Original Article

Low Concentration Trisodium Citrate as a Non-inferior Locking Agent for Non-tunneled Dialysis Catheters in the Asian Setting

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Abstract

Introduction: Unfractionated heparin is the commonly used catheter lock solution in patients with temporary dialysis catheters as hemodialysis access. The effectiveness of trisodium citrate as an alternate catheter lock agent has not been studied in Asian population. **Methods:** In this prospective quasi-experimental study, which included 180 patients with central venous dialysis catheter, patients were randomly allotted to citrate 4.67% and heparin 5000 units/ml arms in the ratio of 2:1. Baseline demographic and dialysis related data, incidence of catheter-related bloodstream infections, and mean catheter days in both the study cohorts were collected and compared. Formal cost analysis for citrate 4.67% use as catheter lock was done. **Results:** The mean age of the total study population was 50.49 ± 14.87 years. Sixty-six females (36.7%) and 80 (44.4%) diabetic patients were included in the study. The overall incidence of catheter-related bloodstream infection (CRBSI) was 11.11%. The majority had nontunneled dialysis catheters (95%; n = 114). On analyzing the data of patients with nontunneled catheters, it was found that the total number of catheter days for the citrate and heparin groups were 4,795 and 2,419 days, respectively. The number of CRBSI episodes per 1,000 catheter days for the citrate and heparin groups were 2.711 and 2.89, respectively. Citrate catheter lock cost only 6% of that of heparin lock. **Conclusions:** The incidence of catheter related bloodstream infections was comparable between the heparin and citrate 4.67% lock cohorts. The use of low concentration citrate as catheter lock was cost-effective when compared with heparin.

Keywords: *Central venous catheter, citrate lock, cost effectiveness, CRBSI, heparin lock*

Introduction

The number of patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis (MHD) is increasing exponentially over the years. Arteriovenous fistulas (AVF) or grafts are the preferred vascular accesses for MHD, and renal health guidelines also insist on early construction of AVF and "fistula first" policy for MHD. But many ESRD patients present to the healthcare facility late often requiring urgent initiation of hemodialysis (HD) through temporary vascular access. The gravity of the problem is more in developing countries with relatively poor access to healthcare.[1,2]

Catheter-related infections (CRI), which include exit site infections and catheter-related bloodstream infections (CRBSI) significantly contribute to morbidity and mortality of ESRD population.[3] Catheter malfunction secondary to kinking and obstruction due to thrombus are common with temporary and or permanent vascular catheters. To prevent thrombosis, the catheter hubs are commonly locked with an anticoagulant like heparin. In view of risks associated with heparin use, another anticoagulant, trisodium citrate (TSC), has been tried in varying concentrations as an alternate locking agent. TSC has the advantage of fewer side effects and lesser cost as compared with heparin. Since there is paucity of published studies from Asia regarding the use of TSC as catheter locks, we intended to study the effectiveness of low concentration TSC in preventing CRBSIs and its cost-effectiveness over heparin in our dialysis unit.

Subjects and Methods

The study was done at the department of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Chennai. The dialysis unit predominantly uses AVF or A-V graft as dialysis access and temporary

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catheters are used for initiating HD before AVF/A-V graft can be cannulated. We use double lumen nontunneled catheter with a length of 13.5 cm for internal jugular vein access [MAHURKAR™ 11.5 Fr/Ch (3.8 mm) × 13.5 cm]. The catheter lumen volume is 1.1 ml in the arterial limb and 1.2 ml in the venous limb. The catheter is placed by nephrology residents, using ultrasound guidance and strict aseptic catheter handling practices are adopted both during catheter placement and whenever HD is initiated. HD is done by trained dialysis technologists.

In this prospective quasi-experimental study, renal failure patients more than 18 years of age and dialyzed with central venous catheter access at jugular site were included. Patients who were initiated on HD through temporary catheter in our unit and underwent MHD elsewhere, patients with catheters at femoral site, patients with comorbid conditions, patients diagnosed with fever of any etiology other than CRBSI, sick patients requiring admission in intensive care units were excluded from the study. The sample size was 180 and it was divided into two groups. Group 1 (n = 120) was the study group and included patients in whom TSC was used as catheter locking agent. Group 2 (n = 60) was the control group and heparin was used as catheter locking agent. The study population was assigned into one of the groups randomly. The study was conducted over a 14 months period from February 2017 to March 2018 in the MHD unit. Commercially available TSC 46.7% (SEROCIT™-46.7%, La Renon Healthcare Pvt. Ltd.) in dilution of 1:10 (final concentration of 4.67%) was used for catheter lock in group 1. Unfractionated heparin (CAPRIN®, Samarth Life Sciences Pvt. Ltd.) in concentration of 5,000 units/ml was used in Group 2. After each HD session, the catheter lumens were flushed with 0.9% saline and locked with the assigned solution (TSC 4.67% and heparin) in required volumes. Exit site dressings were changed under aseptic precautions after each HD session. No intranasal mupirocin was used.

Demographic information of the subjects including age and gender, clinical diagnosis, and comorbid conditions including diabetic status of patients were collected. Data related to HD such as dialysis frequency, types and sites of catheter and total number of days on catheter prior to CRBSI were collected. For patients who had no episodes of CRBSI, the total number of days on catheter prior to catheter removal was taken. All definite, probable, and possible CRBSIs (according to CDC definitions of CRIs) were taken into account in the study.[4] As a protocol, in patients who developed CRBSI, the temporary catheters were removed promptly. The patients were subsequently treated with empirical parenteral antibiotics, which were modified based on culture and sensitivity reports. Temporary catheters were also removed when encountered with any kind of catheter malfunction such as kinking and complete or partial thrombus occlusion. We did not routinely check serum calcium concentration in the study population since only low concentration citrate was used in group 1 and hypocalcemia is unlikely with 4.67% catheter lock. Informed consent was obtained from the patients for the study. Institutional Ethics Committee approval was obtained prior to the study (CSP/15/MAY/41/61).

Statistical analysis was done at the end of the study using SPSS 16. Baseline characteristics of the total study population were described. For comparison between the two groups, Pearson Chi-square test was used for qualitative data and Independent t-test/Mann--Whitney U test was used for quantitative data. Descriptive analysis was done for CRBSI incidence in both the groups. A 'P' value of <0.05 was considered significant.

Results

The study included 180 patients and TSC group (study group) constituted 120 patients and heparin group (control group) constituted 60 patients. The mean age of the total study population was 50.49 ± 14.87 years. Sixty-six females (36.7%) and 80 (44.4%) diabetic patients were included in the population. All the patients were undergoing twice weekly HD. Only a miniscule were AKI patients (n = 4; 2.2%). Six (3.3%) patients underwent HD through double lumen tunneled catheters. The total number of catheter days in the study was 7,544 days. The mean catheter day for the total study population was 41.91 ± 14.56. The overall incidence of CRBSI was 11.11% (n = 20). The number of CRBSI episodes was 2.65 per 1,000 catheter days for the study population.

The majority of the study population had nontunneled dialysis catheters (95%; n = 114). For comparison between the TSC and heparin groups, we included data from patients with nontunneled catheters. Baseline characteristics of both the TSC and heparin lock groups including age, gender, diabetic status, mean catheter days, and CRBSI incidence were comparable. The total number of catheter days for the TSC group was 4,795 and for the heparin group, it was 2,419 days. The incidence of CRBSI in the TSC group was 11.3% (n = 13). Six patients had CRBSI with gram-positive organisms, five had gram-negative organism growth in culture, and two had culture-negative possible CRBSI. In the heparin group, the incidence was 11.86% (n = 7). Three had infection with gram-positive organisms, two with gram negative, and two had culture-negative possible CRBSI. In terms of number of CRBSI episodes per 1,000 catheter days, it was 2.711 for the TSC group and 2.89 for the heparin group [Table 1].

Discussion

Tunneled and nontunneled HD catheters are often used in newly diagnosed ESRD patients initiated on HD or when a functioning AVF or A-V graft fails. The catheter limbs are filled with anticoagulants after HD to prevent thrombus formation. In addition to catheter malfunction secondary

Table 1: Baseline characteristics and comparison of citrate and heparin groups

	4.67% Citrate group	Heparin group	*P*
Number (*n*)	115	59	-
Mean age (years)	51.1±14.24	49.49±15.325	0.492
Female (*n*)	43 (37.4%)	21 (35.6%)	0.816
Diabetics	58 (50.4%)	21 (35.6%)	0.063
Dialysis frequency	Weekly twice	Weekly twice	-
Left side IJV (*n*)	15	11	-
Total catheter days	4,795	2,419	-
Mean catheter days	41.7±15.1	41±13.1	0.739
Incidence of CRBSI (*n*)	13 (11.3%)	7 (11.86%)	0.912
CRBSI episodes/1000 catheter days	2.711	2.89	-
Gram positive organisms	6 *Staph aureus -3 Coagulase neg Staph- 1* *Staph hemolyticus -1 Strep agalactiae-1*	3 *Staph aureus -2* *Strep dysgalactiae- 1*	-
Gram-negative organisms	5 *Pseudomonas aeroginosa- 3* *Klebsiella pneumonia -2*	2 *Klebsiella pneumonia-1* *Pseudomonas aeroginosa- 1*	-
Culture-negative possible CRBSI	2	2	-

to kinks/obstruction by thrombus, CRBSI is a common clinical problem encountered in patients with dialysis catheters.

Heparin, a polysaccharide, exerts anticoagulant effect by accelerating the activity of antithrombin III to inactivate thrombin. This conformational change in antithrombin III inactivates thrombin, factor IXa, and factor Xa. Heparin in concentration of 5,000 to 10,000 units/ml is the standard lock solution in many centers worldwide. Inadvertent spilling of heparin into the bloodstream and subsequent systemic anticoagulation is a concern, especially in uremic patients who are already prone for bleeding. Heparin-induced thrombocytopenia and osteoporosis are other reasons for concern with long term use of heparin.[5] To overcome these issues, an alternate lock solution, TSC in various concentrations was proposed and had been tried in some HD centers.

TSC acts as a local anticoagulant. It chelates ionized calcium present in the blood, which results in blockade of calcium-dependent clotting pathways and a reduction in fibrin formation. It has relatively lower risk of systemic anticoagulation. Also, TSC has some antimicrobial properties and it probably inhibits biofilm formation in the catheters. Studies using TSC have been done with different concentrations varying from 4% to 46.7%. Potential risks including fatal cardiac arrest have been reported with the use of high concentration TSC (46.7%).[6,7] Some antibiotic--anticoagulant locks such as gentamicin--citrate and taurolidine--citrate combinations have shown better outcomes in terms of prevention of CRBSI in HD patients.[8-11] There are no recommendations in renal health guidelines for use of one catheter locking agent over another, and individual HD units have developed practice patterns based on their own experience.

The use of citrate as a low cost agent for catheter lock has been described in several studies from the West.[12-17] Weijmer *et al*. in an RCT including patients with temporary catheters predominantly as study cohorts reported that the use of TSC 30% for catheter locking in HD can contribute importantly to the reduction of catheter-related complications in patients by prevention of premature catheter removal and CRIs.[12] In a retrospective analysis of catheter lock efficacy, Linda Grudziski *et al*. demonstrated the noninferiority of 4% TSC over heparin 10,000 units/ml. The investigators analyzed catheter survival data when heparin was used as catheter lock and compared with the time period when, after a change in unit policy, TSC was used as catheter lock.[13] From another study designed similarly, Charmaine *et al*. concluded that citrate 4% has equivalent or better outcomes with regards to catheter exchange, thrombolytic use, and access-related hospitalizations when compared with heparin 5,000 units/ml.[14] In a prospective cohort analysis of patients with long-term HD catheters, Calantha found that a lock solution of TSC 4% was associated with fewer CRIs and similar effectiveness when compared with heparin 5,000 units/ml.[15] Zhao *et al*., in a meta-analysis of citrate versus heparin lock RCTs, concluded that citrate locks of low to moderate concentrations were superior to heparin locks in preventing CRBSI and citrate locks were noninferior to heparin in the prevention of exit site infection and in preserving catheter patency.[16] From the outcomes of CITRIM trial, it could be inferred that there was no difference in CRBSI-free or dysfunction-free survival between jugular vein dialysis catheter locked with heparin 5,000 units/ml or 30% citrate.[17] Azim *et al*. found that citrate 4% lock solution was equally effective as compared to heparin 5,000 units/ml in maintaining patency of temporary dialysis catheters[18] [Table 2].

Table 2: Studies which compared citrate and heparin as catheter lock solution

	Linda Grudzinski *et al*.[13]	Charmaine E. Lok *et al*.[14]	Calantha K. Yon *et al*.[15]	CITRIM trial[17]	Our study
Year and place of study	2002 to 2004 Canada	2003 to 2004 Canada	2008 to 2010 USA	2012 to 2014 Brazil	2017 to 2018 India
Study design	Retrospective single centre study	Prospective Observational	Prospective single centre cohort analysis	Prospective single centre RCT	Prospective single centre Randomized
Type of dialysis catheter	Double lumen tunneled	Double lumen tunneled	Double lumen tunneled	Double lumen non tunneled	Double lumen non tunneled
Citrate concentration	4%	4%	4%	30%	4.67%
Number of subjects in citrate group	161	129	58	231	120
Number of subjects in heparin group	146	121	60	233	60
Total catheter days in citrate group	37139	17593	13530	6052	4795
Total catheter days in heparin group	30925	16761	10800	6927	2419
CRBSI rates per 1000 catheter days	0.94 in TSC and 0.77 in heparin groups	-	0.81 in TSC and 1.90 in heparin groups	-	2.711 in TSC and 2.89 in heparin groups
Outcomes	Outcomes comparable. Pharamcoeconomic benefits with citrate use	Citrate has better outcomes with regards to catheter exchange and TPA use. Cost effective	Citrate was associated with fewer CRIs and similar effectiveness when compared with heparin	No difference in CRBSI-free/ dysfunction-free survival between groups at jugular site	CRBSI incidence comparable. Use of citrate is cost -efficient

In our study, the CRBSI rates in both the TSC (2.711/1,000 catheter days) and heparin (2.89/1,000 catheter days) groups are comparable and the findings concur with most published literature. CRBSI rates per 1,000 catheter days ranged from 0.81 to 1.1 in the TSC group and 0.77 to 4.1 in the heparin group in similar studies.[12,13,15] Grudzinski *et al*. and Yon *et al*. reported lesser CRBSI rates, but tunneled catheters had been used in the study cohort.[13,15] Also, catheter handling practices may not be uniform across dialysis centers, and this could explain subtle differences in reported CRBSI rates.

Citrate in the desired concentration had been prepared in the local pharmacy in most studies, and pharmacoecomomic analysis done by the investigators favored the use of citrate over heparin.[13,14] Our study findings with low concentration citrate in Indian HD settings are also concordant with those studies. In our center, the heparin vial 5 ml (5,000 units/ml) costs Indian rupees (INR) 212. It can be used as lock after two HD sessions and the cost of heparin lock for one session would be INR 106. For the TSC arm, we used 1:10 dilution solution of the commercially available 5 ml vials of TSC (SEROCIT™ -46.7%). The final concentration that was used for catheter lock was 4.67%. The cost of one vial is INR 129. In the dilution in which we used, it can be used as catheter lock after 20 HD sessions. The cost for one session would be INR 6.45. Low concentration citrate lock comes at only 6% of the heparin lock cost. In high volume centers with significant HD population with tunneled or nontunneled central venous catheters as access, a change in unit policy would be advantageous from the pharmaco economic point of view. Also, we did not manually prepare the low concentration citrate in the local pharmacy as commercial vials were readily available and easily diluted to the desired concentration for use. This saved time of in-hospital pharmacy personnel.

The advantage of the study is that it is a prospective, and probably the first from an Asian population with good sample size that has analyzed the CRBSI incidence with low concentration citrate and heparin catheter locks. Majority of the studies in literature have come to a conclusion based on comparison between two study cohorts from different timeline (historical cohort), which may not be an ideal study design.[13-15] Our study findings are based on head to head comparison between two groups. Also, the study is relevant since it was conducted in patients with temporary dialysis catheter, which is primarily used in majority of the Indian HD units. The findings should encourage other HD centers to try citrate catheter locks in their patients and formulate their own unit policy.

Our study is not without limitations. It is a single center quasi-experimental study and randomization to the groups was done without blinding. The study design would have been much better had we had included another study cohort with higher concentrations of TSC to find difference in CRBSI incidence.

Conclusions

ESRD patients getting dialyzed through nontunneled temporary dialysis catheter constituted majority of the study cohort. The incidence of CRBSI was comparable between both heparin and 4.67% TSC groups. The use of low concentration TSC was cost-effective when compared with heparin. Policy change in individual HD centers recommending the use of low concentration TSC might be a cost-cutting intervention benefitting HD patients with central venous catheter access.

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Conflicts of interest

There are no conflicts of interest.

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