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Comparison of patency of heparin-coated with non-heparin coated catheters in patients under hemodialysis: a randomized clinical trial

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Objective: **to compare the patency and incidence of infection in patients under hemodialysis with the heparin-coated catheter and non-heparin coated catheter.** ***Methods and materials:*** **In this randomized clinical trial (IRCT: N 2016010925918), 100 patients with the end-stage renal disease, referred to the Imam Reza hospital in Kermanshah, Iran, were recruited. The patients were randomized into either Palindrome chronic catheter, 14.5 F-19 cm (Non-heparin coated) or Palindrome H chronic catheter, 14.5 F-19 cm (heparin coated) groups (50 patients in each group). The catheter lines in both groups were filled with 5 ccs of TauroLock (heparin +antibiotic), then in the heparin-coated group, the tip to cuff of catheters were heparinized and the second group left without any more intervention and was considered as control. The patients were followed up for five months (150 days) and the rate of patency and the incidence of infection were compared between two groups.** ***Results:*** **100 patients including 55 males and 45 females, mean age 52.00±15.00 (range 30-80) years old were evaluated. The rate of patency in non-heparin group one month after placement was 83%, and decreased to 72% after three months and 54% after five months. in the heparin-coated catheter group the rate of patency was non-significantly, higher than non- coated and was 90%, 79% and 64% at one, three and five months after procedure, respectively (P=0.87). The incidence of infection in non-heparin coated catheters was significantly higher than heparin coated group (20% vs 10%, P=0.001).** ***Conclusion:*** **We showed that in case of filling of catheters with a TauroLock solution, the heparinization of catheters' tip to cuff does not improve the patency, however, it decreases the incidence of infection.**

INTRODUCTION

The majority of patients with the end-stage renal disease are hemodialyzed, and some of these patients are using the catheters for this purpose (1, 2, 29-31). Thrombosis and infection are two most complications related to these catheters (3), thrombosis may be formed during hours after placement (4), and may develop to the central vein if remain untreated longer (5). The presence of thrombus in hemodialysis catheters may function as a nidus for biofilm formation and initiates the bacterial colonization and infection (6). The thrombus and infection in these catheters can impair the catheter function, restrict dialysis blood flow and decrease the volume and dose of dialysis (7). Unfractionated heparin as a catheter-locking solution is a common agent used in patients with end-stage renal failure under dialysis to prevent thrombosis (8). The comparative studies indicate that heparin decreases the creation of clot and thrombus in the lumen (9), moreover, other studies on the anti-infection effect of heparin in patients under hemodialysis have revealed a lower rate of bacterial colonization, infection, and bacteremia with heparin-coated catheters (10, 11). These investigations have found that heparin decreases the adherence of bacteria to the catheters and subsequently decreases the rate of infection among the patients under hemodialysis (12, 13). However, the findings of previous investigations are not conclusive and some of the studies provided conflicting results with the use of heparin catheter-lock solution (14-16). Therefore, we conducted this randomized clinical trial to compare the patency and incidence of infection of heparin-coated and un-heparinized catheters among patients under hemodialysis with a permanent catheter (tunneled), in Imam Reza hospital in Kermanshah in the west of Iran

METHODS AND MATERIALS

In this randomized clinical trial (IRCT: N 2016010925918), all patients with the end-stage renal disease referred to the Imam Reza hospital in Kermanshah, Iran, were evaluated. Of these, all patients under hemodialysis, who were not under anticoagulant and antiplatelet treatment were enrolled. However, the patients who did not refer for follow up and patients with immune deficiency were excluded from the study. Finally, 100 patients who met including criteria were selected and the study procedure was described for them and signed consents were taken. Moreover, the ethics committee of Kermanshah University of medical science confirmed the study protocol. Then patients were interviewed and demographic data such as sex and age were recorded, moreover, the presence or absence of systemic diseases such as coronary artery disease (CAD), diabetes and systolic and diastolic blood pressure was asked and recorded. Then the patients, based on random numbers

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generated by computer, were randomized into either Palindrome chronic catheter, 14.5 F-19 cm (Non- heparin-coated catheter) as control group or Palindrome H chronic catheter, 14.5 F-19 cm (heparin-coated catheter) as intervention group (50 patients in each group). In the operation room, the catheters were placed under ultrasonography guidance, in the internal jugular by an expert vascular surgeon. Then in the first visit, a surgery resident checked the primary function of the catheters by aspiration of 10 ml of blood, and to check the place of catheter's tip, the chest x-ray was taken. Then the catheter lines in both groups were filled with 5 ccs of TauroLock (antibiotic plus heparin). In the heparin-coated catheter group (intervention group, n=50) the tip to cuff of the catheters were heparinized. On the other hand, the second group left without any more intervention and was considered as a control group (n=50). Next day the patients were visited by surgery resident and the hemostasis and chest radiograph of the patients were evaluated. The patients were followed up for five months (150 days) and the patency and function of the catheters were assessed. Moreover, fistula or graft maturation, catheter replacement, thrombosis of the catheter tip and the infection were measured and recorded in patients files during five months.

Definition

Infection was defined if fever sustains in spite of antibiotic therapy for 2 days. Catheter dysfunction was defined as the inability to deliver adequate flow for dialysis because of thrombosis.

Statistical Analyses

The data were analyzed using SPSS version 22. N (%) shows categorical data and mean ± SD continuous ones. The Chai_2 or Fisher's exact test was used to compare categorical data and the Student's t-test to compare continuous variables. P<0.05 was considered significant.

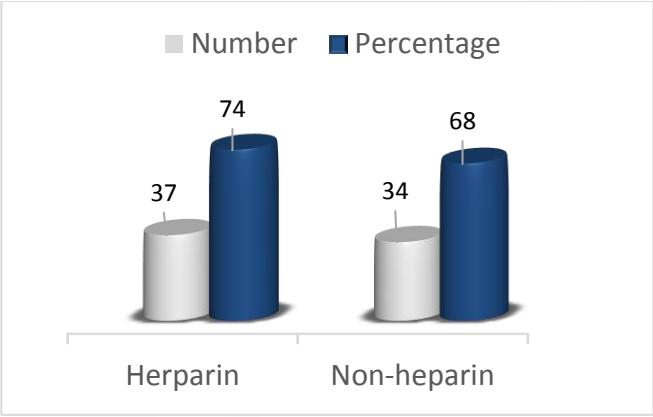

Figure 1 Distribution of the underlying condition of cardiovascular diseases in individuals by type of catheter

RESULTS

100 patients including 55 males and 45 females, mean age 52.00±15.00 (range 30-80) years old were evaluated. The difference between two groups was not significant regarding sex, age and the incidence of hypertension, diabetes mellitus, and coronary artery disease (Fig 1). The rate of patency in non- heparin group during one month after placement of the catheters was 83% and decreased to 72% after three months. The rate of patency decreased to 54% five months after placement of the catheters. On the other hand the rates of patency in the heparin-coated catheter group one month after placement was 90%, 79%, and 64% at one, three and five months later, that is higher than the non-heparin group, however, the difference between two groups was not significant (P=0.87). In this trial, we confirmed that heparin decreases the bacterial adherence, bacterial colonization and consequently the rate of infection. Regarding this fact, the rate of infection in patients with non-heparin coated catheters was 10 (20%) that was significantly lower than the heparin-coated group by 10 % (5 patients), (P=0.001), (Table 1).

Table 1 the mean of age and frequency sex and previous disease and the rate of patency and infection among two groups

		Non-heparin coated catheter	Heparin coated catheter	P
age	year	51.00±14.00	53.00±15	
sex	Male	30(60%)	25(50%)	0.16
	female	20(40%)	25(50%)	
Diabetes mellitus		26(52%)	30(60%)	0.53
Hypertension		46(92%)	47(94%)	1
Coronary Artery Disease		34(68%)	37(74%)	0.21
patency	30 days	83%	90%	0.87
	90 days	72%	79%	
	150 days	54%	64%	
infection		10(20%)	5(10%)	0.001

DISCUSSION

Prevention of thrombosis among the patients under hemodialysis is a matter of concern and to prevent thrombosis and infection the specialists in dialysis centers lock both lumens of the catheter with heparin (1000 to 10,000 units/mL) or other anticoagulant agents such as sodium citrate (14). Heparin has several uses, however, the use of heparin as a catheter lock solution is very common (15). In this randomized clinical trial, we compared the effect of heparin-coated catheters with non-heparin coated catheters on the patency and incidence of infection among 100 patients who were under dialysis in our center. We found that heparin-coated catheter did not influence the patency and catheter's function, however, the rate of infection in heparin-coated catheter group was significantly lower than uncoated heparin catheter group. It seems that heparin coated catheter doesn't prevent thrombus formation at the catheter tip. Catheter related thrombus is a nidus for catheter biofilm formation (6), this may explain how heparin coated could reduce infection without affecting thrombus. In line with our results, a study by Jain et al. in 2009 compared the frequency of thrombosis and infection, among 89 patients with heparin-coated catheters with 86 patients who had non-heparin coated catheters. They revealed that the rate of infection and bacteremia in heparin-coated catheters was lower than non- coated catheters, however, the thrombosis and subsequently, the catheter dysfunction and patency in two groups was the same (16). Harmoniously, a study by Allemang et al. in 2014 failed to show better patency with polytetrafluoroethylene (PTFE) grafts compared to the group without heparin bonding (17). Conversely, Davidson et al. in a controlled study compared, expanded polytetrafluoroethylene (e-PTFE) grafts (N=83) with 67 controls and reported that heparin-binding technology for artificial surfaces improved the rate of patency by 20% in 80 % of patients in a year (18). Although, the exact reason for such discrepancy among the studies are not clear and need more evaluation, however, it may be because of different doses of heparin, different study design and

sample size are possible reasons of these inconclusive findings among the studies across the globe. In addition to the thrombosis, infection among patients under hemodialysis is so serious and the mortality rate and hospitalization due to infection related to the catheters are high among them (14-16). To overcome this complication some studies have added antibiotic to the heparin and reported better outcomes than using heparin alone (14-19). As we mentioned above, in current practice, we coated the catheters in both groups with TauroLock (antibiotic plus heparin), and observed a significant reduction in the rate of infection, So, because the two groups received the TauroLock, it is obvious that heparinization of the catchers' tip to cuff has decreased the rate of infection. Similar to our work, a study by Saxena et al. used cefotaxime-heparin locks solution, in 208 patients under hemodialysis, and reported a significant reduction in catheter thrombosis and in the rate of catheter-related bloodstream infections (CRBSI) (20). Although, some authors have reported a comparable effect with the high and low dose of heparin among the patients under hemodialysis, however, some others indicated that the dose of heparin is an important factor and has a direct impact on the outcome of the procedure. A meta-analysis by Han et al. in 2016, reported a lower incidence of infection and bleeding without any effect on thrombosis and catheter dysfunction with the low dose of heparin (< 5,000 U/mL) (21). However, a study by Thompson et al. reported that heparin 1,000 IU/ml catheter lock solution, decreases the systemic heparinization requirement compared to heparin 5,000 IU/ml, moreover, they showed that heparin 1,000 IU/ml catheter lock solution did not increase the rate of infection and catheter dysfunction in comparison with heparin 5,000 IU/ml (22). These findings are not conclusive and the right dose of heparin with maximum effect and minimum side effect in patients under hemodialysis need more studies. Some adverse effects are not avoidable and limit the use of heparin and heparin should be used with caution, for instance, some of the heparin may leak into the systemic circulation and prolong the partial thromboplastin times (PTT) for hours and subsequently increases the risk of bleeding (23, 24). On the other hand, use of heparin in patients under chronic hemodialysis increased the risks of cardiovascular mortality, due to the heparin antibodies (25, 26). Furthermore, heparin has chondroitin sulfate, that in higher doses, it is toxic and may cause serious diseases and death (27), additionally, heparin may stimulate biofilm formation (28).

Second major complication of applying central vein catheter is bacteremia furthermore insertion of catheter forms bacterial biofilm on inner surface of the catheter. Taurolock (Taurolidine + 4% citrate) will protect against bacterial and fungal adhering to catheter (6).

This was a randomized clinical trial, which was the strength of this work; however, the practice was conducted in a single dialysis center in Kermanshah on a relatively small sample size, therefore the results may not generalize to all patients under hemodialysis. Further multicentric studies with larger series are needed to confirm the findings reported here.

CONCLUSION

The trial revealed that until the lines of catheters are filled by TauroLock solution (heparin+ antibiotic) the heparinization of the catheters' tip to cuff do not improve the rate of patency, although, the heparinization of the catheters' tip to cuff significantly decreases the incidence of infection among patients under hemodialysis.

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Conflicts of interest
The authors declare that they have no competing interest.

Ethical considerations
Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The study was approved by the institutional ethics committee of Kermanshah University of Medical Sciences and was registered in Iranian Registry of Clinical Trials (identifier: IRCT2016010925918N1; http://www.irct.ir/trial/21615). Written informed consent was obtained from all participants too.

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