Taurolidine-based catheter lock regimen significantly reduces overall costs, infection, and dysfunction rates of tunneled hemodialysis catheters

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Catheter-related infections and dysfunction are the main catheter complications causing morbidity and mortality in hemodialysis patients. However, there are no consistent data for the choice of catheter lock solutions for tunneled hemodialysis lines. In this prospective, multicenter, randomized, controlled trial, two lock regimens using three commercial catheter lock solutions were compared in 106 hemodialysis patients with a newly inserted tunneled central catheter. In the taurolidine group, TauroLock™-Hep500 was used twice per week and TauroLock™-U25,000 once a week. In the citrate group, a four percent citrate solution was used after each dialysis. Both groups were compared regarding catheter-related infections, catheter dysfunction, and costs. Over a period of 15,690 catheter days, six catheter-related infections occurred in six of 52 patients in the taurolidine group, but 18 occurred in 13 of 54 patients in the citrate group, corresponding to 0.67 and 2.7 episodes of catheter-related infections per 1000 catheter days, respectively (Incidence Rate Ratio 0.25, 95% confidence interval, 0.09 to 0.63). Catheter dysfunction rates were significantly lower in the taurolidine group (18.7 vs. 44.3/1000 catheter days) and alteplase rescue significantly more frequent in the citrate group (9.8 vs. 3.8/1000 catheter days). These differences provided significant catheter-related cost savings of 43% in the taurolidine group vs. citrate group when overall expenses per patient and year were compared. Thus, use of taurolidine-based catheter lock solutions containing heparin and urokinase significantly reduced complications related to tunneled hemodialysis catheters when compared to four percent citrate solution and was overall more cost-efficient.

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Catheter-related infections (CRIs) and catheter dysfunction are major causes of morbidity and mortality in hemodialysis patients.[1] Infection is the second leading cause of death in dialysis patients and the leading cause of catheter removal and morbidity in patients with end-stage renal disease.[2] The incidence of CRI varies per dialysis unit, site of insertion, type of catheter inserted, and adequacy of catheter care,[2] and ranges between 0.2 and 6.5 cases per 1000 catheter days for tunneled catheters.[3–6]

It has been estimated that 20% to 40% of chronic hemodialysis patients rely on tunneled central venous catheters during the course of their dialysis dependency.[2,7] In addition to CRIs, catheter patency always has been a problem, resulting in low dialysis quality and disturbed electrolyte balances. Thus, preventing catheter dysfunction is equally important as the prevention of CRIs in a chronic dialysis population and the choice of an adequate catheter lock solution (CLS) represents a key decision. Current guidelines state that the use of pure heparin is no longer the gold standard but the guidelines do not provide a clear recommendation regarding the variation and availability of CLS (UK Renal Association 2015,[8] European Renal Best Practice 2010,[9] and ASDIN 2008[10]).

The prophylactic use of urokinase or alteplase can be considered as a CLS to prevent line occlusion.[11] Although alteplase was shown to be an efficient yet costly option in maintaining patency,[5] there is limited experience in using urokinase as a CLS in dialysis catheters. Here, data are based on studies comparing heparin with twice-monthly use of urokinase in pediatric patients with central lines.[12] Antibiotic lock solutions (e.g., gentamicin) reduce the rate of CRIs but have to be combined with heparin or citrate because of a lack of anticlotting properties[6] and are not recommended for routine use in current guidelines. High concentrated trisodium citrate shows both an antithrombotic and antimicrobial effect. Data on the ability of 30% or 46.7% citrate to function as an anticoagulant and prevent CRIs exist,[13] but the use of high concentrated citrate resulted in higher requirements for thrombolytic treatment.[14,15] Moreover, its use is decreasing because of the potential cardiac and embolic risks,[16–18] and because of the Food and Drug Administration warning after a fatality associated with an inadvertent i.v. administration of 46.7% citrate. In contrast, the use of low concentrated citrate

(4%) is safe,[19] but has lower antimicrobial efficacy in *in vitro* studies.[20] Citrate appears comparable with heparin in ensuring patency.[21,22]

Taurolidine, a broad-spectrum, antimicrobial, nontoxic agent that reduces the development of biofilm is a nonantibiotic lock alternative that does not cause bacterial resistance and has no adverse effects, even if it leaks into circulation.[23,24] Studies with taurolidine–citrate locks (a combination of taurolidine with 4% citrate) in tunneled catheters resulted in a reduction of CRI rates.[14,25–27] The addition of heparin to taurolidine–citrate has been shown to strengthen its efficiency regarding patency.[28]

Currently, 4% citrate or taurolidine–citrate combinations are used widely CLSs in dialysis centers. Our study compared both. We therefore studied taurolidine–citrate in combination with heparin and urokinase versus a 4% citrate solution regarding CRIs, patency, and overall costs in a multicenter randomized controlled trial (RCT).

RESULTS

Study population

We assessed 150 patients for eligibility, of whom 44 were excluded because of the exclusion criteria or refusal to participate. The remaining 106 patients underwent randomization; 54 patients were assigned to receive 4% citrate (citrate group [CG]), and 52 were assigned to the taurolidine-based lock protocol (taurolidine group [TG]). A trial flow diagram is provided in Figure 1. There were no significant differences between treatment groups at randomization time in baseline characteristics, including comorbidity and frailty (Table 1). The total observation period was 15,690 catheter days, with 6708 catheter days in the CG and 8982 catheter days in the TG. The mean duration of follow-up evaluation was 124 days in the CG and 173 days in the TG, corresponding to a 29% increase in observation period per patient in the TG owing to a reduced complication rate. No patients were lost to follow-up evaluation. The main results are shown in Figure 2.

Catheter-related infections

A total of 6 CRIs occurred in 6 of 52 patients receiving the taurolidine-based regimen and 18 CRIs occurred in 13 of 54 patients receiving 4% citrate. This corresponded to rates of 0.67 and 2.7 episodes of CRIs per 1000 catheter days in the TG and CG, respectively (incidence risk ratio [IRR], 0.25; 95% confidence interval [CI], 0.09–0.63; $P = 0.003$). Survival without any CRI (including recurrent CRIs) was significantly better in the TG (hazard ratio, 0.27; 95% CI, 0.10–0.73; $P = 0.009$) (Figure 3). Based on the first episode only, survival without a CRI was better in the TG as well (hazard ratio, 0.37; 95% CI, 0.13–0.97; $P = 0.044$). The rate of episodes of antibiotic therapy was significantly lower in the TG (1.1 vs. 2.7 per 1000 person-days; IRR, 0.42; 95% CI, 0.19–0.89; $P = 0.026$). In the CG there were more CRIs caused by gram-negative organisms than in the TG ($P = 0.004$); there was no difference seen for gram-positive organisms ($P = .77$). Microorganisms detected in blood cultures are shown in Table 2. Hospitalization days for CRI events were significantly lower in the TG (3.7 vs. 15.8/1000 catheter-days; IRR, 0.23; 95% CI, 0.16–0.34; $P = 0.001$), as well as hospitalization for all-cause infectious events (0.6 vs. 1.8/1000 catheter-days; IRR, 0.31; 95% CI, 0.11–0.88; $P = 0.028$) (Figure 2).

Catheter dysfunction

The rate of total catheter dysfunctions was significantly lower in the TG (18.7 vs. 44.3/1000 catheter-days; IRR, 0.42; 95% CI, 0.34–0.51; $P = 0.001$). The need for acute management of the dysfunctional tunneled central line by reversal of catheter lines (7.5 vs. 18.2/1000 catheter-days; IRR, 0.41; 95% CI, 0.30–0.55; $P = 0.001$) and using alteplase rescue was significantly less common in the TG (3.8 vs. 9.8/1000 catheter-days; IRR, 0.38; 95% CI, 0.25–0.58; $P = 0.001$) (Figure 2).

Further secondary outcomes

Catheter removal for infectious and mechanical complications occurred 6 times less often in the TG (0.2 vs. 1.2/1000 catheter-days; IRR, 0.19; 95% CI, 0.04–0.88; $P = 0.034$). Exit-site infections (1.4 vs. 1.6/1000 catheter-days; $P = 0.90$) and tunnel infections (both 0.4/1000 catheter-days; $P = 0.996$) were similar in both groups. There were no withdrawals resulting from adverse events or bleeding complications. Hospitalization rates because of cardiovascular reasons were not significantly different between the study groups (0.7/1000 catheter-days; $P = 0.65$) (Figure 2). Four patients in the taurolidine arm and 2 patients in the citrate arm died after cardiovascular events. All events were assessed individually and were found not to be related to the lock regimen or catheter. No patients died after infection-related complications. There was no significant difference in any of the primary and secondary outcomes between study centers.

Cost analysis

The baseline costs of CLS per patient year in the TG were US $1485 compared with US $187 in the CG. The subsequent costs related to management of complications associated with CRI and catheter dysfunction were higher in the CG (US $4309 vs. US $1063) and included alteplase rescue (US $104 per case; removal and replacement of catheter, US $855 per case; outpatient treatment of CRI, US $434 per case; and hospitalization for CRI, US $581 per day). The catheter-related combined yearly expenses, including costs for CLS and treatment of complications associated with CRI and catheter dysfunction, were in the TG 43% lower than in the CG.

DISCUSSION

The data from this RCT show that the combined regular use of 2 commercially available taurolidine-based catheter locks in a 2:1 protocol (TG) reduced the incidence of CRIs and catheter malfunctions in patients with a newly inserted tunneled dialysis catheter when compared with a standard 4% citrate-lock (CG). Because of lower complication rates, overall