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Endovascular Management of Haemodialysis Vascular Access Complications

Manejo Endovascular de Complicaciones en el Acceso Vascular de Hemodiálisis

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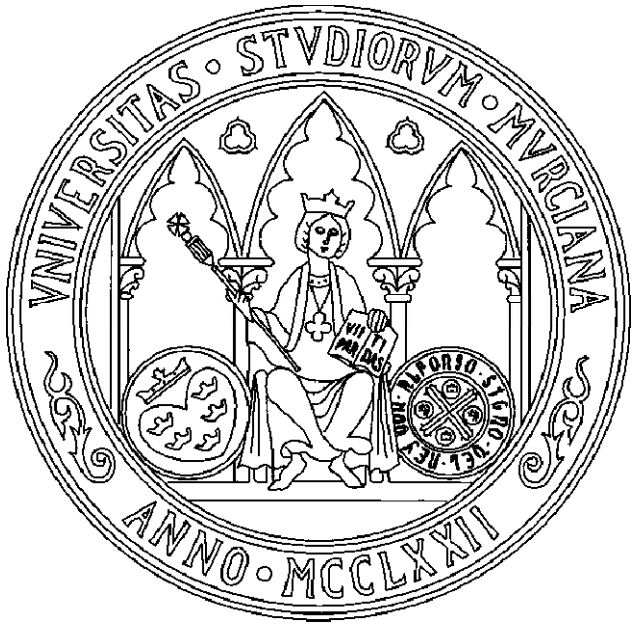

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DOCTORAL DISSERTATION/TESIS DOCTORAL

Endovascular management of haemodialysis vascular access complications

Manejo endovascular de complicaciones en el acceso vascular de hemodiálisis

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Abbreviations

AVF: Arteriovenous fistula

AVG: Arteriovenous graft

CE: Catheter exchange

CKD: Chronic kidney disease

DOPPS: Dialysis Outcomes and Practice Patterns Study

ESRD: End-stage renal disease

ESVS: European Society for Vascular Surgery

FSA: Fibrin sheath angioplasty

GFR: Glomerular filtration rate

HCVC: Haemodialysis central venous catheter

KDOQI: Kidney Disease Outcomes Quality Initiative

PE: Physical examination

RRT: Renal replacement therapies

VA: Vascular access

VRU: Vascular Radiology Unit

Abstract

Background. Over two million people worldwide currently receive renal replacement therapy for end-stage renal disease. Haemodialysis is the most common treatment option, and a well-functioning vascular access (VA) is essential for efficient haemodialysis therapy. The three main types of VA are the arteriovenous fistula (AVF), the AV graft (AVG) and the haemodialysis central venous catheter (HCVC). The AVF is generally the preferred option, but this is not free of complications, and the HCVC may be the only VA option for some patients. As the appearance of VA complications are a main cause of morbimortality in these patients, a comprehensive management of these complications is essential in order to preserve the patient's lifeline. The research aim of this thesis was to analyse the endovascular management of complications in VA for chronic haemodialysis among patients attending a vascular radiology unit (VRU). Specifically, the research analysed performance of physical examination (PE) to detect AVF stenosis, the stent graft utility for treatment of thrombosed aneurysm and residual thrombi in AVF, and compared two endovascular techniques for managing HCVC dysfunction.

Methods. The dissertation comprised three studies of consecutive patients attending the VRU at Reina Sofía University General Hospital in Murcia, Spain, for VA examination between January 2004 and December 2016. The first study used a cross-sectional approach to analyse the performance of PE to detect AVF stenosis in 99 patients between January and March 2015. PE and ultrasonography (the "gold-standard") were blind-performed by different radiologists, and sensitivity, specificity, positive predictive value (PPV) negative predictive value (NPV) value, likelihood ratios (LR) and Cohen's κ value were measured. A second study between January 2004 and December 2016 used a retrospective design to assess the utility of stent grafts as a treatment of thrombosed aneurysm and residual wall-adherent thrombi in AVF by analysing post-

intervention primary patency rates using the Kaplan-Meier log-rank test. Multivariate Cox proportional regression models were performed to determine whether cannulation within the stent graft area was a potential risk factor for occlusion in terms of adjusted hazard ratio (HR). Finally, the third study, comparing catheter exchange (CE) and CE + fibrin sheath angioplasty (FSA) as endovascular techniques for managing dysfunctional tunnelled HCVC, was performed retrospectively and involved 107 patients from August 2005 to December 2016. Kaplan-Meier log-rank test and multivariate Cox regression analyses were performed to determine primary patency rates and risk of obstruction according to type of endovascular procedure.

Results. In the first study, ultrasonography revealed the presence of stenosis in 57 patients (58%) while PE identified 61 cases (62%). For diagnosis of AVF stenosis, PE achieved 82% sensitivity, 67% specificity, 77% PPV, 74% NPV, 2.74 LR+ and 0.26 LR-. There was moderate agreement beyond chance between PE and ultrasonography ($\kappa = 0.5$). The analysis of stent deployment was based on a sample of 27 procedures. At 3, 6, 12, 24, 36 and 72 months after stent deployment, respective primary patency rates (%) were 59, 32, 32, 21, 11 and 5; stent puncture rates were 53, 21, 21, 16, 5 and 0; and no stent puncture rates were 80, 80, 80, 40, 40 and 40. Multivariate analysis showed that cannulation through the stent graft was not significantly associated with increased risk of obstruction (HR = 3.01; P = 0.286). In the third analysis, 73 of 107 patients (68.2%) underwent CE, and 34 of 107 (31.8%) underwent CE + FSA. At 3, 6, 12, 24 and 36 month follow-up after endovascular procedures, primary patency rates (%) were 75, 75, 65, 65 and 65 in the CE + FSA group and 70, 65, 62, 30 and 0 in the CE group. In the adjusted model, endovascular procedure was unrelated to risk of obstruction (HR = 1.34; P = 0.515).

Conclusions. PE for the detection of AVF stenosis exhibited moderate accuracy. In the absence of ultrasonography, haemodialysis units can use PE to optimize VA survival, and professionals

should improve their basic skills. For partially thrombosed aneurysms and residual thrombi in AVF, stent graft treatment may be a feasible procedure. Although fistulas punctured through the stent exhibited lower patency rates, this practice was not associated with higher risk of obstruction. In relation to dysfunctional HCVC, our findings suggested that CE and CE+FSA approaches were equivalent in terms of patency and safety results, and other aspects such as cost assessment, expertise and physician's preference should therefore be considered when choosing one or other technique.

Resumen

Introducción

La enfermedad renal crónica representa un problema de salud pública que afecta al 10% de la población mundial, estado asociada a una alta morbimortalidad. Actualmente, alrededor de 2 millones de personas reciben tratamiento renal sustitutivo para su enfermedad renal terminal, siendo la hemodiálisis la modalidad de tratamiento más frecuente. El funcionamiento correcto del acceso vascular es esencial para la realización de una hemodiálisis eficiente. Hay tres tipos principales de acceso vascular, la fistula arteriovenosa nativa, la fístula arteriovenosa protésica y el catéter venoso central de hemodiálisis. La fistula arteriovenosa nativa es la opción preferida, aunque no está exenta de complicaciones, mientras que el uso del catéter venoso central de hemodiálisis representa la única opción para algunos pacientes. La aparición de complicaciones en el acceso vascular es la principal causa de morbimortalidad de estos pacientes. Es por ello que un manejo integral de las complicaciones del acceso vascular es crucial para preservar la línea de vida del paciente.

La estenosis es la complicación más frecuente en pacientes con fístulas arteriovenosas nativas y protésicas. El diagnóstico y tratamiento tardío puede resultar en la pérdida del acceso vascular, requiriendo la realización de técnicas menos eficientes. La monitorización y vigilancia del acceso vascular puede mejorar la supervivencia y funcionalidad del mismo. La exploración física puede constituir un método accesible y de bajo coste para evaluar el diagnóstico temprano de la estenosis en fístula arteriovenosa nativa. Sin embargo, a pesar del creciente potencial de esta técnica para la evaluación de acceso disfuncional, la literatura previa en relación a su rendimiento como una herramienta diagnóstica para detectar estenosis en fístulas nativas es escasa.

Las complicaciones del acceso vascular pueden requerir de la realización de un tratamiento adecuado mediante técnicas quirúrgicas o procedimientos endovasculares, entre los que se encuentran la angioplastia transluminal percutánea, la implantación de stents y el recambio de catéteres. La inserción de stents constituye una opción terapéutica para preservar la funcionalidad de las fístulas arteriovenosas nativas en casos seleccionados. Los stents recubiertos pueden proporcionar un soporte endoluminal que mantiene la permeabilidad de la pared del vaso además de servir como barrera biocompatible para prevenir el crecimiento celular, pudiendo evitar la migración de coágulos y posibles retrombosis en el vaso. Por lo tanto, el stent cubierto podría ser útil en el tratamiento de los aneurismas parcialmente trombosados y del trombo residual adherido a la pared. Sin embargo, aunque estas lesiones no están incluidas entre las indicaciones del uso de los stents, en la actualidad no hay suficientes estudios para determinar el potencial del stent recubierto es estos escenarios clínicos.

La formación de la vaina de fibrina es una de las complicaciones más frecuentes relacionadas con la disfunción del catéter venoso central de hemodiálisis. El recambio del catéter con la angioplastia de la vaina de fibrina representa una opción terapéutica para el manejo de los catéteres disfuncionantes. Sin embargo, no hay evidencia actual para determinar si este abordaje puede ser más efectivo para preservar la permeabilidad del acceso en comparación con la realización sólo del recambio del catéter.

El objetivo general de esta tesis fue analizar el manejo endovascular de complicaciones en el acceso vascular de hemodiálisis crónica en pacientes que acuden a una Unidad de Radiología Vascular. Específicamente, se analizó el rendimiento de la exploración física en la detección de la estenosis en pacientes con fistula arteriovenosa nativa, la utilidad del stent cubierto como tratamiento de aneurismas parcialmente trombosados y trombo residual en fistula arteriovenosa

nativa, y la comparación de dos técnicas endovasculares para el tratamiento de la disfunción del catéter venoso central de hemodiálisis.

Métodos

Esta tesis fue desarrollada en tres trabajos que incluyeron pacientes que acudieron de forma consecutiva a la Unidad de Radiología Vascular del Hospital General Universitario Reina Sofía (Murcia, España) entre enero 2004 y diciembre 2016 para la revisión de su acceso vascular. El primer trabajo analizó el rendimiento de la exploración física para detectar estenosis en fistula arteriovenosa nativa. Se realizó un estudio transversal con un total de 99 pacientes que acudieron a la consulta entre enero y marzo de 2015. La exploración física y la ecografía (patrón de referencia) fueron realizadas a ciegas por distintos radiólogos. Los datos registrados incluyeron las características de los pacientes, comorbilidades, información del acceso vascular, motivo de consulta y los resultados de la exploración física y de la ecografía. El rendimiento de las pruebas diagnósticas se estimó mediante tablas de contingencia 2x2. Se midieron los valores de sensibilidad, especificidad, valores predictivos positivo y negativo, las razones de verosimilitud positiva y negativa y el grado de concordancia mediante el valor de κ del test de Cohen. Además, a partir de estos índices se realizó la representación visual de la exploración física mediante el nomograma de Fagan.

En relación a la utilidad de los stents cubiertos como tratamiento de los aneurismas parcialmente trombosados y el trombo residual parietal en fistula arteriovenosa nativa, realizamos un estudio de diseño retrospectivo entre enero de 2004 y diciembre de 2016. Durante ese periodo se identificaron un total de 2943 procedimientos de los cuales se incluyeron un total de 27 procedimientos correspondientes a 24 pacientes. Los pacientes fueron intervenidos para el tratamiento de su acceso

disfuncionante mediante técnicas endovasculares donde se implantaron stents recubiertos. Todos los pacientes acudieron a las sesiones de hemodiálisis después de la intervención. Se evitó la canulación a través del stent en las primeras 2-3 semanas excepto en los casos donde no se disponían de otras opciones. La monitorización y vigilancia fue realizada por el nefrólogo de referencia del paciente. Se midió la permeabilidad primaria después de la intervención, definida según los estándares actuales como el intervalo desde la implantación del stent hasta la aparición de una trombosis, una intervención repetida en cualquier lugar del circuito del acceso o el momento de la medición de la permeabilidad. Las tasas de permeabilidad primaria se analizaron mediante el test de Kaplan-Meier log-rank. Se realizaron modelos de regresión de Cox multivariante para determinar si la punción en el área del stent fue un factor de riesgo para la oclusión del acceso vascular mediante el Hazard ratio (HR) ajustado.

Por último, el tercer estudio consistió en la comparación de dos técnicas endovasculares para el tratamiento de la disfunción del catéter venoso central de hemodiálisis tunelizado, el recambio de catéter versus recambio de catéter + angioplastia de la vaina de fibrina. Consistió en un estudio observacional retrospectivo que incluyó un total de 107 pacientes que acudieron a la consulta entre agosto de 2005 y diciembre de 2016. Los pacientes fueron referidos a la consulta de Radiología Vascular por su nefrólogo debido a la sospecha de disfunción de su catéter venoso central. El tratamiento endovascular fue realizado por dos radiólogos vasculares expertos de la Unidad según las guías de la propia Unidad y acorde a los estándares y guías internacionales. Se determinó la permeabilidad primaria tras el procedimiento en base a los estándares internacionales, definida como el intervalo entre la inserción del catéter hasta la disfunción que requirió tratamiento en el catéter.

Se realizó un test de Kaplan-Meier log-rank y análisis de regresión de Cox multivariante para determinar las tasas de permeabilidad primaria y el riesgo de obstrucción según el tipo de procedimiento endovascular realizado.

Todas las pruebas fueron de dos colas y el nivel de significación estadística se estableció en < 0.05. Los análisis de los datos fueron realizados utilizando los programas estadísticos SPSS (Statistical Package for the Social Sciences), EPIDAT 3.1 y Diagnostic test calculator (version 2010042101).

Resultados

El primer trabajo incluyó 99 pacientes con una media de edad de 67.3 años y deviación estándar de 13.5 años. La mediana de edad de la fístula arteriovenosa nativa fue de 17 meses, con un rango intercuartílico entre 4 y 53 meses. La presencia de estenosis se observó en 57 (58%) de pacientes con la ecografía, y 61 (62%) mediante la exploración física. El rendimiento de la exploración física para el diagnóstico de estenosis en fistula arteriovenosa nativa mostró una sensibilidad del 82%, especificidad 67%, valor predictivo positivo 77%, valor predictivo negativo 74%, razones de verosimilitud positiva y negativa de 2,74 y 0,26, respectivamente. El grado de concordancia más allá del atribuible al azar de la exploración física frente a ecografía fue moderado, con un valor de κ = 0.5, intervalo de confianza al 95% de 0.32-0.67 (P <0.001). Al analizar los signos de la exploración física de forma individual con respecto a la ecografía, la pulsatilidad fue el signo que mostró un mayor rendimiento, con una sensibilidad del 70%, especificidad 67%, valor predictivo positivo 74%, valor predictivo negativo 62%, razones de verosimilitud positiva y negativa de 2,11 y 0,45, respectivamente, y un grado de concordancia similar a la exploración física completa, κ = 0.37, intervalo de confianza al 95% de 0.18-0.55 (P <0.001).

En relación al análisis del tratamiento con stents cubiertos, la media de edad de los pacientes incluidos en el estudio fue de 70.8 años con una desviación estándar de 6.9 años. La edad media de la fístula arteriovenosa nativa en el momento de la intervención fue de 1143.1 días con una desviación estándar de 809.8 días. De los 27 procedimientos incluidos, 13 correspondieron al tratamiento del trombo adherido a la pared del aneurisma y 14 al tratamiento del trombo residual en la pared. Un total de 18 procedimientos requirieron adicionalmente la realización de trombectomía y 23 la realización de angioplastia transluminal percutánea. Las tasas de permeabilidad primaria (%) después de la implantación del stent a los 3, 6, 12, 24, 36 y 72 meses fueron, respectivamente: total 59, 32, 32, 21, 11 y 5; punción del stent 53, 21, 21, 16, 5 y 0; no punción del stent 80, 80, 80, 40, 40 y 40. En relación a la canulación a través del stent durante las sesiones de hemodiálisis, 19 fístulas fueron puncionadas a través del stent mientras que las 8 fístulas fueron puncionadas en otros lugares. En los resultados del análisis multivariado, la canulación a través del stent no se asoció de forma estadísticamente significativa con un incremento del riesgo de obstrucción de la fístula, HR = 3,01, intervalo de confianza al 95% de 0.40–22.75.

En el tercer análisis, 73 de 107 pacientes (68,2%) se sometieron al recambio del catéter y 34 de 107 (31,8%) al recambio de catéter + angioplastia de la vaina de fibrina. La edad mediana y desviación estándar de los pacientes del primer grupo fue de 70.0 años y 11.9 años, y del segundo grupo 69.4 años y 13.6 años. La edad del catéter venoso central tuvo una mediana e intervalo intercuartílico de 110.0 días y 48.5-263.5 días para el grupo del recambio de catéter, y de 506.5 días y 325.5-1026.5 días en el grupo de recambio de catéter + angioplastia. Las tasas de permeabilidad primaria después del procedimiento endovascular a los 3, 6, 12, 24 y 36 meses de seguimiento fueron 75, 75, 65, 65 y 65 en el grupo de recambio de catéter + angioplastia de la

vaina de fibrina, 70, 65, 62, 30 y 0 en el grupo de recambio de catéter. El tipo de procedimiento endovascular, recambio de catéter versus recambio de catéter + angioplastia de la vaina de fibrina, no se relacionó con el riesgo de obstrucción del catéter venoso central en el modelo ajustado, HR = 1,34, intervalo de confianza al 95% de 0.56-3.21.

Conclusiones

La exploración física mostró ser una herramienta diagnóstica de utilidad moderada para la detección de estenosis en la fistula arteriovenosa nativa de hemodiálisis. En ausencia de disponibilidad de ecografía en los centros de hemodiálisis, podría representar un beneficio en el manejo óptimo de la supervivencia del acceso, siendo conveniente entrenar al personal de los centros para el desarrollo de habilidades necesarias.

El tratamiento con stent cubierto puede ser un procedimiento factible en aneurismas parcialmente trombosados y en trombo residual de la fistula arteriovenosa nativa. Aunque las fistulas que fueron puncionadas a través del stent durante la sesión de hemodiálisis tuvieron tasas de permeabilidad menores, esta práctica no se asoció con mayor riesgo de obstrucción.

En relación al catéter venoso central de hemodiálisis disfuncionante, nuestros resultados sugirieron que el recambio de catéter y el recambio de catéter + angioplastia de la vaina de fibrina son técnicas equivalentes en términos de permeabilidad y seguridad, por lo que es necesario valorar otros aspectos como los costes asociados, la experiencia o las preferencias del médico para valorar entre ambas técnicas.

List of publications

Maldonado-Cárceles AB, García-Medina J, Torres-Cantero AM. Performance of physical examination versus ultrasonography to detect stenosis in haemodialysis arteriovenous fistula. J Vasc Access. 2017;18(1):30-34. doi: 10.5301/jva.5000616. PMID: 27834455.

Candidate's contribution: literature review, study design, statistical analysis, interpretation of data, drafting the manuscript for scientific publication, corresponding author.

García-Medina J, Maldonado-Cárceles AB, García-Alfonso JJ, Árense-Gonzalo JJ, Torres-Cantero AM. Stent graft deployment in haemodialysis fistula: patency rates in partially thrombosed aneurysm and residual thrombi. Clin Kidney J. 2020;14(3):814-819. doi: 10.1093/ckj/sfz193. PMID: 33777364; PMCID: PMC7986443.

Candidate's contribution: literature review, study design, acquisition of data, statistical analysis, interpretation of data, drafting the manuscript for scientific publication, corresponding author.

Maldonado-Cárceles AB, García-Medina J, García-Alfonso JJ, Árense-Gonzalo JJ, Torres-Cantero AM. Patency rates of dysfunctional central hemodialysis venous catheter: Comparison between catheter exchange alone and catheter exchange with fibrin sheath angioplasty. Diagn Interv Imaging. 2019;100(3):157-162. doi: 10.1016/j.diii.2018.08.013. PMID: 30262173.

Candidate's contribution: literature review, study design, statistical analysis, interpretation of data, drafting the manuscript for scientific publication, corresponding author.

1. GENERAL INTRODUCTION

1.1. Chronic kidney disease and haemodialysis

Chronic kidney disease (CKD) is an irreversible condition characterised by the progressive decline of renal function over time (Bello et al. 2019). CKD is a worldwide public health problem (Bello et al. 2019, Himmelfarb and Ikizler 2019) that affects about ten percent of the population (Institute for Health Metrics and Evaluation 2021), with a 29.3% increase in prevalence between 1990 and 2017 (Bikbov et al. 2020). Globally, it is estimated that this disease accounted for 1.64% of total disability-adjusted life years in 2019 (Institute for Health Metrics and Evaluation 2021), ranking as the twelfth leading cause of death, with 1.2 million deaths in 2017 (Bikbov et al. 2020). The cost of treating this growing epidemic places an enormous burden on families and on society as a whole (Mills et al. 2015); in the United States, for example, Medicare treatment costs exceeded $120 billion in 2017, representing 33.8% of total fee-for-service spending (United States Renal Data System 2019).

CKD is categorized in 5 stages according to the estimated glomerular filtration rate (GFR). When renal function fails (GFR<15 ml/min/1.73m^2), the patient enters end-stage renal disease (ESRD) (Levin et al. 2013), which affects about 0.1% of the world's population (Bello et al. 2019). At this advanced stage, patients require life-saving renal replacement therapies (RRT) (Himmelfarb and Ikizler 2019). More than two million people around the world receive RRT, which are most often used in high-income countries (Liyanage et al. 2015). In 2018, the prevalence of patients per million population (pmp) undergoing RRT was 897 in Europe (ERA-EDTA Registry 2019) and 2,354 in the United States (United States Renal Data System 2019). Moreover, factors such as increased life expectancy or improvements in access to dialysis in countries with

growing economies mean that the number of people undergoing RRT is expected to grow to more than five million by 2030 (Liyanage et al. 2015).

RRT options include renal transplantation, peritoneal dialysis and haemodialysis (Himmelfarb and Ikizler 2019). Despite geographical variations in use, haemodialysis remains the most common treatment option (United States Renal Data System 2020). Haemodialysis is used to treat patients with temporary or permanent loss of renal function by maintaining fluid balance and excretion of toxins (Himmelfarb and Ikizler 2019) in a continuous process that typically requires three four-hour sessions each week (Ashby et al. 2019). The average worldwide prevalence of chronic haemodialysis was 298.4 pmp, increasing to 513.7 pmp in high-income countries (Bello et al. 2019). According to a Spanish Society of Nephrology report on dialysis and kidney transplants, the prevalence of haemodialysis among patients receiving RRT in Spain in 2019 was 555.0 pmp (40.3% of the RRT), with an incidence of 119.4 pmp (78.6% of the RRT) (Registro Español de Enfermos Renales 2019).

1.2. Vascular access for haemodialysis

Among patients undergoing chronic haemodialysis, a vascular access must be created for blood extraction. The ideal haemodialysis access should facilitate safe and effective treatment throughout therapy sessions. The three main access options are the arteriovenous fistula (AVF), the arteriovenous graft (AVG), and the haemodialysis central venous catheter (HCVC) (Himmelfarb and Ikizler 2019). Arteriovenous access involves surgical intervention to establish a link between an artery and a vein, usually in the upper extremity, to implement an easily accessible vessel that supports repeated puncture and ensures adequate blood flow during long-term use. (Schmidli et al. 2018, Himmelfarb and Ikizler 2019). AVF vessels are linked by an autogenous anastomosis while an AVG uses a prosthetic graft (Schmidli et al. 2018). The HCVC is placed into

a central vein or the right atrium, preferably in the upper extremity (Lok et al. 2020), enabling immediate use for haemodialysis (Dumaine et al. 2018, Himmelfarb and Ikizler 2019).

Based on outcomes (complications and patency rates) reported in published observational studies, international guidelines recommend AVF as the preferred option for vascular access, followed by AVG and HCVC (Schmidli et al. 2018, Lok et al. 2020). Given the low use of AVF in the United States, these recommendations prompted the National Access Improvement Initiative, established in 2003 by the Medicare and Medicaid services, leading in turn to the Fistula First Breakthrough Initiative, which was subsequently renamed the Fistula First-Catheter Last Initiative (End Stage Renal Disease National Coordination Center 2020). The aim was to increase the use of AVF among chronic haemodialysis patients (Lee 2017, End Stage Renal Disease National Coordination Center 2020). Europe raised the level of ambition further with the Distal Fistula First initiative based on radial-cephalic and ulnar-basilic microsurgery techniques for forearm AVF (Bourquelot and Pirozzi 2014). However, concerns about study bias and a lack of comparative clinical trials have called this approach into question (Lok et al. 2020). For a subset of patients, AVG and HCVC may represent the best option (Lee 2017), and vascular access should be carefully individualized to ensure the 'right access, in the right patient, at the right time, for the right reasons' (Lok et al. 2020). In its recent guidelines, the KDOQI (Kidney Disease Outcomes Quality Initiative) working group proposed a more patient-centred strategy for developing an end-stage kidney disease (ESKD) life plan, taking account of the patient's access needs, the "ViP ACCeS plan": Vessel important Preservation, Access Creation, Contingency, and ESKD access Succession plans (Lok et al. 2020).

According to international data from the 2012/2013 Dialysis Outcomes and Practice Patterns Study (DOPPS) (Pisoni et al. 2015, 2018), use of different vascular access types varies

widely across countries, with a range of 49-92% for AVF, 2-18% for AVG and 2-49% for HCVC. Recent US data show that AVF use among patients receiving haemodialysis in February 2020 was 63% as compared to rates of 17% and 20% for AVG and HCVC, respectively (Dialysis Outcomes and Practice Patterns Study 2020). The proportion of patients starting chronic haemodialysis with AVF increased moderately over the past decade to 16% in 2018; HCVC use decreased slightly to 81%, and AVG use remained relatively unchanged at 3% (United States Renal Data System 2020). In Spain, the most recent available data (from the 2012/2013 DOPPS) indicate that nearly two-thirds of patients were using AVF for haemodialysis therapy as compared to 6% using AVG and almost 30% using HCVC (Pisoni et al. 2015). The Spanish Society of Nephrology annual reports on dialysis and kidney transplant use do not refer to vascular access types, but it is planned to include this information in future reports (Registro Español de Enfermos Renales 2019).

1.3. Vascular access complications and management

Optimal vascular access management is crucial for achieving and maintaining the requisite functionality for successful haemodialysis therapy, ideally involving both the patient and a multidisciplinary team of healthcare professionals (Kramer et al. 2019, Lok et al. 2020). Any complications that render the access dysfunctional, leading ultimately to loss of the access, may require additional treatments to re-establish its functionality. Among patients undergoing chronic haemodialysis, vascular access complications are the main cause of morbimortality (Adib-Hajbagheri et al. 2014), accounting for up to 20% of hospital admissions among these patients (Schmidli et al. 2018). For that reason, comprehensive management is needed to track complications through monitoring and surveillance and to deploy the necessary treatment strategy to preserve the patient's lifeline.

Different types of complications may compromise the functionality of the vascular access. This dissertation has focused on specific complications and challenges in management of the vascular access for chronic haemodialysis among patients attending the Vascular Radiology Unit, including performance of physical examination to detect AVF stenosis, utility of the stent graft for treatment of thrombosed aneurysm and residual thrombi in AVF and the relative merits of two endovascular techniques for fibrin sheath treatment in cases of dysfunctional HCVC.

1.3.1. Stenosis and physical examination in arteriovenous fistula

Stenosis is a common complication in patients with AVF and AVG (Pirozzi, Garcia-Medina, and Hanoy 2014, Himmelfarb and Ikizler 2019), arising predominantly from neointimal hyperplasia, causing progressive luminal narrowing of 50% as compared to the normal adjacent vessel segment, which may lead to intra-access flow impairment (Kramer et al. 2019, Lok et al. 2020). Thrombosis is usually the final complication in a progressive stenosis (García-Medina et al. 2009, Schmidli et al. 2018, Himmelfarb and Ikizler 2019), which may cause loss of the vascular segment, making the vascular access unsuitable for dialysis (García-Medina et al. 2009) and requiring the use of less efficient techniques. Early detection and correction of AVF dysfunction prior the occurrence of the thrombotic event may increase AVF survival and functionality (Tessitore et al. 2004).

Physical examination (PE) involves a clinical monitoring strategy to identify any underlying stenosis of the vascular access prior to flow dysfunction (Schmidli et al. 2018, Lok et al. 2020). This has been proposed as an accessible and cost-efficient method that has been proposed for early detection of AVF stenosis (Coentrão and Turmel-Rodrigues 2013, Schmidli et al. 2018, Lok et al. 2020). The recent KDOQI guidelines (Lok et al. 2020) recommend regular monitoring using PE to check the AVF for access flow dysfunction caused by underlying pathologies

including stenosis and thrombosis, based on evidence of moderate quality. Other clinical bodies, including The Renal Association (UK Renal Association 2015) and the European Society for Vascular Surgery (ESVS) (Schmidli et al. 2018) have also published guidelines recommending routine recommends performing routine PE. If monitoring indicates the presence of a lesion that may be clinically significant, a confirmatory evaluation should be performed for early diagnosis and prompt treatment where needed (UK Renal Association 2015, Lok et al. 2020).

Although the potential of PE as a tool for assessing early vascular access dysfunction (Coentrão and Turmel-Rodrigues 2013) is increasingly acknowledged by international guidelines and recommendations, regular PE is not routinely performed in haemodialysis units (Schmidli et al. 2018). As in other medical disciplines, technology has taken precedence to the detriment of PE (Harrison and Longo 2012), which requires skilled and specifically trained caregivers (Lok et al. 2020). As there are few existing studies of the performance of PE as a diagnostic tool for detecting AVF stenosis, further research is needed in this area (UK Renal Association 2015, Kramer et al. 2019, Lok et al. 2020).

1.3.2. Partially thrombosed aneurysms and residual thrombi and stent graft deployment in arteriovenous fistula

Aneurysm is a common vascular malformation in the AVF (UK Renal Association 2015), ranging in incidence from 5% to 60% in clinical series (Lok et al. 2020). It is defined as a circumscribed dilation of all three layers of the vessel, with a diameter of >18 mm (Baláž and Björck 2015, Lok et al. 2020), resulting from disease or trauma in the vessel wall (Lok et al. 2020). Diagnosis by clinical examination can be confirmed by ultrasonography (Schmidli et al. 2018, Lok et al. 2020), which can detect associated lesions such as stenosis and wall-adherent thrombi (Schmidli et al. 2018).

The majority of aneurysms are asymptomatic and are generally managed conservatively, with no need for intervention and avoiding cannulation within aneurysmal areas (Rokosny, O'Neill, and Baláž 2018, Lok et al. 2020). However, some aneurysms may involve multiple lesions (Lok et al. 2020) that can cause complications for the AVF by increasing the risk of life-threatening bleeding and compromising adequate blood flow, leading to vascular access dysfunction (Baláž and Björck 2015, Lok et al. 2020).

Several techniques have been proposed for treating symptomatic aneurysms, using either surgical techniques or endovascular procedures (García-Medina et al. 2009, Pirozzi, Garcia-Medina, and Hanoy 2014, Schmidli et al. 2018, Lok et al. 2020, Baláž et al. 2020). Surgical procedures are the main option for treating such lesion (Schmidli et al. 2018, Baláž et al. 2020) including resection with substitution, remodelling and ligation (Rokosny, O'Neill, and Baláž 2018). Among endovascular procedures, stent graft deployment is the treatment of choice (Rokosny, O'Neill, and Baláž 2018). Current guidelines published by the Society of International Radiology, the ESVS and KDIGO address various indications for the use of stent grafting in AVF (Dariushnia et al. 2016, Schmidli et al. 2018, Lok et al. 2020) (e.g., in-stent re-stenosis, treatment of ruptured venous stenotic segment). Implantation of a stent graft for aneurysm exclusion is recommended only as an alternative procedure in highly selective cases. Once the stent is implanted in the AVF, cannulation through the stent segment is not advisable (Lok et al. 2020).

Aneurysms can be accompanied by large thrombi (Bent et al. 2010, Schmidli et al. 2018). The presence of wall-adherent thrombi can make catheter aspiration difficult (Hung et al. 2014), leaving a remaining clot with high risk of re-thrombosis (Funaki 2004). Use of a stent graft may provide support for the vessel wall, maintaining AVF patency and reducing the risk of cellular ingrowth (Falk et al. 2016). It follows that although partially thrombosed aneurysms and residual

wall-adherent thrombi are not at present regarded as indicating stent graft use, the available data are insufficient for evaluation of the impact of this minimally invasive technique in such cases. Moreover, the limited published literature in this area means that current indications for the management of AVF aneurysm are based on clinical experience rather than scientific evidence (UK Renal Association 2015, Inston et al. 2017), as the majority of techniques are reported as individual case studies (Rokosny, O'Neill, and Baláž 2018). As a consequence, recommendations for optimal treatment are still lacking, and there is little evidence regarding the impact of stent grafts in other case scenarios.

1.3.3. Fibrin sheath and endovascular techniques in haemodialysis central venous catheter dysfunction

Fibrin sheath formation is among the most frequent complications in dysfunctional tunnelled HCVC (Masud et al. 2018, Lok et al. 2020) and is the main cause of late dysfunction (Himmelfarb and Ikizler 2019). It comprises smooth muscle cells and connective tissue at the point of contact between the catheter and vessel wall that extends along the catheter surface (Lok et al. 2020). Developing over days or even months after HCVC placement (Himmelfarb and Ikizler 2019, Lok et al. 2020), incidence is up to 75% at 90 days after insertion (Shanaah, Brier, and Dwyer 2013). Although the pathophysiology is not fully understood, fibrin sheath is probably a response to the impact suffered by the endothelium and turbulent blood flow around the HCVC (Li et al. 2020). This may compromise patency and HCVC survival and may be associated with other complications such as thrombosis and catheter-related infection (Miller et al. 2016, Himmelfarb and Ikizler 2019, Kumbar and Yee 2019, Lok et al. 2020).

Several endovascular strategies have been proposed for the restoration of tunnelled HCVC functionality, including fibrin sheath stripping, internal snare manoeuvres, over-the-wire catheter

exchange (CE) and fibrin sheath angioplasty disruption (FSA) (Janne d'Othée, Tham, and Sheiman 2006, Kennard et al. 2017, Lok et al. 2020). According to recent KDOQI guidelines (Lok et al. 2020), CE should be performed (with or without FSA), and any decision about fibrin sheath disruption should be based on the operator's discretion and best clinical judgment. These recommendations are based on the consensus of expert opinion, as the current evidence is not sufficiently rigorous to commend one strategy rather than another (Lok et al. 2020). A Cochrane systematic review published in 2017 (Kennard et al. 2017) suggested that using both techniques (FSA previous to CE) rather than CE alone produced better results in terms of catheter survival time, but previous studies reported no statistically significant differences between the different approaches (Janne d'Othée, Tham, and Sheiman 2006, Oliver et al. 2007). In short, the available evidence is insufficient to determine which approach might prove more effective for managing dysfunctional HCVC (Kennard et al. 2017).

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2. BRIEF RATIONALE

Chronic kidney disease is a public health problem affecting 10% of the global population, and it is associated with high morbimortality. About two million people worldwide currently receive renal replacement therapy for end-stage renal disease, for which haemodialysis is the most frequent treatment option. This modality requires a functioning vascular access (VA) for blood extraction and purification, which is considered the patient's lifeline. Of the different types of VA—arteriovenous fistula (AVF), arteriovenous graft (AVG) and the haemodialysis central venous catheter (HCVC) —the AVF is generally the preferred option.

Maintenance of VA functionality is one of the main objectives for optimal care of patients undergoing chronic haemodialysis therapy. As VA-related complications may compromise the efficiency of haemodialysis sessions and are the main cause of morbidity in these patients, appropriate management of these complications is crucial.

Stenosis is the most common complication in patients with AVF and AVG. Late diagnosis and treatment may result in VA loss and a need to resort to less efficient techniques. Conscientious monitoring and surveillance may improve VA survival and functionality, and physical examination (PE) is an inexpensive and accessible method for early diagnosis of AVF stenosis. However, despite the potential of PE assessment of VA dysfunction, few studies have investigated PE as a diagnostic tool for detecting AVF stenosis. For that reason, the first thesis study compared PE to the "gold-standard" of ultrasonography on several diagnostic performance parameters.

VA complications may appropriate surgical or endovascular intervention (e.g., percutaneous transluminal angioplasty, stent deployment, catheter exchange). As a therapeutic option, stent deployment can preserve the AVF functionality in selected cases. The second thesis

study addressed the use of stent grafts, which are not currently indicated for use in partially thrombosed aneurysms or residual wall-adherent thrombi. Theoretically, stent grafts may provide endoluminal support to maintain vessel wall patency in combination with a biocompatible barrier to prevent cellular ingrowth, clot migration and re-thrombosis. However, the available clinical data are insufficient to assess the potential of this procedure in such cases.

The development of fibrin sheath is among the most common complications in HCVC dysfunction. While catheter exchange with fibrin sheath angioplasty is a possible treatment option, there is no evidence that this approach is more effective in terms of patency outcomes than catheter exchange alone. To address this gap, the third thesis study compared these two approaches in terms of patency rates and risk of HCVC obstruction.

3. RESEARCH AIM AND OBJECTIVES

3.1. General aim

The general aim of the dissertation was to analyse the management of vascular access for haemodialysis and associated complications among patients attending a vascular radiology unit.

3.2. Specific objectives

- To compare the accuracy of physical examination and ultrasonography as methods of detecting stenosis in patients with arteriovenous fistula for haemodialysis.

- To analyse patency rates of post-interventional covered stent deployment when treating partially thrombosed aneurysms or residual wall-adherent thrombi in arteriovenous fistula for haemodialysis.

- To assess differences in patency rates when arteriovenous fistulas were punctured through the stent during dialysis sessions.

- To investigate patency rates and risk of obstruction for catheter exchange (CE) and CE with fibrin sheath angioplasty in cases of tunnelled haemodialysis central venous catheter dysfunction.

4. CONCLUSIONS

- While physical examination (PE) may be of moderate utility as a tool for stenosis detection in arteriovenous fistula for haemodialysis, it is not a substitute for ultrasonography, and patients with a positive PE-based diagnosis should be subsequently assessed for stenosis by US. Nevertheless, PE can be useful in haemodialysis units, especially where US is not available, and teaching PE skills to health professionals with haemodialysis-related responsibilities can help to improve VA quality management.
- In the present study, the use of stent grafts for treatment of partially thrombosed aneurysms and residual thrombi for haemodialysis fistulas exhibited acceptable primary patency rates and may prove effective in managing arteriovenous fistulas for haemodialysis.
- Arteriovenous fistulas cannulated through the stent exhibited lower patency rates than stent area avoidance during dialysis, but this practice was unrelated to risk of fistula occlusion.
- Treatment of haemodialysis central venous catheter dysfunction using catheter exchange (CE) showed equivalent patency and safety results to CE plus fibrin sheath angioplasty. These findings suggest that cost assessment should be among the factors considered when choosing between these techniques.

5. SCIENTIFIC PUBLICATIONS

Performance of physical examination versus ultrasonography to detect stenosis in haemodialysis arteriovenous fistula

Journal: The Journal of Vascular Access

Abstract:

Purpose: The overall purpose of this study is to compare the accuracy of physical examination (PE) versus ultrasonography (US) in people with arteriovenous fistula (AVF).

Methods: This is a cross-sectional study with a total of 99 patients attended by the vascular radiology unit for AVF evaluation during January - March 2015. PE and ultrasonography were blinded performed by different radiologists. For complete and individual signs of PE, sensitivity, specificity, predictive positive (PPV) and negative (PNV) value, likelihood ratios (LR) and Cohen's κ value were measured.

Results: According to ultrasonography, the presence of stenosis was identified in 57 (58%) patients, and 61 (62%) by PE. The accuracy of PE for the diagnosis of AVF was sensitivity 82%, specificity 67%, PPV 77%, NPV 74%, LR 2.74 and 0.26. There was a moderate agreement beyond chance between PE and ultrasonography (κ = 0.5).

Conclusions: PE has shown a moderate accuracy to detect stenosis. With non-ultrasonography availability Haemodialysis Units can get benefit to optimize VA survival and professionals should improve its basic skills.

Website address:

https://journals.sagepub.com/doi/abs/10.5301/jva.5000616?rfr_dat=cr_pub%3Dpubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&journalCode=jvaa

Stent graft deployment in haemodialysis fistula: patency rates in partially thrombosed aneurysm and residual thrombi

Journal: Clinical Kidney Journal

Abstract

Background. Current evidence is insufficient to determine the contribution of stent grafts as treatment in partially thrombosed aneurysms or residual wall-adherent thrombi in arteriovenous fistulae (AVFs) for haemodialysis. The overall purpose of this study was to analyse patency rates of post-interventional covered stent deployment in those cases. We also assessed if patency rates differed when fistulas were punctured through the stent during dialysis sessions.

Methods. We conducted a retrospective study between 2006 and 2014 analysing post-intervention primary patency rates using the Kaplan–Meier log-rank test. Multivariate Cox proportional regression models were performed to determine if cannulation within the stent graft area was a potential risk factor for occlusion, by adjusted hazard ratio (HR).

Results. A total of 27 procedures were included in the study. Primary patency rates (%) after stent deployment at 3, 6, 12, 24, 36 and 72 months were, respectively: total 59, 32, 32, 21, 11 and 5; stent puncture 53, 21, 21, 16, 5 and 0; and no stent puncture 80, 80, 80, 40, 40 and 40. Cannulation through the stent graft was not significantly associated with increased risk of obstruction in multivariate analysis (HR = 3.01; P = 0.286).

Conclusion. Stent graft treatment may be a feasible procedure in partially thrombosed aneurysms and residual thrombi in AVF. Although fistulas punctured through the stent presented lower patency rates, this practice was not associated with a higher risk of obstruction. Giving the impossibility of comparing with similar approaches, further studies are needed to confirm or refute the advantages of this procedure.

Website address:

https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfz193/5733045

Patency rates of dysfunctional central hemodialysis venous catheter: Comparison between catheter exchange alone and catheter exchange with fibrin sheath angioplasty

Journal: Diagnostic and Interventional Imaging

Abstract

Purpose. The purpose of this study was to compare patency rates and risk of obstruction of catheter exchange (CE) with that of CE with fibrin sheath angioplasty (CE + FSA) in dysfunctional tunneled central hemodialysis venous catheter (CHVC).

Materials and methods. A total of 107 consecutive patients with dysfunctional CHVC were retrospectively included. There were 66 men and 41 women with a mean age of 67.8 ± 12.5 (SD) years (range: 23.0–86.0 years). Seventy-three of 107 patients (68.2%) underwent CE procedure and 34 of 107 (31.8%) underwent CE + FSA. Kaplan–Meier log-rank test and multivariate Cox regression analyses were performed to determine patency rates and risk of obstruction according to type of endovascular procedure.

Results. Patency rates after endovascular procedures at 3, 6, 12, 24 and 36 months follow up were 75%, 75%, 65%, 65% and 65% in CE + FSA group and 70%, 65%, 62%, 30% and 0% in CE group. Mean time until obstruction of CHVC was 778.4 days after CE + FSA and 497 days after CE ($P = 0.211$). Endovascular procedure was unrelated to risk of obstruction in adjusted model (HR = 1.34; $P = 0.515$).

Conclusions. Our findings suggest that both techniques are equivalent in terms of patency and safety results, so other aspects as cost assessment should be considered when choosing between both techniques.

Website Address:

https://www.sciencedirect.com/science/article/pii/S2211568418301980?via%3Dihub

6. APPENDIX

Communications to scientific meetings

- "Estudio comparativo entre la exploración clínica y la ecografía en las fístulas de diálisis" (Noviembre 2015). Maldonado Cárceles AB, García Medina J, Torres Cantero AM. II Congreso de la Sociedad Española de Acceso Vascular. Colegio Oficial de Médicos. Madrid, España.
- "Etude comparative entre l'examen clinique et l'écho doppler dans les fistules d'hémodialyse" (Junio 2016). García Medina J, Maldonado Cárceles AB, Torres Cantero AM. 21º Cours Congrès de la Société Francophone de l'Abord Vasculaire: Abords vasculaires pour hémodyalise. Palais des Congrès d'Ajaccio. Ajaccio, Francia.
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