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Comparison of Catheter Related Blood Stream Infections in Hemodialysis Patients Treated with Trisodium Citrate as Catheter Locking Solution vs Heparin as Conventional Locking Method

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Author`s Contribution

[1,4]Substantial contributions to the conception or design of the work; or the acquisition, [2]analysis, or interpretation of data for the work, [3,6]Drafting the work or revising it critically for important intellectual content,[5] Data Analysis, Literature review

Funding Source: None
Conflict of Interest: None

Received: May 30, 2023
Accepted: Sept 04, 2023

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ABSTRACT

Objective: To compare the frequency of temporary catheter related blood stream infections using sodium citrate as catheter locking solution with heparin as standard in hemodialysis patients.

Methodology: A randomized controlled trial was conducted at a nephrology department's hemodialysis unit in Pakistan Institute of Medical Sciences (PIMS) between August 2022 and February 2023. Total 110 consecutive end-stage renal disease patients, aged above 18 years, undergoing hemodialysis with temporary central venous catheters, were divided into two groups. Group-I received trisodium citrate 46.7% as a lock solution, while Group-II received heparin 2000 U/ml (control).

Results: The average age of patients in both groups was 51.98±13.57 years. The average duration of dialysis in both groups was 4.01±3.1 months and mean catheter time in Group-I was 13.65±8.29 days and in group-II was 13.40±8.33 days with statistically insignificant ($p \geq 0.05$). The rate of CRBSI per 1000 catheter days was 3.12 days for group I and 5.14 days for group II ($p = 0.001$). The cumulative mean infection-free catheter survival in the trisodium citrate group was lower than the heparin group (log rank = 2.31, $p = 0.128$). Cox regression survival analysis between two groups; the difference in group I & II was insignificant (HR = 1.6, CI = 0.49–1.17, $p = 0.201$).

Conclusion: There is insignificant difference between trisodium citrate 46.7% and heparin as a catheter lock solution in the survival rate of tunneled hemodialysis catheters in end-stage renal disease.

Keywords: Catheter-related infections; Central venous catheter thrombosis; Hemodialysis solutions; Heparin; Trisodium citrate.

Cite this article as: Karmani JK, Mir S, Naveed SM, Shah SAA, Javaid MK. Asim F. Ahmad A. Comparison of Catheter Related Blood Stream Infections in Hemodialysis Patients Treated with Trisodium Citrate as Catheter Locking Solution vs Heparin as Conventional Locking Method. Ann Pak Inst Med Sci. 2023; 19(3):307-312. doi. 10.48036/apims.v19i3.877

Introduction

Patients undergoing hemodialysis, especially those using a central venous catheter (CVC), are indeed at an increased risk of infection compared to those using arteriovenous fistulae (AVF).[1] The recommendations favoring AVF as the preferred vascular access for hemodialysis, there has been a growing reliance on catheters due to the rapid increase in patients with end-stage renal disease (ESRD) requiring hemodialysis.[2]

Catheter-related bloodstream infection (CRBSI) is a major threat to the survival of patients on hemodialysis. In addition, the use of catheter lock solution containing heparin is associated with bleeding and thrombocytopenia.[3] Catheters can be a pathway for

bacteria to enter the bloodstream and are associated with mortality in patients with ESRD. Catheter-related infections are the second leading cause of death in ESRD patients. CRBSI is associated with high rates of hospitalization,[4] treatment related costs,[5] and significant morbidity and mortality and in many cases requires the removal of the catheter.[4]

There are different mechanisms involved in the development of CRBSIs. These mechanisms include bacterial migration from exiting site of infections, contamination of catheter core, and internal colonization of catheter by biofilm-forming organisms.[6] Heparin is used as the standard intradialytic locking solution for catheters, mainly because of its anticoagulant properties. However, it should be noted that there is no strong evidence to support the efficacy and safety of lock solution heparin.[7] Complications of heparin include inadvertent systemic anticoagulation, disturbances and laboratory evaluation of platelet aggregation, heparin-mediated thrombocytopenia, and an increased risk of bleeding, especially in uremic patients at risk of coagulopathy.[8]

In vitro, sodium citrate has the potential to inhibit biofilm formation by certain bacteria, including Staphylococcus aureus and Staphylococcus epidermidis, especially on materials used for dialysis catheters.[9] High concentration of trisodium citrate (TSC) have been supported for hemodialysis catheter locking due to its local anticoagulant properties and potential antimicrobial effects. TSC Ca^{2+} and Mg^{2+} buffers can prevent this biofilm formation and colonization. Presently, there is limited evidence of high concentrations of TSC in clinical practice.[10] Sodium citrate concentrations ranging from 0.3% to 47% have been reported for their anticoagulant properties and potential to prevent the formation of staphylococcal biofilms.[11]

Medical research in Pakistan regarding optimal use of antibiotic lock solutions (ALS) is currently lacking and incidence of catheter related blood stream infection is so common in our setup, so there is need to work in this area. In our dialysis unit at PIMS we receive significant numbers of patients who are put on emergency dialysis via double lumen catheters so we want to perform a study to analyze and compare the rates of CRBSI using different lock solutions. This will allow us to gain conclusive evidence, in the light of which we can formulate further infection preventing policies regarding catheter related infections in this particular population of patients. The study objective was to compare the frequency of temporary catheter related blood stream infections using sodium citrate as catheter locking solution with heparin as standard in hemodialysis patients.

Methodology

A comparative randomized control trial was conducted at hemodialysis unit of nephrology department, Pakistan Institute of Medical Sciences (PIMS) Islamabad between August 2022 and February 2023. After approval of the Institutional Review Board (IRB) of the hospital and informed written consent, total 110 patients consecutively with end stage renal disease (ESRD), aged above 18 years undergone hemodialysis using temporary central venous catheter (CVC) as vascular access irrespective of etiology of renal failure were included. Hemodialysis patients with pre-existing infections, and abnormal coagulopathy were excluded.

Total 110 patients sample size was calculated with WHO sample size and the following parameters were used; CRBSI rate was 7.69%,[12] confidence level was 95% and alpha margin of error was 5%. The patient population enrolled in the study was assigned into two groups of equal sizes (n=55, each group) by lottery method. Group-I (Trisodium citrate) was administrated with lock solution of trisodium citrate 46.7%, whereas Group-II (Heparin) was administrated with lock solution of heparin 2000 U/ml (as control).

The volume of locking solution was injected by an experienced nephrologist to match the exact volume of the ports of the catheter so as to prevent any entry into the blood stream. The CVC was inserted under all possible aseptic measures. All protocols were followed that entitles both groups to follow the same exit site care. Patient's follow ups were done after insertion of CVC and clinical assessment at each dialysis visit to closely examine the clinical events. Catheter related infections were identified in patients if they presented with fever, rigors, hypotension or altered mental state that subsequently had positive blood cultures and absence of an altered source of bacteremia.

The lock infusion was prepared at a separate site, and lock solution equal to the intraluminal volume marked on the catheter was administered each time to the resident nurse (who was not involved in data collection).

The primary endpoints of this study were the CRBSI rate, measured as the number of CRBSI episodes observed per 1000 catheter days between two groups: group-I (trisodium citrate) and group-II (heparin). Secondary endpoints were the number of catheters with thrombosis, catheter infection, and bleeding episodes.

The basic demographic and clinical data were collected, including age, male/female ratio, weight, comorbidities (e.g., diabetes, hypertension, ischemic heart disease, hepatitis B & C), duration of dialysis, and catheter location. Laboratory data were obtained as hemoglobin, urea, creatinine, serum albumin and ferritin.

All data were analyzed using SPSS software v 23. Results were expressed as mean ± SD or frequency (percent). Means and percentages were calculated by patient age and sex. For normal distribution of data between two groups Kolmogorov-Smirnov test was used. Statistical analysis of continuous variables between groups applying independent sample t-test, and chi-square was applied for categorical variables. Survival rate of catheter was measured by Cox regression analysis, and data were presented as hazard ratios with 95% confidence intervals. Kaplan-Meier test was applied for survival curves with log-rank test. The probability p-value ≤ 0.05 was measured as significant.

Results

One hundred & ten patients with hemodialysis were received CVC and enrolled equal numbers into two groups. The average age of patients in both groups was 51.98±13.57 years. The average weight of patients in both groups was 68.78±14.13 kg. The average duration of dialysis in both groups was 4.01±3.1 months and mean catheter time in Group I was 13.65±8.29 days and in group II was 13.40±8.33 days with statistically insignificant ($p \geq 0.05$). The demographic characteristics was not significant between two groups. The catheter insertion site, in femoral, subclavian, and jugular was insignificant ($p \geq 0.05$) between two groups (Table I). The laboratory parameters were recorded and analyzed at baseline in both groups (Table II).

The rate of CRBSI per 1000 catheter days was 3.12 days for group I and 5.14 days for group II ($p = 0.001$). In all cases of CRBSI, the catheter was removed and appropriate IV antibiotics administered. Empiric antibiotic therapy initially included vancomycin and topical antibiotics based on gram-negative bacilli according to CDC guidelines. There were no deaths due to CRBSI.

Table II: Descriptive statistics of laboratory parameters at baseline in both groups. (n=110)

Baseline laboratory	Group-I (trisodium citrate)	Group-II (heparin)	p-value*
Hb (g/dL)	10.2±1.9	10.1±2.0	.061
Creatinine (mg/dL)	11.4±5.1	10.7±3.9	.060
Urea (mg/dL)	106.6±41.9	106.6±33.6	.060
Albumin (g/dL)	177.3±92.4	182.9±88.6	.065
Ferritin (ng/mL)	2.9±0.8	3.0±0.8	.061

**Independent sample t-test*

During CRBSI episodes, the isolated pathogens were mainly Gram-negative. In Gram-positive, predominantly S. aureus was cultured (n=26) during CRBSI episodes. In heparin group 14 Gram-positive (S. aureus) cultured during CRBSI episodes (Table III).

Table III: During CRBSI episode isolated pathogens.(n=110)

Microorganisms		Group-I (trisodium citrate)	Group-II (heparin)
No growth		19	9
Gram positive	S. Aureus	12	14
Gram negative	E. Coli	6	8
	Coagulase (-) Staphylococcus	6	8
	Klebsiella	5	7
	Pseudomonas	7	9

The cumulative mean infection-free catheter survival in trisodium citrate group was lower than heparin group (log rank = 2.31, p = 0.128), (Figure 2). Cox regression survival analysis between two groups; the difference in group I & II was insignificant (HR = 1.6, CI = 0.49–1.17, p = 0.201).

Discussion

This study analyzed 110 tunneled hemodialysis CVCs comparing survival between CRBSI and trisodium citrate

Table I: Descriptive statistics of baseline data of all patients. (n=110)

Baseline variables		Group-I (trisodium citrate)	Group-II (heparin)	p-value*
Age (years)	Mean±SD	54.3±14.6	49.6±12.2	.077
Gender	Male	31 (56.4%)	34 (61.8%)	.091
	Female	24 (43.6%)	21 (38.2%)	
Comorbidities	Hypertension	27 (49.1%)	25 (45.5%)	.084
	Diabetes	26 (47.3%)	26 (47.3%)	
	CVA	1 (1.8%)	2 (3.6%)	
	Hep. B & C	1 (1.8%)	2 (3.6%)	
Catheter types inserted	Femoral	9 (16.4%)	10 (18.2%)	.104
	Subclavian	10 (18.2%)	9 (16.4%)	
	Jugular	36 (65.4%)	36 (65.4%)	

**Kolmogorov-Smirnov test*

46.7% and heparin lock solution groups. The study found, there are advantages of trisodium citrate in terms of survival rates between lock groups and increased CRBSI-free survival in the lock group of heparins. The frequency of CRBSI rate per 1000 catheter days was 3.12 days for trisodium group and 5.14 days for heparin group (p = 0.001). These findings are comparable with Correa Barcellos et al study results, who randomized patients with non-tunneled catheter, and the rate of CRBSI was 5.2 per 1000 catheter days in the trisodium group and 3.4 per 1000 catheter days in the heparin group.[13] A study conducted by Quenot et al randomized patients with non-tunneled catheters, and event-free survival was 7 days in the citrate group and 5 days in the heparin group (p = 0.51).[14]

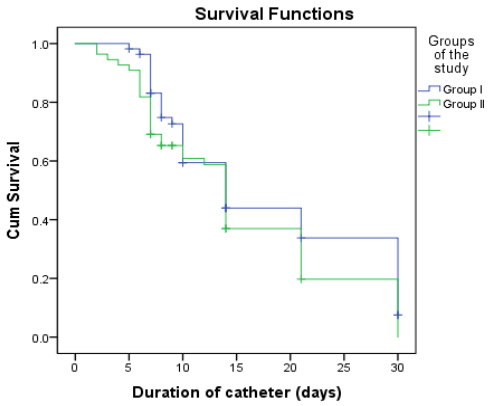

Figure 2. Kaplan-Meier curve compared the catheter infection-free survival in the heparin group and the trisodium citrate group.

Due to the limitations associated with small studies, the existing evidence comparing citrate with heparin as locking solutions for tunneled hemodialysis catheters is not sufficient to draw definitive conclusions about their safety and efficacy.[15] Trisodium citrate 4% is commonly used as a lock solution in patients undergoing chronic renal replacement therapy with long-term tunneled catheters. Its use aims to prevent catheter dysfunction and reduce the risk of infection.[16] Heparin is commonly considered the reference locking solution for non-tunneled hemodialysis catheters. However, the available evidence regarding the safety and efficacy of heparin as a locking agent in critically ill patients is limited.[17] The potential contraindications to heparin in critically ill patients, citrate locking solutions could hold promise as an alternative option.

The study by Betges et al which demonstrated a significant longer sepsis-free survival for tunneled catheters locked with citrate, suggests a potential benefit of using citrate as a locking solution in this specific subset of patients.[18] Studies investigating the use of citrate as a lock solution in hemodialysis CVC have reported heterogeneous results.[19] Many studies investigating the use of citrate as a lock solution in hemodialysis catheters focus primarily on tunneled catheters or do not include non-tunneled catheters.[20]

In group-I resulted in a significantly lower risk of catheter dysfunction compared to group-II, and there was also a lower incidence of infection in group-I. However, insignificant difference was observed in CRBSI between two groups. The study conducted by Parienti et al, which utilized trisodium citrate 46.7% as a lock solution, reported a nonsignificant risk of infection in the trisodium group compared with the heparin group.[21] Additionally, the study found no significant difference in the mean duration of non-tunneled hemodialysis catheters between the two groups. In Parienti's study, the use of trisodium citrate as a lock solution was 46.7% associated with less catheter dysfunction compared to the heparin group. This finding is consistent with the results reported by Hermite et al in their study, which also showed a higher rate of catheter dysfunction in the heparin group compared to the trisodium citrate group.[22]

Grudzinski et al meta-analysis study, compare the benefits and potential harms of trisodium versus heparin locking solutions for non-tunneled hemodialysis catheters. Mortality and CRBSI were lower with trisodium locking solutions compared to heparin. However, the pooled effect estimates did not reach statistical significance.[23] Whereas, in our study there is no death record due to CRBSI. Grudzinski et al study showed insignificant difference in catheter replacement, thrombolysis, or all-cause hospitalizations between the trisodium locking solutions and heparin groups in the pooled analyses.[23] However, it is worth noting that trisodium lock solution is associated with fewer bleeding episodes than heparin. Regarding the lack of significant differences in general or local infections, including CRBSI, between groups, it is important to consider that systemic antimicrobials were likely used in the study. Lastly, it is noted that the study was not specifically powered to detect significant differences in this secondary end point, which could have influenced the findings.

There were some limitations in our study. The first limitation is the lack of analysis regarding the costs associated with the use of trisodium as a catheter lock solution, including considerations of cost-effectiveness. The second limitation is related to the specific patient population included in the study, mainly comprising end-stage renal disease patients with a high rate of systemic antibiotic use. This may limit the generalizability of the

findings to other clinical situations and patient populations. Lastly, the exclusion of patients with a contraindication to anticoagulant therapy is mentioned as a limitation.

Conclusion

The study concluded that there was insignificant difference between trisodium citrate 46.7% and heparin as a catheter lock solution in terms of survival rates of tunneled hemodialysis catheters in end-stage renal disease patients. However, it is important to consider the limitations of the study and the need for further research to confirm these findings.

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