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Cefazolin–gentamicin versus taurolidine–citrate for the prevention of infection in tunneled central catheters in hemodialysis patients: A quasi-experimental trial

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ABSTRACT

Background: Catheter-related bloodstream infection (CR-BSI) is one of various complications related to hemodialysis (HD). As a result of the high rate of infection, the use of lock solutions for the prevention of CR-BSI has been studied. However, adverse effects of lock solution, such as increased emergence of strains resistant to antibiotics, which is an important concern, need to be investigated further. The aim of this study was to compare the efficacy of lock solution using a combination of cefazolin and gentamicin versus taurolidine and citrate in reducing CR-BSI in patients undergoing HD and to identify any adverse effects.
Methods: A prospective observational study was performed at two dialysis centers. Patients using new tunneled central venous catheters (CVC) for HD were included. Patients with a tunneled CVC were assigned to receive either antibiotic lock solution (group 1: gentamicin 7 mg/ml + cefazolin 12 mg/ml + heparin 3500 IU/ml) or lock solution with TauroLock-Hep500 (group 2: taurolidine citrate 4% + heparin 500 IU/ml) during the inter-dialysis period. The patients were allocated to these groups according to the hemodialysis center they were attending.
Results: A total of 145 CVCs were implanted in 127 patients and were followed for 15 months: 77 CVCs (65 patients) were placed in group 1 and 68 CVCs (62 patients) in group 2. There was no difference between the two groups with regard to CR-BSI (events per 1000 catheter-days: group 1 = 0.79, group 2 = 1.10; $p = 0.18$) or exit site infection rates (events per 1000 catheter-days: group 1 = 2.45, group 2 = 1.83; $p = 0.37$). The groups differed in ESI pathogens, with gram-positive oxacillin-resistant pathogens more frequent in group 1 (31.8% vs. 5.0%; $p = 0.003$). The two groups were similar in mechanical complications. In the Cox regression analysis, the internal jugular vein site was a protective factor for all catheter removal complications (hazard ratio (HR) 0.41, 95% confidence interval (CI) 0.19–0.91) and mechanical complications (HR 0.16, 95% CI 0.065–0.41); only ESI was a risk factor for all catheter removal complications (HR 1.79, 95% CI 1.04–3.07) and mechanical complications (HR 5.64, 95% CI 1.65–19.3).
Conclusions: The efficacy of both lock solutions was similar in preventing infections related to tunneled CVCs for HD. However, there were more oxacillin-resistant strains in patients who received antibiotic lock solution. Further studies are required to determine the optimal drug regimen and concentrations for lock solution and the associated adverse effects.

Introduction

Hemodialysis (HD) is the most widely used dialysis therapy in the world, and vascular access represents an important risk factor for bacteremia, hospitalization, and mortality (Sesso et al., 2016; Niyyar, 2012; Lok and Mokrzycki, 2011; Al-Balas et al., 2017; Vascular Access 2006 Work Group, 2006). In particular, catheter-

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related bloodstream infection (CR-BSI) is a severe complication that requires hospitalization, systemic antibiotic therapy, and removal, reinsertion or replacement of the catheter (The NIH, 2016; Lee, 2017; Sequeira et al., 2017). Various measures have been studied for the prevention of CR-BSI, one of which is the use of lock solutions (Katneni and Hedayati, 2007; Böhlke et al., 2015). This measure consists of instilling solutions with antithrombotic and antimicrobial properties into the catheter lumen at concentrations 100–1000 times greater than the minimum inhibitory concentration commonly used for systemic therapy, in an attempt to prevent the main mechanisms of morbidity and mortality associated with central venous catheters (CVCs): dysfunction due to thrombosis and infection (Katneni and Hedayati, 2007; Böhlke et al., 2015; Betjes, 2011; Niyyar and Lock, 2013; Labriola and Pochet, 2017).

In recent decades, meta-analyses and systematic reviews have shown the benefits of prophylactic lock therapy compared to heparin for reducing the incidence of CR-BSI in HD patients (Labriola et al., 2008; Jaffer et al., 2008; Yahav et al., 2008; Rabindranath et al., 2009; Snaterse et al., 2011; Zhao et al., 2014; Liu et al., 2013; Liu et al., 2014; Wang et al., 2016; Zang et al., 2017; Zcharioudakis et al., 2014). The ideal solution for locking prophylactic therapy, as well as its long-term adverse effects, is yet to be determined.

Solutions for locking prophylactic therapy can include antibiotic or non-antibiotic antimicrobial agents. The former are bactericidal and bacteriostatic agents (Lok and Mokrzycki, 2011; Lee, 2017). Bactericidal drugs cause death and disruption of the bacterial cell and include drugs that primarily act on the cell wall (e.g., β-lactams), cell membrane (e.g., daptomycin), or bacterial DNA (e.g., fluoroquinolones). Bacteriostatic agents inhibit bacterial replication without killing the organism, and most act by inhibiting protein synthesis; these include sulfonamides, tetracyclines, and macrolides. The distinction is not absolute; some agents that are bactericidal against certain organisms may only be bacteriostatic against others and vice versa (Katneni and Hedayati, 2007; Böhlke et al., 2015).

Recent publications have reported the emergence of antibiotic/antimicrobial-resistant bacteremia in HD patients. One way to solve this problem is to use non-antibiotic antimicrobial catheter locks, such as those with high concentrations of citrate and taurolidine, which are able to eradicate biofilms and have broad-spectrum activity against both gram-positive and gram-negative organisms enclosed in biofilms generated in vivo (Katneni and Hedayati, 2007; Böhlke et al., 2015; Betjes, 2011; Niyyar and Lock, 2013; Labriola and Pochet, 2017).

These non-antibiotic drugs inhibit microbial growth in a different manner. They may have direct antimicrobial activity, increasing the efficiency of an antibiotic if given together by acting as helper compounds; they can also change the pathogenicity of microorganisms or the physiological response to them, such as modulating macrophage activity (Lok and Mokrzycki, 2011). Non-antibiotic biocides, on the other hand, are composed of heterogeneous groups of natural and synthetic substances, such as disinfectants and antiseptics, which can deter, render harmless, or exert a controlling effect on microorganisms by biological or chemical means (Betjes, 2011; Niyyar and Lock, 2013; Labriola and Pochet, 2017).

The aim of this study was to compare the efficacy of lock solution using gentamicin–cefazolin–heparin (antibiotic antimicrobial agents) vs. taurolidine–citrate (non-antibiotic antimicrobial agents) in reducing CR-BSI in patients undergoing chronic HD with a tunneled CVC and to identify the associated adverse effects.

Methods

Study design and patients

This was a quasi-experimental trial conducted from November 2014 to February 2016 that included patients enrolled in two Brazilian University Hospitals: Botucatu School of Medicine (dialysis unit, group 1) and Bauru State of Sao Paulo Hospital (dialysis unit, group 2). The patients were not randomized and were allocated to the two lock therapy groups according to their HD center. The antibiotic group (group 1) received a mixture of 12 mg/ml cefazolin, 7 mg/ml gentamicin, and 3500 IU/ml heparin during the inter-dialysis period. Group 2 received a solution containing taurolidine, citrate 4%, and 500 IU/ml heparin (TauroLock-Hep500). In both groups, the solutions were used to fill the lumen of the catheter according to its size. The volume of fluid was an exact fill.

The protocol was approved by the institutional ethics committee (protocol number 4323-201) and registered as a Brazilian clinical trial (RBR-6vfg7r). Written informed consent was obtained from the patients or their next of kin.

Patients were eligible for enrolment if they were undergoing chronic HD with a new tunneled catheter while waiting for placement and maturation of an arteriovenous fistula (AVF) or graft. Exclusion criteria included patients under 18 years of age, pregnant women, patients who already had an infection or who were on antibiotic therapy, and those with tunneled catheters implanted before November 2014. An intervention nephrologist inserted the tunneled central catheters (Tal Palindrome, Kendall, Tyco Healthcare Division, Mansfield, MA, USA) into the right or left internal jugular, subclavian vein, or femoral vein under fluoroscopic guidance. Inserted catheters were managed using infection prophylaxis protocols in accordance with the Guidelines for the Prevention of Intravascular Catheter-Related Infections (2011) (O'Grady et al., 2011). Transparent dressings with controlled permeability were used routinely in both services, and antibiotic prophylaxis was provided with 2 g cefazolin at the time of catheter insertion.

The primary end-point of the trial was CR-BSI, the definition for which was based on the Manual of Diagnostic Criteria and Guidance System for Epidemiological Surveillance of Nosocomial Infections in Sao Paulo State, which describes it as the presence of at least one of the signs or symptoms associated with infection, such as fever, tremors, or hypotension (systolic blood pressure <90 mmHg) without another apparent focus of infection, with a negative blood culture if one is performed (Silva et al., 2012).

For patients who were experiencing their first CR-BSI and who had not been hospitalized in the last 3 months, the treatment of CR-BSI was conducted using intravenous (IV) administration of 2 g cefazolin after HD sessions. For patients with severe symptoms, such as septic shock, and those with previous use of broad-spectrum antibiotics or who had been hospitalized in the last 3 months, IV administration of 15 mg/kg vancomycin in combination with 500 mg levofloxacin or 2 g ceftazidime was given after HD sessions. The treatment time was 21 days, and antimicrobial drug dosages were adjusted according to the results of an antibiogram. Exit site infection (ESI) was defined as the presence of purulent discharge or erythema and edema at the exit site below the cuff (Mermel et al., 2009). Secretions were collected for culture using the swab technique after treatment with a first-generation cephalosporin was initiated. Catheter removal was indicated in the presence of septic shock, metastatic infectious complications, or the absence of improvement after 48 h of treatment.

Complications related to lock solution use were evaluated, such as the emergence of strains resistant to antibiotics, defined as an increase in the number of infections caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and strains resistant to gentamicin. The rate of catheter removal by mechanical complication (catheter occlusion) was also evaluated, which was defined as the impossibility of maintaining catheter flow above 250 ml/min during the hemodialysis session, without an adequate response to thrombolytic drugs, necessitating catheter change.

Other variables included age, sex, etiology of chronic kidney disease (CKD), presence of diabetes mellitus and cardiovascular disease, HD start date, and catheter insertion date and site.

Statistical analyses

A sample size of at least 59 patients per group was determined based on the hypothesis that the difference in mechanical complications or the emergence of strains resistant to antibiotics would be 20% lower in group 2, with a two-tailed α error of 0.05 and study power of 0.80.

All analyses were performed on an intention-to-treat basis. Data are presented as the mean ± standard deviation or median and range. The Student *t*-test and Kruskal–Wallis test were used to compare parametric and non-parametric patient characteristics, respectively. The Chi-square test and Fisher's exact test were used to compare proportions. Rates of CR-BSI (measured in events per 1000 catheter-days) were compared using the log rank test. Cumulative infection-free survival and mechanical complication-free catheter survival were determined using the Kaplan–Meier method and compared using the log rank test. These were censored for CVC removal for fistula use, change of dialysis method, transplantation, transfer of dialysis center, and death.

p-Values of <0.05 were considered statistically significant. Cox regression analysis was performed to assess the impact of the variables, including age, group, comorbidities, catheter site, baseline disease, and time on HD until CVC implantation ended in catheter withdrawal for any reason (transplantation, death, AVF use, and mechanical and infectious complications).

Results

During the study period, 145 tunneled CVCs were inserted in 127 patients with stage 5 CKD. Sixty-five patients were enrolled in group 1 (77 CVCs) and 62 patients in group 2 (68 CVCs). The patients had a mean age of 60.8 ± 15.0 years and were predominantly male (57.4%). Diabetes was the main etiology of CKD (42.5%), and the comorbidities hypertension, smoking, and cardiovascular disease (CVD) presented in 90.6%, 29.1%, and 41.7% of the patients, respectively. The median time on dialysis prior to tunneled CVC implantation was 54 days (range 12–846 days) and the internal jugular vein was the main site (93.0%).

There was no statistically significant difference between the two groups in relation to age, diabetes, or kidney disease as the main cause of CKD, or the presence of comorbidities, such hypertension and diabetes mellitus. There was a significant difference between the two groups in regard to smoking, which was more frequent in group 2 (group 1 = 20.0%, group 2 = 38.7%; $p = 0.014$).

The duration of HD treatment until catheter implantation was variable, but without a significant difference between the two groups (median (range): group 1 = 31 (6–944), group 2 = 93 (36–827) days; $p = 0.09$). The clinical characteristics of group 1 and group 2 patients are shown in Table 1.

In both groups, the main site of CVC implantation for the 145 implanted catheters was the internal jugular vein, but it was more frequent in group 2 (group 1 = 85.7%, group 2 = 98.5%; $p = 0.013$). There was a predominance of CVC in the direct jugular vein when compared to left jugular vein in both groups (74.0% and 79.0%, respectively; $p = 0.87$). No catheter was inserted in the subclavian vein and there was no difference between the two groups in the prevalence of ESI (40.0% vs. 29.4%; $p = 0.17$) or CR-BSI (12.9% vs. 17.6%; $p = 0.43$).

Prior to this study using antibiotics/antimicrobials, the use of only heparin (concentration 5000 UI/ml) in the lock solution resulted in 9.80 ESI events and 1.97 CR-BSI events per 1000 catheter-days in group 1. In group 2, there were 3.50 ESI events and 1.74 CR-BSI events per 1000 catheter-days. After the introduction of antibiotics/antimicrobials into the lock solution, the two groups displayed an overall reduction in, and similar rates for, CR-BSI (group 1 = 0.79, group 2 = 1.10 events per 1000 catheter-days; $p = 0.18$) and ESI (group 1 = 2.45, group 2 = 1.83 events per 1000 catheter-days; $p = 0.37$). The infection-free time was also similar in the two groups (median (range): group 1 = 106 (40–184), group 2 = 147 (40–189) days; $p = 0.59$). There were differences in group 1 and group 2 before and after the introduction of lock solution therapy, as shown in Table 2.

Table 1
Clinical characteristics of 127 patients with long-term hemodialysis catheters in groups 1 and 2.

Characteristics	Group 1 $n = 65$	Group 2 $n = 62$	*p*-Value
Sex, male	33 (50.8%)	40 (64.5%)	0.39
Age (years)	60.2 ± 15.7	61.5 ± 14.3	0.56
Causes of CKD			
Diabetes mellitus	25 (38.4%)	29 (46.8%)	0.44
Hypertension	11 (16.9%)	11 (17.7%)	0.90
Glomerulonephritis	10 (15.4%)	4 (6.4%)	0.18
Unknown	7 (10.8%)	5 (8.1%)	0.82
Other	12 (18.5%)	13 (21%)	0.89
Comorbidities			
Diabetes mellitus	32 (49.2%)	35 (56.4%)	0.52
Cardiovascular disease	31 (47.7%)	22 (35.5%)	0.22
Hypertension	59 (90.8%)	56 (90.3%)	0.83
Smoking	13 (20%)	24 (38.7%)	0.014
Time of dialysis (days)	31 (6–944)	93 (26–827)	0.09
Colonization, GP methicillin-resistant	5 (7.7%)	3 (4.8%)	0.78
Colonization, GN multi-resistant	2 (3.1%)	0 (0%)	0.81

CKD, chronic kidney disease; GP, gram-positive; GN, gram-negative. Results are presented as the number (%), mean ± standard deviation, or median (interquartile range).

In the outcome analysis, the two groups had similar cure rates for both ESI (96.8% vs. 95.0%; $p = 0.75$) and CR-BSI (80.0% vs. 75.0%; $p = 0.78$), as shown in Tables 3 and 4. The two groups were similar for the etiological microbes associated with CR-BSI episodes, with a predominance of gram-negative cultures in both groups (80.0% vs. 58.4%; $p = 0.38$), followed by gram-positive cultures (10.0% vs. 33.3%; $p = 0.32$). There were also large numbers of gram-negative cultures associated with ESI episodes (32.2% vs. 50.0%; $p = 0.33$), as shown in Tables 3 and 4; however, gram-positive agents were the most frequently seen in ESI for both groups (38.7% vs. 20.0%; $p = 0.27$). There was no difference in the resistance to the antimicrobials in CR-BSI. However, for ESI, the prevalence of oxacillin-resistant gram-positive strains was significantly higher in group 1 than in group 2 (38.7% vs. 5.0%; $p = 0.017$). The colonization status with oxacillin-resistant gram-positive strains prior to enrolment was similar in the two groups (7.7% in group 1 and 4.8% in group 2; $p = 0.81$).

Regarding catheter removal, there was no difference between the two groups (49.3% vs. 52.9%; $p = 0.85$). The etiology of removal differed, with mechanical complications more frequent in group 1 (52.6% vs. 25.0%; $p = 0.028$) and the use of AVF more frequent in group 2 (0% vs. 33.3%; $p < 0.001$).

The groups did not present significant differences in infection-free time for CR-BSI or ESI, or mechanical complication-free catheter survival (Figures 1–3). Multiple logistic regression analyses were performed to identify the factors associated with CR-BSI, ESI, and mechanical complications. No CR-BSI-associated variables were identified, while the number of days with the CVC was associated with ESI (odds ratio 7.79, 95% confidence interval (CI) 1.02–1.12; $p = 0.0052$) and mechanical complications (odds ratio 11.98, 95% CI 0.98–0.99; $p = 0.0006$).

Table 2
Rates of exit site infection (ESI) and catheter-related bloodstream infection (CR-BSI) before and after lock solution.

	Group 1		Group 2		*p*-Value (after G1 vs. G2)	*p*-Value (after G1 vs. G1)	*p*-Value (after G2 vs. G2)
	Before LS	After LS	Before LS	After LS			
CR-BSI/1000 CVC-days	1.97	0.79	1.74	1.1	0.18	0.01	0.3
ESI/1000 CVC-days	9.80	2.45	3.50	1.83	0.59	0.02	0.07

CVC, central venous catheter; LS, lock solution; G1, group 1; G2, group 2.

Table 3
Outcome and etiology of exit site infection (ESI).

	Group 1 $n=31$	Group 2 $n=20$	*p*-Value
Outcome			
Resolution	30 (96.8)	19 (95)	0.75
CVC removal	1 (3.2)	1 (5)	0.99
Agents			
Gram-positive	12 (38.7)	4 (20)	0.27
Gram-negative	8 (25.8)	4 (20)	0.74
Negative culture	10 (32.1)	10 (50)	0.33
Not collected	1 (3.3)	2 (10)	0.55
Gram-positive, methicillin-resistant	12 (38.7)	1 (5)	0.017
Gram-negative, multi-resistant	2 (6.4)	0 (0)	0.51

CVC, central venous catheter.

Table 4
Outcome and etiology of catheter-related bloodstream infection (CR-BSI).

	Group 1 $n=10$	Group 2 $n=12$	*p*-Value
Outcome			
Resolution	8 (80)	9 (75)	0.78
CVC removal	2 (20)	3 (25)	0.99
Agents			
Gram-positive	1 (10)	4 (33.3)	0.32
Gram-negative	1 (10)	1 (8.3)	0.99
Negative culture	8 (80)	7 (58.4)	0.38
Gram-positive, methicillin-resistant	1 (10)	2 (16.7)	0.99
Gram-negative, multi-resistant	1 (10)	0 (0)	0.45

CVC, central venous catheter.

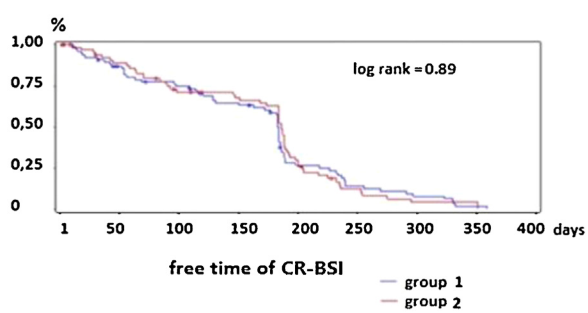

Figure 1. Infection-free time for catheter-related bloodstream infection (CR-BSI).

In the Cox regression analysis, the jugular vein site was a protective factor for catheter removal in all causes (hazard ratio 0.41, 95% CI 0.19–0.91) and mechanical complications (hazard ratio 0.16, 95% CI 0.06–0.41; $p<0.001$), as shown in Table 5.

Discussion

The reduction in CR-BSI rates using lock solution has been evidenced in various trials and meta-analyses published recently, yet the best prophylactic lock therapy option is still the subject of

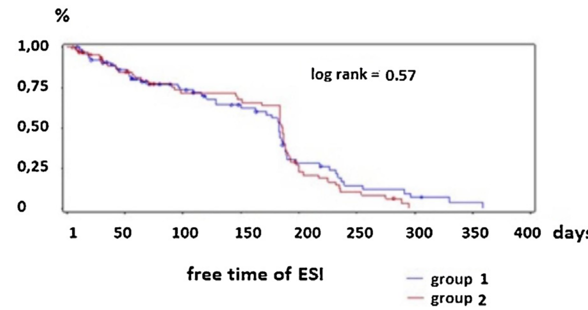

Figure 2. Infection-free time for exit site infection (ESI).

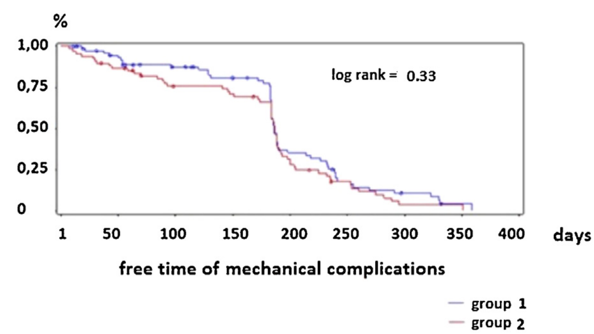

Figure 3. Mechanical complication-free catheter time.

Table 5
Multivariate Cox regression analysis: hazard ratio and 95% confidence interval for tunneled central venous catheter removal for any cause and for mechanical complication.

CVC removal	HR	95% CI	*p*-Value
Any cause			
Group (1 vs. 2)	1.11	0.98–2.35	0.77
DM	1.24	0.97–3.31	0.58
ESI	1.79	1.04–3.07	0.018
BSI	1.29	0.98–2.99	0.90
Smoking	1.08	0.97–1.97	0.75
Site (IJV vs. others)	0.41	0.19–0.91	0.028
Time on HD	1.31	0.97–2.14	0.87
Mechanical complication			
Group (1 vs. 2)	1.17	0.98–2.19	0.24
DM	1.27	0.96–3.17	0.98
ESI	5.64	1.65–19.33	0.006
BSI	1.91	0.98–4.99	0.56
Smoking	1.18	0.99–2.68	0.39
Site (IJV vs. others)	0.16	0.065–0.41	<0.001
Time on HD	1.24	0.97–3.21	0.76

CVC, central venous catheter; HR, hazard ratio; 95% CI, 95% confidence interval; DM, diabetes mellitus; ESI, exit site infection; BSI, bloodstream infection; IJV, internal jugular vein; HD, hemodialysis.

study (Silva et al., 2012; Filiopoulos et al., 2011; Weijmer et al., 2005; Zwiech et al., 2016; Solomon et al., 2010; Murray et al., 2014; Takla et al., 2007; Vercaigne et al., 2016; Maki et al., 2011; Dogra et al., 2002; Kim et al., 2006; Nori et al., 2006; Al-Hwiesh and

Abdul-Rahman, 2007; Campos et al., 2011; Moran et al., 2012; Moore et al., 2014; Hemmelgarn et al., 2011; Wasse, 2008). In this study, the use of prophylactic lock therapy was studied only in catheters tunneled for HD, with a follow-up of at least 6 months, comparing solutions containing antibiotics (gentamicin + cefazolin) versus antimicrobial solutions (taurolidine + citrate); these solutions presented similar results in reducing CR-BSI and ESI.

There is only one clinical study in the literature comparing antimicrobial and antibiotic drugs. The study by Filiopoulos et al. (2011) was performed in non-tunneled HD catheters using gentamicin–heparin, taurolidine–citrate, or heparin only (historical control group) with a 3-month follow-up. They found similar rates of CR-BSI among the groups that used gentamicin and taurolidine, and rates were higher in the heparin-only group. There was no difference in thrombosis rate. In the present study, the etiological agents of CR-BSI were similar in the gentamicin–cefazolin and taurolidine–citrate groups, without a greater number of gram-positive infections detected, suggesting that taurolidine also has an effect on infections by these agents. This effect was also found in a previous study that detected a reduction in bacteremia by comparing 23 positive blood cultures in HD catheters during the use of heparin, with all cultures negative after a mean of 33.8 days of taurolidine–citrate–heparin lock therapy. All positive blood cultures were gram-positive and most contained *S. aureus*, demonstrating the action of taurolidine against gram-positive strains (Zwiech et al., 2016).

In contrast with previous results presented by Liu et al. (2014) and Solomon et al. (2010), this study detected the presence of similar mechanical complications between the groups, after the exclusion of AVF as a cause for removal.

Winnicki et al. (2018) reported the results of a randomized multicenter study that evaluated the role of prophylactic therapy using two different treatments: taurolidine–citrate–heparin twice a week and 4% citrate three times a week. In addition to a significant reduction in CR-BSI and mechanical dysfunction in the taurolidine group, there was no difference between the groups in the number of gram-positive bacterial agents ($p = 0.77$).

Many investigators have selected gentamicin as one of the antibiotics to include for preventive purposes. In the meta-analysis published by Labriola et al. (2008), lock therapy resulted in a reduced rate of CR-BSI, and stratified subgroup analysis for the presence of diabetes, duration of follow-up, serum albumin, serum ferritin level, proportion of tunneled catheters, intranasal use of mupirocin, and the use of citrate or gentamicin showed that the type of solution influences the final efficacy. Gentamicin proved more effective than the others, although the use of this antibiotic in different concentrations and often in association with citrate makes it difficult to compare the work.

In this study, the use of antimicrobial solutions and antibiotics in prophylactic lock therapy resulted in similar incidence and outcomes of infectious and mechanical complications and did not influence the withdrawal of tunneled CVCs. Cox analysis revealed that the patients' treatment group had no impact on outcomes and identified the presence of ESI as a variable associated with CVC removal from all causes and mechanical complications, while the internal jugular site was a protective factor for CVC removal. The risk factors associated with CVC survival are poorly evaluated in the literature, but a previous study also showed that the use of the internal jugular vein was a protective factor, promoting longer catheter permanence (Develter et al., 2005).

There is also growing concern about increased bacterial resistance and the presence of adverse effects with the prolonged use of antibiotics in lock therapy. The emergence of multidrug-resistant (MDR) organisms is an important cause of infections associated with healthcare, and MDR infections are associated with poorer results when compared to infections caused by strains susceptible to the same antibiotics (Calfee, 2013). The colonization status with oxacillin-resistant gram-positive strains prior to enrolment was similar in the two groups (9.2% in group 1 and 4.8% in group 2; $p = 0.78$), showing that the rate of MDR in the antibiotic lock group could have been associated with the intervention.

Regarding complications related to prophylactic lock therapy, there was a difference between the two groups in the emergence of oxacillin-resistant strains. These were more prevalent in the gentamicin + cefazolin group. This differs from the results of the analysis of these agents performed in a previous study in the same dialysis centers published in 2012 (Silva et al., 2012), which compared the use of gentamicin + cefazolin versus heparin lock therapy and showed lower CR-BSI rates in the intervention group (with antibiotics) and no difference in resistant strains. Taurolidine is a disinfectant, not an antibiotic agent; therefore, bacterial resistance to taurolidine has not been reported to date (Labriola and Pochet, 2017).

Conflicting results have been reported in relation to the development of resistance to gentamicin. Dogra et al. (2002) used lock therapy with 40 mg/ml gentamicin and Moran et al. (2012) with 320 μg/ml gentamicin, yet neither found evidence of the emergence of strains resistant to this medication. Meanwhile the emergence of gentamicin-resistant strains was reported by Landry et al. (2010), who used 4 mg/ml gentamicin + 5000 IU/ml heparin. The number of negative cultures was high in the present study, with predominance in both groups and with a proportion of 80% for CR-BSI in group 1. This fact makes it difficult to identify the etiological pathogens of infections, as well as to evaluate the emergence of strains resistant to the antimicrobials used in lock therapy. We questioned whether the use of lock solution with consequent extravasation to the bloodstream could have been responsible for the high prevalence of negative cultures in group 1, since the presence of serum concentrations of these antimicrobials could inhibit bacterial growth.

This study has some limitations, mainly because it was not randomized and it included a small number of patients. It also considered the clinical criterion for the diagnosis of CR-BSI, unlike previous studies, which have adopted the diagnostic criteria for CR-BSI recommended by the US Centers for Disease Control and Prevention (CDC) (O'Grady et al., 2011). Lastly, there may have been other differences in the quality of infection control measures and expertise of the medical and nursing staff between the two dialysis units and this was not explored in the baseline analysis; this could have affected the comparisons between studies and units.

In spite of these limitations, this prospective, comparative study conducted in two centers showed that the efficacy of antibiotic therapy in locking was similar to solutions containing taurolidine and citrate in preventing infections related to catheters tunneled for HD. Although there was a greater presence of oxacillin-resistant strains in the antibiotic agent group, there was no difference in the incidence of occlusion between the two groups.

In conclusion, the results of this study show that the introduction of either antibiotic or antimicrobial lock solution was associated with a reduced incidence of CR-BSI and ESI. There was an equivalent incidence of CR-BSI and ESI and mechanical complications with antibiotic and non-antibiotic antimicrobial lock agents and a higher incidence of bacterial resistance with the antibiotic lock.

Ethical approval

The protocol was approved by the institutional ethics committee (protocol number 4323-201) and was registered as a Brazilian clinical trial (RBR-6vfg7r). Written informed consent was obtained from the patients or their next of kin.

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Conflict of interest

The authors disclose the absence of conflict of interest.

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