Prophylaxis against Dialysis Catheter–Related Bacteremia with a Novel Antimicrobial Lock Solution

Michael Allon
Division of Nephrology, University of Alabama at Birmingham, Birmingham

Catheter-related bacteremia, a frequent complication in patients who are undergoing hemodialysis, may be prevented by eradication of the catheter biofilm. Catheter lock solution (CLS) is an investigational preparation containing taurolidine, a biocompatible antimicrobial agent, and citrate, an anticoagulant agent. CLS was instilled into the catheter lumens after each dialysis session for 20 catheter-dependent hemodialysis patients. Catheter outcomes were compared with those observed in 30 concurrent control patients whose catheters were instilled with heparin. Bacteremia-free survival at 90 days was higher among patients who received CLS than among control patients who received heparin (94% vs. 47%; \( P < .001 \)). Unassisted catheter patency (without tissue plasminogen activator instillation) was lower among patients who received CLS than among control patients (32% vs. 76%; \( P < .001 \)). CLS dramatically reduces the frequency of catheter-related bacteremia among patients undergoing hemodialysis, although there is an increased requirement for thrombolytic interventions to maintain catheter patency.

Patients undergoing hemodialysis require a reliable vascular access (fistula or graft) for performance of regular dialysis treatments. Approximately 20% of US patients who are undergoing hemodialysis use a tunneled central vein catheter for vascular access [1, 2], either while waiting for placement and maturation of a fistula or graft or because they have run out of options for a permanent vascular access. Dialysis catheters are associated with 2 major complications: bacteremia and thrombosis [1]. Most central vein catheters develop a bacterial biofilm on their inner surface as early as 24 h after their placement [3–6]. Catheter-related bacteremia often arises from this biofilm and is usually refractory to treatment with systemic antibiotics alone [7]. For this reason, successful treatment of catheter-related bacteremia usually requires catheter replacement in conjunction with systemic antibiotics [8–11]. Alternatively, instillation of a concentrated antibiotic solution into the catheter lumen after dialysis may eradicate the bacterial biofilm in many cases and obviate the need for catheter removal [12]. However, this strategy may promote Candida infections in some patients [13]. Regardless of the specific method used to treat catheter-related bacteremia, there is a high likelihood of a subsequent bacteremic episode [11, 13]. Catheter thrombosis can be treated by instilling a thrombolytic agent (such as urokinase or tissue plasminogen activator [tPA]) into the lumen [14, 15]. If this does not resolve the thrombosis, the occluded catheter is exchanged for a new one over a guidewire.

Ideally, one would like to prevent catheter-related
complications, rather than treat them after they occur. To prevent catheter thrombosis, an anticoagulant agent (heparin or citrate) is routinely instilled into both catheter lumens after each dialysis session. There is currently no approved pharmacologic agent for prophylaxis against catheter-related bacteremia. Theoretically, catheter-related bacteremia may be prevented by instillation of an antimicrobial agent into the catheter lumen after each dialysis session to eradicate the biofilm. Recently, Dogra et al. [16] reported that instillation of a concentrated solution of gentamicin in citrate reduced catheter-related bacteremia by >90%, compared with instillation with citrate alone. However, long-term antibiotic prophylaxis may select for antibiotic-resistant organisms. Moreover, ~10% of the patients receiving the gentamicin lock solution developed vestibular toxicity.

Taurolidine, a derivative of the amino acid taurine, is a potent, biocompatible antimicrobial agent with broad-spectrum bactericidal activity [17, 18]. In vitro experiments have demonstrated its efficacy in eradicating the catheter biofilm caused by a variety of gram-positive and gram-negative bacteria, as well as Candida albicans [19]. Moreover, preliminary observations of patients in whom a subcutaneous dialysis device or a central vein catheter is used for total parenteral nutrition suggest that instillation of taurolidine into the catheter lumens may prevent catheter-related bacteremia [20, 21].

Catheter lock solution (CLS) is an investigational agent containing the antimicrobial agent taurolidine as well as the anticoagulant citrate. The goal of the present study was to evaluate the efficacy and safety of CLS instilled into the catheter lumens after each dialysis session in the prevention of catheter-related bacteremia and thrombosis among patients who have a long-term need for hemodialysis.

PATIENTS AND METHODS

Patient enrollment. Adult patients with a long-term need for hemodialysis were eligible for enrollment in this investigational study protocol if they underwent dialysis with a tunneled dialysis catheter; if they expected to remain catheter dependent for at least 90 days; and if their catheters were patent. The major exclusion criteria included positive blood cultures or antibiotic therapy within 2 weeks of enrollment, evidence of an exit-site infection, known history of an atrial thrombus, unstable malignancy, cirrhosis with encephalopathy, untreatable bleeding diathesis or hypercoagulable state, or current participation in another investigational protocol. So that the efficacy of CLS for both primary and secondary prophylaxis against catheter-related bacteremia could be evaluated, patients with catheters of all ages were eligible.

The CLS study patient outcomes were compared with those observed in a nonrandomized, concurrent group of patients who were undergoing hemodialysis at University of Alabama at Birmingham who were also catheter dependent but who had standard heparin solution (5000 U/mL), rather than CLS, instilled into dialysis catheters. The 2 patient groups were similar in terms of age, sex, race, diabetic status, baseline serum albumin concentration, catheter age, and catheter type (table 1).

Research protocol. The study was approved by the University of Alabama at Birmingham Institutional Review Board, and all subjects provided written, informed consent. CLS (1.35% taurolidine and 4% sodium citrate) was instilled into both catheter lumens at the end of each dialysis session and then withdrawn from the catheter lumens before initiation of the next hemodialysis session. Patients remained in the study protocol for up to 90 days.

The skin around the tunneled catheter was inspected before each dialysis session for evidence of an exit-site infection. If the patient had a fever (temperature >37.8°C) before or during a dialysis session, blood was obtained from a peripheral vein for culture, and systemic antibiotics were administered to the patient, with continued instillation of CLS into the catheter lumens. If the blood cultures yielded no growth at 5 days, the systemic antibiotics were discontinued. If the results of culture were positive, the patient received a total of 3 weeks of systemic antibiotics, in conjunction with instillation of an antibiotic lock solution into the catheter [13]. CLS instillation was stopped (1.35% taurolidine and 4% sodium citrate) was instilled into both catheter lumens at the end of each dialysis session and then withdrawn from the catheter lumens before initiation of the next hemodialysis session. Patients remained in the study protocol for up to 90 days.

Table 1. Demographic and clinical characteristics of patients undergoing hemodialysis who received catheter lock solution (CLS) and control patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CLS (n = 20)</th>
<th>Heparin control (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total catheter days</td>
<td>1679</td>
<td>2760</td>
<td></td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>58 ± 14</td>
<td>58 ± 18</td>
<td>1.00</td>
</tr>
<tr>
<td>Female sex, % of patients</td>
<td>55</td>
<td>70</td>
<td>.22</td>
</tr>
<tr>
<td>Black race, % of patients</td>
<td>85</td>
<td>93</td>
<td>.30</td>
</tr>
<tr>
<td>Diabetes, % of patients</td>
<td>55</td>
<td>50</td>
<td>.86</td>
</tr>
<tr>
<td>Serum albumin concentration, mean g/dL ± SD</td>
<td>3.6 ± 0.3</td>
<td>3.4 ± 0.5</td>
<td>.15</td>
</tr>
<tr>
<td>Catheter age, no. (%) of patients</td>
<td></td>
<td></td>
<td>.76</td>
</tr>
<tr>
<td>&lt;15 days</td>
<td>3 (15)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>15–45 days</td>
<td>4 (20)</td>
<td>5 (17)</td>
<td></td>
</tr>
<tr>
<td>46–90 days</td>
<td>4 (20)</td>
<td>10 (33)</td>
<td></td>
</tr>
<tr>
<td>&gt;90 days</td>
<td>9 (45)</td>
<td>12 (40)</td>
<td></td>
</tr>
<tr>
<td>Catheter age, median days</td>
<td>82</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Catheter type, no. (%) of patients</td>
<td></td>
<td></td>
<td>.86</td>
</tr>
<tr>
<td>Ash-splita</td>
<td>12 (60)</td>
<td>20 (67)</td>
<td></td>
</tr>
<tr>
<td>Opti-flowb</td>
<td>6 (30)</td>
<td>8 (27)</td>
<td></td>
</tr>
<tr>
<td>Tesioa</td>
<td>2 (10)</td>
<td>2 (7)</td>
<td></td>
</tr>
</tbody>
</table>

* Manufactured by Medcomp.  
  b Manufactured by Bard Access Systems.
when blood culture results were positive. Control patients were evaluated for infection by the same protocol.

Catheters with flow problems that limited the ability to perform dialysis were instilled with tPA (2 mg into each catheter lumen). The tPA was left in the catheter overnight, and dialysis was attempted on the next day. If tPA instillation failed to restore catheter patency, the patient was referred for exchange of the catheter over a guidewire by the Interventional Radiology Department.

Study end points. The primary end point of the study was the occurrence of catheter-related bacteremia. The 2 secondary end points were tPA instillation and catheter exchange to restore catheter patency. An independent medical monitor reviewed all adverse events in patients who received CLS and determined whether these events were related to the study medication.

Data analysis. We collected prospective data for both the CLS and heparin control groups with regard to patient demographics, clinical characteristics, adequacy of dialysis, episodes of bacteremia, and need for tPA instillation or catheter exchange that was attributable to loss of patency. In addition, the clinical outcomes for the patients receiving CLS were compared with the historical control for these patients for the 90 days preceding their participation in the study (pre-CLS) and for the 90 days after completion of study participation (post-CLS). Information about all catheter events was collected prospectively and placed in a computerized database by the University of Alabama at Birmingham dialysis access coordinators [22].

Statistical analysis. The differences in baseline clinical and biochemical features between the study patients and the control group were analyzed by Student’s t test or by χ² analysis. Kaplan-Meier survival curves were generated to plot bacteremia-free survival, unassisted catheter patency (without tPA instillation), and assisted catheter patency (without catheter exchange). The log-rank test was used to evaluate the statistical significance of the differences between the survival curves. Finally, the frequency of each catheter event (bacteremia, tPA instillation, or catheter exchange) was compared between groups by Poisson analysis.

RESULTS

Twenty patients were enrolled in the CLS study protocol. CLS instillation into the catheter lumens occurred after 97.9% of the dialysis sessions. It was not provided in a small number of sessions, either because of inadvertent instillation of heparin or because of catheter patency issues requiring tPA instillation or catheter exchange. Fourteen patients completed the study protocol, and 6 withdrew from the study early. One of these 6 patients was hospitalized on day 17 because of a gangrenous gallbladder. This patient required prolonged continuous venovenous hemodialysis, and his catheter was used to administer numerous blood products. A second patient withdrew from the study on day 61 because of a mature arteriovenous fistula. Two patients left the study (on days 75 and 84, respectively) because of recurrent catheter patency problems. A fifth patient underwent catheter removal at the nephrologist’s request on day 80 because of suspected catheter-related bacteremia. Both the peripheral and catheter blood cultures yielded no growth, and ultimately, the patient’s symptoms were attributed to a rectal abscess. Finally, a sixth patient withdrew from the study on day 85 after receiving a diagnosis of catheter-related bacteremia (Enterococcus). Thus, 17 of the 20 pilot patients had at least 80 days of follow-up while CLS was being used.

Bacteremia-free survival at 90 days was much higher among the patients who received CLS than among control patients (94% vs. 47%; P < .001; figure 1). Only 1 episode of catheter-related bacteremia (Enterococcus) was observed among the 20 patients receiving CLS. In contrast, among the 30 concurrent control patients whose catheters were instilled with heparin, bacteremia occurred in 16 patients during the 90 days of follow-up. The likelihood of bacteremia was similar among patients whose catheter age was ≤90 days, compared with patients whose catheter age was >90 days (50% vs. 56%; P = .76). A single gram-positive coccus grew on culture of samples from 14 patients (9 with Staphylococcus epidermidis, 1 with Staphylococcus aureus, and 4 with Enterococcus). One culture grew Pseudomonas, and 1 patient had polymicrobial bacteremia (S. epidermidis and Escherichia coli).

Unassisted catheter patency (without tPA instillation) was significantly lower among the CLS study patients than among the control patients (32% vs. 76%; P < .001; figure 2). Because most tPA instillations were successful in restoring catheter patency, the likelihood of assisted catheter patency (without requiring catheter exchange) was comparable between the patients who received CLS and the concurrent control patients.

Figure 1. Effect of catheter lock solution (CLS) on bacteremia-free survival among patients undergoing hemodialysis. Survival is shown for patients receiving CLS (solid line) and concurrent control patients receiving heparin (dashed line). P < .001, for comparison between survival curves (log-rank test).
Figure 2. Effect of catheter lock solution (CLS) on unassisted catheter patency (without requiring tissue plasminogen activator instillation or catheter exchange) among patients undergoing hemodialysis. Patency is shown for patients receiving CLS (solid line) and concurrent control patients receiving heparin (dashed line). 

Figure 3. Effect of catheter lock solution (CLS) on assisted catheter patency (without requirement for catheter exchange) among patients undergoing hemodialysis. Patency is shown for patients receiving CLS (solid line) and concurrent control patients receiving heparin (dashed line).

DISCUSSION

The high frequency of catheter-related bacteremia (5.6 cases/1000 patient-days) observed among our patients with standard heparin locks was comparable to that reported in several previous studies [7, 13, 23] and persists despite implementation of infection control measures to prevent intravascular catheter–related infections [24]. We observed a dramatically lower (~90% lower) frequency of hemodialysis catheter–related bacteremia among patients whose tunneled catheters were instilled with CLS (figure 1). Although the present study was not randomized, the control patients were derived from the same dialysis population as the study patients and were similar in terms of demographic and clinical characteristics (table 1). Moreover, the 2 groups did not differ in baseline serum albumin concentration, the only significant risk factor for catheter-related bacteremia previously identified in our dialysis population [11]. Further evidence for the beneficial effect of CLS in preventing bacteremia can be inferred from comparison of the frequency of bacteremia in study patients receiving CLS with the frequencies in the periods before and after their participation in the CLS study, during which they received heparin (figure 4).

The majority of patients had catheters already in place at the time of enrollment (table 1), and catheter biofilm would already have been established [3–6]. Moreover, many of these patients had already experienced an episode of catheter-related bacteremia in the 90-day period preceding their enrollment in the CLS protocol. Thus, our observations suggest that taurodilide may eradicate an established catheter biofilm, which is consistent with recent in vitro observations with this compound [19]. Alternatively, it is possible that CLS did not inactivate the catheter biofilm but simply killed the organisms released from the

(74% vs. 83%; \( P = .40 \); figure 3). Measurements of dialysis adequacy (\( Kt/V \) [dialyzer clearance \( \times \) time/volume of distribution of urea]) during the study period were similar between the 2 treatment groups (mean \pm SD, 1.47 \pm 0.25 vs. 1.42 \pm 0.29; \( P = .56 \)).

Catheter outcomes in the CLS study patients were also compared with the pre-CLS and post-CLS outcomes for these patients (figure 4). The frequency of catheter-related bacteremia was 5.6 per 1000 patient-days in the pre-CLS period, decreased by ~90% after the patients were switched from heparin to CLS, and increased to the previous levels after the patients were switched back from CLS to heparin (figure 4A). The frequency of tPA instillation was 4.9 events/1000 patient-days during the pre-CLS period, increased ~4-fold after the switch from heparin to CLS, and then decreased to previous baseline values after the switch back from CLS to heparin (figure 4B). Finally, the frequency of catheter exchange due to loss of patency tended to increase after the switch from heparin to CLS and to decrease after the switch back from CLS to heparin, although these changes failed to achieve statistical significance (figure 4C).

No adverse events related to CLS instillation were observed. A total of 14 hospitalizations occurred in 10 patients enrolled in the CLS study. Only 1 of these hospitalizations, which was due to catheter-related bacteremia, was judged by the independent medical monitor to be related to CLS. The remainder were the result of unrelated medical illnesses, including upper gastrointestinal bleeding, deep venous thrombosis, chest pain, ascites, ruptured gallbladder, gangrene due to peripheral vascular disease, volume overload, and hyperkalemia.

Figure 4. Effect of catheter lock solution (CLS) on assisted catheter patency (without requirement for catheter exchange) among patients undergoing hemodialysis. Patency is shown for patients receiving CLS (solid line) and concurrent control patients receiving heparin (dashed line). \( P = .40 \), for comparison between survival curves (log-rank test).
biofilm. These findings have important clinical implications, because CLS could be used for secondary prophylaxis against catheter-related bacteremia, rather than being restricted to newly placed catheters.

Bacteremia was documented in febrile patients undergoing hemodialysis when the results of blood cultures obtained from peripheral veins were positive. We did not obtain concurrent cultures from the catheter lumens to specifically document that these episodes of bacteremia were catheter related. However, none of these patients had clinical evidence of an alternative source of bacteremia. Moreover, instillation of an antimicrobial agent into the catheter lumen would only be expected to prevent bacteremia that was catheter related. Thus, the dramatic decrease of bacteremia events in study patients, compared with control patients, suggests that CLS can prevent catheter-related bacteremia.

It could be argued that the lower frequency of catheter-related bacteremia in the CLS pilot patients was the result of more meticulous nursing techniques in the study population. However, this explanation would be at odds with the substantially lower unassisted catheter patency in the patients who received CLS (figure 2) and also would not explain the marked decrease in frequency of tPA instillation when the patients left the study and resumed treatment with standard heparin locks (figure 4B).

The antimicrobial action of taurolidine is the result of methyol groups that bind irreversibly to the cell wall of bacteria and fungi, thereby resulting in its activity [19]. Extensive in vitro studies have demonstrated broad-spectrum activity of taurolidine against gram-positive and gram-negative bacteria, as well as Candida, with no instances of observed antimicrobial resistance [18]. Moreover, prolonged exposure of several bacterial strains to subinhibitory concentrations of taurolidine failed to produce evidence of resistant bacteria [25]. These observations suggest that prolonged instillation of CLS into dialysis catheter lumens is not likely to promote emergence of drug-resistant bacterial or fungal infections.

Catheter flow problems requiring tPA instillation occurred more commonly in catheters instilled with CLS than in those instilled with heparin. This difference was evident when we compared unassisted catheter patency in the CLS study patients to that observed in the concurrent control patients (figure 2). Moreover, among the study patients, the frequency of tPA instillation increased when patients switched from heparin to CLS and decreased after they switched back from CLS to heparin (figure 4). CLS uses the anticoagulant 4% sodium citrate; it is possible that citrate is a less potent anticoagulant than heparin in this clinical setting. A small, short-term study reported that heparin and citrate, at concentrations similar to those used in the current study, were equally efficacious in preventing thrombosis in tem-

---

Figure 4. Effect of catheter lock solution (CLS) on the frequency of bacteremia (top), tissue plasminogen activator instillation (center), and catheter exchange (bottom) among patients undergoing hemodialysis. Data for patients receiving CLS are compared with the historical control for these patients for the 90 days preceding participation in the study (pre-CLS) and for the 90 days after completion of study participation (post-CLS). *P<.02, vs. pre-CLS and post-CLS.
porary, single-lumen dialysis catheters [26]. Likewise, a recent study observed similar frequencies of tPA requirements in patients with double-lumen tunneled catheters instilled with either citrate or heparin. It is possible that taurolidine itself promotes catheter thrombosis by an undefined mechanism.

Bacteremia is a serious complication of use of dialysis catheters that often leads to major systemic complications, including endocarditis, osteomyelitis, epidural abscess, septic arthritis, and even death [7, 10, 11, 13, 23, 27, 28]. The frequent use of antibiotics for treatment of catheter-related bacteremia has contributed to the emergence of multiple antibiotic–resistant infections among patients undergoing hemodialysis [29], including the first reported case of vancomycin-resistant *S. aureus* [30]. The use of CLS in our pilot study dramatically reduced the occurrence of catheter-related bacteremia in this patient population. CLS use also increased the frequency of catheter thrombosis. Catheter patency was usually restored by thrombolytic instillation, but catheter exchange occasionally was required. Given the dire clinical consequences of catheter-related bacteremia, most physicians would likely accept the trade-off required. Given the dire clinical consequences of catheter-related bacteremia, most physicians would likely accept the trade-off

Acknowledgments

Norma Miller provided expert technical assistance in performing this study. Michelle Michela assisted with the statistical analysis of the data.

References