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

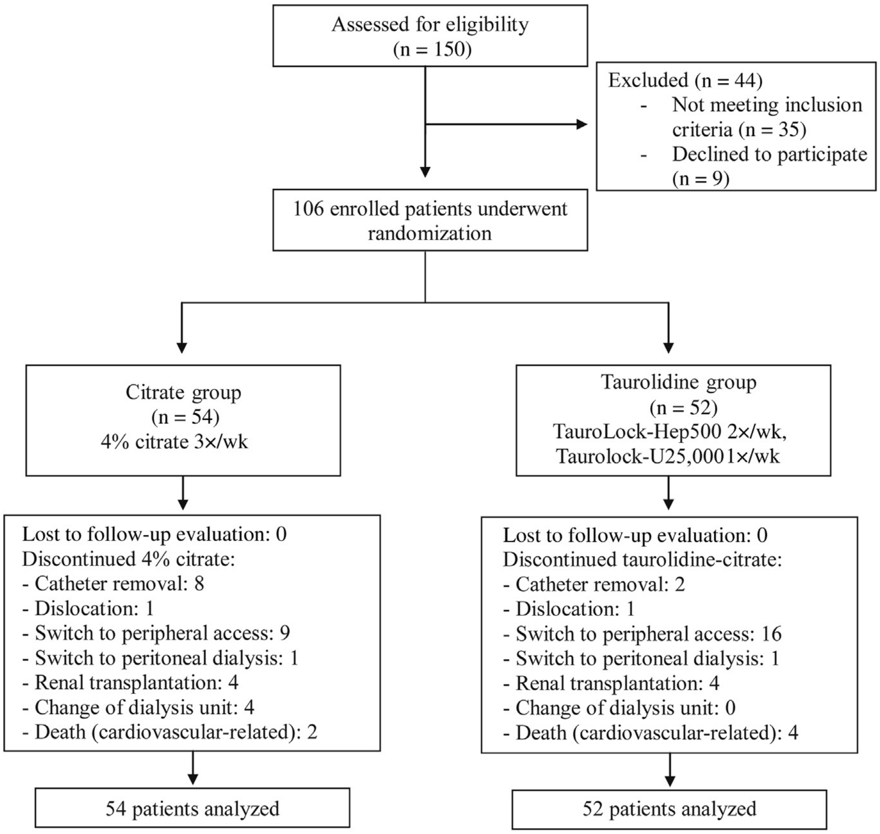

Figure 1 | Trial flow diagram.

costs per patient year in the TG were reduced by 43% when compared with the CG. The premature catheter removal rate was very low in both groups owing to strict implantation and care standards, but was significantly lower in the TG. No catheter-related adverse events were observed in either group.

In the TG we found beneficial effects on the incidence of CRIs and survival without CRIs. This is consistent with findings by other investigators, although they used heparin and not 4% citrate as a control group.[14,26–29] Even though some studies stated that 4% citrate and heparin have similar results in occurrences of CRIs,[21,22] recent meta-analyses did not clarify the ability of 4% citrate to reduce CRIs because they did not differentiate 4% citrate solutions from mixtures of 4% citrate with additional antimicrobial compounds (e.g., gentamicin or taurolidine).[30]

There also seems to be an effect of fibrinolytics, such as urokinase and alteplase, on the reduction of CRIs. This assumption was based on the findings by Hemmelgarn *et al.*[5] The use of alteplase once a week and heparin twice a week as a dialysis catheter lock reduced CRIs compared with heparin used 3 times per week. Fibrin sheath or small blood clots that can act as a nidus for organisms may be reduced by fibrinolytics, leading to improved catheter patency and fewer infection rates.

In our study, CRIs were comparatively rare, with rates between 0.7 and 2.7 episodes per 1000 catheter-days. The low baseline rates probably not only are attributable to the CLS used, but also reflect our compliance with standards regarding insertion and care of catheters according to checklists.[31,32]

Because of the multicenter design of the study, including a stand-alone unit, it could not be guaranteed that blood culture bottles from all included patients could be incubated within 6 hours after blood draw to generate valid differential time to positivity results.[33,34] Thus, to ensure the uniformity of diagnostic procedures we defined CRIs as a positive blood culture taken from a symptomatic dialysis patient with a tunneled line with no other source of infection.[33] This may have led to an underestimated reduction of CRIs in the TG in this study.

According to our analysis on the organisms isolated in patients with CRIs, gram-negative organisms were less likely to cause an infection in the TG. Because taurolidine is bactericidal on gram-negative and gram-positive organisms,[24] it could be hypothesized that the source of the gram-positive organisms was endogenous.

Although the number of exit site and tunnel infections was comparable in both groups, the rate of dysfunction owing to poor flow and the need for line reversal or for alteplase rescue was significantly lower in TG patients. It is necessary to discuss which antithrombotic (citrate, heparin) or fibrinolytic (urokinase) constituent of the taurolidine-based regimen is relevant for improved patency. Because citrate is reported to be comparable with heparin regarding patency[21,22] and also is present in both groups, urokinase might be the relevant agent.

Table 1 | Baseline characteristics of study patients

Characteristic	Taurolidine group (n = 52)	Citrate group (n = 54)	*P* value
Age (yr)	56.2 ± 15.3	58.4 ± 15.5	0.58
Male sex, n (%)	30 (57.7)	27 (50.0)	0.43
White, n (%)	49 (94.2)	51 (94.4)	0.96
Cause of end-stage renal disease, n (%)			
Diabetic nephropathy	8 (15.4)	10 (18.5)	0.80
Glomerulonephritis	6 (11.6)	8 (14.8)	0.78
Polycystic kidney disease	2 (3.8)	1 (1.9)	0.61
Hypertension or vascular disease	12 (23.1)	14 (25.9)	0.82
Postrenal complication	7 (13.4)	4 (7.4)	0.35
Other	17 (32.7)	17 (31.5)	0.99
Co-existing or prior illness, n (%)			
Heart failure	13 (25.0)	14 (25.9)	0.91
Coronary heart disease	15 (28.8)	17 (31.5)	0.76
Cerebral vascular disease	6 (11.5)	11 (20.4)	0.22
Peripheral arterial occlusive disease	11 (21.2)	14 (25.9)	0.56
Arterial hypertension	45 (86.5)	50 (92.6)	0.31
Diabetes mellitus (insulin-dependent)	11 (21.2)	14 (25.9)	0.56
Diabetes mellitus (non–insulin-dependent)	6 (11.5)	5 (9.3)	0.70
Chronic obstructive pulmonary disease	6 (11.5)	7 (13.0)	0.82
Smoker	13 (25.0)	11 (20.4)	0.57
History of cancer	10 (19.2)	13 (24.1)	0.55
History of immunosuppression	6 (11.5)	11 (20.4)	0.22
History of alcohol abuse	1 (1.9)	0 (0)	0.31
History of drug abuse	0 (0)	2 (3.7)	0.16
Charlson Comorbidity Index[36]	3.77 ± 1.97	3.96 ± 1.75	0.36
WHO Performance Status[37]	0.79 ± 0.67	0.69 ± 0.75	0.32
Laboratory parameters			
C-reactive protein (mg/dl)	2.1 ± 2.2	1.8 ± 2.1	0.51
White blood count (G/L)	7.3 ± 2.3	7.6 ± 3.1	0.85
Hemoglobin (g/dl)	9.5 ± 1.6	9.1 ± 1.5	0.20
Serum albumin (g/dl)	31.8 ± 7.8	33.4 ± 6.9	0.46
PTH (ng/l)	392.7 ± 330.5	327.5 ± 352.2	0.16
Serum calcium (mmol/l)	2.1 ± 0.2	2.1 ± 0.2	0.76
Serum phosphate (mmol/l)	1.8 ± 0.6	1.7 ± 0.8	0.29
Transferrin saturation (%)	19.1 ± 13.8	18.6 ± 12.7	0.75
Serum ferritin (ng/ml)	351 ± 690.8	313.6 ± 328.6	0.45
Platelet count (G/L)	219.5 ± 89.0	234.9 ± 90.4	0.55
Normotest (PTZ)	97.0 ± 28.0	102.5 ± 26.6	0.23
S aureus nasal carriage	15	17	0.77
Catheter localization			
Right internal jugular vein	30	29	0.70
Left internal jugular vein	15	13	0.66
Right subclavian vein	5	9	0.39
Left subclavian vein	2	3	0.99

PTH, parathyroid hormone; WHO, World Health Organization.
Means ± SD are shown; numbers in parentheses indicate percentages.

This is in accordance with results from an RCT with the fibrinolytic agent alteplase once weekly showing improved catheter patency.[5] Nevertheless, studies to determine the role of urokinase independent from taurolidine in this setting are underway.

Important strengths of this study include the following: (i) randomized controlled design, (ii) inclusion of patients showing comparable comorbidity and frailty characteristics and only with newly inserted tunneled catheters without side holes, (iii) strict adherence to hygiene standards during catheter insertion and follow-up care[31,32] and therefore low infection rates in general, (iv) trial size with 106 patients and 15,690 catheter-days including complete follow-up information for each patient, and (v) well-defined objective outcome criteria analyzed by blinded study assessors.

The most significant limitation of this study was its partially blinded design, which was in part compensated by objective outcome parameters; clear documentation; and blinding of patients, laboratory staff, and assessors, which left little room for interpretation and bias. Another shortcoming was that a significant proportion of study patients discontinued the study during the course of the trial. However, this was an expected phenomenon and has been described in previous studies involving hemodialysis patients.[5,35] This is usually because dialysis patients receive an arteriovenous fistula or undergo a change of renal replacement therapy to a renal graft or to peritoneal dialysis. Despite comparable study discontinuation rates as a result of these 3 factors in both groups, taurolidine-based CLS extended the follow-up duration for each patient by 29% because of a reduction in catheter-based complications.

In conclusion, this RCT compared a catheter lock regimen of taurolidine–citrate in combination with heparin and urokinase with 4% citrate solution in tunneled hemodialysis catheters. Our data show clear benefits of the taurolidine-based regimen compared with 4% citrate regarding CRIs, catheter patency, and costs. Thus, use of this catheter lock regimen may be favorable with regard to complication rates and morbidity of dialysis patients with central lines.

METHODS

Study design

This prospective multicenter RCT compared a taurolidine-based catheter-lock regimen versus 4% citrate on the incidence of CRIs and catheter malfunctions in patients with a newly inserted tunneled hemodialysis catheter. A cost analysis was performed on expenditures for CLS and for overall costs including treatment of complications per patient year. The study was partially blinded: patients, laboratory personnel, and study assessors were blinded, whereas physicians and nurses on duty were not.

Study population, recruitment, and randomization

Recruitment and randomization took place at the Medical University of Vienna starting in January 2012. Follow-up evaluations were performed at 3 dialysis centers (Medical University of Vienna, Dialysis Centre Vienna, and University Hospital of St. Pölten) until August 2016.

Adult incident hemodialysis patients were eligible to join this study after implantation of a tunneled dialysis catheter in the upper central venous system, allowing sufficient blood flow (≥300 ml/min) after the first dialysis session. Patients were in a standard chronic dialysis regimen with 3 treatments per week. The Charlson Comorbidity Index[36] and World Health Organization performance status[37] were documented for the study population. Exclusion criteria for study patients were as follows: age younger than 18 years,

	Taurolidine group (n = 52)	Citrate group (n = 54)	*P* Value	IRR (95% CI)
Catheter days	8982	6708		
Outcomes for infections				
Catheter-related infection *	6	18		
-No. per 1000 catheter days	0.7	2.7	0.003	0.25 (0.09–0.63)
Episodes of antibiotic therapy	10	18		
-No. per 1000 catheter days	1.1	2.7	0.026	0.42 (0.19–0.89)
Hospitalization days for catheter-related infectious event	33	106		
-No. per 1000 catheter days	3.7	15.8	0.001	0.23 (0.16–0.34)
Hospitalization for all-cause infectious event	5	12		
-No. per 1000 catheter days	0.6	1.8	0.028	0.31 (0.11–0.88)
Outcomes for catheter patency				
Catheter dysfunction	168	297		
-No. per 1000 catheter days	18.7	44.3	0.001	0.42 (0.34–0.51)
Need for reversal of catheter lines	67	122		
-No. per 1000 catheter days	7.5	18.2	0.001	0.41 (0.39–0.55)
Need for alteplase rescue	34	66		
-No. per 1000 catheter days	3.8	9.8	0.001	0.38 (0.25–0.58)
Further secondary outcomes				
Catheter removal for infectious and mechanical complication	2	8		
-No. per 1000 catheter days	0.2	1.2	0.034	0.19 (0.04–0.88)
Exit-site infection	13	11		
-No. per 1000 catheter days	1.4	1.6	0.9	0.95 (0.43–2.09)
Tunnel infection	4	3		
-No. per 1000 catheter days	0.4	0.4	0.996	0.99 (0.22–4.45)
Hospitalization for cardiovascular event	6	5		
-No. per 1000 catheter days	0.7	0.7	0.65	0.75 (0.22–2.58)

* primary outcome

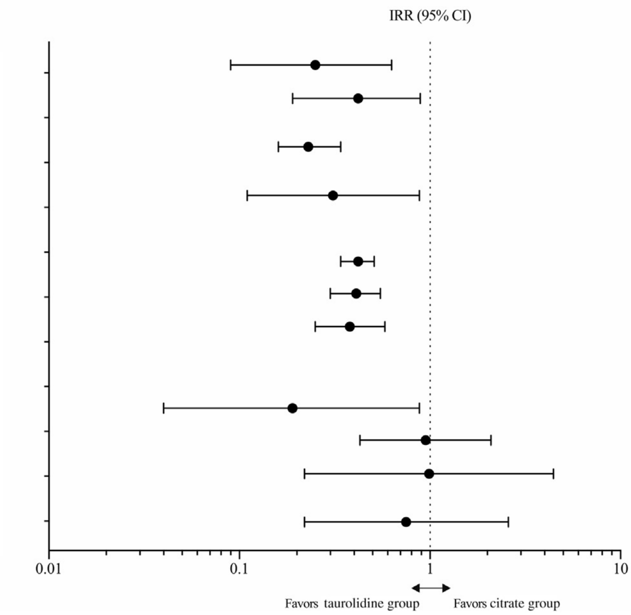

Figure 2 | Clinical outcomes. CI, confidence interval; IRR, incidence rate ratio for the taurolidine group.

systemic anticoagulant therapy, current use of antibiotic therapy as a result of bacteremia in the previous 21 days, major hemorrhage or intracranial bleeding in the previous 3 months, pregnancy, and known allergies or contraindication to the CLS used. Randomization was performed using a random number table in a 1:1 ratio. Treatment assignments were concealed in sealed envelopes.

Study procedures

Catheter insertion. A tunneled double-lumen silicone catheter without side holes (Doppellumen-Vorhof-Katheter; VMP, Iserlohn, Germany) was placed in all study participants in the operating room in the right internal jugular vein whenever possible.[38] Study patients were screened for nasal carriage of *Staphylococcus aureus*

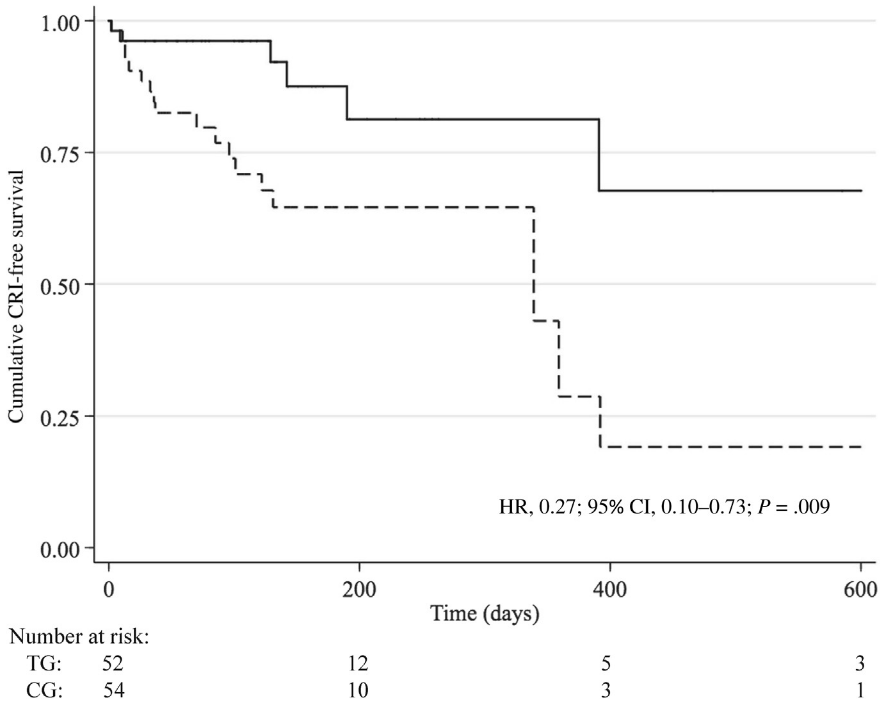

Figure 3 | Kaplan-Meier analysis for cumulative catheter-related infection-free survival for taurolidine- (solid line) and citrate-group (dashed line). Survival without a catheter-related infection (CRI) was significantly better in the taurolidine group (hazard ratio, 0.27; 95% confidence interval [CI], 0.10–0.73; $P = 0.009$). CG, citrate-group; HR, hazard ratio; TG, taurolidine-group.

Table 2 | Microorganisms involved in catheter-related infections

	Taurolidine group	Citrate group	*P* value
Gram-positive			
S aureus	3	2	0.68
Staphylococcus epidermidis	0	1	0.99
Staphylococcus haemolyticus	1	0	0.49
Propionibacterium acnes	0	1	0.99
Corynebacterium jeikeium	0	1	0.99
Total gram-positive	4	5	0.77[a]
Gram-negative			
Escherichia coli	1	1	0.99
Enterococcus faecalis	1	6	0.11
Klebsiella pneumoniae	0	1	0.99
Pseudomonas aeruginosa	0	4	0.12
Burkholderia	0	2	0.46
Enterobacter cloacae	1	3	0.62
Citrobacter	0	1	0.99
Proteus mirabilis	0	1	0.99
Serratia marcescens	1	0	0.49
Total gram-negative	4	19	0.004[a]

P values were from the Fisher exact test.
[a]Wald test was based on robust SE.

before catheter placement and were treated with mupirocin ointment twice daily until culture results were available. Patients with positive nasal cultures were treated for an additional 2 weeks.

Catheter lock procedure. After dialysis, lumens were flushed with saline solution and blocked with 2.3 ml CLS. The instillation of CLS was based on the regimen shown in Figure 4.

TauroLock-Hep500 (1.35% taurolidine, 4% citrate, and 500 IU/ml heparin) and TauroLock-U25,000 (1.35% taurolidine, 4% citrate, and 25,000 IU urokinase) were purchased from Tauropharm (Waldbüttelbrunn, Germany). CitraFlow 4% was from MedXL (Montreal, Canada).

Catheter maintenance protocol. Care of the tunneled catheter in the study sites followed established standards including dressing changes, exit site care, and hygiene without any change over the study period.[31,32] After each hemodialysis session the exit site was inspected and covered with a 2.0% chlorhexidine dressing (Tegaderm CHG; 3M, Neuss, Germany). No patient reacted to the topical chlorhexidine patch and no antibiotic ointments were used.

Diagnosis and treatment of catheter-related infections (standard protocol). A CRI was defined as a positive bacterial blood culture drawn from the dialysis catheter in a symptomatic patient with fever or chills associated with dialysis and no apparent other source of infection.[33] Blood cultures were taken using an aseptic technique from each lumen of the tunneled catheter, and in addition, from a peripheral vein whenever possible. If the same microorganism was isolated in blood cultures taken fewer than 3 weeks apart it was considered to be the same infection[39] and not a recurrent event. Infections were treated by the attending nephrologist starting with vancomycin and, in more critical clinical states, the addition of cefepime. The treatment was adjusted based on culture results thereafter. In case of an inadequate response to antibiotic therapy or recurrence of a CRI, the catheter was removed and the observation period was stopped. Exit site and tunnel infections were defined as previously described.[40,41]

Diagnosis and treatment of catheter dysfunction (standard protocol). Catheter dysfunction was defined as inadequate blood flow during dialysis (blood flow <200 ml/min or >30% less than the average of the previous 10 sessions), and, if present before or during dialysis, patient repositioning or a reversal of catheter lines was performed. If unsuccessful, 2 mg of alteplase (Actilyse Cathflo; Boehringer Ingelheim, Ingelheim, Germany) were instilled per lumen either with a 30-minute dwell time before dialysis or as CLS in the interdialytic time as rescue. If alteplase was not effective after repeated use then the catheter was removed.

	Monday Tuesday	Wednesday Thursday	Friday Saturday	
Taurolidine-citrate-heparin 500	X	X		Taurolidine group
Taurolidine-citrate-urokinase 25,000			X	
				versus
4% Citrate	X	X	X	citrate group

Figure 4 | Trial profile. Comparison of 2 lock regimens using 3 commercially available catheter lock solutions.

Laboratory diagnostics for routine parameters

All laboratory parameters were determined at the laboratories of the respective center, which operate according to certified (ISO 9001:2008) and accredited (ISO 15189:2008) quality management systems.

Outcomes

The primary outcome was the total number of CRIs. Secondary outcomes were defined for infections (CRI-free survival, episodes of antibiotic therapy, hospitalization days for a catheter-related infectious event, hospitalization for an all-cause infectious event) and for patency (catheter dysfunction, need for reversal of catheter lines, rescue with alteplase). Further secondary outcomes were catheter removal owing to infectious and mechanical complications, exit-site or tunnel infections, hospitalization for a cardiovascular event, and death and bleeding complications (defined as bleeding requiring any type of intervention: extended observation in the hospital, additional sutures, surgical consults, or blood transfusions).

Cost analysis

A cost analysis was performed on the basis of the pricing policy of our study sites. Cost factors related to treatments and short-term complications included the following: (i) CLS, (ii) rescue with alteplase, (iii) removal and replacement of the catheter, (iv) complete treatment of a CRI in an outpatient setting,[42] and (v) inpatient treatment of a CRI per day.[43]

Statistical analyses

We present categorized data as absolute counts and relative frequencies. Continuous data are presented as means $\pm$ SD.

The sample size calculation was based on the results of a monocentric pilot study. One hundred patients were required to detect a decrease in the primary outcome from 35% in the control group to 10% in the experimental group, with a power of 80% at a 2-sided type I error level of 5% using the Fisher exact test with a randomization ratio of 1.

To compare randomization success we compared treatment groups qualitatively and used the chi-squared test or the Fisher exact test for categorized variables and the Mann-Whitney *U* test for continuous data to test the null hypothesis of no difference between treatment groups. The primary outcome was the occurrence of CRI events. We calculated the incidence rates based on the total follow-up time per patient using a Poisson model with a CRI event rate as the outcome and treatment group as the covariate to calculate the

IRR with a 95% CI. To account for differences in follow-up time between recurrent CRI events, the Andersen and Gill[44] method was applied. We modeled recurrent CRI events in a proportional hazards Cox model with CRI events as the outcome and treatment group as the covariable. Time variables were set to continue the observation time after the occurrence of an event. Efron's method for handling ties was used. To account for correlated data structures we used robust SEs based on Huber/Whites/sandwich estimator variance components for the calculation of the CIs. We compared hospital days resulting from infectious events using the Mann-Whitney *U* test.

Follow-up data were gathered at the end of the study (time of catheter removal, switch to alternative dialysis access or to alternative renal replacement therapy, or patient's transfer to a dialysis unit not involved in the study or death, whichever came first).

To assess differences in microorganisms involved in CRIs, we used the Fisher exact test for pairwise comparisons or for overall comparisons accounting for the correlational structure of the data a logistic regression model with robust SEs and the *P* value from the Wald test.

For data management and analysis we used MS Excel for Mac and Stata 14 for Mac (Stata Corp, College Station, TX). A 2-sided *P* value of 0.05 or less was considered statistically significant.

Approval and registration

The study protocol was performed in accordance with the Helsinki Declaration and was approved by the Ethics Committee of the Medical University of Vienna. All study participants provided written informed consent. The study was registered at ClinicalTrials.gov (ID: NCT02789501).

DISCLOSURE

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