hecho de que el angioTAC carezca de potencial terapeútico hace que en ocasiones sean necesarios otros métodos hemostáticos como la endoscopia o la arteriografía.

En conclusión, nuestros resultados demuestran la habilidad del angioTAC para mostrar con exactitud la morfología aberrante de estas frecuentes lesiones vasculares, proporcionando un

diagnóstico fiable. Este procedimiento diagnóstico es seguro, bien tolerado, mínimamente invasivo y ampliamente disponible. Por lo tanto puede ser un alternativa diagnóstica apropiada cuando la endoscopia no consigue establecer el diagnóstico, evitando una arteriografía invasiva. Este hallazgo aumenta el potencial diagnóstico del angioTAC a el punto que puede convertirse en la técnica de elección en el diagnóstico de la hemorragia digestiva de origen oscuro. Sin embargo, son necesarios estudios comparativos prospectivos con otras técnicas de imagen digestiva para establecer el papel definitivo del angioTAC en la evaluación de las lesiones vasculares del intestino.

Estudio 3: **Increased plasma fibrinolytic activity in bleeding gastrointestinal angiodysplasia.**

Los resultados del presente estudio muestran cambios característicos en los parámetros de coagulación de los pacientes con hemorragia digestiva por angiodisplasia. Estos pacientes presentan un aumento en la actividad fibrinolítica plasmática como se demuestra por el aumento en los niveles de D-dímero y en la actividad t-PA. Además, bajos niveles plasmáticos de PAI-1 pueden constituir un factor de riesgo de recidiva hemorrágica en pacientes con angiodisplasia.

Varios trastornos de la hemostasia, en particular la enfermedad de von Willebrand han sido implicados en la tendencia hemorrágica de estas lesiones vasculares (119,120). Sin embargo en nuestra serie, y de acuerdo con otra serie prospectiva de 22 pacientes consecutivos, ningun paciente fue diagnosticado de enfermedad de von Willebrand (121). De hecho, en nuestro estudio la media de los niveles plasmáticos del factor de von Willebrand fue superior a la de los pacientes con hemorragia digestiva por ulcus péptico. Este hecho probablemente esté relacionado con las enfermedades isquémicas asociadas que están presentes en la mayoría de los pacientes con hemorragia por angiodisplasia, como ha sido demostrado en estudios previos (14). De hecho, el aumento en los niveles plasmáticos del factor de von Willebrand, un marcador fiable de lesión endotelial, está asociado a accidente cerebrovascular tromboembólico, enfermedad isquémica coronaria, y arteriopatía periférica obstructiva (122). Además dichos procesos isquémicos, estimulan la síntesis de factores angiogénicos (96), que a su vez pueden estimular la síntesis del factor de von Willebrand por las células endoteliales (123).

Evidencias indirectas basadas en la eficacia del tratamiento antifibrinolítico en pacientes con hemorragia digestiva por angiodisplasia (11,65), sugieren que una hiperfibrinolisis subyacente puede contribuir a la hemorragia por estas lesiones vasculares. Nosotros ahora mostramos como estos pacientes presentan un aumento en la actividad fibrinolítica plasmática como se demuestra por el aumento de los niveles plasmáticos de D-dímero y en el aumento en la actividad plasmática t-PA. Esta hiperfibrinolisis plasmática es una característica de una serie de procesos como la telangiectasia hereditaria hemorrágica (65), el carcinoma de próstata (124), la cirrosis hepática (125) y el trasplante ortotópico de higado que tienen como denominador común la hemorragia recidivante. La hiperfibrinolisis probablemente causa o predispone a la hemorragia ya que reduce la adhesión y la agregación plaquetaria via degradación del factor de von Willebrand y de los receptores de fibrina de las plaquetas (glicoproteína I y IIb-IIIa) (126) provocando asíla lisis del coágulo por desagregación plaquetaria y ruptura del tapón hemostático (127). Aunmás, puede provocar un retraso en la activación de la coagulación debido al consumo de los factores de coagulación y a la inhibición de la polimerización de la fibrina (128). La hiperfibrinolisis puede también favorecer los episodios hemorrágicos mediante la activación de enzimas con actividad metaloproteinasa que pueden degradar la pared vascular. La matriz extracelular de los sanguíneos esta provista de abundante plasminógeno y zimógenos como la colagenasa, la estromelisina y la elastasa los cuales exhiben actividad metaloproteinasa cuando son activadas por el VEGF (factor de crecimiento endotelial vascular) y la plasmina (129,130).

Todos los mecanismos expuestos podrían estar implicados en la hemorragia por angiodisplasia pero el origen exacto del estado de hiperfibrinolisis en la angiodisplasia es desconocido. Una posible explicación podría derivarse del reciente hallazgo del aumento en la

expresión de los factores de crecimiento endotelial vascular (VEGF) y del factor de crecimiento fibroblástico básico (bFGF) en el endotelio de la angiodisplasia de colon humana (131). Ambos factores han demostrado su capacidad de estimular la síntesis y secreción de t-PA y su inhibidor natural, el PAI-1 (99).

Aunque los niveles plasmáticos del PAI-1 en pacientes con angiodisplasia gastrointestinal fueron similares a los controles, los niveles de PAI eran significativamente más bajos en los pacientes angiodisplásicos con alta tasa hemorrágica, en comparación con los de baja tasa hemorrágica ($p<0.05$). En condiciones normales la actividad fibrinolítica del t-PA está equilibrada por su inhibidor natural, el PAI-1. Por tanto nuestros hallazgos apoyan la hipótesis de que la alta tendencia hemorrágica en la angiodisplasia se debe a la imposibilidad de que bajos niveles de PAI-1 acomplejen completamente el aumento en la actividad t-PA.

En este punto sólamente podemos especular sobre la causa de los bajos niveles de PAI-1 en un subgrupo de pacientes con angiodisplasia con más altas tasa de sangrado. Sin embargo el hecho de que el PAI-1, al igual que el factor de von Willebrand (vWf), sea sintetizado por las células endoteliales (133), sugiere que la asociación de bajos niveles de PAI-1 y niveles elevados de vWf en pacientes con angiodisplasia podría ser el resultado de daño celular endotelial. De hecho nuestros resultados están en analogía con los datos reportados en la retinopatía diabética, un proceso angiogénico dependiente que se asocia a un aumento en la actividad fibrinolítica, bajos niveles plasmáticos de PAI-1, elevados niveles de factor de von Willebrand (133), y niveles aumentados de VEGF (134).

De forma alternativa, los niveles reducidos de PAI-1 podría ser debidos a una disminución en su síntesis. Shatos et al. han demostrado que el t-PA y otros activadores del plasminógeno conducen a una disminución en la elaboración del PAI-1 por las células

endoteliales de forma específica. Este efecto es mediado al nivel de transcripción o en la estabilización del ARN mensajero, y no está influido por la plasmina o el sitio catalítico del t-PA (135). El bloqueo en la síntesis de PAI-1 deja al endotelio expuesto a la acción del t-PA, puede hacer a los vasos susceptibles al daño y tener como consecuencia la hemorragia digestiva (135). De hecho varios estudios apoyan el argumento que la hiperfibrinolisis favorece el sangrado en caso de daño vascular (136,129). Esta vulnerabilidad endotelial al daño proteolítico aumenta cuando existe un daño endotelial establecido, siendo este hecho un factor relevante dado que la enfermedad aterosclerótica vascular se asocia con frecuencia a la angiodisplasia.

Koh y colaboradores (137) también han demostrado que el tratamiento a corto plazo con un estrogeno conjugado oral o combinado con un progestágeno reduce los niveles de PAI-1 aproximadamente al 50% y aumenta los niveles plasmáticos de D-dímero y la actividad t-PA en mujeres postmenopáusicas. Sin embargo en nuestro estudio no detectamos diferencias en ninguno de estos parámetros entre los pacientes tratados y no tratados con una combinación de estrógenos y progestágenos. La presencia de pacientes varones en nuestra serie y la diferencia en el tiempo de tratamiento pueden explicar las diferencias con el estudio de Koh. Asimismo la activación de la coagulación por la vía extrínseca no parece jugar un papel en la recidiva hemorrágica de la angiodisplasia gastrointestinal, pues los niveles plasmáticos de FVIIa-RTF y TFPI fueron similares en ambos grupos.

En conclusión nosotros hemos mostrado que los pacientes con hemorragia digestiva por angiodisplasia presentan un aumento en la actividad fibrinolítica plasmática que puede contribuir al sangrado de estas lesiones vasculares. Estos hallazgos proporcionan el mecanismo que explicaría el efecto beneficioso del tratamiento antifibrinolítico. Otro hallazgo importante de

este estudio es el valor de los niveles de PAI-1 como factor predictivo de riesgo hemorrágico asociado a la angiodisplasia gastrointestinal. Este hecho es especialmente remarcable pues otras variables como el D-dímero y el t-PA que se habían descrito previamente como factores predictivos de hemorragia (138,139) no tuvieron valor pronóstico. Asimismo la identificación de un subgrupo de pacientes con angiodisplasia de alto riesgo hemorrágico puede ayudar a la selección de pacientes que requieran un abordaje terapeútico más invasivo.

Estudio 4: **A multicenter, randomized, controlled, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia.**

Los resultados del presente estudio indican que el tratamiento con una combinación oral de estrógenos y progestágenos no es superior al placebo en la prevención de la recidiva hemorrágica por angiodisplasia. Este tratamiento hormonal no consiguió reducir los requerimientos trasfusionales ni de hierro y causó más efectos adversos. Además el analisis de regresión multivariado descartó al tratamiento hormonal como factor predictivo en la prevención de la recidiva hemorrágica.

Casos aislados (140-142), series retrospectivas (4,143,144) y un único estudio controlado con un número limitado de pacientes y seguimiento a corto plazo (58), habán convertido al tratamiento hormonal en una alternativa prometedora al tratamiento quirúrgico o endoscópico en la prevención de la recidiva hemorrágica por angiodisplasia (145). Sin embargo todos estos estudios se enfrentaban con una historia natural de la angiodisplasia poco conocida, en la cual la presentación de la hemorragia puede ser intermitente, con periodos libres de hemorragia muy variables (5,8). Esta variabilidad en la historia natural de la enfermedad puede dificultar la evaluación de cualquier tratamiento cuando el ensayo clínico no es controlado, o cuando el seguimiento no es prolongado. Bajo estas premisas nosotros realizamos este ensayo clinico multicéntrico y doble ciego con el objetivo de evaluar la eficacia a largo plazo del tratamiento hormonal en la prevención de la recidiva hemorrágica por angiodisplasia.

Nosotros observamos prevención de la hemorragia en el 60% de los pacientes con tratamiento hormonal y en el 54% de los tratados con placebo. Estos resultados son similares

a los obtenidos por Lewis y colaboradores (59) en un estudio de cohortes donde la prevención del resangrado fue similar en los pacientes en tratamiento hormonal y los tratados con placebo (50% vs 44% respectivamente). Por otra parte nuestros resultados contrastan con el efecto beneficioso del tratamiento hormonal comunicado por Van Cutsem y colaboradores en un estudio cruzado (58). Sin embargo, los criterios de selección empleados, el escaso número de pacientes incluidos,y el seguimiento a corto plazo (6 meses en cada tratamiento) pueden explicar las diferencias. Asíen el estudio de Van Cutsem et al. el 50% de los pacientes tenían enfermedad de Rendu-Osler-Weber, una entidad en la cual la patogenia de las lesiones vasculares es diferente de la angiodisplasia adquirida del anciano (146), y que probablemente presente una respuesta diferente al tratamiento hormonal (63). Consecuentemente nosotros realizamos el estudio en una población homogénea de pacientes ancianos con angiodisplasia adquirida. Los pacientes cirróticos no fueron incluidos en nuestro estudio porque las lesiones vasculares que desarrollan estos pacientes tiene distintos mecanismos patogénicos (147) y distintas características histomorfométricas (148).

Otra diferencia con el estudio de Van Cutsem está en relación con la dosis empleada. De hecho estos autores sugirieron que el efecto del tratamiento hormonal en la prevención de la recidiva hemorrágica era dosis dependiente (149). Sin embargo, en el presente estudio no observamos un efecto beneficioso utilizando una dosis doble que en el estudio de Van Cutsem.

La razón de la utilización del tratamiento hormonal en la prevención de la recidiva hemorrágica se apoyaba en datos clínicos y experimentales. Estudios previos demostraron que el tratamiento hormonal reducía la hiperemia gástrica en 2 modelos experimentales de hipertensión portal (54) y de uremia (150), dos entidades en las que las angiodisplasias son comunes.

Otras acciones del tratamiento hormonal como la disminución del tiempo de sangría observadas en pacientes con insuficiencia renal crónica (56,57) podría contribuir a su efecto hemostático. Sin embargo, otras observaciones no apoyan el uso del del tratamiento hormonal en la prevención de la recidiva hemorrágica. Así recientemente Koh y colaboradores han demostrado que el tratamiento a corto plazo con un estrogeno conjugado oral o combinado con un progestágeno produce un aumento de la actividad fibrinolítica como se demuestra con el aumenta los niveles plasmáticos de D-dímero y de la actividad t-PA (137). Esta hiperfibrinolisis plasmática es una característica de una serie de procesos como la enfermedad de Rendu-Osler-Weber (124), el carcinoma de próstata (125), la cirrosis hepática (126,139) y la angiodisplasia gastrointestinal (151) que se asocian a hemorragias recidivantes.

Uno de los principales inconvenientes del tratamiento a largo plazo del tratamiento con estrógenos-progestágenos esta relacionado con sus múltiples y potenciales efectos adversos que podrían haber limitado su uso,en especial en el anciano. De hecho, en nuestro estudio los efectos adversos fueron superiores en el grupo de tratamiento hormonal alcanzado el 44%. Sin embargo el tratamiento hormonal fue bien tolerado ya que los acontecimientos adversos fueron en general leves, siendo la metrorragia el efecto adverso más común. Estos resultados concuerdan con el ensayo clínico randomizado controlado con placebo que incluyó el número más importante de pacientes hasta la fecha (152), en el que se concluyó que los efectos de los estrógenos y progestágenos sobre el sistema cardiovascular son neutrales o ligeramente beneficiosos. De la evaluación conjunta de estos estudios se extrae la conclusión que los efectos a corto y a largo plazo del tratamiento hormonal sobre los lípidos, la presión arterial, factores de coagulación, riesgo de trombosis venosa, infarto de miocardio y accidentes cerebrovasculares reportados en la

decada de los 70 (153) estaban relacionados con las dosis más altas utilizadas durante ese periodo (154).

Nuestro estudio también aporta nuevos aspectos sobre la historia natural de la angiodisplasia gastrointestinal. La historia natural de esta enfermedad no es bien conocida, y está basada en estudios retrospectivos que indican que tras un primer episodio hemorrágico ésta sigue un curso crónico recidivante que afecta hasta el 50% de los pacientes en los 3 primeros años tras el sangrado inicial (5,8). En nuestro estudio prospectivo, la probabilidad acturial de permanecer libre de sangrado despues de 2 años de seguimiento fue del 55% (IC: 36%-74%) en el grupo de tratramiento hormonal y 36% del grupo placebo (IC:14%-58%)(log-rank test, p=0.649). Además nosotros hemos demostrado que el número previo de hemorragias digestivas y la insuficiencia renal crónica son factores predictivos de recidiva hemorrágica en un análisis de regresión multi o bivariado. Siete de 8 pacientes (87.5%) con insuficiencia renal crónica presentaron nuevos episodios hemorrágicos durante el seguimiento, una proporción significativamente más alta que la observada en los pacientes sin insuficiencia renal (24/60= 40%; p=0.019). Está mayor tendencia hemorrágica en pacientes con insuficiencia renal crónica y angiodisplasia (155,156), se relaciona con la disfunción plaquetaria, el uso de heparina durante la hemodiálisis y la toma de aspirina (38). Aunque en estos pacientes con insuficiencia renal crónica el resangrado fue independiente del tratamiento recibido, el escaso número de pacientes con esta patología incluidos en este estudio nos impide sacar una conclusión definitiva sobre el posible efecto beneficioso del tratamiento hormonal en este subgrupo específico de pacientes.

En conclusión el tratamiento continuado con una combinación oral de estrógenos y progestágenos no es útil en la prevención de la recidiva hemorrágica por angiodisplasia. La

identificación de factores predictivos específicos de resangrado como la historia previa de hemorragia digestiva y la insuficiencia renal crónica puede ayudar a mejorar el manejo de estos pacientes. Finalmente será necesario la investigación de otras alternativas farmacológicas que puedan prevenir la hemorragia por angiodisplasia en especial cuando ocurre tras el tratamiento endoscópico o quirúrgico.

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