Internal Medicine and Medical Investigation Journal
E-ISSN: 2474-7750
Homepage: www.imminv.com

ORIGINAL ARTICLE

Effects of Heparin on Early Patency of Arteriovenous Fistula in Angioaccess Surgery of Patients with End-stage Renal Disease

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ARTICLE INFO

Article history
Received: Aug 14, 2017
Accepted: Oct 21, 2017
Published: Feb 08, 2018
Volume: 3
Issue: 1

Conflicts of interest: None
Funding: None

Key words
Arteriovenous Fistula,
Heparin,
Vascular Patency,
Chronic Kidney Disease

ABSTRACT

Background: Arteriovenous fistula (AVF) is the optimal method for obtaining vascular access for dialysis. Measures such as systemic anticoagulation have been proposed as means of increasing patency rates, but not enough evidence exists to support their application. In this study, we evaluated the efficacy of preoperative heparin injection on the patency of AVF during the first 24 hours after surgery and determined whether this measure can be used to prevent early thrombosis of the vascular access. **Methods:** This study was conducted on 150 patients admitted to Shohada-e-Tajrish Hospital for permanent vascular access placement during 2011-2012. Seventy-five patients were randomly assigned to receive 100 units/kg of heparin intraoperatively and at 24 hours after surgery. The AVF patency rate was assessed and compared to the control group. **Results:** All 75 patients who received heparin intraoperatively had a patent AVF 24 hours after surgery; this showed a statistically significant difference compared to the control group, among which only 69 (92%) patients had a functioning AVF (P=0.028). **Conclusion:** Systemic anticoagulation with heparin can be an effective option for preventing vascular access failure. However, considering the contradictory data on the usefulness of heparin injection, larger trials are needed to evaluate efficacy and adverse effects of systemic intraoperative anticoagulation in patients with end-stage renal disease before qualifying it as a method for increasing AVF patency.

INTRODUCTION

Chronic kidney disease is a global health issue with increasing prevalence (1). It is defined by the presence of kidney damage or decreased kidney function for at least 3 months, irrespective of the cause (2). In advanced cases, renal replacement therapies, including hemodialysis, peritoneal dialysis, hemofiltration, and renal transplantation, are suggested for patients as life-extending measures (3).

With the advances in the supportive treatment of chronic renal insufficiency and the increasing number of patients suffering from chronic kidney disease (4), vascular access placement surgeries, which are needed to perform dialysis, have become a very common surgical procedure throughout the world. Several vascular access techniques are available. If the patient is to be on dialysis for a short time, a double lumen catheter is an appropriate choice; but to obtain permanent vascular access, the three available options are arteriovenous fistula (AVF), arteriovenous graft, and venous catheter. AVF is considered the best long-term vascular access for hemodialysis (5) because it provides adequate blood flow and lasts a long time. Moreover, despite the observed complications such as infection, pseudo-aneurysm formation, hemorrhage, venous hypertension, neuropathy, limb ischemia, and cardiac failure (6), this technique has a lower complication rate compared to other types of vascular access, making it a more suitable choice (7). Grafts are prone to frequent stenosis and thrombosis. Most arteriovenous access failures result from endothelial cell injury, sta-

Published by Mehrabani Publishing LLC.

http://dx.doi.org/10.24200/imminv.v3i1.108

sis, and hypercoagulability, the latter being a major cause since patients with renal failure requiring hemodialysis are frequently at increased risk for hypercoagulable states, making these patients vulnerable to thrombosis and subsequent access failure (8). The available options for reversing AVF occlusion are costly and might result in technical failure (9); therefore, preventing and reducing vascular access failure is a priority. AVF patency is affected by many factors, including but not limited to vessel diameter, patient age, and concomitant vascular disorders such as diabetes (10). Use of adjuvant medical therapies such as intraoperative heparin administration (11-12), anti-platelet therapy (13-14), topical glyceryl trinitrate injection (15), and postoperative flow monitoring (16) have been proposed as means of increasing patency rates, but not enough evidence currently exists to support their use, especially considering the costs and probable side effects, such as increased risk of bleeding.

We conducted the current study to assess the effect of heparin on the early patency of AVF. We evaluated the efficacy of preoperative heparin injection on patency of the AVF during the first 24 hours after surgery and determined whether this measure can be used to prevent early thrombosis of the vascular access.

METHODS

This open-label randomized controlled trial, which is registered in the clinicaltrials.gov database (ID: NCT02493504), was conducted on patients admitted to Shohada-e-Tajrish Hospital in Tehran, Iran, for permanent vascular access placement. From April 2011 to September 2012, using a convenience sampling method, all patients referred by a nephrologist for AVF placement were included. Therefore, the need for this procedure was determined by the patients' own physician, and we, the authors, did not reevaluate the patients. Exclusion criteria consisted of having a contraindication for administration of anticoagulant agents and being candidate for arteriovenous graft or central venous catheter placement. A total of 174 patients were found to be eligible, of whom 24 were not willing to participate and withdrew from the study. Eventually, 150 patients were enrolled.

All patients were operated on by a single surgeon. The distal vascular system of the non-dominant upper extremity (mostly the left arm) was generally used unless unfavorable vasculature or previous fistula placement changed the preference. To assess the arterial circulation of the forearm and hand, radial and ulnar pulses were checked, and Allen's test was performed. In cases with abnormal findings of these evaluations, Doppler ultrasound was done. Local anesthesia was induced by percutaneous injection of 4 mg/kg lidocaine hydrochloride 0.5% solution. The anastomosis technique was either end-to-side or side-to-side. Continuous sutures were taken using a number 6.0 prolene suture. Through a simple randomization method, 75 patients were assigned to receive 100 units/kg of intravenous heparin after dissection prior to anastomosis; the other 75 received no intraoperative heparin injection. Auscultation of bruit and palpation of thrill were used to assess AVF patency in the first 24 hours after AVF placement. Concurrently, patients were evaluated regarding early complications of surgery, including hemorrhage, hematoma, and wound dehiscence.

Data were analyzed with SPSS v. 13 software using independent sample t-tests, the chi-squared test, and Fisher's exact test as needed. *P* values less than 0.05 was considered statistically significant.

Patient enrollment was voluntary, and no costs were imposed on the patients. Study protocol was in accordance with the 1975 Declaration of Helsinki, and written informed consent was obtained from the included patients.

RESULTS

Mean age was 54.63±19.71 for patients in the control group and 52.37±15.78 years for patients in the intervention group. Fifty-four patients (66.7%) in the control group and 50 patients (72%) in the intervention group were men. In the control group, 50.7% of patients had diabetes, whereas in the intervention 37.3% of patients had diabetes. In the control group, 77.3% of patients had a history of hypertension, whereas 70.7% of patients in the intervention group had a history of hypertension. In the control group, 9.3% of patients were cigarette smokers, whereas 20% of patients in the intervention arm were cigarette smokers. In the control group, 9.3% of patients had undergone previous fistula placement, whereas 18% of patients in the intervention group had undergone previous fistula placement. As for the anastomosis technique, 10.7% of patients in the control group and 21.3% of patients in the intervention arm were end-to-side, with the rest being side-to-side (Table 1). No significant differences were observed between the two groups regarding the mentioned variables ($P>0.05$). Moreover, none of the patients presented with bleeding, hematoma, or wound dehiscence.

Table 1. Correlation between evaluated variables and intravenous heparin administration

All 75 patients who had received heparin intraoperatively had a patent AVF 24 hours after surgery, which showed a statistically significant difference compared to the control group, among which only 69 (92%) of patients had a functioning AVF ($P=0.028$) (Table 1). Since no patients in the intervention group presented with AVF failure, the odds ratio could not be calculated to evaluate the correlation between heparin administration and AVF patency.

DISCUSSION

AVF is the optimal method of obtaining vascular access for dialysis, and measures to increase patency rates of AVF have become a subject of interest for researchers. One of the proposed techniques to reduce vascular access failure is systemic anticoagulation. Unfortunately, there are not enough studies available on the efficacy of heparin in preventing access occlusion.

In our study, we evaluated the effect of intraoperatively administered heparin on the patency of AVF 24 hours after surgery. Our results showed a statistically significant difference between the patency rates of AVF in patients who had received 7500 units of heparin prior to anastomosis (100% patency in the intervention group vs. 92% patency in the control group) ($P= 0.028$).

Table 1. Correlation between evaluated variables and intravenous heparin administration

Variables	Intravenous heparin		*P* value
	Negative	Positive	
Age (Mean±SD)	54.63±19.71	52.37±15.78	>0.05
Sex, N (%)			
Men	50 (66.7)	54 (72)	>0.05
Women	25 (33.3)	21 (28)	
Diabetes, N (%)			
Positive	38 (50.7)	28 (37.3)	>0.05
Negative	37 (49.3)	47 (62.7)	
Hypertension, N (%)			
Positive	58 (77.3)	53 (70.7)	>0.05
Negative	17 (22.7)	22 (29.3)	
Smoking, N (%)			
Positive	7 (9.3)	15 (20.0)	>0.05
Negative	68 (90.7)	60 (80.0)	
Previous Fistula, N (%)			
Positive	7 (9.3%)	14 (18.7)	>0.05
Negative	68 (90.7)	61 (81.3)	
Current Fistula Type, N (%)			
End-to-Side	8 (10.7)	16 (21.3)	>0.05
Side-to-Side	67 (89.3)	59 (78.7)	
Function after 24 Hours. N (%)			
Patent	69 (92.0)	75 (100)	0.028
Not Patent	6 (8.0)	0 (0.0)	

Our results agreed with several other studies on the same subject. In 2007, Sharatkumar et al. examined the efficacy of a specific thromboprophylaxis protocol on the patency of AVF in 22 pediatric patients in Michigan (17). The protocol consisted of 5-10 units/kg/hr unfractionated heparin infusion postoperatively, followed by subcutaneous low-molecular-weight heparin until AVF was matured. They observed that the incidence of thrombosis was lower in patients who received the protocol (12.5% compared to 83%; $P<0.05$) and concluded that anticoagulation can be considered feasible in preventing early thrombosis at AVF (17).

In another study by Ravari et al. (11), which was conducted on 198 end-stage renal disease patients in Iran in 2005, the patency rate 2 weeks after surgery showed a statistically significant difference between those who received heparin and those who did not (85% vs. 74%; $P=0.046\%$). Therefore, they concluded by recommending the routine use of intraoperative heparin in AVF operations (11).

However, other trials have yielded different results regarding the efficacy of heparin administration on access patency. In their 2008 study conducted on 50 patients in Nepal, Bhomi et al. observed that the patency rate 6 weeks after surgery was 96% for patients who received 5000 units of heparin and 92% for those who did not (18). They concluded that systemic coagulation during vascular access surgery offers no benefit in terms of primary patency, while increasing the risk of hemorrhagic complications.

A 2008 study by D'Ayala et al. (19), conducted on 115 patients in New York, evaluated the efficacy of systemic anticoagulation on patency of both AVF and arteriovenous grafts. According to the results of this study, at 1 month and 3 months after surgery, the patency of the vascular access did not increase significantly in patients who had received heparin (84% vs. 86% at 1 month and 68% for both groups at 3 months), while perioperative bleeding complications did increase ($P=0.008$) (19).

In 2010, Wang et al. published the results of a double-blind randomized controlled trial, which had been conducted on 48 patients undergoing AVF creation (20). Their results suggested that intraoperative administration of heparin had no statistically significant effect on patency rates (92% vs. 86%; $P=0.65$) or postoperative bleeding complications ($P=0.61$) (20).

In 2011, Charlton-Ouw et al. compared the patency of AVF with heparin-bonded and conventional grafts (21). Evaluating the outcomes of 64 brachiocephalic fistula, 21 brachioaxillary heparin-bonded, and 21 brachioaxillary conventional AV grafts, they found the 1-year cumulative patency rates of these methods to be 83%, 44%, and 67%, respectively $P=0.001$).

Therefore, given that no consensus has been reached on this matter and considering the number of conflicting trials, a meta-analysis of the trials, including the present survey, is recommended.

This study's limitations include lack of blinding and lack of assessment of AVF patency beyond 24 hours after surgery.

CONCLUSION

We found a statistically significant difference between the patency rates of AVF at 24 hours after surgery in patients who received heparin prior to anastomosis ($P=0.028$). Considering the contradictory data on the usefulness of heparin injection and the limitations of our study, larger trials with different follow-up durations are needed to evaluate the efficacy and adverse effects of systemic intraoperative anticoagulation in end-stage renal disease patients, to determine whether intraoperative heparin administration can be an effective method for increasing AVF patency.

ACKNOWLEGMENTS

This research was conducted as part of Dr. Fatemeh Hoseinzadegan's dissertation.

AUTHOR CONTRIBUTIONS

Study concept and design: Mozafar, Hoseinzadegan
Acquisition of data: Hoseinzadegan, Solatpour
Statistical analysis and interpretation of data: Hoseinzadegan, Lotfollahzadeh, Baikpour
Drafting of the manuscript: Lotfollahzadeh, Baikpour, Amraei

Critical revision of the manuscript for important intellectual content: Baikpour
Administrative, technical, and material support: Baikpour, Amraei
Study supervision: Mozafar

CONFLICT OF INTEREST

The authors have no financial interest related to the material in the manuscript and declare no conflicts of interest. The study received no funding.

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