

Taurolock versus saline 5% on preventing infection and dysfunction of hemodialysis catheters; a randomized, double blind controlled clinical trial

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ABSTRACT

Introduction: Despite the higher rate of morbidity and mortality, the use of central venous catheters has increased significantly compared to arteriovenous fistula. So far, no ideal organic solution has been identified for the prevention of thrombosis and catheter-related infection in patients undergoing hemodialysis.

Objectives: This study aimed to evaluate the efficacy of Taurolock versus saline 5% on the prevention of catheter dysfunction and catheter-related infections.

Patients and Methods: Seventy patients with chronic kidney disease, who requiring hemodialysis or those with permanent hemodialysis catheters referring to hemodialysis centers of Ahvaz, were selected and randomly divided into two groups, while 68 patients remained until the end of the study. In the first group, saline 5% was inserted into the lumen of catheter after each hemodialysis, and then catheter was blocked. In the second group, Taurolock solution (TauroLock™ -Hep 500®: Taurolidine; antimicrobial agent), citrate 4% and heparin (UI/mL) were used as antibiotics. **Results:** No significant difference between the catheter-related infection and positive blood culture in both saline and Taurolock groups was detected (2.94% versus 2.94%; $P > 0.05$). Moreover, the catheter-related dysfunction in the saline 5% group was 5% less than the Taurolock group (2.94% versus 11.76%, $P = 0.365$).

Conclusion: The results showed that saline 5% is at least as effective as a Taurolock solution for prevention of infections and catheter dysfunction. Saline is an effective, inexpensive, safe and readily available in various settings. Therefore, it could be considered as a proper alternative solution for reduction of dialysis-related side effects and costs.

Trial Registration: Registration of trial protocol has been approved in Iranian registry of controlled trials (identifier: IRCT20190304042918N1; <https://en.irct.ir/trial/38055>, ethical code# IR.AJUMS.REC.1397.412).

Implication for health policy/practice/research/medical education:

In a randomized, double blind controlled clinical trial on patients undergoing hemodialysis to find the efficacy of Taurolock versus saline 5% for preventing infection and dysfunction of hemodialysis catheters; we found saline 5% is at least as effective as the Taurolock solution for prevention of infections and catheter dysfunction. Saline is an effective, inexpensive, safe and readily available in various settings. Therefore, it could be considered as a proper alternative solution for reduction of dialysis-related side effects and costs.

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Introduction

The use of catheters in dialysis patients has been rising since the early 21st century. In 2001, the use of hemodialysis was 900 per one million in the American patients due to end-stage renal disease (ESRD). Although arteriovenous fistulas or grafts are preferred for longer

periods of hemodialysis, it is preferable to use the catheter until the fistula is developed or dialysis is initiated (1,2). Given the need for continuous use of catheters, this device faces two major problems including catheter infections and decreased blood circulation during dialysis.

Due to these complications, over 50% of the catheters

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should ultimately be removed and replaced since they might lead to bacteremia. Various studies have shown that the use of catheters to perform hemodialysis has a 10-fold greater risk of bacteremia and topical infections than AV fistulas (3,5).

The most obvious complication of catheter placement is the development of catheter related bacteremia that is associated with morbidity and mortality, which is varying in different studies from 3.4 to 6.5 episodes per 1000 catheter-days (2). Gram-positive bacteria play a major role in these infections. The most famous type of such bacteria is known as *Staphylococcus aureus* (6,7). Numerous studies have shown that infection with these bacteria in catheters leads not only to higher treatment costs and longer duration of admission but also a higher mortality rate than other microorganisms (8,9).

Various substances are used to prevent catheter-related complications, including heparin, antibiotics and hypertonic and hypersomal substances (10).

Several studies have been conducted on the combination of these materials and their effectiveness, either individually or in combination. Currently, many studies have focused on the use of antibiotics in various combinations to prevent catheter complications as well as high treatment costs. Although antibiotics can effectively prevent bacteremia in the laboratory environment, it is very difficult to use them practically in desired concentrations. Accordingly, the main problems for using antibiotics are outlined as follows:

- Failure to prevent bacteremia in the body
- High costs for the production of antibiotics in the form of an antibiotic block with effective concentrations
- Side effects caused by the administration of high concentrations of antibiotics
- Antibiotic resistance in bacterial colonies of catheters (5,11).

Given the main problems for using antibiotics which mentioned above, some simpler materials that are capable of preventing complications of catheter placement, have been the focus of some studies. The most important of which is trisodium citrate solutions. This substance, which was originally used for coagulation to prevent catheter dysfunction, has the ability to prevent colonization of bacteria in hypertonic forms. As a result, it can have significant preventive effects (bacteremia and sepsis) (5,11). According to some studies, in addition to superiority over heparin, it can be used in conjunction with antibiotics as well as antibiotics alone (12).

Other studies have shown that hypertonic saline solution such as trisodium citrate has similar effects to heparin in preventing the catheter dysfunction and bacteremia, due to the hyperosmolarity and preventing bacterial colonization.

The authors consider it necessary for the following reasons:

- Studies have been conducted on the effects of hypertonic saline in preventing the colonization of bacteria showed a significant reduction in catheter related bacteremia (13).
- Few studies have compared the effects of saline 5% solution versus antibiotics. Meanwhile, many studies have shown the effectiveness of trisodium citrate in preventing bacterial colonization, compared to heparin and some other antibiotics (5,11-13).
- This solution is not only readily available, but also it is more economical.
- The possibility of developing bacterial resistance for all antibiotics, including Taurolocks, is not unlikely. It is therefore necessary to choose a suitable alternative for these substances.
- Better or even equal effectiveness as saline 5% will cut down costs for health-care systems and patients.
- Unfortunately, there are limited data to prove this case.

Objectives

The aim of the present study to evaluate the effectiveness of saline 5% as a proper substance with high availability versus taurolidine antibiotic for preventing infection and catheter dysfunction in patients undergoing hemodialysis.

Patients and Methods

Study design

This study is a randomized, double blind controlled clinical trial conducted on 70 patients undergoing hemodialysis at two educational centers of Ahvaz Jundishapur University of Medical Sciences.

The patients were randomly assigned (by remote computerized randomization) to either saline 5% or TauroLock groups (TauroLock™ -Hep 500®) (n=35). The patient, the physician and the person who evaluates the results did not have any information on groups. The study population is randomly divided into two groups of A and B. The medication was given by the nurse in the treatment room. In both hospitals, the nurses were injecting Taurolock and saline 5% into the lumen of the catheter equally, and observing sterility. The lumen of the catheters was not used for drug injection or blood sampling at all. Patients in both groups underwent training to reduce the rate of infection and were followed for three months. The authors used targeted sampling in this study. Taurolock contains taurolidine (antimicrobial agent), 500 units of heparin and 4% citrate. [Figure 1](#) shows how this study is organized.

Inclusion criteria

- Male and female patients over the age of 18; requiring hemodialysis three times a week
- Having a semi-permanent catheter for hemodialysis
- Willingness to participate in the study

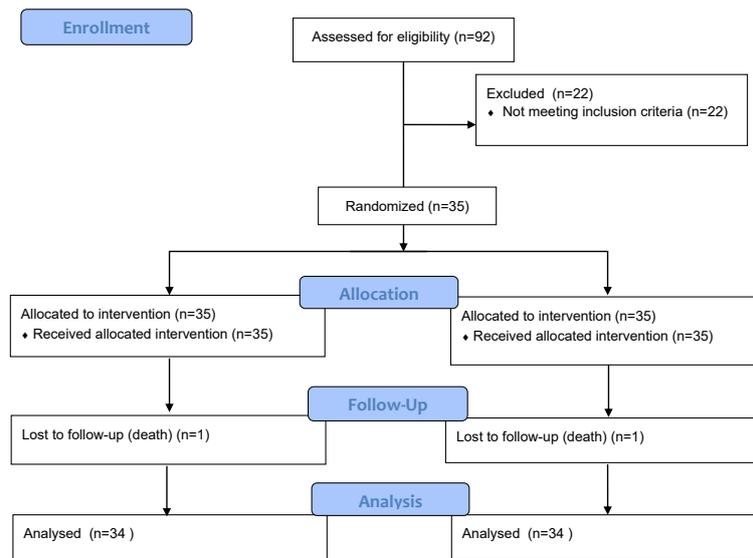


Figure 1. CONSORT flow chat diagram.

Exclusion criteria

- Patients undergoing antibiotic treatment
- Patients who need to change the catheter during the study
- Patients with sepsis

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The ethics committee of Jundishapur University of Medical Sciences approved this study (IR.AJUMS.REC.1397.412). The study protocol was also registered as a clinical trial at Iranian Registry of Clinical Trials (identifier: IRCT20190304042918N1; <https://irct.ir/trial/38055>). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from the internal medicine residential thesis of Maryam Afkane at this university.

Data analysis

Quantitative variables were used to describe the data center mean and standard deviation was used to describe the data distribution. Frequency and percentage were used to describe the data. Normal distribution of data was evaluated by the Shapiro-Wilk test and Q-Q graph. Chi-square test, independent *t* test and simple logistic regression were used to analyze the data. Multivariate logistic regression was used to analyze the data. Due to the multiple linearity problem between the two variables of diabetes and hypertension, diabetes was included in the model. For statistical analysis, SPSS (version 22) was used. The significance level in the tests was 0.05.

Results

In this study, 70 hemodialysis patients aged 24 to 81 years were enrolled. There was no significant difference between

the two groups in terms of age, gender and underlying diseases such as hypertension and diabetes ($P > 0.05$). Around 68 patients remained until the end of the study (Table 1). Table 2 shows the results of the use of saline 5% and Taurolock.

The results of catheter dysfunction in both saline and Taurolock groups are presented in Table 3. According to the table, the Taurolock group experienced dysfunction

Table 1. Baseline characteristics of patients with tunneled hemodialysis catheters^a

	Taurolock	Saline 5%
Prevalent hemodialysis patients	34	34
Dialysis via tunneled catheter	34 (100%)	34 (100%)
Site of catheter (jugular)	34 (100%)	34 (100%)
Male	23 (67.6%)	24 (70.6%)
Female	11 (32.4%)	10 (29.4%)
Age (y) (mean ± SD)	51.88±11.48	54.41±10.91
Presence of diabetes	12 (35.3%)	13 (38.2%)
Presence of hypertension	26 (76.5%)	29 (85.3%)

^a There was no significant difference between two groups.

Table 2. Comparison of outcomes of intervention in Taurolock and saline groups

Outcome/Group	Saline (n=34)	Taurolock (n=34)	P value ^a
Dysfunction	1 (2.94)	4 (11.76)	0.356
Infection	1 (2.94)	1 (2.94)	1.000
Positive blood culture	1 (2.94)	1 (2.94)	1.000

^a Chi-square test.

Table 3. Average catheter dysfunction time in saline and Taurolock groups

Variable	Saline (n=1)	Taurolock (n=1)
Duration of dysfunction (days)	48	50 ± 12.24

after 50 days on average. Meanwhile, one person in the saline group suffered from dysfunction after 48 days.

Accordingly, 4 cases (11.76%) in the Taurolock group and one case in the saline 5% group (2.94%) had catheter dysfunction, however, there was no significant difference between the two groups ($P=0.356\%$). There were no significant differences between the two groups in terms of infection or positive blood culture.

The results of catheter dysfunction in both saline and Taurolock groups are presented in Table 3. According to the table, the Taurolock group experienced dysfunction after 50 days on average. Meanwhile, one person in the saline group suffered from dysfunction after 48 days.

The results of catheter dysfunction prediction based on variables are presented in Tables 4 and 5. As shown in Table 4, the effect of gender, age, hypertension, diabetes and receiving saline or Taurolock alone were not significant in the catheter dysfunction.

Discussion

Hemodialysis in people with chronic diseases of the kidney is dependent on vascular access, which may include arteriovenous fistula or central venous catheters. Despite higher morbidity and motility, the use of central venous catheters has increased significantly compared to AV fistula (14,19). Given the infectious diseases, the formation of clots and fibrinous pods, catheter dysfunction is expected, since these issues limit their life span (15, 18). Although various strategies have been considered, including heparin, antibiotics and solution, to reduce the incidence of catheter-induced infection (11,20,21), so far there is no approach to prevent catheter dysfunction and catheter-related infections, especially in people with long-term use of the catheter. However, some studies have suggested the role of thrombolytic drugs in preventing catheter inappropriate functioning (19).

Given the important role of central venous catheters in hemodialysis patients, administration of the accumulated solutions to these catheters is an important option for the prevention and treatment of catheter-related infections (4,21).

The effectiveness of Taurolock solution or taurolidine-containing solutions in the prevention of infection and catheter-related dysfunction has been studied and confirmed in several studies. Accordingly, these solutions are commonly used in clinical trials for the prevention of infection and hemodialysis catheter dysfunction. Martinez et al, for example, showed that taurolidine-containing solutions can significantly reduce the catheter-related dysfunction and infection and also will reduce the thrombotic events and thereby improving the dialysis efficacy (14).

The superiority of taurolidine to heparin in reducing the infection and obstruction of dialysis catheters was also reported by Olthof et al. Given the significant difference

Table 4. Catheter dysfunction prediction based on variables (univariate logistic regression)

Variable	No	Yes	OR	P value
Gender				
Female	19 (90.5)	2 (9.5)	1.54	0.649
Male	44 (93.6)	3 (6.4)		Ref
Age (mean \pm SD)	53.18 \pm 11.48	57.20 \pm 5.45	1.22	0.369
Hypertension				
No	12 (92.3)	1 (7.7)	1.06	0.908
Yes	51 (91.27)	4 (7.3)		Ref.
Diabetes mellitus				
No	39 (90.7)	4 (9.3)	2.46	0.433
Yes	24 (96)	1 (4)		Ref.
Group				
Saline	30 (88.2)	4 (11.8)	4.40	0.196
Taurolock	33 (97.1)	1 (2.9)		Ref.

Table 5. Catheter dysfunction prediction based on variables (multivariate logistic regression)

Variable	Group	OR	CI 95%	P value
Gender	Female	1.84	0.25-13.69	0.554
	Male		Reference	
Age (mean \pm SD)		1.32	0.800-2.18	0.276
Diabetes	No	3.13	0.27-36.07	0.360
	Yes		Reference	
Group	Taurolock	4.99	0.49-50.25	0.172
	Saline		Reference	

in the catheter infection that can lead to bacteremia, sepsis and increased mortality, Olthof et al suggested to use taurolidine as a better solution instead of heparin (15).

Although all these studies indicate that taurolidine-containing solutions significantly reduce the complications of hemodialysis catheters, it is necessary to identify some effective, accessible and safe substances. It should be pointed out that these solutions may have a high cost, relatively low-accessibility and some other complications. Recent studies have shown that hypertonic solutions such as trisodium citrate, sodium bicarbonate and saline solution can prevent colonization of bacteria, bacteremia, sepsis and catheter dysfunction (5,11-13).

Currently, the use and effectiveness of Taurolock as a common but expensive medication have not been evaluated. Therefore, this double-blind randomized clinical trial was conducted to evaluate the effectiveness of saline 5% solution as a cheap and easily available and suitable substance, compared to taurolidine-containing Taurolock (antimicrobial agent) to prevent catheter-related infection and dysfunction.

In this study, there were no significant differences between the two groups in terms of age, gender, hypertension and diabetes, suggesting that these variables do not affect the results.

The present study showed, no significant difference between the two groups regarding catheter-related

infection and positive blood culture in the hemodialysis patients receiving saline versus Taurolock.

In previous studies, hypertonic saline has been used as an antimicrobial agent due to its high concentration to prevent colonization of bacteria and to reduce the catheter infection. For example, Oguzhan et al showed that bacteremia and catheter-related infection in hemodialysis patients were not significantly different between saline and heparin groups (13). This result is consistent with the finding of our study.

Oguzhan et al showed that catheter-related dysfunction was significantly lower in heparin-treated patients than in patients receiving hypertonic saline. The results suggest that hypertonic saline has no significant effect on catheter infection and dysfunction compared to heparin containing solutions. The antibacterial and anticoagulant properties of hypertonic saline have the potential to replace heparin (13).

Our investigation also showed that the catheter dysfunction in the Taurolock group was higher than the saline group (11.76% versus 2.94%). However, this difference was not significant. Taurolock group experienced dysfunction after 50 days on average. Meanwhile, one person in the saline group suffered from dysfunction after 48 days.

The effectiveness of taurolidine or Taurolock solution (containing taurolidine, heparin and 4% citrate) and saline solutions in the prevention of catheter-related infection and dysfunction have been investigated separately in various studies. However, no studies have compared the two treatments. Accordingly, there are few studies comparing the effectiveness of saline solution and antibiotics. Numerous studies have shown the effectiveness of trisodium citrate as a substance that prevents colonization of bacteria. For example, Weijmer et al and Winnet et al showed the effectiveness of hypertonic trisodium citrate solution at concentrations of 30% and 46%, compared to heparin (2,5). Furthermore, the amount of bleeding after catheter placement in the heparin recipient group was significantly higher than that of the trisodium citrate group (2,5). Therefore, the administration of hypertonic solutions, in addition to higher effectiveness for hemodialysis patients, is much more economical.

In our study, saline 5% had the same preventive effect as TauroLock. Since heparin can increase the risk of hemorrhage in many hemodialysis patients, it is essential to find an alternative to heparin in hemodialysis patients with a high risk of hemorrhage. In this regard, Chen et al showed that the risk of hemorrhage in the early stages of dialysis in patients receiving heparin was significantly higher than that of saline group. Although this finding was not different significantly in 30 minutes after dialysis, this risk was still lower in the saline group (18). Therefore, hypertonic saline can be very helpful for patients who are

at risk of bleeding/hemorrhage and require dialysis. No bleeding was observed in the saline group in the present study.

Additionally, El-Hennawy et al found that hypertonic sodium bicarbonate solution is safe and is superior to normal saline in preventing catheter dysfunction. It can also be used to prevent infection and catheter-related thrombosis in hemodialysis patients (16). Arechabala et al showed that solutions differ in the prevention of infection, thrombosis and catheter-related dysfunction, since no specific superiority has been reported for different solutions. These results suggest that the evidence in this area is not sufficient while more studies are needed to select and validate an alternative method with high safety and effectiveness (17).

Furthermore, the amount of saline hypertonicity used in our study was 5% and was lower compared to similar studies (in other studies saline solution was used up to 10% and 26%) (13,18). This also suggests that lower-density solutions can also prevent infectious and non-infectious catheter complications.

Finally, the present study showed that saline 5% is at least as effective as Taurolock within three months, will not have serious side effects and can be used as a cheap and safe drug for the prevention of infection and catheter dysfunction in dialysis patients.

Finally, it should be noted that our study compared the effectiveness of Taurolock and saline in reducing infections and catheter dysfunction in hemodialysis patients. However, there were some limitations. For example, only short-term effects (three months of follow-up) of treatment were investigated, while the long-term effects of using these solutions were not investigated. The small number of samples in each group was another limitation. Further studies with greater sample size can lead to reliable results.

Conclusion

According to the results, saline solution is readily available and economical. Given the bacterial resistance to all antibiotics such as Taurolock, it is therefore an alternative option for Taurolock in the clinical field. However, given the limited studies on the role of antibiotic accumulation solutions, including Taurolock and saline in the prevention of catheter-related complications in hemodialysis patients, further studies are needed in this regard.

Limitations of the study

The limitations of the study are the low sample size in each group. Further studies with larger sample size and multicenter results can be obtained. In this study only short-term effects (three months follow-up) were investigated and the effects of using long-term solutions were not investigated.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, double publication) have been completely considered by the authors.

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