

The Effect of Heparin Lock and Topical Antibiotics on Catheter-Related Bloodstream Infection Events in Chronic Kidney Disease with Short-Term Double-Lumen Catheter Patients

Hery Siswanto¹, Muhammad Nuralim Mallapasi^{2,3}, Mulawardi¹, Jayarasti Kusumanegara^{2,3}, Umar Usman², Burhanuddin Bahar⁴, Haerani Rasyid⁵, Muhammad Faruk¹

¹Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

²Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.

³Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Wahidin Sudirohusodo Hospital, Makassar, Indonesia

⁴Department of Biostatistics, Public Health Faculty, Hasanuddin University, Makassar, Indonesia

⁵Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

***Corresponding author:**

Jayarasti Kusumanegara, MD
Division of Thoracic and cardiovascular
Surgery, Department of Surgery
Faculty of Medicine
Hasanuddin University
Jalan Perintis Kemerdekaan KM 11
Makassar, South Sulawesi, 90245
Indonesia
Telephone: +62411585984
Fax: +62411585984
E-mail: jayarasti@gmail.com

ABSTRACT

Introduction: Catheter-related bloodstream infection (CRBSI) is a complication that can occur in hemodialysis patients, especially when a double-lumen catheter (DLC) is used. This study aimed to investigate the effect of heparin lock and topical antibiotics on the incidence of CRBSI in chronic kidney disease (CKD) patients using DLC.

Methods: This randomized, pre–post-control design study was conducted on adult patients undergoing routine hemodialysis. Patients were divided equally into two groups. In addition to the standard protocol, the first group was given a combination therapy of heparin lock (20 mg/mL heparin left in DLC for 4 hours) and mupirocin 5% cream at the DLC exit area, and the second group was only given a single heparin lock. The diagnosis of CRBSI was made based on the Infectious Diseases Society of America criteria. Numerical data were analyzed using the t-test and Mann–Whitney U test. Categorical data were analyzed using the chi-square test. A p-value of <0.05 was considered significant.

Results: Of the 40 patients (20 male and 20 female) in this study, 62.5% were between the ages of 41–60 years. CRBSI was found in 10 patients (25%), with a higher incidence in the single-therapy group (8 cases; $p < 0.05$). The single-therapy group also tended to have CRBSI faster, with a hazard ratio of 7.61.

Conclusion: The application of the topical antibiotic mupirocin might be effective in reducing the risk of CRBSI in CKD patients using DLC.

Key words: vascular access, double-lumen catheter, catheter-related bloodstream infection, insertion site, randomized-controlled trial

INTRODUCTION

Vascular access (VA) is imperative in the hemodialysis process. Some available options are arteriovenous (AV) fistula, AV graft, and catheter (1,2). Due to its improved long-term patency, higher performances, and fewer problems in

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most patients, AV fistula remains the preferred VA strongly recommended by best practice recommendations (2,3). A catheter may be used if hemodialysis is needed urgently. It can be placed in a large vein, such as the subclavian, internal jugular, or femoral vein. A double-lumen catheter (DLC) provides temporary access for hemodialysis. This was created in 1987 and is made from silicone or polyurethane. Some complications might arise from DLC insertion, such as infection, thrombosis, arrhythmia, entrapped guidewire, and malposition (4). Infection arising from DLC infection is known as catheter-related bloodstream infection (CRBSI) (5). In Indonesia, CRBSI is found in 2.1–30.3 cases per 1,000 days of central venous catheter (CVC) usage (6).

Antibiotic lock solutions (e.g., gentamicin, vancomycin, minocycline, cefazolin, cefotaxime) and nonantibiotic lock solutions (e.g., sodium citrate, taurolidine) can help avoid CRBSI by locking catheter lumens. Antimicrobial lock solutions (antibiotic or nonantibiotic) are sometimes used in conjunction with an anticoagulant (typically heparin) and, rarely, another antibiotic (7). Antibiotics as a catheter locking solution (CLS) agent might increase the risk of bacterial resistance, low effectivity, and high toxicity in the bloodstream. However, antibiotic CLS can prevent biofilm formation inside the catheter.

Heparin lock administration is a strategy to prevent blood clotting, so it may help prevent catheters from blocking or from causing pulmonary embolism (8), to prevent bacterial colonization dysfunction of the catheter (9). According to a recent survey of intensive care units in the United States, 64.6% of respondents used normal saline and 31% used heparin. The most common heparin concentrations were 100 IU/mL (37.5%) and 10 IU/mL (29.7%), and the most common catheter locking intervals were every 8 hours and after each use (74.4%) (8).

Topical antibiotics, such as mupirocin, prevent up to 85% of CRBSI. However, their usage can increase the risk of antimicrobial resistance (9). Mupirocin has shown effectivity to suppress bacterial skin colonization at the CVC exit site and tip and prevent CRBSI. It is strongly effective for Gram-positive cocci but not non-fermented Gram-negative cocci. However, in some studies, mupirocin has been effective against both Gram-positive and Gram-negative bacteria (10).

This study aimed to investigate the effect of a heparin lock intervention with and without topical antibiotic application (mupirocin 2% cream) in terms of CRBSI events in chronic kidney disease (CKD) patients with DLC.

METHODS

Study design

This experimental study with a randomized pre-post-controlled design was conducted from 1st – 31st October 2021 in the Hemodialysis Center, Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. Study participants were divided into two treatment groups: (i) heparin lock group and (ii) mupirocin 2% cream combined with heparin lock treatment group.

Population and sample

Patients were enrolled from the hemodialysis center. The inclusion criteria were routine hemodialysis adult patients (above 18 years old) who used DLC for VA during dialysis and agreed to participate. The exclusion criteria were history of allergy to mupirocin 2% cream, history of infected DLC, duration of DLC usage of more than 3 months, and close contact with and/or symptoms of and/or confirmed COVID-19. A minimum sample size of 18 patients for each group was determined by the Federer formula, with an additional 10% for the possibility of drop-out, so the total sample size for each group was 20 patients.

Study protocol

All participants were given information regarding the research. A simple randomization method used flipping a coin (heads: heparin lock group; tails: mupirocin group). The DLCs were inserted by a cardiothoracic-vascular surgeon and a vascular surgeon.

Participants with diabetes mellitus (DM) comprised those with a history of DM and newly diagnosed DM patients (fasting blood glucose >126 mg/dL, glucose tolerance test >200 mg/dL, 2-hour post-prandial glucose >200 mg/dL, or HbA1C test >7%).

Chlorhexidine 2% was applied on healthy skin and observed for 30 minutes. In case of hypersensitivity signs such as shortness of breath, wheezing, shock, edema, pruritus, or redness, we used povidone-iodine instead. Then, if contraindications to mupirocin 2% cream were excluded for participants in both treatment groups, mupirocin 2% cream was applied to the DLC insertion site, and it was wrapped with sterile gauze. Standard wound care was performed with a 3-times medial-to-lateral disinfection process within a 30-cm area surrounding the DLC insertion site, using chlorhexidine 2% or povidone-iodine. NaCl 0.9% was used to rinse blood clots and slough. Heparin lock (heparin 20

mg/mL) was administered in the DLC in both groups, and mupirocin 2% cream was applied in the disinfected area in the heparin lock + antibiotic group. This area was covered with sterile gauze in both groups. These procedures were repeated within 4 weeks of study, and CRBSI signs were observed.

CRBSI

The Infectious Diseases Society of America criteria for CRBSI are bacteremia or fungemia in a patient with an intravascular catheter with at least one positive blood culture, as well as clinical signs and symptoms of infection (fever, chills, and/or hypotension) and no other obvious source of the bloodstream infection than the catheter, plus the same organism (species and antibiogram) isolated from the catheter segment and peripheral blood in a positive semiquantitative (>15 CFU/catheter segment) or quantitative (>10² CFU/catheter segment) culture (5,11).

Statistics

Data were taken and analyzed with IBM SPSS Statistics for Windows, Version 20. Data were presented as age, gender, DLC duration, DM type 2, and CRBSI event. Numerical data were tested using the t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Categorical data were analyzed with the chi-square test. The accepted level of significance was p < 0.05.

Ethics

This study obtained ethical approval from the Ethical Committee of Faculty of Medicine, Hasanuddin University (Number: 728/UN4.6.5.31/PP36/2021).

RESULTS

A total of 40 participants were enrolled and divided into two groups by simple randomization: 20 in the heparin lock group and 20 in the heparin lock + antibiotic group. The basic characteristics of the participants are shown in *table 1*.

Most participants were 41–60 years old (n = 25, 62.5%). The mean age was 46.15 years (SD ± 11.99). Fifty percent of the participants were male (n = 20). Most had a body mass index of 25–29.9 kg/m² (n = 14; 35%). DM was found in most participants (n = 33; 82.5%).

Among the 40 participants, 3 (7.5%) had pus at

Table 1 - Basic Characteristic of the Participants

Variable	Frequency (%)
Age (Years)	
≤ 20	2 (5.0)
21–40	10 (25.0)
41–60	25 (62.5)
>60	3 (7.5)
Gender	
Male	20 (50.0)
Female	20 (50.0)
Nutritional Status	
Underweight (BMI <18.5 kg/m ²)	2 (5.0)
Normal weight (18.5–24.9 kg/m ²)	8 (20.0)
Overweight (25–29.9 kg/m ²)	14 (35.0)
Obesity I (30–34.9 kg/m ²)	8 (20.0)
Obesity II (35–39.9 kg/m ²)	4 (10.0)
Obesity III (≥ 40 kg/m ²)	4 (10.0)
Diabetes Mellitus	
Yes	33 (82.5)
No	7 (17.5)
Immunosuppressive Disease	
Yes	2 (5.0)
No	38 (95.0)
Other Vascular Disease	
Yes	0 (0.0)
No	40 (100.0)
Fever	
Yes	40 (100.0)
No	0 (0.0)
Shivering	
Yes	40 (100.0)
No	0 (0.0)
Pus Appeared in DLC Insertion Site after Treatment	
Yes	3 (7.5)
No	37 (92.5)
Microbial Culture	
Positive	10 (25.0)
Negative	30 (75.0)
Microorganism	
<i>Staphylococcus aureus</i>	9 (22.5)
<i>Streptococcus sobrinus</i>	1 (2.5)
No microorganism found	30 (75.0)
DLC Location	
Femoral	25 (62.5)
Subclavian	15 (37.5)
History of Prior DLC Insertion	
Yes	9 (22.5)
No	31 (77.5)
Treatment	
Heparin lock	20 (50.0)
Heparin lock + mupirocin	20 (50.0)
Total	40 (100.0)

BMI = body mass index; DLC = double-lumen catheter

the DLC insertion site. Ten participants (35.0%) had a positive blood culture: 9 (22.5%) had *Staphylococcus aureus*, and 1 (75.0%) had *Streptococcus sobrinus*. Most participants had the DLC inserted in the femoral vein (n = 25; 62.5%) and had no prior history of DLC insertion (n = 31; 77.5%).

Table 2 shows factors that might affect CRBSI. We

Table 2 - Analysis of Factors Associated with CRBSI Event

Variable	CRBSI						p
	Yes		No		Total		
	n	%	n	%	n	%	
Age (years)							
≤ 20	1	50.0	1	50.0	2	100.0	^c 1.000
21–40	2	20.0	8	80.0	10	100.0	
41–60	6	24.0	19	76.0	25	100.0	
>60	1	33.3	2	66.7	3	100.0	
Gender							
Male	4	20.0	16	80.0	20	100.0	^b 0.716
Female	6	30.0	14	70.0	20	100.0	
Nutritional Status							
Underweight (BMI <18.5 kg/m ²)	0	0.0	2	100.0	2	100.0	^c 0.999
Normal weight (18.5–24.9 kg/m ²)	3	37.5	5	62.5	8	100.0	
Overweight (25–29.9 kg/m ²)	4	28.6	10	71.4	14	100.0	
Obesity I (30–34.9 kg/m ²)	2	25.0	6	75.0	8	100.0	
Obesity II (35–39.9 kg/m ²)	0	0.0	4	100.0	4	100.0	
Obesity III (≥ 40 kg/m ²)	1	25.0	3	75.0	4	100.0	
Diabetes Mellitus							
Yes	8	24.2	25	75.8	33	100.0	^b 1.000
No	2	28.6	5	71.4	7	100.0	
Immunosuppressive Disease							
Yes	1	50.0	1	50.0	2	100.0	^b 0.441
No	9	23.7	29	76.3	38	100.0	
DLC Location							
Femoral	5	20.0	20	80.0	25	100.0	^b 0.457
Subclavian	5	33.3	10	66.7	15	100.0	
History of Prior DLC Insertion							
Yes	2	22.2	7	77.8	9	100.0	^b 1.000
No	8	25.8	23	74.2	31	100.0	
Treatment							
Heparin lock	8	40.0	12	60.0	20	100.0	^a 0.028*
Heparin lock + mupirocin	2	10.0	18	90.0	20	100.0	

BMI = body mass index; DLC = double-lumen catheter. ^aChi-square test; ^bFisher's exact test; ^cKolmogorov–Smirnov test

found no association of CRBSI event with age, gender, nutritional status, DM, immunosuppressive disease, pus existence, DLC insertion site, or history of prior DLC insertion ($p > 0.05$). In contrast, a significant difference was found with different treatments. The heparin lock group had 8 participants with CRBSI, and the heparin lock + antibiotic group had 2 participants with CRBSI ($p < 0.05$).

Table 3 shows the leukocyte count and DLC usage duration by CRBSI event. For participants with CRBSI, the mean leukocyte count was higher ($17.21 \times 10^3/\mu\text{L}$) than those without CRBSI ($15.33 \times 10^3/\mu\text{L}$). Participants

with CRBSI had a higher mean DLC usage duration (13.86 days) than those without CRBSI (12.10 days). However, these differences were not statistically significant ($p > 0.05$).

Table 4 shows the difference in pus finding between the heparin lock and heparin lock + antibiotic groups. Three participants (15.0%) had pus at the DLC insertion site in the heparin group, and no pus was found in the heparin lock + antibiotic group. This difference was not statistically significant ($p > 0.05$).

The heparin lock group showed a significantly higher mean leukocyte count compared to the heparin

Table 3 - Leukocyte Count and DLC Duration Usage (Days) by CRBSI Event

Variable	CRBSI (Mean ± SD)		p
	Yes	No	
Leukocyte Count ($10^3/\mu\text{L}$)	17.21 ± 4.60	15.33 ± 3.77	^b 0.233
DLC Duration Usage (Days)	12.10 ± 5.38	13.86 ± 5.48	^a 0.206

DLC = double-lumen catheter; ^aindependent t-test; ^bMann–Whitney test

Table 4 - Pus Appearance at DLC Insertion Site After Treatment With Heparin Lock Alone Compared to Heparin Lock and Mupirocin Combination Treatment

Variable	Pus Appearance at DLC Insertion Site					p	
	Yes		No		Total		
n	%	n	%	n	%		
Treatment							
Heparin lock	3	15.0	17	85.0	20	100.0	*0.231
Heparin lock + mupirocin	0	0.0	20	100.0	20	100.0	

DLC = double-lumen catheter. *Fisher's exact test

lock + antibiotic group ($17.36 \times 10^3/\mu\text{L}$ vs. $14.24 \times 10^3/\mu\text{L}$; $p < 0.05$). The DLC usage duration was significantly longer in the heparin lock + antibiotic treatment group compared to heparin lock treatment alone (17.6 days vs. 9.25 days; $p < 0.05$) (table 5).

Figure 1 shows a Kaplan–Meier curve for the two treatment options with the probability of CRBSI. Participants with heparin lock treatment alone had a higher probability of CRBSI compared to heparin lock + antibiotic treatment. Hence, the survival rate was higher in combination therapy. The hazard ratio of CRBSI in heparin lock therapy alone was 7.61. According to the log-rank test, a significantly higher probability for CRBSI existed in the heparin lock alone treatment group compared to the heparin lock + antibiotic treatment group ($p < 0.05$).

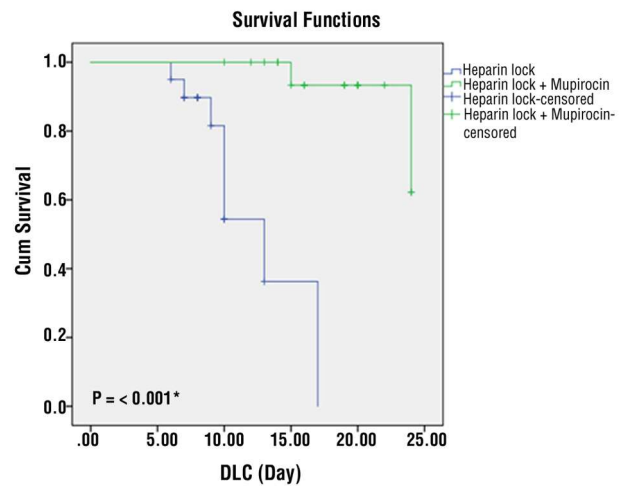


Figure 1 - Kaplan–Meier analysis of the probability that a patient will experience CRBSI based on the type of therapy given. P-value is calculated using the log-rank test*

DISCUSSION

The incidence of CRBSI ranges from 10–18 cases per 1,000 days of catheter usage and is related to longer length of stay and increased morbidity and mortality (12). In one observational study of nearly 500 new hemodialysis patients, the cumulative risk of CRBSI increased by more than half in just 6 months (13). Empirical research has found that CRBSI is mostly (40%–80%) caused by Gram-positive bacteria (*Staphylococcus aureus*) (14). Unstable hemodynamics, mental status alterations, catheter dysfunction, hypothermia, nausea, vomiting, and malaise might be caused by CRBSI (15).

A study by Xu et al. showed that the mean age of CRBSI patients was 71.1 ± 16.7 years, and most were

male (16). Most participants in our study were 41–60 years old ($n = 25$), and CRBSI-positive participants were mostly in this age group (6 out of 10). Six out of 10 CRBSI-positive participants were female. Nahla et al. found more than half (53.8%) of CRBSI participants had DM (17). However, neither DM nor immunosuppressive diseases showed statistically significant differences in CRBSI events in our study. However, 8 out of 10 CRBSI-positive participants had DM.

The leukocyte count was higher and DLC usage duration was shorter in CRBSI participants, but both statistical analyses were not significant ($p > 0.05$). This is in contrast to Xu et al., who found the leukocyte count

Table 5 - Leukocyte Count and DLC Usage Duration by Treatment Given

Variable	Treatment (Mean ± SD)		p
	Heparin lock	Heparin lock + Mupirocin	
Leukocyte ($10^3/\mu\text{L}$)	17.36 ± 4.03	14.24 ± 3.43	^a 0.021*
DLC Usage Duration (Days)	9.25 ± 2.69	17.60 ± 4.12	^a <0.001**

DLC = double-lumen catheter. *Mann–Whitney test

was lower in CRBSI patients compared to non-CRBSI patients ($13.85 \pm 7.1 \times 10^3/\mu\text{L}$ vs. $15.38 \pm 5.6 \times 10^3/\mu\text{L}$; $p = 0.246$) (16). In our study, the mean leukocyte count was significantly higher in the group receiving heparin lock alone compared to the combination treatment with topical mupirocin group ($17.36 \times 10^3/\mu\text{L}$ vs. $14.24 \times 10^3/\mu\text{L}$; $p = 0.028$). Moreover, DLC usage duration was longer in participants with the combination treatment compared to heparin lock alone (17 days vs. 9 days; $p < 0.001$). Heparin prevents bloodstream dysfunction, and mupirocin prevents bacterial colonization (especially by *Staphylococcus*) (9,18).

Our findings are in line with a meta-analysis by Dang et al. that found that gentamicin with citrate anti-coagulant (OR 2.92, 95% CI 1.32–6.42) and cloxacillin and heparin (OR 2.07, 95% CI 1.19–5.49) were effective to prevent CRBSI. Cloxacillin was highly effective (84.2%) to prevent CRBSI, following EDTA (84.4%). Furthermore, CRBSI prevention at the exit site was shown to be effective by a combination of minocycline and EDTA. Cefotaxime and heparin were the most effective to prevent catheter-related thrombosis (19).

Tao et al. showed that mupirocin topical administration significantly reduced cannulation of the wound site and decreased skin colonization at the CVC insertion site. Bacterial colonization was significantly reduced at the CVC tip (RR=0.316; $p=0.001$) after topical mupirocin application, as were CRBSI events (5.3 vs. 29.1 per 1,000 catheter-days; $p < 0.001$) (18). Mupirocin has also been shown to be effective against Gram-positive and Gram-negative bacteria, even though theoretically it is only effective against Gram-positive cocci (10,18). Another meta-analysis by Salim et al. also showed that CRBSI events were significantly lower with CLS with antibiotics compared to heparin alone (RR = 0.28, 95% CI (0.21–0.37); $p < 0.0001$) (20).

Our study has several limitations. Requirements needed for regression analysis were not fulfilled; hence, regression analysis was not done to evaluate heparin lock + antibiotic therapy for CRBSI events without being influenced by other independent variables such as comorbidities, DLC location, and DLC usage duration. Moreover, we did not study the effectivity of other topical antibacterial such as bacitracin, ethanol, or povidone-iodine as a comparison with mupirocin for increasing DLC usage duration. Further study is needed to evaluate more varied basic characteristics of patients, and other topical antibiotics should be studied. Further research should assess the time of bacterial colonization by swabbing around the DLC insertion site so a predictive analysis can be carried out on the onset of CRBSI between heparin lock treatment

alone and heparin lock + topical antibiotics combination treatment.

CONCLUSION

The application of the topical antibiotic mupirocin to the DLC insertion site might be effective in reducing the incidence of CRBSI and prolonging the duration of DLC use. However, further study with larger sample sizes is required. Therefore, the addition of mupirocin to heparin-locked DLC depends on the clinician's decision.

Conflicts of interests

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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