https://nephropathol.com DOI: 10.34172/jnp.2025.27589 J Nephropathol. 2025;14(3):e27589

Journal of Nephropathology

Citrate versus heparin lock in hemodialysis catheter's complications; a randomized clinical trial

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 24 Oct. 2024
Revised: 31 Dec. 2024
Accepted: 12 Mar. 2025
Published online: 15 Apr. 2025

Keywords:
Hemodialysis
Catheter-related infections
Citra-Lock
Heparin-Lock

ABSTRACT

Introduction: Permanent central venous catheters (CVCs) are utilized in patients undergoing chronic hemodialysis who lack alternative vascular access or are awaiting kidney transplantation or the development of a long-term vascular access. The primary complications associated with CVCs include catheter-related infections (CRIs) and catheter lumen thrombosis, collectively contributing to catheter dysfunction.

Objectives: This study aimed to compare the efficacy of 4% sodium citrate and heparin lock solutions in maintaining hemodialysis catheters, focusing on catheter dysfunction and infection, coagulation parameters, and serum calcium levels.

Patients and Methods: This randomized clinical trial included 58 patients undergoing chronic hemodialysis, who were randomly assigned into two parallel groups. The intervention group (Citra-Lock; n = 29) received a lock solution containing 4% sodium citrate, while the control group (Heparin-Lock; n = 29) was administered a heparin 5000 IU lock. Data regarding hemorrhagic or coagulation events (e.g., prolonged partial thromboplastin time [PTT]), infections, catheter-related obstructions, and bleeding at the catheter site were prospectively collected and analyzed in both groups. Data were analyzed using SPSS software version 27, with a P value < 0.05 considered statistically significant.

Results: The male-to-female ratio in the study population was 1.52. A significant difference was observed in PTT changes between Citra-Lock and heparin-lock groups ($P<0.001$). However, no significant differences were found in platelet counts or international normalized ratio (INR) levels (186750±9580 versus 175586±10424 and 1.00 versus 1.00; $P=0.247$, $P=0.326$ respectively). Besides, there were no statistically significant differences in catheter related complications ($P=0.669$).

Conclusion: In patients with durable hemodialysis catheters, the administration of a 4% sodium citrate lock solution was associated with fewer changes in PTT compared to heparin locks, without increasing the risk of infections or other catheter-related complications.

Trial registration: The trial was approved by the Iranian registry of clinical trial (identifier: IRCT20231018059761N1; https://irct.behdasht.gov.ir/trial/75555, ethical code; IR.IUMS.FMD.REC.1402.459).

Original Article

Implication for health policy/practice/research/medical education:
Sophisticated maintenance of central venous catheters (CVCs) is crucial for patients on hemodialysis, which can reduce further serious complications that needs salvage or exchanging catheters. At this condition, anticoagulant lock solutions such as the heparin lock are used widely and have specific considerations. This study was conducted to compare 4% sodium citrate and heparin lock in this population. Our findings suggest that both 4% sodium citrate (Citra-Lock) and heparin are comparable in maintaining catheter patency and preventing complications in hemodialysis patients, with no significant differences observed in catheter-related complications, coagulation parameters except for partial thromboplastin time (PTT) which shows drastic changes in heparin group compared to Citra-Lock.

Please cite this paper as: Kohansal Vajargah M, Saddadi F, Fallahkohan MH, Ossareh Sh. Citrate versus heparin lock in hemodialysis catheter's complications; a randomized clinical trial. J Nephropathol. 2025;14(3):e27589. DOI: 10.34172/jnp.2025.27589.

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Introduction

Stable and reliable vascular access is essential for patients undergoing hemodialysis (1). The arteriovenous fistula (AVF) is the preferred vascular access for maintenance hemodialysis, offering a long lifespan with minimal malfunction and infectious complications. Other types of vascular access include arteriovenous grafts and central venous catheters (CVCs) (2). Patients requiring CVCs for maintenance hemodialysis often face significant challenges, including risks of catheter-related obstruction, bleeding, and lumen infection (3).

To enhance catheter functionality and minimize complications such as thrombosis and infection, catheter lock solutions such as heparin are commonly administered (4). Heparin, traditionally used for anticoagulation, reduces these complications through its systemic effects. However, heparin administration is associated with several risks, including increased systemic anticoagulation properties, which may exacerbate bleeding complications (5,6). Additionally, heparin has anti-inflammatory properties but may lead to significant adverse events, such as heparin-induced thrombocytopenia (7,8).

Recent research suggests that sodium citrate (4%) is a safer and more effective alternative to heparin as a catheter lock solution in hemodialysis patients (9). Sodium citrate (4%) has demonstrated both antibacterial and anticoagulant properties, limiting complications such as infection and bleeding (10). Numerous studies have indicated the effectiveness of sodium citrate (4%) in preventing catheter-related infections (CRIs) and bleeding compared to heparin (11).

Objectives

This study aimed to compare the effectiveness of 4% sodium citrate (Citra-Lock) and heparin as catheter lock solutions in terms of reducing CRIs, catheter obstruction, and bleeding in patients undergoing hemodialysis and effects on coagulation indices.

Patients and Methods

Study design

This study was conducted as a randomized, single-center, parallel-group clinical trial involving chronic hemodialysis patients with CVCs. A total of 58 patients undergoing maintenance hemodialysis at a single dialysis center were enrolled and randomly assigned in one of two intervention groups. The trial lasted three months, during which catheter-related complications were monitored. All patients used permanent dual-lumen catheters for their hemodialysis treatments.

Inclusion and exclusion criteria

Eligible participants were adults aged 18 to 80 years who underwent hemodialysis three times per week using a functional CVC (internal jugular, subclavian, or femoral vein) and had normal coagulation parameters as determined by partial thromboplastin time (PTT). Patients were excluded if they had systemic or CRIs within two weeks prior to enrollment, used arteriovenous fistulae or grafts, were pregnant or breastfeeding, had abnormal coagulation tests, had known allergies to heparin or sodium citrate, had coagulopathies, or were receiving immunosuppressive therapy.

Randomization and allocation

Participants were randomly assigned in a 1:1 ratio into either the Citra-Lock group (n=29) or the Heparin-Lock group (n=29). The intervention group received a 4% sodium citrate solution, while the control group received a heparin solution at a concentration of 5000 units/mL.

Blinding

The study was conducted as an open-label trial, meaning that both clinicians and patients were aware of the assigned catheter lock solution. However, laboratory staffs analyzing blood samples and cultures were blinded to the intervention groups to minimize bias in outcome assessments.

Intervention

During each hemodialysis session, 2–3 mL of either heparin or sodium citrate was instilled into the venous and arterial lines of the catheter to act as a lock solution. The sodium citrate solution was sourced commercially from Mana Teb Daya under license by Dirinco, the Netherlands. Patients were clinically monitored during all hemodialysis sessions over the three-month study period for signs of infection, bleeding, and catheter occlusion.

Outcomes

The primary outcomes included the coagulation parameter changes, incidence of CRIs, catheter obstruction, and catheter site bleeding. The frequency of these complications was compared between the two groups.

Data collection

Clinical assessments were performed at each dialysis session, recording complications such as CRIs, catheter obstruction due to clotting, and catheter site bleeding. CRIs were defined based on clinical symptoms and positive blood cultures with no other identifiable source of infection. Catheter obstruction was assessed using ultrasound and quantified based on the volume of thrombolytic agents required to restore blood flow. Bleeding at the catheter site was monitored and recorded during each session.

Sampling

Blood samples were collected at baseline and monthly to evaluate coagulation indices, including activated partial thromboplastin time (APTT), prothrombin time (PT), and international normalized ratio (INR). Additional cultures from both the catheter lines and peripheral blood cultures were performed if catheter infections were suspected.

Statistical analysis

Data were reported as means ± standard deviations or percentages, as appropriate. The sample size of this study measured using G*Power version 3.1.9.2 software. For statistical analysis, the Mann-Whitney U test was conducted to compare differences in non-normally distributed continuous or ordinal variables between the two groups. Pearson's chi-squared test was employed to evaluate categorical data and determine associations between catheter lock measures and variables, such as the frequency of catheter infections. The student's T-test was employed to assess differences in continuous variables between the two groups. All statistical analyses were performed using SPSS software, version 27.0 (IBM Corp., Armonk, NY, USA).

Results

In this study, a total of 58 patients undergoing hemodialysis were divided into two groups; the Heparin-Lock group (n = 29) and the Citra-Lock group (n = 29). One participant in the Citra-Lock group was lost to follow-up due to death from heart disease, leading to 28 analyzed cases in that group. The Heparin-Lock group had no exclusions (Figure 1). The mean age of the participants was 60.8 years, with a mean age of 62.8 years in the Citra-Lock group and 58.8 years in the heparin-Lock group, a difference that was not statistically significant ($P = 0.39$). The gender distribution of the participants in Citra-Lock group were 17 males and 12 females, while in the Heparin-Lock group 18 males and 11 females were included. The male-to-female ratio was 1.52, with no significant difference between the two groups ($P = 0.79$).

Baseline characteristics

Prior to the intervention, there were no statistically significant differences between the groups regarding body mass index ($P = 0.24$), prevalence of diabetes mellitus (P= 0.58), hypertension ($P = 0.06$), catheter insertion sites (the right subclavian vein was used in 84.4% of cases, P=0.33), history of catheter replacement ($P = 0.75$), catheter blockage ($P = 0.68$), or antibiotic therapy ($P = 0.68$). Baseline blood sample analyses for calcium levels, platelet counts, INR, and PTT showed no significant differences between the groups (Table 1).

Post-intervention effects on coagulation factors

Following the intervention, a statistically significant

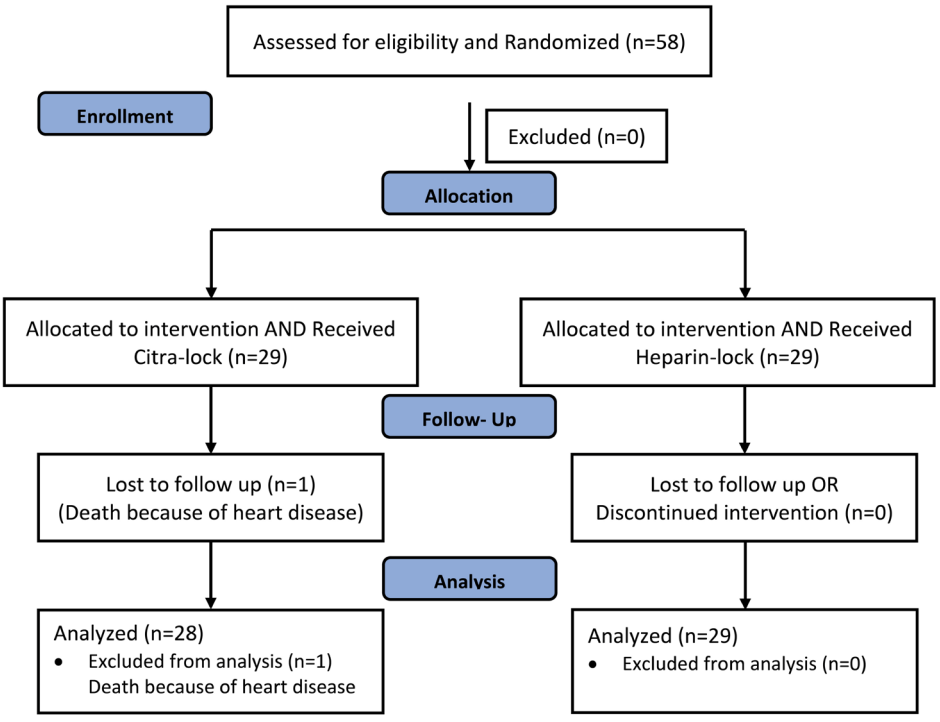

Figure 1. Consort flowchart of the study.

Table 1. Distribution of baseline laboratory values prior to the intervention

Laboratory values	Citra-Lock		Heparin- Lock		Total	*P* value[a]
	Mean	Standard Error	Mean	Standard Error	Mean	
Calcium (mg/dL)	9.8	0.2	9.9	0.2	9.8	0.530
Platelet (/µL)	186750	9580	175586	10424	181070	0.247
INR	1.00	0.00	1.00	0.00	1.00	0.326
PTT (s)	28	1	29	1	29	0.148

INR: International normalized ratio; PTT: Partial thromboplastin time.
[a] Mann-Whitney test.

Table 2. The effect of Citra-lock and Heparin-lock on the changes in coagulation factors over time

Laboratory Values	Citra-lock		Heparin-lock		Total	*P* value[a]
	Mean	Standard Error	Mean	Standard Error	Mean	
Platelet (1st month) (/µL)	7178.57	3089.95	3620.69	2768.32	5368.42	0.614
Platelet (2nd month) (/µL)	55740.74	52217.59	285.71	2271.20	27509.09	0.241
Platelet (3rd month) (/µL)	124592.59	83380.09	500.00	1991.72	61418.18	0.561
INR (1st month)	0.00	0.00	0.00	0.00	0.00	0.326
INR (2nd month)	0.00	0.00	0.07	0.07	0.04	0.564
INR (3rd month)	0.00	0.00	0.00	0.00	0.00	0.317
PTT (1st month)	0.39	0.28	30.45	7.50	15.68	0.025
PTT (2nd month)	0.22	0.15	37.54	7.18	19.00	0.001
PTT (3rd month)	1.19	0.82	37.93	7.86	18.73	0.001

INR: International normalized ratio; PTT: Partial thromboplastin time.
[a] Mann-Whitney test.

difference was observed in trends of PTT changes between the two groups across study timeline. However, no significant differences were found in trends of changes in other coagulation parameters; platelet counts and INR levels in the same period ($P=0.145$ and $P=0.376$ respectively; Figure 2, Table 2). Additionally, changes in serum calcium levels between the groups were not statistically significant ($P=0.673$; Figure 3).

Catheter-related complications

Post-intervention analysis of catheter-related complications showed no significant differences between the heparin-Lock and Citra-Lock groups in terms of the number of catheter obstruction and replacement (n = 6 versus 4, $P=0.669$), catheter infection and catheter site bleeding in both groups during timeline of conducting this study (n = 0, $P=$ NA; Table 3).

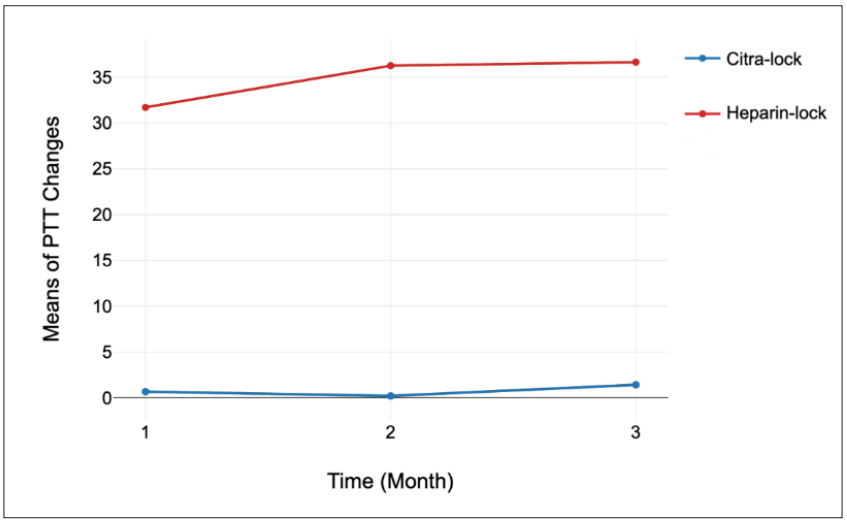

Figure 2. The trends of changes in PTT, between Citra-Lock and Heparin-Lock groups over time ($P< 0.001$).

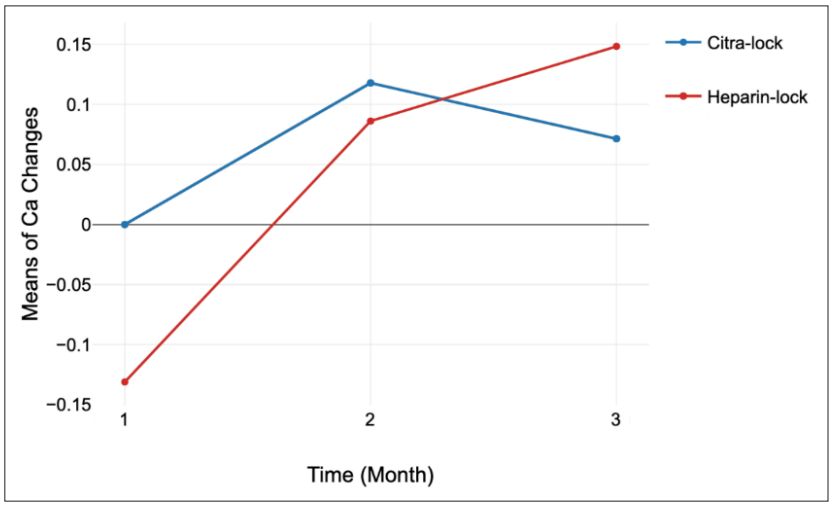

Figure 3. The trends of changes in serum calcium levels between Citra-Lock and Heparin-Lock groups over time ($P = 0.673$).

Discussion

An AVF remains the preferred vascular access for hemodialysis patients due to its low complication rates and long-term reliability (12). However, CVCs are often used as a rapid solution for initiating maintenance hemodialysis when AVF preparation is not immediately feasible (13). Despite their convenience, CVCs are associated with significant late complications, including infections caused by biofilm-forming pathogens such as *Staphylococcus aureus* and catheter dysfunction (14). The administration of heparin as a catheter lock solution has been the standard approach to reduce these complications (15).

This study compared the effectiveness of sodium citrate 4% and sodium heparin as catheter lock solutions in hemodialysis patients. The results revealed no significant differences between the groups regarding baseline characteristics such as body mass index or comorbid conditions, including diabetes and hypertension. These findings align with those of Moore et al that also reported the effectiveness of both solutions in preventing catheter-related dysfunction and infections (16).

One key finding was the significant difference in APTT changes between the heparin-Lock and Citra-Lock groups, whereas changes in INR levels were not significant over time (Table 2). Thompson et al, previously demonstrated a surge in APTT levels 10 minutes after catheter heparin locking, underscoring the potential systemic anticoagulant effects of heparin, even when administered locally (17). This highlights the importance of careful monitoring of APTT in patients with coagulopathies when using heparin locks.

The current study's findings are also consistent with the work of Yon et al, who demonstrated that sodium citrate 4% is a safe and effective lock solution in hemodialysis patients with long-term catheters. Their results, showed that sodium citrate 4% effectively minimizes CRIs while presenting fewer systemic anticoagulation effects (3). We did not find a lower CRI rate, as there were no infections in the studied groups.

Collectively, these findings contribute to the growing evidence supporting the use of Citra-Lock as a viable alternative to heparin locks, particularly in terms of safety and effectiveness in managing catheter-related complications in dialysis patients.

Table 3. Comparison of occurrence of catheter related complications in Heparin-Lock and Citra-Lock groups

Catheter related complication		Heparin- lock	Citra-lock	Total	*P* value[a]
Catheter infection	Yes	0	0	0	N/A
	No	29	28	57	
Catheter obstruction	Yes	3	2	5	0.669
	No	26	26	52	
Catheter replacement	Yes	3	2	5	0.669
	No	26	26	52	
Catheter bleeding	Yes	0	0	0	N/A
	No	29	28	57	

[a] Chi-square test.

Conclusion

This study demonstrated that both Citra-Lock and Heparin-Lock yield similar results across most measured parameters and catheter-related complications. No significant differences were observed between the two groups, including body mass index, diabetes, blood pressure, catheter insertion sites, history of catheter replacement, catheter blockage, and antibiotic use. Furthermore, no significant differences were found in changes to calcium, albumin, platelet counts, or INR changes.

However, a significant difference in APTT changes was observed, indicating that Heparin-Lock has a distinct impact. Despite its local use, heparin may cause systemic effects, as evidenced by changes in APTT, necessitating careful monitoring in patients with coagulopathies or other bleeding risks. These findings underscore the importance of tailoring anticoagulation strategies for hemodialysis patients, with sodium citrate 4% emerging as a safer alternative for reducing complications while maintaining efficacy.

Limitations of the study

This study faced some limitations. The small sample size may restrict the generalizability of the findings. Additionally, timely management and cooperation of participants posed challenges, potentially impacting the consistency of data collection. It is recommended for the future research, involve larger samples (multi- centers), and implement strategies to enhance participant engagement and adherence to study timelines.

Authors' contribution

Conceptualization: Mahsa Kohansal Vajargah, Fereshteh Saddadi, Shahrzad Ossareh.
Data curation: Mahsa Kohansal Vajargah.
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Funding acquisition: Mahsa Kohansal Vajargah, Fereshteh Saddadi.
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Supervision: Fereshteh Saddadi, Shahrzad Ossareh.
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Writing–original draft: Mahsa Kohansal Vajargah, Fereshteh Saddadi, Mohammad Hassan Fallahkohan.
Writing–review & editing: Fereshteh Saddadi, Shahrzad Ossareh, Mohammad Hassan Fallahkohan.

Conflicts of interest

This study was fully funded by Mana Teb Daya under license by Dirinco, the Netherlands, which also provided the sodium citrate solution used in the experiments. The authors declare no additional financial or personal relationships with this company that could have influenced the work reported in this paper.

Ethical issues

This study was conducted in compliance with the principles outlined in the Declaration of Helsinki and was approved by the Human Ethics and Research Ethics Committees of the Iran University of Medical Sciences (Ethical code# IR.IUMS.FMD.REC.1402.459) and was registered in Iranian registry of clinical trial (identifier: IRCT20231018059761N1). Informed consent was obtained from all participants before their inclusion in the study. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was supported by Mana Teb Daya Company (Grant nubmer: 517623).

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