

Effect of Intra Operative Intravenous Injection of Heparin on Patency Rate of Radio Cephalic Autogenous Arteriovenous-Fistula in Chronic Renal Failure Patients

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Background: Currently, there is no standard for the use of systemic heparin during creation of Arteriovenous (AV) fistula to decrease the incidence of postoperative thrombotic complications.

Objectives: The goal of this study was to evaluate the effects of intra-operative IV heparin on patency rate and postoperative bleeding complications in patients undergoing surgery for AV fistula.

Patients and Methods: A prospective, randomized controlled study was performed on 50 patients undergoing AV fistula creation, who were randomly divided in two groups. The control group received no systemic heparin and the heparin group received 5,000 units of intravenous heparin before clamping of the artery.

Results: There was a significant difference in patency rate between the heparin and control groups (96% vs. 72%, $P = 0.021$), and there were no significant differences in operative time ($P = 0.55$). Perioperative bleeding was not significantly different between the two groups.

Conclusions: The results suggest that intra operative administration of heparin has statistically significant effects on patency rates yet not on postoperative bleeding complications. Larger trials with longer follow-up durations and assessment of maturation rates are needed to determine this effect on fistula outcome.

Keywords: Patency Rate; AV Fistula; Systemic Heparin

1. Background

Despite impressive advances in medicine, increasing chronic kidney disease in modern societies is alarming (1). Nevertheless there has been progress in the fields of renal transplantation and hemodialysis, with these methods being the most common treatment strategies for patients with renal insufficiency (2, 3).

The mainstay in chronic dialysis is an adequate vascular access for dialysis that could provide at least 300 mL of blood per minute with good short-term and long-term performance and minimum complications (2, 4). Arteriovenous fistula is still the standard route for patients requiring chronic dialysis vascular access (5).

Every patient has a few anatomic sites for creation of arteriovenous fistula, and because of constant use, fistulas usually have a time-limited performance. Several factors can influence the performance and patency of Arteriovenous (AV) fistula, such as history of previous catheterization, underlying hypercoagulopathy and co-morbidities like diabetes and hypertension (6).

The use of systemic heparin preoperatively, is one of the most common measures in patients undergoing

vascular surgery (7) yet the need for intraoperative use of anticoagulants during AV fistula formation has not been mentioned explicitly in previous studies. The use of heparin can reduce early anastomotic thrombosis, yet on the other hand, it could increase time of operation due to increased chance of bleeding during surgery and need for more hemostasis (8).

2. Objectives

This study aimed to evaluate the efficacy and side effects of systemic anticoagulants on patency rate of radio-cephalic AV fistula and incidence of post-operative and intra-operative complications.

3. Patients and Methods

This study included 50 patients, with chronic renal failure requiring hemodialysis, which were candidates for arteriovenous fistulas at a radio-cephalic site. The patients were enrolled and randomly divided to two groups. The first group (heparin group) received intra-operative in-

travenous heparin (5,000 units), while the second group (control group) received no routine anticoagulants. Next, intra-operative complications and post-surgical outcome in the two groups were compared. Surgery was performed under the supervision of a surgeon.

Patients with a history of previous fistula surgery or patients, who were candidates for fistula construction at another location, were excluded from the study. In addition, patients who had a history of anticoagulant consumption and one patient with underlying vasculitis (lupus) were also excluded. Venous mapping was performed pre-operatively by Doppler ultrasound in only one patient, who had a history of manipulation and ipsilateral subclavian vein catheterization. Other patients were evaluated by considering their history and physical examination, to select the site of fistula.

The non-dominant hand was chosen in all patients because it has a larger cephalic vein diameter. All surgical procedures were performed under local anesthesia with 2% lidocaine without epinephrine. Patients in the heparin group received a single dose (5,000 IU) of intravenous heparin, right before arterial clamping. Hydrostatic dilation of cephalic vein was done before anastomosis, in all patients. Washing of vein and artery with heparinized normal saline was performed in both groups during the anastomosis. All anastomoses were done side to side with a suture material polypropylene 7 - 0 as the running suture. After surgery, all patients were hospitalized for at least 24 hours to clear early complications such as post-operative bleeding and hematoma.

After 24 hours, the amount of fistula blood flow was measured with color Doppler ultrasound and patients were discharged for weekly examination and evaluation of fistula performance at the end of six weeks. Fistula performance was examined with a touch of local thrill and engorgement of superficial veins in the involved arm. The two groups were matched regarding underlying diseases such as diabetes, hypertension, coronary heart disease and hyperlipidemia and hyper-coagulopathy.

Patients were recruited after providing an informed consent. Data were analyzed using the SPSS version 18 software.

4. Results

Fifty patients with chronic renal failure were randomly divided in two groups of 25 subjects. In the group receiving heparin, 15 (60%) patients were male and 10 (40%) patients were female and in the other group not receiving heparin, 17 (68%) patients were male and 8 (33%) patients were female. The mean age of patients in the heparin

group was 57.5 ± 15.8 standard deviation (SD) and in the other group this was 53 ± 15 SD. There were no significant differences between the two groups for demographic segmentation. In terms of age, sex and underlying disease leading to kidney failure, there was no significant difference between the two groups and the two groups were matched in this regard. There were no significant differences regarding the cause of chronic renal failure between the two groups (Table 1).

In the study group, 11 patients (44%) had a history of previous dialysis while in the control group 9 patients (36%) had a history of previous dialysis ($P = 0.56$). There was no fistula failure in the 11 patients receiving heparin yet in the control group, there were seven failed fistulas including 4 patients (57%) with a history of previous dialysis ($P = 0.17$); this indicated that a history of previous hemodialysis had no significant effect on the performance of fistula in both groups. It can be concluded that heparin during hemodialysis used for catheter washing has no effect on fistula patency rate.

In terms of comorbidities, there were no significant differences between two groups:

1. Diabetes was present in ten patients (40%) of the study group versus six patients (24%) of the control group ($P = 0.22$).

2. Hypertension in the study group was observed in 24 patients (96%) while in the control group it was found in 21 (84%) patients ($P = 0.34$).

3. Coronary heart disease was seen in seven (28%) of the heparin cases and four (16%) of the control cases ($P = 0.3$).

4. Hyperlipidemia was observed in two patients of the heparin group (8%) and two of the control group ($P = 1$).

Frequency of postoperative complications in patients who entered the study were as follows (Table 2):

Hematoma was seen in three (12%) patients of the study group and one (4%) patient of the control group, ($P = 0.29$) with no statistical differences. In all patients hematoma managed conservatively with no need to drainage.

Bleeding was observed in one case in each group (4%) with no difference between the two groups. The patient who had received heparin underwent reoperation to evaluate the site of bleeding and there was no active bleeding and it was controlled with packing. For the patient who had not received heparin, conservative management was done without surgery. In none of these patients the fistula had failed. In the group that had received heparin, none of the patients showed early postoperative thrombosis while early thrombosis was observed in seven patients (28%) of the group that had not received heparin ($P = 0.004$). There was a meaningful difference between the two groups.

Table 1. Distribution of the Underlying Etiological Disease ^a

| Group | Diabetes | Hypertension | Polycystic Kidney | Pyelonephritis | Glomerulonephritis | Nephrolithiasis | Unknown | P Value |
|---------|----------|--------------|-------------------|----------------|--------------------|-----------------|---------|---------|
| Heparin | 10 (40) | 3 (12) | 1 (4) | 4 (16) | 1 (4) | 1 (4) | 5 (20) | 0.71 |
| Control | 5 (20) | 2 (8) | 2 (8) | 7 (28) | 2 (8) | 2 (8) | 5 (20) | 0.71 |

^a The values are presented as No. (%).

Table 2. Frequency of Surgical Complications^a

| | Heparin Group | Control Group | P Value |
|------------------|---------------|---------------|---------|
| Early | | | |
| Hematoma | 3 (12) | 1 (4) | 0.29 |
| Bleeding | 1 (4) | 1 (4) | 1.0 |
| Oozing | 5 (20) | 2 (8) | 0.22 |
| Early thrombosis | 0 | 7 (28) | 0.004 |
| Late | | | |
| Late thrombosis | 1 (4) | 2 (8) | 0.55 |
| Infection | 1 (4) | 0 | 0.31 |

^a The values are presented as No. (%).

Post-operative blood oozing was observed in five (20%) of the patients in the study group who had received heparin and in two (8%) patients from the control group ($P = 0.22$). This difference was not statistically meaningful. The fistulas did not fail in any of these patients.

Delayed complications including infection and thrombosis:

Late thrombosis was observed in one patient (4%) in the group that received heparin and in two patients (8%) of the control group; ($P = 0.55$) the difference was not statistically significant. Wound infection was observed in one patient (4%) of the study group and no patient in the control group ($P = 0.31$). There was no significant difference regarding wound infections between the two groups. There was only one case with wound infection, which was the same patient in the heparin group that had undergone reoperation for bleeding. Fistula did not fail after reoperation.

Performance of the fistula was evaluated by the presence of thrill or bruit, 24 hours, three and six weeks after the operation. At the same time, distal arterial pulses were examined and the following results were obtained:

During the first 24 hours, the patency of fistula was confirmed by touching the surgical area and presence of thrill in 24 patients (96%) from the group that had received heparin versus 18 (72%) patients from the control group ($P = 0.021$). Also in the first 24 hours, distal pulses were detected in 100% of patients who had received heparin, and 84% (21 individuals) of patients who had not received heparin ($P = 0.037$). Thus there was a significant difference between the two groups in the first 24 hours, with better results for the heparin group.

After three weeks, fistula was patent (thrill +) in 22 patients (88%) in the heparin group versus 16 patients (64%)

in the control group ($P = 0.047$). Also, after three weeks, pulses were detected in 100% of patients from the case group and 21 patients (84%) of the control group ($P = 0.037$). Thus there was a significant difference after three weeks regarding thrill and pulses, with better results found for the heparin group.

After six weeks, 22 (88%) patients in the heparin group and 15 (60%) patients from the other group had patent fistula with thrill ($P = 0.024$). Also, after six weeks, 24 (96%) patients in the heparin group had distal pulses versus 19 (76%) patients in the control group. ($P = 0.042$); again there was a statistically meaningful difference with better results for the heparin group after six weeks regarding thrill and pulses.

The mean operative time was 41 ± 7.4 minutes for the heparin group and 40 ± 4.7 minutes for the group that did not receive heparin ($P = 0.55$).

After 24 hours, blood flow (flow rate) of arteriovenous fistula was measured with Doppler ultrasound and the average flow in the heparin group was 566.04 ± 143.21 and in the control group was 572.22 ± 206.83 ($P = 0.9$, no difference).

There was no statistically significant difference between the two groups regarding aspirin consumption (6 (24%) patients in the heparin group versus 5 (20%) patients in the group without heparin) ($P = 0.73$) (Table 3).

None of the patients had a history of arterial thrombosis or intraoperative bleeding.

In predicting factors affecting failure of fistula function, among intervening factors (diabetes, patient's age and sex, hypertension, hyperlipidemia, coronary heart disease, history of anti-coagulant use and post-operative hematoma) based on a logistic regression, coronary artery disease and intra-operative heparin were significantly more effective on patency rate.

Table 3. Fistula Performance and Distal Pulses After Surgery^a

| | Heparin Group | Control Group | P Value |
|-----------------------|---------------|---------------|---------|
| After 24 hours | | | |
| Thrill + | 24 (96) | 18 (72) | 0.021 |
| Pulse + | 25 (100) | 21 (84) | 0.037 |
| After 3 weeks | | | |
| Thrill + | 22 (88) | 16 (64) | 0.047 |
| Pulse + | 25 (100) | 21 (84) | 0.037 |
| After 6 weeks | | | |
| Thrill + | 22 (88) | 15 (60) | 0.024 |
| Pulse + | 24 (96) | 19 (76) | 0.042 |

^a The values are presented as No. (%).

5. Discussion

Creating and maintaining arteriovenous fistula is still a very important issue and has high costs for patients allocated to a dialysis program, in addition, the closure of fistulas in dialysis patients leads to major complications. Classically embedding an AV fistula is started from distal extremities and if it fails, proximal sites are considered. National kidney foundation-disease outcome quality initiative (NKF-DOQI) guidelines offer anastomosis between the radial artery and cephalic vein in the distal section of the forearm as the first choice for vascular access in patients undergoing hemodialysis (9). Also based on these guidelines patient's vessels are preferred over synthetic vascular grafts. Vascular anastomoses per second are associated with a risk of premature failure. However, the percentage of success is not exact, yet it has been reported to be between 36 and 56%. This study concluded that a lack of success was seen in 9 (16%) of fistulas, which may be the result of low sample number or selection of distal fistula.

A literature review on the use of systemic intra-operative anticoagulants showed different patterns; while some surgeons use systemic anticoagulants routinely, others preferred heparinized saline for local washing of anastomosis site (10-17).

In a study conducted during 2006 by Yevzlin et al. (18), it was shown that the use of anti-platelet drugs such as aspirin, dipyridamole and ticlopidine was associated with worsened outcomes on AV fistula. Another study conducted by Flye et al. (19) showed that taking aspirin before surgery and after surgery results in better function of the fistula. In our study, aspirin had no effect on patency rate of fistula, however, due to the low number of patients taking aspirin, other studies are required to confirm or refute this conclusion.

In a study conducted during 2008 by D'Ayala et al. (20) complications related to bleeding during and after surgery were significantly higher in the group that received heparin ($P = 0.008$). In our study there was no significant statistical difference in bleeding, hematoma and oozing

intra-operatively or post-operatively between the two groups. In a study conducted during 2010 by Wang et al. (7), postoperative hematoma was seen in three patients receiving heparin (12%) and one patient from the control group (5%), with no significant difference ($P = 0.61$). In another study by Bhomi et al. (8) in 2008, postoperative bleeding in patients receiving anticoagulants was significantly higher than the control group ($P < 0.001$).

In none of the studies, post-operative thrombosis was assessed at 24 hours (21-23). In this study, early postoperative thrombosis occurred in seven patients (28%) of the control group, who had not received heparin, and none of the patients that had received heparin. Four out of seven patients underwent repeated surgery, and fistula was located in another place. In one patient, angioaccess was made with Gore-Tex graft. The mean operative time was not significantly different in any of the groups, which is compatible with the results of previous studies (8, 20).

In this study performance of fistula was evaluated with existence of thrill or bruit after 24 hours, three and six weeks, and there was a significant difference between the two groups, indicating patency rate was higher in the group that received systemic heparin during the procedure. This result was confirmed by the study of Flye et al. (19) yet the study of Wang et al. (7) and Bhomi et al. (8) did not verify these results. Also, in a study by Sharathkumar et al. (24) performed on children, use of prophylactic heparin followed by anticoagulant was effective for decreasing rate of fistula thrombosis.

The use of heparin significantly lowers chance of fistula failure based on logistic regression analysis, while not having a history of heart disease makes fistula less likely to fail. Other variables related to age and gender in this study could not predict fistula failure, which is due to the random selection of samples. In total, using intra-operative systemic heparin in radio-cephalic AV fistula has no effect on hemorrhagic complications during surgery and does not prolong operative time while it increases fistula patency rate.

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