J Surg Med. 2020;4(9):716-719.
DOI: 10.28982/josam.788906

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effectiveness and safety of using a novel endothelial damage inhibitor in arteriovenous fistula formation

Arteriovenöz fistül oluşturulmasında yeni endotelyal hasar inhibitörü kullanılmasının etki ve güvenirliği

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Ethics Committee Approval: The ethic approval of the present the study was obtained from Ethical Committee of Ordu University, School of Medicine. (Approval number: 2020/165 Date: 8/20/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışmanın etik onayı Ordu Üniversitesi Tıp Fakültesi Etik Kurulundan alınmıştır. (Onay numarası: 2020/165 Tarih: 20.08.2020). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/11/2020
Yayın Tarihi: 11.09.2020

Abstract

Aim: Patients with end-stage renal disease need accurate and effective vascular access for hemodialysis. Although renal transplantation is the golden standard treatment that provides a life without hemodialysis, an arteriovenous (AV) fistula is the most frequent method for sustaining long-term hemodialysis because of insufficient renal donors. In the current study, we aimed to compare patency rates of AV fistulae created with or without the endothelial protection solution.

Methods: This single-center case-control study was conducted between August 2018 and August 2019. Patients with end-stage renal disease requiring AV fistula access for hemodialysis (n=49) were included in the study and divided into two groups. During the creation of an AV fistulae, endothelial protection solution was used in 27 patients, who constituted Group A, and not used in 22 patients, who were included in Group B (the control group). All fistulae anastomoses were performed by the same surgical team. The demographical data, maturation time, mean flow volume, complications, basal metabolism index (BMI), and patency rates at the 3rd and 6th months were compared.

Results: There was no significant difference between the two groups regarding demographical findings ($p>0.05$). The patency rates were higher in group A at both the 3rd and 6th months (96% and 93%) when compared with group B (64% and 27%) ($P<0.05$).

Conclusion: AV fistulae created with endothelial protection solution has higher patency rates compared to conventionally created AV fistulae.

Keywords: End stage renal disease, Arteriovenous fistula, Endothelial protection solution, Patency rate

Öz

Amaç: Son dönem böbrek hastalığı olan hastalar, hemodiyaliz için doğru ve etkili damar erişimine ihtiyaç duymaktadır. Böbrek nakli, hemodiyaliz gereksinimi olmadan yaşamın sürdürülmesini sağlayan kesin tedavi yöntemi olsa da, yetersiz böbrek donörü nedeniyle uzun süreli hemodiyalizin sürdürülmesinde en sık kullanılan yöntem arteriyovenöz (AV) fistüldür. Bu çalışmada, endotel koruma solüsyonu ile veya solüsyonsuz oluşturulan AV fistülün açıklık oranlarını karşılaştırmayı amaçladık.

Yöntemler: Bu tek merkezli vaka control çalışması Ağustos 2018 ile Ağustos 2019 arasında gerçekleştirilmiştir. Hemodiyaliz için son dönem böbrek hastalığı olan hastalar (toplam 49 hasta) çalışmaya dahil edilmiştir. Hastalar grup A (endotel koruma solüsyonu ile oluşturulan AV fistüller çalışma grubu olarak, n=27) ve grup B (endotel koruma solüsyonu olmadan oluşturulan AV fistüller control grubu olarak, n=22) olarak iki gruba ayrıldı. Tüm fistül anastomozları aynı cerrahi ekip tarafından yapıldı. 3. ve 6. aydaki demografik veriler, olgunlaşma süresi, ortalama akış hacmi, komplikasyonlar, bazal metabolizma indeksi (VKİ) ve açıklık oranları karşılaştırıldı.

Bulgular: Demografik bulgular açısından iki grup arasında fark yoktu ($P>0,05$). Grup A'da 3. ve 6. ayda (%96 ve %93) B grubuna (%64 ve %27) göre daha yüksek açıklık oranları saptandı ($P<0,05$).

Sonuç: Endotelyal koruma solüsyonu ile oluşturulan AV fistül, geleneksel AV fistül oluşturma ile karşılaştırıldığında daha yüksek açıklık oranlarına sahip gibi görünmektedir.

Anahtar kelimeler: Son dönem böbrek hastalığı, Arteryo-venöz fistüller, Endotelyal koruma solüsyonu, Açıklık oranı

How to cite/Atıf için: Khalil E, Akalın Ç. Effectiveness and safety of using a novel endothelial damage inhibitor in arteriovenous fistula formation. J Surg Med. 2020;4(9):716-719.

Introduction

Although renal transplantation is the best treatment method for end stage renal disease, hemodialysis is important until transplantation, and considered the last treatment method for patients who cannot find donors [1-3]. In patients requiring a hemodialysis access site, autogenous AV fistulae are the optimum method for dialysis access. National Kidney Foundation Department Outcomes Quality Initiative guidelines suggest that AV fistulae are the most sustainable and effective option for patients who require hemodialysis for a long time [3]. The artery and vein selection for AV fistula creation should start distally in the upper limbs. Hence, the common preferred site is the distal radiocephalic zone and can progress proximally if the artery and vein are not appropriate for the required procedures. Brachiocephalic site is the other popular option in patients who do not have appropriate vessels in the radiocephalic zone [3-5].

The surgical procedure, the experience of the surgeon, the quality of arteriovenous structures, and advanced strategies are the main factors that determine the patency rates of created AV fistulae. After creation of an AV fistula, arterial endothelium migrates to vein wall, which gets affected by increased blood flow and pressure. Hypoxia, hemodynamic shear stress, and inflammation are considered the main additional factors which cause the pathophysiologic changes on the vein wall. These factors lead to venous neointimal hyperplasia which can result in the failure of the AV fistula [4-6]. Endothelial protection solutions are preservation solutions used for the vein wall, containing antioxidant material to systematically protect the endothelium against these stress factors. They can be used for coronary or peripheral vascular reconstruction with autologous vascular grafts. Published studies suggest that these solutions can improve endothelial functions and increase the patency rates of vascular grafts [7,8].

In the current study, we aimed to investigate the midterm patency rates of created AV fistulas with or without endothelial protection solution.

Materials and methods

This single-center case-control study was conducted in Ordu University Training and Research Hospital. Patients with end-stage renal disease were included in the study prior to AV fistulae creation between August 2018-August 2019. Ethics Approval was obtained from the local ethics committee of Ordu University, School of Medicine (Approval number: 2020/165). All AV fistulae were created by the same surgical team and patients who did not give consent to be included in the study were excluded. During the creation of an AV fistulae, endothelial protection solution (NOESIS®, Noegenix, Ankara, Turkey) was used in 27 patients, who constituted Group A, and not used in 22 patients, who were included in Group B (the control group). All patients were followed up for 6 months. Age, gender, body mass index (BMI), accompanying diseases (diabetes mellitus [DM] and hypertension [HT]) were recorded. All patients underwent clinical evaluation and preoperative Duplex scans to assess the patency of superficial veins. A functionally mature AVF is defined per Kidney Disease Outcome Quality Initiative (KDOQI) guidelines as one that can be easily cannulated and undergoes at least six successful consecutive dialysis sessions [1,3]. AV fistulae were routinely created under a local anesthetic field block. Magnifying loupes were used for all cases. The upper extremity vein graft was identified first and clamped after injection (Figure 1) of NOESIS® [Noegenix, Ankara, Turkey] in patients in Group A. The arterial site was explored, and the artery was prepared for anastomosis. Before AV anastomosis, the vein graft was unclamped and end to site anastomosis was performed. Similar procedures were performed in group B except NOESIS® administration to the vein graft. After anastomoses, mean flow on vein graft was evaluated with duplex scans, and complications, along with patency rates at the 3rd and 6th months were recorded. The vein endothelium was visualized with color duplex scans and compared.

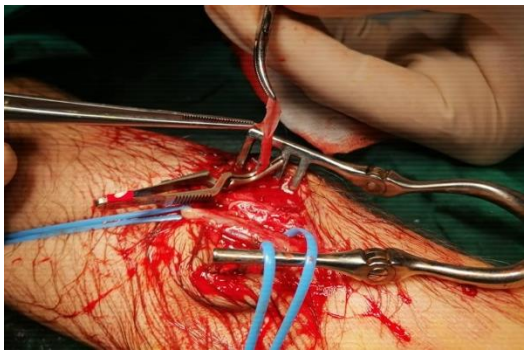

Figure 1: Preparation of a vein conduit and artery for creation of an AV fistula

Statistical analysis

Analysis of the data was conducted using SPSS (Statistical Package for Social Science) for Windows 15.0 package program. Descriptive statistics were presented as mean (standard deviation) for continuous variables, the differences between which were evaluated with Mann-Whitney U Test. Discrete variables were compared with Pearson Chi-square test. The comparison of groups was made with the Fisher exact test. $P<0.05$ was considered statistically significant.

Results

The groups were similar in terms of age, gender, and BMI values. There were 19 (70%) patients with DM in group A and 17 (77%) patients in group B. The number of patients with hypertension was 23 (85%) and 19 (86%) patients in groups A and B, respectively. The demographic findings are summarized in Table 1.

Table 1: Comparison of demographic variables between two groups

	Group A (n:27)	Group B (n:22)	*P*-value
Age mean (standard deviation)	55.88 (16.14)	60.63 (13.86)	0.334
Gender (n of males/%)	17/63	10/45	0.349
BMI mean (standard deviation)	27.74 (6.89)	26.00 (6.20)	0.537
Diabetes (n/%)	19/70	17/77	0.586
Hypertension (n/%)	23/85	19/86	0.582

BMI: Body mass index

There were 16 patients with radiocephalic (59%) and 11 patients with brachiocephalic (41%) anastomoses in group A and the distribution of fistula sites was similar with group B (Table 2). Mean (standard deviation [SD]) flows were 492.59 (135.60) mL/min and 537.05 (163.16) mL/min in groups A and B, respectively. Thrombosis was detected in 3 (11%) patients in group A and 4 (18%) patients in group B (Table 2). The 3rd month patency rates were significantly higher in group A (n=26, 96%) when compared with group B (n=14, 64% (P=0.007). Furthermore, the fistulae were patent at the 6th month in 25

(93%) (Figure 3) and 6 (27%) patients in groups A and B, respectively (P<0.001) (Table 2).

The walls of veins were more regular in Group A than those in Group B, as detected by duplex scans (Figure 2A, B). Figure 3 shows effective blood flow in the AV fistula which was created using the endothelium protection solution at the 6th month.

Table 2: Operational and follow-up findings of AV fistulae created with or without endothelial protection solution

	Group A (n:27)	Group B (n:22)	*P*-value
Fistula Type			
Radiocephalic n(%)	16 (59)	14 (64)	0.986
Brachiocephalic n(%)	11 (41)	8 (36)	0.779
Postoperative Findings			
Mean Flow on Vein After Anastomoses mean (standard deviation) (mL/min)	492.59 (135.60)	537.05 (163.16)	0.537
Complication (early thrombosis) n(%)	3 (11)	4 (18)	0.685
Patency on 3rd month n(%)	26 (96)	14 (64)	0.007
Patency on 6th month n(%)	25 (93)	6 (27)	<0.001

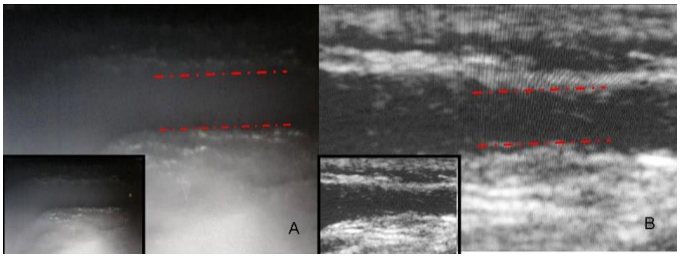

Figure 2: A: Small frame: The ultrasonographic visualization of arteriovenous (AV) fistula vein graft which was created using the endothelium protection solution, Big frame: The dashed red line shows the regularity of endothelial wall. B: Small frame: The ultrasonographic visualization of AV fistula vein graft which was transplanted without using an endothelium protection solution, Big frame: The dashed red line shows the irregularity of endothelial wall.

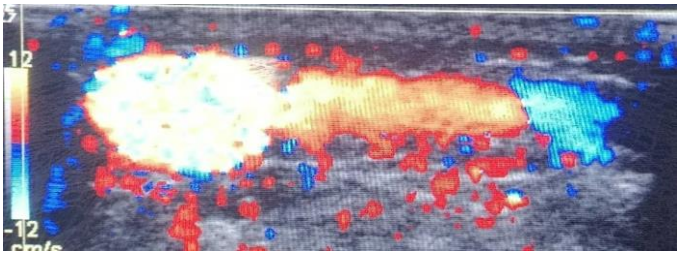

Figure 3: Effective blood flow in the AV fistula at 6th month, which was created using an endothelium protection solution

Discussion

To the best of our knowledge, this is the first study which compares the patency rates of AV fistulae that were created with or without endothelial damage inhibitor solution. Our results indicate that AV fistula creation with endothelial protection solutions yield higher patency rates. This solution seems to improve endothelial functions and provide regular venous endothelial wall, protecting the venous endothelium against neointimal hyperplasia.

AV fistula is still the best method for maintaining dialysis, which is why longer patency durations are important. The main determinants of patency are the quality of surgical anastomosis, the structures of vein and arterial endothelium, and venous endothelial hyperplasia [9-11]. Regardless of the quality of anastomosis, the vein endothelium exposed to arterialized blood flow undergoes hyperplasia and deformation along with oxidative stress factors, and occlusion begins on the venous side [10-12]. During surgery, mechanical harm may be done to the vein due to handling, harvesting and anastomotic repositioning, which leads to structural and functional damage of the grafted venous endothelium. These factors trigger three mechanisms after the creation of AV fistula: 1. Early thrombosis within hours, 2. Thrombosis due to intimal hyperplasia within months, and 3. Thrombosis in the late phase due to atherosclerosis within years [8,12]. Endothelial damage inhibitor solutions reduce these factors and prolong the patency of grafted veins. The key roles of solutions include preserving the venous conduit until implantation and protecting the endothelia against thrombosis and neointimal hyperplasia following implantation. Autologous blood, balanced saline or ringer solutions were used in the prior studies and significant results were reported [13,14]. However, determining of the best endothelium protection solution in which the conduit is stored until the time of implantation has been a major point of controversy with regards to the contents. The biocompatibility and antioxidant properties of endothelium protection solutions determine the protective capacity against ischemia-reperfusion and cellular damage, viability, and integrity during maladaptive processes due to handling, harvesting, and repositioning [8,12]. The recent studies about special endothelial protection solutions encourage their usage for harvested conduits. Haime et al. reported that utilizing endothelium protection solutions in saphenous venous grafts (before anastomosing to coronary artery) in patients undergoing coronary bypass surgery reduces the risk of long-term adverse events [15]. Moreover, some studies point the beneficial effects of hyaluronic-acid-containing products. Mochizuki et al. reported that hyaluronic acid glycosaminoglycans can regulate the endothelial functions by inducing the release of nitric oxide in canine femoral arteries. They concluded that "the hyaluronic acid (HA) glycosaminoglycans in the glycocalyx layer function as a shear-stress detection mechanism for shear-induced NO production" [16]. The disease related stress increases hyaluronidase activity, which is responsible for dissolving hyaluronic acid, and induces the generation of reactive oxygen species (ROS), causing damage to the endothelial glycocalyx. Studies claim that components of HA play a crucial role in the maintenance and enhancement of vascular integrity [17]. Bahcivan et al. studied the effect of hyaluronic acid-carboxymethyl cellulose on neointimal hyperplasia experimentally. They claimed that HA prevents the development of neointimal hyperplasia on vein grafts through a positive effect on tissue repair due to its barrier-forming nature [18]. Thus, we studied the effects of a HA-based endothelial protection solution for vein grafts for the creation of AV fistulas. The obtained results indicate that HA-based endothelial protection solution improves early and midterm patency rates of AV fistulae.

Conclusions

The HA based solutions can exert protective effects by enhancing endothelial functions and preventing neointimal hyperplasia against venous conduit occlusion in AV fistula patients. However, our study presents macroscopic findings and the cellular effects should be clarified with micro-analysis studies.

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