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Short Report

Efficacy of heparin—vancomycin—amikacin combination lock in preventing catheter-related infections in haemodialysis patients: a double-blind randomized clinical trial

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SUMMARY

Background: Haemodialysis patients with tunnelled central venous catheters (CVCs) are at high risk for catheter-related infections (CRIs), which can lead to serious complications, prolonged hospitalizations, and increased healthcare costs. The use of antibiotic lock solutions may help prevent these infections. This study evaluates the efficacy of a heparin—vancomycin—amikacin combination lock solution in preventing CRIs compared with heparin alone in haemodialysis patients.

Methods: This single-centre, double-blind randomized clinical trial involved 60 haemodialysis patients with tunnelled CVCs. Patients were randomly assigned to receive either a heparin 5000 units/mL lock (Group A) or a combination of heparin 5000 units/mL, vancomycin 500 mg/mL, and amikacin 500 mg/mL lock (Group B). The primary outcome was the incidence of CRIs, diagnosed using CDC criteria, over a 6-month follow-up period.

Findings: Group B demonstrated a significantly lower incidence of CRIs compared to Group A (P=0.001). Additionally, the mean number of CRI episodes per patient and the CRI rate per 1000 catheter days were significantly lower in Group B (P=0.028 and 0.042, respectively). The rate of catheter removal due to infection was also significantly reduced in Group B (P=0.029). No significant differences in infection timing were observed, although Group B showed later infection onset. No adverse drug reactions were reported.

Conclusions: The heparin—vancomycin—amikacin combination lock solution was more effective in preventing CRIs than heparin alone in haemodialysis patients. Further studies with larger sample sizes and longer follow-up are needed to confirm its long-term benefits and assess potential risks, including antibiotic resistance.

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Introduction

Haemodialysis is a life-saving treatment for patients with end-stage renal disease (ESRD), often relying on tunnelled central venous catheters (CVCs) for vascular access when arteriovenous fistulas or grafts are unavailable or unsuitable [1]. However, the use of CVCs is associated with a significant risk of catheter-related infections (CRIs), a leading cause of morbidity and mortality in this population. CRIs not only compromise patient outcomes but also contribute to prolonged hospitalizations, increased healthcare costs, and a higher risk of catheter failure and systemic complications such as sepsis [2,3].

To reduce the risk of CRIs, various strategies have been developed, including the use of catheter lock solutions. Antibiotic lock, which involves instilling a concentrated antimicrobial solution into the catheter lumen, aims to prevent bacterial colonization and biofilm formation, effectively reducing infection rates [4]. Among the antibiotics commonly used, vancomycin and amikacin have demonstrated potent activity against Gram-positive and Gram-negative pathogens frequently implicated in CVC infections, making them promising candidates for preventing CRIs [5,6].

Heparin, a commonly used anticoagulant in haemodialysis patients, is often used in catheter lock solutions to prevent thrombus formation. However, the efficacy of heparin alone in preventing infections remains uncertain [7]. As such, the combination of heparin with antibiotics may offer a more effective approach in reducing infection rates in tunnelled CVCs.

The aim of this study was to assess and compare the efficacy of a heparin-only lock solution versus a combination of heparin with vancomycin and amikacin in preventing CRIs in tunnelled CVCs among haemodialysis patients. By evaluating these two strategies, the trial seeks to provide critical insights into the potential advantages of heparin—antibiotic lock solutions for reducing infection rates and improving clinical outcomes in this high-risk patient population.

Methods

This clinical trial was conducted at a tertiary dialysis centre in Iran. The study protocol received approval from the Biomedical Ethics Committee of Ardabil University of Medical Sciences (IR.ARUMS.REC.1399.632). Written informed consent was obtained from all participants before enrollment.

The inclusion criteria were adult patients with ESRD undergoing chronic haemodialysis as outpatients, with a history of at least two months of dialysis, and the placement of a new tunnelled CVC for haemodialysis, without signs of inflammation or infection at the vascular access site. Exclusion criteria included patients undergoing kidney transplantation or peritoneal dialysis, those receiving systemic antibiotics or immunosuppressive therapy, individuals with a history of allergic reactions to the lock solution, patients who missed two or more haemodialysis sessions, and those who declined to participate in the study.

Patients were randomly assigned to one of two groups. Block randomization was performed using a random number table. Group A received heparin 5000 units/mL in each catheter lumen, while Group B received a combination of heparin 5000 units/mL, vancomycin 500 mg/mL, and amikacin 500 mg/mL in each catheter lumen. At the end of each dialysis session, the solutions were instilled into both catheter lumens, left in place during the interdialytic period, and withdrawn before the subsequent session. This procedure was repeated throughout the study. Both patients and researchers assessing the outcomes were blinded to group assignments. Patients were followed for up to six months and were monitored at each dialysis session by nephrologists and nurses. They were assessed three times per week for signs of infection and instructed to report any symptoms, including fever, redness, or pain at the catheter insertion site. Additionally, they received written guidelines and a contact number for concerns between sessions.

The primary outcome was CRI, diagnosed using CDC criteria [8]: (1) clinical exit site infection with inflammation within 2 cm of the exit site; (2) definite bloodstream infection with a significant organism isolated from both catheter and peripheral blood, with no other infection source; (3) probable bloodstream infection with symptom resolution after antibiotic therapy or catheter removal, where blood culture confirms infection but the catheter tip does not, or *vice versa*, with no other infection source identified; (4) possible bloodstream infection with symptom resolution after antibiotic therapy or catheter removal in a symptomatic patient, but with negative cultures and no other identified infection source.

Repeat episodes of possible and probable CRBSIs were defined as new infections occurring after catheter replacement. Exit-site infections were treated as separate entities from CRBSIs. In cases of suspected CRBSI, blood cultures were obtained from both the catheter lumen and a peripheral vein, with at least two sets of cultures sent for microbiological analysis. Investigations and management decisions, including catheter removal, were based on clinical judgement, microbiological findings, and the patient's response to treatment. Infections were categorized by onset as occurring within the first 4 weeks or later.

Catheters were exchanged or removed in cases of progressive infection despite systemic antibiotic therapy, evidence of metastatic infection, or catheter dysfunction. All removed catheters were cultured, and the catheter tip was specifically swabbed for microbiological analysis using a quantitative method to identify potential pathogens. Catheter cultures were performed using appropriate agar media to detect organisms present.

Descriptive statistics were used to summarize participant characteristics and outcomes. The Mann—Whitney U-test was used for continuous variables, and Fisher's exact test for categorical variables. Data analysis was performed using SPSS version 26, with a significance level set at 0.05.

Results

A total of 60 patients were included in the study, with 30 patients in each group. The mean age of participants was 59 years (range: 24—84). No significant differences were observed between the groups in terms of mean age (P=0.37), age categories (adult (20—39 years), middle-aged adult (40—59 years), and geriatric (60+ years)) (P=0.78), or gender (P=1). The mean number of dialysis sessions for the two study groups was similar

(70 ± 3 in Group A and 71 ± 2 in Group B, P=0.13). Additionally, there was no significant difference in the mean number of catheter days per patient (114 ± 15 days for Group A and 162 ± 14 days for Group B; P=0.08).

A total of 28 CRI episodes were observed in 18 patients in Group A, compared with five episodes in four patients in Group B (P=0.001). The mean number of episodes per patient was significantly lower in Group B (1.25) than in Group A (1.56) (P=0.042) (Table I). Additionally, the CRI rate per 1000 catheter days was significantly reduced in Group B (5.00) compared with Group A (9.33) (P=0.028). Catheter removal due to infection occurred in 11 patients in Group A, while only two patients in Group B required removal (P=0.029). In one Group B patient, the catheter was exchanged due to dysfunction. Of the 11 catheters removed due to infection in Group A, six yielded positive cultures, indicating the presence of pathogens. The negative catheter cultures were observed in cases of probable CRBSI and possible CRBSI, where infection was suspected but not confirmed microbiologically. In these cases, clinical judgment and symptom resolution after catheter removal were considered sufficient for diagnosing the infection.

The time to first CRI did not differ significantly between the groups (P=0.18), but the onset of infection was later in Group B (25.0 ± 6.8 days) compared with Group A (20.5 ± 5.4 days). Similarly, no significant difference in infection timing was observed between the groups (P=0.599), although most infections occurred during the third week. Details on infection types and timing are provided in Table II.

Micro-organisms isolated from catheter cultures included three cases of *Staphylococcus aureus*, one case of *Staphylococcus epidermidis*, one case of *Pseudomonas aeruginosa*, and one case of *Klebsiella pneumoniae*. Blood cultures identified *S. aureus* in two cases.

Regarding infection rates across age groups, no significant differences were found between the groups (P=0.13 in Group A and P=0.7 in Group B). However, in Group A, women experienced significantly more infections than men (P=0.03), whereas this difference was not observed in Group B (P=1).

Table I
Comparison of catheter-related infection (CRI) outcomes between Groups A and B

Outcome	Group A (heparin lock) $N = 30$	Group B (heparin + antibiotic lock) $N = 30$	P
Total CRI episodes	28	5	**0.001**
Mean number of episodes/patient	1.56	1.25	**0.042**
CRI rate, per 1000 catheter days	9.33	5.00	**0.028**
Time to first CRI, days	20.5±5.4	25.0±6.8	0.18
Catheter removal due to infection, N (%)	11 (36.7%)	2 (6.7%)	**0.029**

Bold values indicate statistically significant differences (P<0.05) between the two groups.

Discussion

This randomized clinical trial demonstrates that the heparin—vancomycin—amikacin combination lock solution is more effective in preventing CRIs in haemodialysis patients compared with heparin alone. Our findings show a significantly lower incidence of CRIs and a reduced need for catheter removal due to infection in the group receiving the antibiotic lock solution. These results align with previous studies indicating the effectiveness of antibiotic lock solutions in preventing infections associated with CVCs in haemodialysis patients [9,10]. The combination of vancomycin and amikacin provides broad-spectrum coverage against common pathogens, including *Staphylococcus aureus* and *Staphylococcus epidermidis*, which probably contributed to the lower infection rates observed in Group B [11].

In our study, the most common types of CRIs were exit-site infections and probable CRBSI, followed by possible CRBSI, and a small number of definite CRBSI. These findings are consistent with prior studies on CVC-related infections in haemodialysis patients, where exit-site infections are frequently observed as an early manifestation, often progressing to more severe infections if not promptly managed [12,13].The use of the heparin—antibiotic lock solution appears to significantly reduce the incidence of exit-site infections, which are a major concern in haemodialysis patients, potentially preventing progression to more serious infections such as bloodstream infections [14].

Table II
Details of infection types and time to first infection between Groups A and B

Outcome	Group A (heparin lock) $N = 30$	Group B (heparin + antibiotic lock) $N = 30$	P
Exit site infection	12 episodes (in 7 patients)	2 episodes (in 2 patients)	**0.03**
Definite CRBSI	2 episodes (in 2 patients)	0 episodes	0.30
Probable CRBSI	5 episodes (in 3 patients)	0 episodes	0.08
Possible CRBSI	9 episodes (in 6 patients)	3 episodes (in 2 patients)	**0.02**
Time to first infection			
1st week	4 episodes	1 episode	0.518
2nd week	3 episodes	1 episode	
3rd week	12 episodes	3 episodes	
4th week or later	9 episodes	0 episodes	

CRBSI, catheter-related bloodstream infection.
Bold values indicate statistically significant differences (P<0.05) between the two groups.

Beyond the direct reduction in infection rates, the use of an antibiotic lock solution has significant implications for improving patient outcomes in haemodialysis. Catheter removal due to infection is a serious complication that not only harms the patient but also leads to increased hospitalizations, prolonged treatments, and higher healthcare costs [15]. Although differential time to positivity (DTP) was not specifically applied for catheter removal in our study, decisions were made based on standard clinical guidelines. By reducing the need for catheter removal, the combination lock solution may help alleviate these adverse consequences, improving both patient survival and reducing the economic burden of care [16]. While the time to first CRI did not significantly differ between groups, Group A did show an earlier onset of infection, suggesting that the antibiotic lock solution may delay infection progression or reduce its severity, even if the onset time is not substantially altered [17].

Our subgroup analysis revealed that, within Group A, women experienced significantly higher infection rates than men. These findings are consistent with previous studies that have shown a higher prevalence of CRIs in women [18], which may warrant further investigation. Interestingly, this gender-based difference was not observed in Group B, where both men and women had similar infection rates. This suggests that the antibiotic lock solution may mitigate gender-related differences in infection susceptibility, offering additional benefits for women who are more prone to infections.

Amikacin, when combined with heparin alone or with vancomycin in solution, has shown stability and efficacy [17]. While other studies have evaluated the efficacy of combination antibiotic lock therapies, such as vancomycin-gentamicin [19], to the best of our knowledge, this is the first study to assess the heparin—vancomycin—amikacin combination for preventing CRIs in haemodialysis patients. The stability of amikacin in combination with heparin and vancomycin suggests that this regimen could be a viable option for preventing infections in this vulnerable patient population.

In addition to the use of heparin—antibiotic lock solutions, it is crucial to emphasize the importance of reducing the reliance on tunnelled catheters by promoting the creation of arteriovenous (AV) fistulas whenever possible. AV fistulas are the preferred method for vascular access in haemodialysis patients and significantly reduce the risk of CRIs. The use of tunnelled catheters should be minimized, as prolonged use of CVCs increases the risk of infections and may contribute to the development of antibiotic resistance [20,21]. While our study focused on improving infection outcomes with a heparin—antibiotic lock solution, efforts to reduce the need for tunnelled catheters through proactive AV fistula creation should be an integral part of the overall infection prevention strategy in haemodialysis patients.

Although antibiotic resistance rates were not directly compared, the identified organisms were consistent with typical CRBSI pathogens in haemodialysis patients. Treatment was adjusted based on susceptibility patterns, with Gram-negative organisms (*P. aeruginosa* and *K. pneumoniae*) sensitive to amikacin, and *S. aureus* treated with vancomycin. Exit-site infections were managed with topical antibiotics.

Despite these promising findings, several limitations must be considered. The sample size of 60 patients is relatively small, and the 6-month follow-up may not capture the long-term effects of the heparin—antibiotic lock solution. Larger, multi-centre studies with extended follow-up are necessary to confirm these results and evaluate the long-term safety and efficacy of this intervention. Furthermore, our study did not assess the potential risks of prolonged antibiotic use, particularly concerning the development of antibiotic resistance. While no adverse effects were observed in this study, future research should monitor resistance patterns and assess the long-term safety of antibiotic lock solutions.

In conclusion, our study supports the use of a heparin—vancomycin—amikacin combination lock solution as an effective strategy for preventing CRIs in haemodialysis patients. Further research involving larger sample sizes, longer follow-up periods, and surveillance for antibiotic resistance is needed to confirm the long-term benefits of this approach and to ensure its safety and cost-effectiveness in clinical practice.

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Authorship statement

We, the undersigned authors, have made substantial contributions to the study and manuscript as follows, and confirm our authorship and willingness to publish the work:

1. **Amir Ahmad Arabzadeh**: Conceptualization, Methodology, Supervision, Writing — Original Draft, Writing — Review & Editing.
2. **Maryam Iranikia**: Data Curation, Formal Analysis, Writing — Review & Editing.
3. **Farhad Pourfarzi**: Investigation, Resources, Writing — Review & Editing.
4. **Bita Shahrami**: Investigation, Writing — Original Draft, Writing — Review & Editing.
5. **Susan Mohammadi Kebar**: Conceptualization, Methodology, Project Administration, Writing — Review & Editing.

Each author has reviewed and approved the final version of the manuscript and agrees to be accountable for all aspects of the work. We acknowledge and confirm our authorship and our willingness to publish the manuscript in its current form.

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Conflict of interest statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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