Approaches to Prolong the Use of Uncuffed Hemodialysis Catheters: Results of a Randomized Trial

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Key Words
Catheter-related bacteremia · Hemodialysis · Lock solutions · Uncuffed catheters · Taurolidine · Thrombosis

Abstract
Background: Use of uncuffed catheters (UCs) in hemodialysis patients is common practice. An antibiotic lock has been recommended to prevent catheter-related bacteremia (CRB), although insufficient data are available about the appropriate antimicrobial agent and dose with prolonged use of UCs. Methods: This open-label randomized study was conducted to compare gentamicin/heparin (group A) and taurolidine/citrate (group B), as catheter-lock solutions, in 119 chronic hemodialysis patients in whom a total of 150 UCs were placed. A well-matched historical control group (heparin) included 67 UCs in 58 patients (group C). Results: CRB episodes developed in 6 and 8 patients in groups A and B, respectively, significantly fewer than in group C (20 patients). Cumulative CRB-free catheter survival at 90 days was 82% for A and 78% for B, which is significantly higher than the 26% for C. Similar Gram-positive infection rates were found in all groups. The Gram-negative infection rate was significantly lower in B compared to C. No significant differences in thrombosis rates were observed between the groups. Conclusions: Gentamicin/heparin and taurolidine/citrate, used for locking UC, were similarly effective at preventing CRB and catheter thrombosis for up to 3 months, until a functional permanent vascular access became available. Both antimicrobial lock solutions were superior to heparin in CRB prevention with similar thrombosis rates.

Introduction

Central venous catheters are essential in hemodialysis (HD) current practice. They are temporarily used in acute kidney injury and in a substantial proportion of incident and prevalent HD patients until their permanent vascular access becomes available [1, 2]. According to the Dialysis Outcomes and Practice Patterns Study (DOPPS), 60% of incident patients in the USA and 31% in Europe began HD with a catheter [3]. In prevalent HD patients, catheter use was 17% in the USA and 8% in Europe [3]. Widespread application of catheters exposes patients to an enhanced risk for catheter-related infections, a major cause of increased morbidity and mortality [1]. In particular, catheter-related bacteremia (CRB) is a severe complication that requires hospitalization, systemic antibiotic therapy and catheter removal or replacement [2]. Therefore, CRB prevention is crucial. Interdialytic catheter locking with antimicrobial agents has been recommended in an attempt to prevent intraluminal coloniza-
Long-Term Use of Uncuffed HD Catheters

Patients and Methods

Patients

Between April 2008 and November 2009, 119 adult patients with chronic kidney disease stage 5 (CKD-5) requiring an UC insertion for starting or maintaining chronic HD at our center were enrolled. Only patients with a newly inserted, well-positioned UC that was expected to be needed for at least 1 week could be included. Patients with active or recent infection as well as those under antibiotic therapy or immunosuppressive medications were excluded. The study was performed in accordance with the Declaration of Helsinki and with the approval of the local ethics committee. All patients gave informed written consent before enrollment.

58 adult patients with CKD-5 requiring HD via an UC in a previous period, between March 2007 and March 2008, were used as historical controls. Patients’ clinical characteristics are shown in table 1.

Study Design

The study design is a prospective, open-label randomized trial conducted at a single medical center. Patients were randomly assigned to receive interdialytic catheter locking with either gentamicin/heparin (40 mg/ml gentamicin and 5,000 U/ml unfractionated heparin; ratio 1:3) (group A) or taurolidine/citrate (1.35% taurolidine and 4% sodium citrate; TauroLock™, TauroPharm GmbH) (group B) at the end of each dialysis session and continuously since catheter insertion. The randomization procedure was performed using a computer-generated table of random numbers. Finally, the catheter-lock solution in the historical control group contained unfractionated heparin alone at a concentration of 5,000 U/ml (group C).

Catheters were inserted at bedside by experienced nephrologists and under strict aseptic conditions. A single type of UC was used throughout the study (Mahurkar dual lumen catheter with curved extension, Quinton, Va., USA). The preferred site for insertion was the right internal jugular vein, followed by the left internal jugular vein and the subclavian veins. Femoral catheters were excluded. Antibiotic prophylaxis was not given. A post-procedure erect X-ray was performed to exclude complications and assess catheter tip position.

The lock solution was prepared by dialysis nurses at the end of each dialysis session, immediately before instillation into the catheter lumen, according to clear instructions and each administration was reported in the patient’s dialysis chart. 2-ml syringes were used, one for each catheter lumen (0.5 ml of gentamicin and 1.5 ml of heparin for group A, 2 ml of TauroLock for group B and 2 ml of heparin for group C). The adherence to the study protocol was regularly checked by the attending physician. The lock solution was withdrawn before each dialysis session and the catheter was locked after dialysis with a volume equal to the dead space of each catheter port lumen as it is listed by the manufacturer. Gentamicin/heparin solutions were checked for turbidity after constitution. Exit-site care involved inspection of the catheter exit site at each dialysis, cleaning with chlorhexidine or iodine and covering with a new transparent, air-permeable dry dressing. Connecting and disconnecting of the dialysis catheter to the bloodlines was done under strict aseptic conditions. All adverse events were systematically assessed and recorded at each dialysis session. The attending physician determined whether
these events were related to the study medications. In particular, the patients were subjected to direct clinical inquiry of any evidence of aminoglycoside ototoxicity, although formal hearing tests were not performed, and of potential citrate toxicity (digital and facial paresthesias).

In case a catheter was replaced due to dysfunction, patients could continue in the same arm of the study. As reasons for study discontinuation were considered: catheter permanent removal for any reason, kidney transplant, conversion to peritoneal dialysis, transfer to another dialysis unit, death or withdrawal from the study by the patient or attending physician.

The catheter care protocol and patient monitoring during the previous period of the historical control group were similar to those applied during the study and mentioned above. Our institutional policy regarding HD catheter care had been established a sufficient period of time before the study was conducted.

**Outcomes and Definitions**

The primary end-point of the study was the time to the first CRB episode. CRB was defined as positive blood culture obtained, using an aseptic technique, during dialysis through the dialysis circuit linked to the catheter in a symptomatic patient and after other potential sources of infection had been excluded through the appropriate clinical and laboratory testing. Blood-culture bottles are processed at a local laboratory. Exit from the study for any non-CRB-related cause was treated as a censored observation for the purposes of survival analysis. Catheter use was defined as the number of days from catheter insertion to diagnosis of CRB or censored observation. Patients were followed up until the study end-point of CRB was reached or a censored observation occurred.

The secondary end-point was catheter thrombosis defined by catheter dysfunction with blood flow <200 ml/min in three consecutive dialysis sessions and after other potential causes, such as malposition or kinking, had been excluded.

**Statistics**

All analyses were performed on an intention-to-treat basis. Data are presented as means ± standard deviations or as medians and ranges. The Student’s t-test and the Mann-Whitney U test were used to compare continuous variables between groups and χ² test to compare categorical variables between groups. Cumulative CRB-free catheter survival was determined using the Kaplan-Meier method and compared using the log-rank test. p values <0.05 were considered statistically significant.

**Results**

**Patient Allocation and Follow-Up**

A total of 119 patients were enrolled where 150 catheters were inserted. No patient was lost to follow-up or discontinued the catheter-lock solution. During the study period, patient survival was 100%. The historical control group comprised 58 patients in whom 67 catheters were inserted.

**Patients’ Baseline Characteristics**

The clinical characteristics of patients in the gentamicin/heparin group (group A) and taurolidine/citrate

### Table 1. Patients’ characteristics by type of catheter-lock solution

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>60</td>
<td>59</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>72 (50–80)</td>
<td>75 (36–95)</td>
<td>70 (42–84)</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>29/31</td>
<td>33/26</td>
<td>30/28</td>
<td>NS</td>
</tr>
<tr>
<td>Incident/prevalent HD patients, n</td>
<td>35/25</td>
<td>36/23</td>
<td>38/20</td>
<td>NS</td>
</tr>
<tr>
<td>Mean HD duration for prevalent patients ± SD, months</td>
<td>37 ± 25</td>
<td>34 ± 28</td>
<td>41 ± 27</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetics, n (%)</td>
<td>40 (67)</td>
<td>38 (64)</td>
<td>36 (62)</td>
<td>NS</td>
</tr>
<tr>
<td>Indication for catheter insertion, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start or maintain HD for CKD-5</td>
<td>42</td>
<td>45</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>Reinsertion due to dysfunction</td>
<td>14</td>
<td>17</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular access failure</td>
<td>18</td>
<td>14</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Catheters, n</td>
<td>74</td>
<td>76</td>
<td>67</td>
<td>NS</td>
</tr>
<tr>
<td>Internal jugular</td>
<td>62</td>
<td>63</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>Subclavian</td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Median duration of catheter use (range), days</td>
<td>30 (18–88)</td>
<td>30 (20–90)</td>
<td>30 (17–89)</td>
<td>NS</td>
</tr>
<tr>
<td>Catheters in place for</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–40 days, n (%)</td>
<td>59 (79.72)</td>
<td>56 (73.68)</td>
<td>56 (83.58)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;40 days, n (%)</td>
<td>15 (20.28)</td>
<td>20 (26.32)</td>
<td>11 (16.42)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;60 days, n (%)</td>
<td>3 (4.05)</td>
<td>3 (3.94)</td>
<td>2 (2.98)</td>
<td>NS</td>
</tr>
</tbody>
</table>

p = NS for all comparisons. For all p > 0.05, NS is used.

NS = Not significant; HD = hemodialysis; CKD-5 = chronic kidney disease stage 5.
Table 2. Incidence of CRB

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 60)</th>
<th>Group B (n = 59)</th>
<th>Group C (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>6 (10)</td>
<td>8 (13.5)</td>
<td>20 (34.48)</td>
</tr>
<tr>
<td>Total number of CRB episodes</td>
<td>6*</td>
<td>8**</td>
<td>20* **</td>
</tr>
<tr>
<td>CRB rates per 1,000 catheter-days</td>
<td>2.74</td>
<td>3.67</td>
<td>9.92</td>
</tr>
</tbody>
</table>

A vs. B: non-significant differences. 
* $\chi^2 = 6.62$, p = 0.01; ** $\chi^2 = 4.34$, p = 0.03.

Table 3. Characteristics of patients with CRB

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>3/3</td>
<td>6/2</td>
<td>15/5</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>71 (58–76)</td>
<td>77 (36–78)</td>
<td>70 (32–88)</td>
</tr>
<tr>
<td>Diabetics, n (%)</td>
<td>3 (50)</td>
<td>5 (62.50)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Internal jugular/subclavian catheters, n</td>
<td>5/1</td>
<td>7/1</td>
<td>17/3</td>
</tr>
<tr>
<td>Days to CRB after catheter insertion, median (range)</td>
<td>29 (22–38)</td>
<td>30 (21–40)</td>
<td>31 (21–42)</td>
</tr>
<tr>
<td>Organisms isolated, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive</td>
<td>S. aureus (3)</td>
<td>S. aureus (8)</td>
<td>S. aureus (4)</td>
</tr>
<tr>
<td></td>
<td>E. faecalis (1)</td>
<td></td>
<td>S. epidermidis (5)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>P. aeruginosa (2)</td>
<td></td>
<td>P. aeruginosa (4)</td>
</tr>
<tr>
<td></td>
<td>E. coli (4)</td>
<td></td>
<td>E. coli (4)</td>
</tr>
<tr>
<td></td>
<td>K. oxytoca (2)</td>
<td></td>
<td>K. oxytoca (2)</td>
</tr>
<tr>
<td></td>
<td>S. marcescens (1)</td>
<td></td>
<td>S. marcescens (1)</td>
</tr>
</tbody>
</table>

$p = \text{NS for all comparisons between groups except for Gram-negative infections between groups B and C} (\chi^2 = 3.95, p = 0.04)$. No Gram-negative infections were noted in group B. All staphylococci were methicillin-sensitive strains.

group (group B), as well as in the historical control group (group C) are shown in table 1. No significant differences were found between groups.

**CRB Rates**

There was no statistically significant difference in the incidence of CRB between groups A and B, whereas CRB episodes and rates differ significantly when anti-microbial lock solutions were separately compared to historical heparin-alone lock solution (table 2). No significant changes were noted in the results after subclavian catheters had been excluded from analysis (data not shown). The clinical characteristics of patients diagnosed with CRB are listed in table 3. Of note, all CRB episodes occurred more than 3 weeks after catheter insertion.

**CRB-Free Catheter Survival**

Kaplan-Meier analysis showed that cumulative CRB-free catheter survival at 90 days was 82% for group A, 78% for group B, and 26% for group C. However, since only 3 catheters per group were in place for more than 60 days in groups A and B, and only 2 in group C (table 1), the timeline in Kaplan-Meier curve was not extended beyond 60 days (fig. 1). There was no difference in survival between groups A and B (log-rank 0.44, p = 0.65). Both antibiotic lock solutions statistically prolonged the CRB-free period compared to heparin alone (log-rank 3.03, p = 0.002 for group A vs. group C and log-rank 2.63, p = 0.008 for group B vs. group C).

**Catheter Thrombosis Rates**

Thrombosis developed in 11 (14.86%), 9 (11.84%) and 6 (8.95%) catheters of groups A, B and C, respectively.
differences are statistically non-significant ($\chi^2 = 0.23$, $p = 0.63$ for group A vs. group B; $\chi^2 = 0.91$, $p = 0.33$ for group A vs. group C, and $\chi^2 = 0.26$, $p = 0.61$ for group B vs. group C).

**Adverse Effects**

No adverse events related to catheter locks were reported in all study groups. No patients complained of any symptoms that might be attributable to gentamicin or citrate toxicity. No compatibility issues were noted in the gentamicin/heparin concentrations used in our study.

**Discussion**

The results of the present study suggest that gentamicin/heparin and taurolidine/citrate, used for locking newly inserted UCs, were similarly effective at preventing CRB and catheter thrombosis for up to 3 months of follow-up. This is the first randomized study that compares directly gentamicin/heparin, one of the most commonly used antibiotic-based lock solutions, and taurolidine/citrate, a non-toxic broad-spectrum antimicrobial agent, as catheter locks in a large number of HD patients and for a long duration of follow-up. Although taurolidine/citrate appears to be a safe and effective alternative to the established antimicrobial agents, the present study failed to demonstrate its superiority in terms of CRB prevention. Our study confirms that the use of antimicrobial lock solutions significantly decreases the incidence of CRB with similar catheter thrombosis rates compared to a well-matched historical control group. Gram-positive infection rate was similar in all groups. No Gram-negative infections were noted in the taurolidine/citrate group, whereas there was no significant difference in the infection rate for Gram-negative organisms between the other two groups. In addition, it appears that taurolidine/citrate had limited or no effect on the prevention of CRB caused by *Staphylococcus aureus* in our patients.

We evaluated CRB prevention in UCs, a temporary vascular access that is frequently used until adequate permanent access is available [3]. Patients dialyzing through an UC are exposed to an important infection risk [1]. Therefore, CRB prevention remains a significant challenge in the management of this form of vascular access. However, the efficacy of various antimicrobial locks in UCs is significantly underevaluated. Only one previous randomized study [8] included solely UCs, three [12, 17, 18] included both UCs and TCCs, although the former were underrepresented, and the majority of studies included exclusively TCCs [4, 5, 7, 9, 10, 15]. The results of our study clearly demonstrate that UCs can be safely used for longer periods than those recommended by the international guidelines [2].

There is increasing evidence that antimicrobial locks applied within the catheter lumen are effective at preventing CRB [1, 2, 9] and their use for TCCs has been advocated in the recent ERBP position statement [2]. Of note, most of the studies to date have focused largely on TCCs and, thus, it is not always clear how far their conclusions can be extrapolated to UCs. Two recent meta-analyses of prophylactic antimicrobial locking solutions that included TCCs and small numbers of UCs have demonstrated at least a threefold reduction in the incidence of CRB by using a variety of such locks compared to heparin alone [9, 19]. In addition, marked decrease in morbidity and mortality from CRB has also been shown under this treatment [2, 9, 19]. However, debate continues on the appropriate antimicrobial agent, as well as its optimal concentration, to eradicate a wide variety of organisms. At the same time, concerns for ultimate bacterial resistance and systemic toxicity together with reimbursement issues have been shown to be significant barriers in the widespread use of antimicrobial lock solutions [20]. Undoubtedly, the determination of the safest and most efficient antimicrobial lock solution requires direct, head-to-head comparisons among them, as is the case in the present study.

We chose gentamicin/heparin as the antibiotic-based locking solution on the basis of cost, convenience, chem-
ical stability and safety. At present, gentamicin appears to be the least expensive and most available among many alternative antimicrobial agents and heparin is similarly so in comparison to 4% citrate. In addition, the gentamicin-containing antibiotic lock is definitely the most extensively tested [9, 19]. It is used in 4 out of 8 randomized controlled trials included in a recent meta-analysis [9]. Furthermore, in a subgroup analysis using a random-effects model, the overall efficacy in terms of CRB prevention was better in studies that used gentamicin-containing lock solutions versus those that tested other lock solutions [9].

There is a variation in gentamicin concentrations, either in combination with heparin or citrate, used in previous studies [4–10, 19]. Gentamicin was shown to be an effective antimicrobial lock at both high and low concentrations [9, 20]. In the older literature, concerns have been raised about chemical instability of solutions containing gentamicin, especially at high concentrations, with heparin, resulting in precipitation and, subsequently, in a gentamicin concentration insufficient to be active as an antimicrobial, as well as in potentially reduced long-term catheter function and patency [21, 22]. However, no solubility issues were reported in recent studies with gentamicin/heparin locks [5, 7, 8]. The final solution in our study contains 10 mg/ml gentamicin, a concentration higher than that used by Nori et al. [5] and McIntyre et al. [7] in TCCs and by Kim et al. [8] in UCs. In an attempt to further ensure the stability and compatibility of the final solution, the gentamicin/heparin solutions were made up, throughout our study, just before instillation. No turbidity of the solutions was reported by dialysis staff or the attending physician throughout our study.

The other arm of our study is taurolidine/citrate (TauroLock), a non-antibiotic antimicrobial agent that has demonstrated both in vitro and in vivo high efficacy in eradicating the catheter biofilm caused by a variety of Gram-positive and Gram-negative bacteria, as well as Candida albicans [11–15]. Due to its unique mechanism of action and the low concentration of citrate present, taurolidine/citrate is largely deprived of most adverse effects potentially associated with the use of antibiotic-based locks, such as systemic toxicity and emergence of antibiotic resistance [13, 14]. Therefore, taurolidine/citrate seems to be preferable to the established antibiotic-based or high-concentration citrate locks. However, no superiority of taurolidine/citrate lock over an established antibiotic-based lock in terms of CRB prevention was demonstrated in our study.

Concerns on the efficacy of taurolidine/citrate catheter locks have been raised in a recent randomized double-blind controlled trial conducted in HD patients with newly inserted TCCs [15]. No significant benefit of taurolidine/citrate versus heparin catheter lock in the primary outcome of time to first bacteremia was demonstrated. Moreover, taurolidine/citrate was associated with a greater need for thrombolytic treatment to maintain catheter patency [15]. More than 50% of patients in the taurolidine/citrate group needed thrombolytic therapy at least once during the study. The use of taurolidine/citrate locking solution has been already associated with increased frequency of catheter thrombosis since the publication of a pilot non-randomized controlled study by Allon [11]. Although significantly higher CRB-free survival at 90 days was observed with taurolidine/citrate than with heparin 5,000 U/ml (94 vs. 47%), almost 70% of the patients in the former group required thrombolytics to maintain catheter patency [11].

In our study, UCs thrombosis rates are relatively low and similar in all groups. Indeed, in absolute numbers there were more events of catheter thrombosis in the gentamicin/heparin as compared to taurolidine/citrate group and catheter thrombosis rates appear to be even lower, although non-significantly, in the historical control group. The concentration of heparin in our final gentamicin/heparin solution was relatively low, at 3,750 U/ml, and may explain, at least in part, the aforementioned observation. Increased catheter thrombosis rates could be a limitation to antibiotic locks that reduce the dose of heparin. This concern is not confirmed in our study. Besides, most of the studies on antibiotic-based locking solutions and heparin alone did not find any difference in terms of catheter thrombosis rates. The only exception is a randomized controlled study by Saxena et al. [23] in diabetic HD patients with TCCs that showed superior thrombosis-free survival at 365 days in the group with cefotaxime/heparin catheter lock [9, 10, 19].

Bleeding complications or other symptoms, potentially related to catheter-lock toxicity, were not reported in our study. A plausible explanation for that is the relatively short-term use of UCs compared to TCCs that were predominantly used in previous studies, as well as the fact that the inadvertent spillage of catheter-lock solution into the systemic circulation was minimized in our patients and undesirable events, such as systemic anticoagulation and gentamicin- or citrate-associated toxicity, largely prevented by our protocol, in contrast to other studies that purposefully instill up to 20% more catheter-lock solution than the catheter volume in order to secure a suf-
fficent bactericidal and anticoagulation effect [24]. Our finding is largely consistent with other previously published studies using either gentamicin-based or tauro-
idine/citrate locks [4–15]. On the contrary, symptoms compatible with ototoxicity, potentially related to genta-
icin-containing locks, were reported in about 10% of patients in a single study by Dogra et al. [4] that tested a gentamicin/citrate lock in TCCs used for long periods and at high gentamicin concentration of 27 mg/ml in the final solution. Adverse events related to citrate-contain-
ing locks were reported only in studies using high con-
centrations of citrate (30% of trisodium citrate and 46.7% of sodium citrate) [17, 25].

CRB rates in our groups using antimicrobial lock solu-
tions are in the acceptable range reported in the literature for UCs [1]. Furthermore, they are approximately three-
fold lower than those observed in our well-matched his-
torical control group, a finding that is consistent to previ-
ous literature [1, 9, 19]. However, these rates are higher than those reported in previous studies [8–12]. A first ex-
planation for this difference is that previous studies have focused largely on TCCs and, thus, direct comparisons cannot be made. Also, several studies reporting lower rates applied additional techniques of CRB prevention, such as intranasal mupirocin [4, 12, 17], routine antimicro-
bial body washes [15] or exit-site antimicrobial oint-
ments [9, 19]. Furthermore, our study group comprised a large number of diabetic patients compared to previous studies, a fact that may have contributed to our increased CRB rates [4–8, 11, 12].

Finally, we might have overestimated the CRB rates by the CRB definition criteria we used, although in accor-
dance with the recent ERBP recommendations [2] that were published after our study was concluded. The simulta-
aneous sampling from the peripheral vein and from the catheter, proposed by the Infectious Diseases Society of America (IDSA) in order to differentiate CRBs from bloodstream infections of other etiology, is considered difficult to implement in HD patients as it is highly desir-
able to avoid unnecessary venipuncture in order to pre-
serve venous capital for future access creation [2, 26]. Of
note, we made every effort to further minimize the po-
tential bias caused by the CRB diagnosis criteria by ex-
cluding alternative sources of infection via history-tak-
ing, clinical examination, imaging and targeted labora-
tory testing.

The CRB-causative organisms isolated in our study included both Gram-positive and Gram-negative bacte-
ria at a ratio 2:1 in the gentamicin/heparin group and exclusively *S. aureus* in the tauroldine/citrate group. Similar ratios of Gram-positive and Gram-negative mi-
croorganisms were isolated in the heparin control group. The bacteriologic profile in all groups is similar to previous
studies [4–12], although the finding of a single caus-
ative organism in the tauroldine/citrate group has not been previously reported. Gentamicin-based catheter locks have been shown, not unexpectedly, to be more ef-
effective for the prevention of CRBs caused by Gram-nega-
tive bacteria than those caused by Gram-positive bacte-
ria [4–8]. However, although gentamicin is inactive against *Staphylococcus* at levels reached in the serum, it is toxic to this coccus at the higher levels used in catheter locks [24]. Regarding tauroldine/citrate catheter locks, previous studies [11, 12, 15] have demonstrated a de-
crease in the incidence of CRB caused by Gram-nega-
tive organisms, a finding that is confirmed by our study. Furthermore, *S. aureus* was isolated in the majority of CRB episodes (6 out of 11) in a randomized controlled study using tauroldine/citrate, although the incidence of Gram-positive organisms, including *S. aureus*, was simi-
lar in the heparin control group in this study [15]. Al-
though in vitro results indicate that the tauroldine con-
centration is sufficient to eradicate *S. aureus* [13, 14], one possible explanation of this finding is that *S. au-
reus* possibly ingress via a different portal, such as the exit site [15]. However, irrespective of the potential mech-
nism, the preponderance of *S. aureus* CRBs in the tau-
rolidine/citrate group is highly undesirable, as septice-
mia caused by *S. aureus* in HD patients is associated with the greatest in-hospital and post-discharge mortality risks [1]. Fortunately, in our study, in contrast to previous ones [11, 12, 15], all *S. aureus* were methicilin-sensitive strains.

Our study has several limitations. The heparin control group was a historical one and this could have biased our results. However, this group is well matched to the other two study groups in terms of patients’ clinical character-
istics and duration of catheter use. Taking into consider-
at the high CRB rates observed in our heparin-alone group and the fact that the preventive use of antimicro-
bial lock solutions is recommended by international guidelines, our decision was to exclude the heparin-alone control group from the randomization and to use a his-
torical group instead. Furthermore, our study was not blinded because of the requirement to make up the genta-
icin-locking solution just before instillation, as there was a lack of sufficient stability data. There were no ad-
verse reactions attributable to gentamicin or citrate toxic-
ity in our study. However, limited follow-up of our study does not exclude the onset of adverse events with longer
use of antimicrobial lock solutions. In addition, drug level monitoring in order to identify systemic exposure was not carried out. Finally, the antimicrobial locks tested in our study were applied at certain dosing regimens and this might limit the generalization of the results.

In conclusion, our study supports the equivalence in the prevention of CRB and catheter thrombosis between tested interdialytic lock solutions of gentamicin/heparin and taurolidine/citrate for a prolonged use of UCs in CKD-5 patients on chronic HD. Therefore, taurolidine/citrate application at increased costs appears unjustified by our data in addition to its questionable efficacy in preventing *Staphylococcus* CRB. Both antimicrobial lock solutions were found superior to standard heparin-alone lock in CRB prevention with no significant difference in the thrombosis rates. Our study is the first performing a head-to-head comparison between a widely used, well-established antibiotic-based lock and taurolidine/citrate, an antimicrobial agent that is considered to offer unique characteristics and excellent safety profile in the context of a protocol for long-term use of UCs. Potential advantages of taurolidine/citrate have not been translated into superior clinical benefit in our study patients. Our results also support the safe use of UCs – longer than advised by international guidelines – under the appropriate antimicrobial lock until a permanent vascular access is established. Interestingly, these favorable outcomes were demonstrated in a predominantly diabetic group of patients. Furthermore, a successful longer use of temporary UCs for HD, as described above, could reduce the higher cost and inconvenience associated with the widespread use of TCCs.

**Disclosure Statement**

The authors have no conflicts of interest to declare.


