Taurolidine-citrate-heparin lock reduces catheter-related bloodstream infections in intestinal failure patients dependent on home parenteral support: a randomized, placebo-controlled trial

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ABSTRACT

Background: In patients with intestinal failure who are receiving home parenteral support (HPS), catheter-related bloodstream infections (CRBSIs) inflict health impairment and high costs.

Objective: This study investigates the efficacy and safety of the antimicrobial catheter lock solution, taurolidine-citrate-heparin, compared with heparin 100 IE/mL on CRBSI occurrence.

Design: Forty-one high-risk patients receiving HPS followed in a tertiary HPS unit were randomly assigned in a double-blinded, placebo-controlled trial. External, stratified randomization was performed according to age, sex, and prior CRBSI incidence. The prior CRBSI incidence in the study population was 2.4 episodes/1000 central venous catheter (CVC) days [95% Poisson confidence limits (CLs): 2.12, 2.71 episodes/1000 CVC days]. The maximum treatment period was 2 y or until occurrence of a CRBSI or right-censoring because of CVC removal. The exact permutation tests were used to calculate P values for the log-rank tests.

Results: Twenty patients received the taurolidine-citrate-heparin lock and 21 received the heparin lock, with 9622 and 6956 treatment days, respectively. In the taurolidine-citrate-heparin arm, no CRBSIs occurred, whereas 7 CRBSIs occurred in the heparin arm, with an incidence of 1.0/1000 CVC days (95% Poisson CLs: 0.4, 2.07/1000 CVC days; $P = 0.005$). The CVC removal rates were 0.52/1000 CVC days (95% Poisson CLs: 0.17, 1.21/1000 CVC days) and 1.72/1000 CVC days (95% Poisson CLs: 0.89, 3.0/1000 CVC days) in the taurolidine-citrate-heparin and heparin arm, respectively, tending to prolong CVC survival in the taurolidine arm ($P = 0.06$). Costs per treatment year were lower in the taurolidine arm (€2348) than in the heparin arm (€6744) owing to fewer admission days related to treating CVC-related complications ($P = 0.02$).

Conclusions: In patients with intestinal failure who are life dependent on HPS, the taurolidine-citrate-heparin catheter lock demonstrates a clinically substantial and cost-beneficial reduction of CRBSI occurrence in a high-risk population compared with heparin. This trial was registered at clinicaltrials.gov as NCT01948245. *Am J Clin Nutr* 2017;106:839–48.

INTRODUCTION

In the United States, it is estimated that 10,000–20,000 patients with chronic intestinal failure (IF) may depend on a life-long provision of home parenteral support (HPS; i.e., nutrients and/or fluid and electrolyte supplements) through a long-term central venous catheter (CVC) (1, 2). Although life sustaining, the presence of the CVC poses an ever-imminent risk of the catheter-related complications (2–4) [e.g., exit-site and tunnel infections; catheter-related venous thrombosis; mechanical CVC problems, and catheter-related bloodstream infections (CRBSIs)]. This may restrict the spontaneous lifestyle of the patients, and the actual need for repetitive admissions for antimicrobial therapy and repeated CVC replacements is a burden to the patients, increases their morbidity, increase the health care–associated costs, and potentially increases even their mortality. Therefore, prevention of catheter-related complications is a cornerstone in achieving the best quality of care and improving patient outcomes.

Primary preventive strategies include evidence-based guidelines recommending appropriate education, training, and implementation of "primary prevention bundles" on CVC insertion (5, 6) and catheter care maintenance protocols (7). Despite these primary prevention measures, chronic IF patients remain at high risk for developing repetitive CRBSIs. The main pathogenesis of CRBSI in relation to tunneled CVCs is believed to be a contamination of the catheter hub, leading to intraluminal colonization and biofilm formation. The subsequent detachment of microorganisms from

the biofilm into the bloodstream triggers the systemic symptoms of infection (8). It has been reported that between 42% and 77% of a HPS population never experience a CRBSI, whereas others are prone to repetitive CRBSIs (3, 9). Secondary prevention with instillation of an antimicrobial lock solution could be an important intervention for these high-risk patients receiving HPS.

Various catheter lock solutions have been investigated; solutions containing antibiotics have demonstrated efficacy, but there is a risk of developing antimicrobial resistance (10). Ethanol-containing solutions are attractive due to broad range antimicrobial effects and the lack of emergence of antimicrobial resistance (11), but structural CVC damage and risk of catheter occlusions may jeopardize the catheter patency (12). Taurolidine-containing lock solutions have a broad spectrum of antimicrobial activity, inhibit microbial adhesion to surfaces, inactivate microbial toxins (13), resist the emergence of microbial resistance (14, 15), and demonstrate clinical efficacy in reducing the CRBSI incidence in hemodialysis (16, 17) oncology and/or hematology (18, 19), and HPS populations (20–24). However, in the HPS population, taurolidine-containing lock solutions have thus far been evaluated only in open-label or retrospective studies with a low methodologic strength.

Therefore, this prospective, double-blinded, placebo-controlled, single-center trial was conducted to compare the efficacy of taurolidine-citrate-heparin and heparin 100 IU/mL catheter lock solutions with respect to the occurrence of CRBSIs and other catheter-related complications in a high-risk HPS population with a proven susceptibility to CRBSIs.

METHODS

Study design and settings

This investigator-initiated, single-center study was conducted at the tertiary referral intestinal failure unit at Rigshospitalet, Copenhagen, Denmark. Patients were recruited from November 2013 until June 2014. The patients were identified through the Copenhagen Intestinal failure database (25), which contains information about all CRBSI episodes in our HPS cohort. Before randomization, patients were stratified and paired according to age, sex, and prior CRBSI incidence to obtain 2 comparable groups with respect to prior CRBSI incidence. Randomization was performed by a validated external source with an electronic randomization system (Regional Pharmacy of the Capital region, Denmark). Study participants were blinded and subjected to identical catheter care procedures. Study staff was blinded in the implementation process, during data collection, and during outcome adjudication. The study was conducted in accordance with the Declaration of Helsinki, approved by the Scientific-Ethical Committee of the Capital region of Denmark (protocol no. H-4-2013-127) and the Danish Data protection Agency (jr.no. 30-1112; I-Suite-no. 02566), and registered at clinicaltrials.gov (NCT01948245).

The primary end point was number of CRBSIs per 1000 catheter days in the 2 groups. Secondary end points were as follows: median time to a CRBSI (infection-free period); number, frequency, and median time to CVC removals because of catheter-related complications; number and frequencies of exit-site infections and catheter occlusions; patient satisfaction with the assigned catheter lock; number and frequency of adverse events; and an analysis of associated health care costs.

The maximum treatment period was 2 y, but the patients ceased further participation in the case of a verified CRBSI or in the case of CVC removal due to a secondary end point. Before unblinding, all infectious episodes that could be regarded as a primary or secondary end point were discussed in the study group, and consensus was reached on how to categorize the events.

Protocol amendments

In May 2014, protocol amendments (protocol-anm.no.42685) were made with extension of the treatment period from 1 to 2 y, because an overall lack of primary end points (CRBSIs) was observed in the study. A new informed consent was obtained for participation in the extension period. Furthermore, there were difficulties with inclusion of the patients receiving HPS with the highest CRBSI risk, because the initial inclusion criteria required a tunneled CVC to be older than 3 mo, and all patients with a previous catheter-related venous thrombosis were excluded. Thus, the inclusion and exclusion criteria were modified: the age of the tunneled CVC at enrollment was reduced from 3 to 1 mo, and patients who had experienced a catheter-related venous thrombosis >3 mo ago were allowed to be included if anticoagulant treatment was stable. Elaborate details on the inclusion, exclusion criteria, and protocol are provided at www.clinicaltrials.gov (NCT01948245).

Patient population

Adult patients (18–80 y of age) with chronic IF (dependent on parenteral nutrition or intravenous fluid ≥1 y), receiving HPS through a tunneled CVC for a minimum of 2 times/wk were eligible for study participation. The patients included had evidenced a high risk of CRBSIs, defined as having experienced ≥1 CRBSI episode within the last 4 y and having a tunneled CVC >1 mo, thereby increasing their probability of having an intraluminal biofilm. Patients with active malignant disease were not eligible.

Study locks and catheter procedures

Active treatment consisted of the catheter lock taurolidine-citrate-heparin solution [TauroLockHep100 consisting of (cyclo)-taurolidine 1.35%, sodium-citrate 4%, and heparin 100 IU/mL; TauroPharm GmbH]. The placebo comparator was heparin 100 IU/mL (Amgros I/S), which was the standard catheter lock used in the IF unit. Both study locks were supplied in identical blinded and transparent 5-mL ampoules, which were customized.

The catheter lock instillation procedure steps were as follows: parenteral solution (PS) infusion followed by saline 0.9% flush (10 mL), study lock instillation (2–4 mL) with an intraluminal dwell time >8 h, repeated saline 0.9% flush (10 mL), and subsequent PS infusion. The twice-daily 0.9% saline flushes were implemented at study initiation. The study lock instillation procedures were performed at home by the patient, relatives, or home community nurses who had been trained in the aseptic nontouch catheter care technique after a standardized protocol (26).

Catheter characteristics and care

All enrolled patients had a single-lumen, subcutaneously tunneled, dacron-cuffed, silicone CVC (Broviac, 6.6-Fr diameter; BARD Medical). CVC insertions were performed by anesthesiologists

with ultrasound guidance and a chest X-ray to control CVC tip placement. The CVC was a dedicated central line for PS, which was requested not to be used for regular blood sampling. The catheter care procedures followed the IF unit's standardized protocol (25).

Definition of catheter-related complications

A CRBSI was defined by the presence of clinical and paraclinical signs of infection with elevation of C-reactive protein or white cell count and positive blood culture from the CVC or from a peripheral vein in the absence of another proven focus explaining the infection. This is a modified CRBSI definition applied in the Copenhagen Intestinal failure database (27), which differs slightly from the standard CRBSI definition (2, 28) and is more similar to the definition of a central line–associated bloodstream infection (29).

A local infection was defined as an exit-site infection or tunnel infection determined by the extend of the erythema, induration, purulent drainage, and/or tenderness around the exit site (28). The mechanical CVC problems that occurred were divided into the following: catheter occlusions (failure to flush, aspirate, or infuse sufficiently on the CVC), catheter displacement (visible cuff, accidental auto-removal), and catheter defects (visible breakage or weakness of the silicone material). For microbiological diagnostics, the qualitative, automated blood culture system BACTEC-9240 (Becton Dickinson) was used, microbial identification was with the matrix assisted laser desorption ionization–time of flight (MALDI-TOF) technique (Bruker), and antimicrobial susceptibility was estimated by disk diffusion (Neosensitablets; Rosco). Urine and sputum cultures were handled according to hospital standard procedures.

Statistical analysis

The number of recruited patients was based on power calculations using findings from the study by Bisseling et al. (20). Twenty-one patients should have been recruited for each arm, reflecting a goal statistical power of 80% at 5% significance, to detect a true mean difference of 1.5 between the 2 arms (2-sided, 2-sample t test) and with an anticipated dropout rate of 20%. For categorical data, regarding descriptive statistics of the baseline characteristics, numbers and percentages are provided. Continuous data are presented as means and SDs or medians [minimum-maximum (min-max)] as appropriate according to the distribution of data. The statistical analysis were performed with triple-blinded study staff, meaning the unblinding was only performed by dividing participants into a group allocation, without an unblinding regarding which catheter lock solution each group received. The log-rank test was used to compare incidence rates between groups. The log-rank test is based on asymptotic properties. To ensure that the P values obtained from the log-rank tests were valid, we recalculated the P values with the use of exact permutation tests. An exact permutation test does not depend on sample size and could be conducted within the patient pair, thereby increasing the statistical power with the use of stratified randomization. For a group comparison of ordinals, categorical data Goodman and Kruskal's γ-coefficient and a Wilcoxon's rank-sum test was used. A 2-sided $P < 0.05$ was considered statistically significant. All incidence rates are presented as episodes per 1000 CVC days with 95% Poisson confidence limits (CLs). The statistical analysis was performed with the use of R software version 3.3.2 (package survival version 2.40-1; R Core Team).

RESULTS

Study population

A total of 41 patients (mean age: 56.4 y) were eligible and enrolled in stratified pairs [20 taurolidine-citrate-heparin; 21 heparin arm; see the Consolidated Standards of Reporting Trials (CONSORT) flow diagram in **Supplemental Figure 1**]. Baseline characteristics are presented in **Table 1**. Groups were well balanced except for the finding that the median total parenteral energy requirements (including glucose, lipid, and amino acid energy requirements) and mean PS volume (milliliters per day) were higher in the taurolidine-citrate-heparin arm. The HPS infusion frequency, as an indicator of number of CVC manipulations, was comparable between groups. The study population had received HPS for a total of 309.1 CVC years (median: 5.4; min-max: 1.03–25.8) and had presented with a high mean CRBSI incidence of 2.4 episodes/1000 CVC days [95% Poisson CLs: 2.12, 2.71 episodes/1000 CVC days; Table 1].

CRBSIs

The CRBSI incidence rate in the taurolidine-citrate-heparin arm was 0 during 9622 treatment days. Seven CRBSI episodes occurred in the heparin arm during 6956 treatment days, resulting in a CRBSI incidence rate of 1.0 CRBSI/1000 CVC days (95% Poisson CLs: 0.4, 2.07 CRBSIs/1000 CVC days). The overall CRBSI incidence rate in the study population was 0.42 CRBSIs/1000 CVC days (95% Poisson CLs: 0.17, 0.87 CRBSIs/1000 CVC days; **Table 2**). For the patients who experienced a CRBSI, the median time to a CRBSI was 154 d (min-max; 87–438 d), with cumulative hazard curves for CRBSIs presented in **Figure 1**. Instead of evaluating the difference in mean CRBSI incidence rates, we evaluated the probability of experiencing this outcome or something even more unlikely, if there were no effect of treatment on the occurrence of CRBSIs. First, by analyzing this with the use of the log-rank test, a significantly different CRBSI occurrence in the taurolidine-citrate-heparin arm was demonstrated compared with the heparin arm (P-log-rank = 0.0034). Thus, if there truly was no effect of taurolidine-citrate-heparin on CRBSI occurrence, the probability of observing something at least as skewed as our findings is 0.34%. An exact permutation test was conducted, resulting in P-exact = 0.0052, supporting the original conclusion.

Overall, 15 episodes with positive blood cultures were observed during the study, including the 7 CRBSIs in the heparin arm. In the taurolidine-citrate-heparin arm, 7 episodes were categorized as contaminants or colonization (without systemic symptoms; Table 2). Five of these patients in the taurolidine-citrate-heparin arm never received antimicrobial therapy, 1 patient received antimicrobial therapy for a concomitant urinary tract infection (different microorganism), and 1 patient initially received antimicrobial therapy because of elevated C-reactive protein without any CVC-related symptoms. However, further clinical and endoscopic evidence clearly suggested activity in the patient's Crohn disease (patient 4). The last episode in the

TABLE 1
Patient and central venous catheter characteristics[1]

	Total	Taurolidine-citrate-heparin	Heparin 100 IU/mL	P
Patient characteristics				
n	41	20	21	—
Sex (F/M), n	21/20	10/10	11/10	—
Age at baseline, y	56.4 ± 13.4[2]	58.1 ± 12.4	54.7 ± 14.4	—
BMI, kg/m²	22.1 ± 4.03	21.7 ± 3.7	22.6 ± 4.4	—
Smokers, n (%)	23 (56)	12 (60)	11 (52.4)	—
HPS administration form, n (%)				
Patients	29 (70.7)	13 (65)	16 (76.2)	—
Home community nurses	11 (26.8)	6 (30)	5 (23.8)	—
Relatives	1 (2.4)	1 (5)	0	—
Opioid users, n (%)	24 (59)	14 (70)	10 (47.6)	0.21[3]
Anticoagulant therapy users, n (%)	9 (22)	5 (25)	4 (19)	0.72[3]
Immune-suppressant users,[4] n (%)	7 (17)	4 (20)	2 (9.5)	0.41[3]
Diagnosis classification, n (%)				
IBD	20 (48.8)	9 (45)	11 (52.4)	—
Complications to non-IBD, noncancer abdominal surgery	5 (12.2)	3 (15)	2 (9.5)	—
Complication to gastrectomy	4 (9.8)	1 (5)	3 (14.3)	—
Mesenteric vascular events	5 (12.2)	3 (15)	2 (9.5)	—
Other causes of intestinal failure	6 (14.6)	3 (15)	3 (14.3)	—
Former cancer	1 (2.4)	1 (5)	0 (0)	—
Pathophysiologic classification, n (%)				
Short bowel syndrome	23 (56)	12 (60)	11 (52.4)	—
Intestinal fistulae	1 (2.4)	1 (5)	0 (0)	—
Intestinal dysmotility	7 (17.1)	4 (20)	3 (14.3)	—
Mechanical obstruction	3 (7.3)	1 (5)	2 (9.5)	—
Extensive mucosal disease	4 (9.7)	1 (5)	3 (14.3)	—
Combinations	3 (7.3)	1 (5)	2 (9.5)	—
Patients with an ostomy, n (%)	30 (73.2)	17 (85)	13 (62)	0.16[3]
HPS infusion frequency, d/wk	7 (2–7)[5]	7 (2–7)	7 (4–7)	
7 times/wk, n (%)	31 (76)	16 (80)	15 (71.4)	—
6 times/wk, n (%)	4 (10)	1 (5)	3 (14.3)	—
5 times/wk, n (%)	1 (2)	1 (5)	0 (0)	—
4 times/wk, n (%)	4 (10)	1 (5)	3 (14.3)	—
2 times/wk, n (%)	1 (2)	1 (5)	0 (0)	—
Daily total energy,[5] KJ	5043 (0–9316)	6466 (1455–9316)	2540 (0–9044)	0.051[6]
Glucose	3349 (0–6650)	4671 (989–6650)	1860 (0–6403)	0.039[6]
Lipids	598 (0–1909)	733 (0–1737)	239 (0–1909)	0.14[6]
Amino acids	960 (0–1680)	1181 (227–1470)	441 (0–1680)	0.043[6]
Daily volume,[2] mL	2538 ± 1514	3092 ± 1412	2011 ± 1447	0.02[7]
CVC and prior CRBSI characteristics				
Total CVC years in study population before study start	309.1	140.9	168.2	—
CVC years per patient[5]	5.4 (1.03–25.8)	5.5 (2.1–19.4)	5.4 (1.03–25.8)	—
Total CVC days before baseline visit in study population	111.219	50.451	60.768	—
CVC days per patient[5]	1934 (343–9399)	1965.50 (744–6979)	1934 (343–9399)	—
Tunneled CVC placement,[8] n (%)				0.005[3]
Upper right-sided	26 (63)	8 (40)	18 (86)	
Upper left-sided	14 (34)	11 (55)	3 (14.3)	
Vena femoralis dexter	1 (2.4)	1 (5)	0 (0)	
Tunneled CVC placement, n (%)				0.41[3]
Vena jugularis	16 (39)	8 (40)	8 (38)	
Vena subclavia	23 (56)	10 (50)	13 (62)	
Vena femoralis/upper dexter	2 (4.9)	2 (10)	0 (0)	

(Continued)

TABLE 1 (*Continued*)

	Total	Taurolidine-citrate-heparin	Heparin 100 IU/mL	P
CVC age at baseline,[5] d	306 (40–1652)	345.5 (92–1652)	229 (40–904)	0.46[6]
CRBSIs in tunneled CVCs before enrollment, n	5 (1–39)	5 (1–32)	5 (1–39)	—
Overall prior CRBSI incidence[9]	2.4 (2.12, 2.71)	2.7 (2.3, 3.2)	2.2 (1.8, 2.6)	—

[1] *P* values testing the null hypothesis, no difference between groups, 2-sided *P* < 0.05 was considered statistically significant. Nonparametric statistics were determined with the use of Fisher's exact test for categorical data and Wilcoxon's rank-sum test for continuous data. CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; HPS, home parenteral support; IBD, inflammatory bowel disease.

[2] Mean ± SD (all such values).

[3] Determined by Fisher's exact test.

[4] Immunosuppression users: azathioprine, *n* = 3; prednisolone >15 mg, *n* = 5; mycophenolatmofetil, *n* = 1; and tacrolimus, *n* = 1.

[5] Median; minimum–maximum in parentheses (all such values).

[6] Determined by Wilcoxon's rank-sum test.

[7] Determined by 2-sample *t* test.

[8] Single-lumen, cuffed, silicone (Broviac; BARD Medical).

[9] Values are episodes/1000 CVC days (95% Poisson confidence limits).

taurolidine-citrate-heparin arm was assessed as bacteremia caused by a pulmonary focus (patient 34; **Supplemental Tables 1** and **2**).

Mechanical catheter complications and local infections

The number of patients experiencing mechanical CVC complications (MCs; *n* = 13; 32%), the type of MCs, and median time to the first registered MC are presented in Table 2. No difference in the MC incidence rates was detected between the taurolidine-citrate-heparin (0.74; 95% Poisson CLs: 0.27, 1.6) and heparin arms (1.18; 95% Poisson CLs: 0.47, 2.44; *P*-exact = 0.395; **Supplemental Figures 2** and **3**).

A difference was detected in local infection incidence rates between the taurolidine-citrate-heparin (0.49; 95% Poisson CLs: 0.13, 1.25) and heparin arms (1.58; 95% Poisson CLs: 0.72, 3.0; *P*-exact = 0.07; **Supplemental Figure 4**). Two patients experienced an exit-site infection concurrent with a CRBSI; in one of the cases there was an identical microorganism in the exit-site swab and blood cultures (extended spectrum beta-lactamase producing *Escherichia coli*).

Catheter survival

All catheter-related complications had effects on CVC survival time. The most frequent CVC complication leading to CVC replacement was MCs (*n* = 8). However, in the heparin arm, the infectious complications [CRBSIs (*n* = 4); local infections (*n* = 3)] were the most frequent (Table 2). A tendency to longer CVC survival time was observed in the taurolidine-citrate-heparin arm (*P*-exact = 0.061; **Figure 2**).

Side effects and patient satisfaction with the assigned catheter lock

No hypersensitivity reactions were observed. Side effects were reported by 13 patients (31.7%; Table 2), with most of these patients describing an abnormal or metallic taste sensation at catheter lock instillation (*n* = 8). Three patients reported short-lasting (<10 s) paresthesia (a tingling sensation) in the oropharyngeal region,

hands, or chest. Three patients, 2 of whom received taurolidine-citrate-heparin, withdrew consent because of reported side effects, such as nausea and vomiting (taurolidine-citrate-heparin arm) and dizziness (heparin arm). Regarding patient satisfaction with their assigned study lock, evaluated on the study termination visit, no difference between the 2 groups was observed (*P*-exact = 0.48; **Supplemental Figure 5**).

Cost of catheter locks and the associated cost of treating catheter-related complications

The catheter lock and catheter-related complication costs are evaluated in **Table 3**. The associated costs were almost 3 times lower in the taurolidine-citrate-heparin arm (€2347.7/treatment year) compared with the heparin arm (€6743.9/treatment year), primarily because of a difference in admission days to treat catheter-related complications between the taurolidine-citrate-heparin arm (20 d) and the heparin arm (131 d) (*P*-paired *t* test = 0.02).

DISCUSSION

This is the first prospective, randomized controlled, and double-blind study in a high-risk HPS population demonstrating a significant reduction in CRBSI occurrence with the use of a taurolidine-citrate-heparin catheter lock compared with heparin 100 IU/mL (*P* = 0.0052). All 7 CRBSIs were found in the heparin arm. This was accompanied by a tendency toward prolonged CVC survival (*P* = 0.061) and without any indications of increased risk of mechanical complications. This supports evidence that taurolidine-citrate-heparin is an effective antimicrobial lock in high-risk IF patients receiving HPS.

In general, these findings support the previous studies evaluating different taurolidine-containing locks, predominantly demonstrating encouraging results with a convincing and substantial reduction in CRBSI incidence (18, 22, 24, 30). To date, studies on patients receiving HPS have been either retrospective, uncontrolled, open-labeled, or small-sample-sized studies (14, 20, 22, 25, 31), with meta-analyses indicating methodologic weaknesses, large heterogeneity, and lack of power (32, 33). Chronic intestinal failure is a rare condition, with a low prevalence of patients

TABLE 2
Characteristics of catheter-related complications during the study[1]

	Total	Taurolidine-citrate-heparin	Heparin 100 IU/mL	P value
Patients at baseline, n	41	20	21	
Active patients at end-of-study, n	16	11	5	
Total treatment time, d	16,578	9622	6956	0.12[2]
Treatment time per patient	337 (10–756)[3]	592 (10–756)	207 (25–755)	
CRBSI episodes, n	7	0	7	
Gram-positive bacteria				
Staphylococcus capitis (CVC 1/1, peripheral 3/3) (CVC 1/1, peripheral 2/2)[4]	2	—	2	
Staphylococcus hominis (CVC 4/4, peripheral 2/2)	1	—	1	
Staphylococcus epidermidis (CVC 2/2, peripheral 2/2)	1	—	1	
Gram-negative bacteria				
ESBL *Escherichia coli* (CVC 4/4, peripheral 2/2)	1	—	1	
Serratia fonticola (CVC 3/3, negative peripheral)	1	—	1	
Fungemia				
Candida glabrata (CVC 2/2 flasks twice, negative peripheral)	1	—	1	
CRBSI incidence rate	0.42 (0.17, 0.87)	0	1.0 (0.4, 2.07)	0.0052[5]
Positive blood culture, n	15	8	7	
CRBSI, n	7	0	7	
Contamination (1 *Brevundimonas* species and 6 CoNS, all CVC BCs 1/2 flasks and peripheral no growth)	7	7	0	
Other infectious focus (pneumonia) (peripheral BC 1/2 flasks *Streptococcus salivarius*)	1	1	0	
Local infection, n (exit-site/tunnel infections)	13 (11/2)	4 (4/0)	9 (7/2)	
Time to first local infection,[3] d	91 (14–348)	273 (14–348)	77 (18–266)	
CVC consequence, n				
Accidental autoremoval	1	0	1	
Planned replacement	3	0	3	
Acute removal (CRBSI)	1	0	1	
Left in situ	8	4	4	
Local infection incidence rate	0.94 (0.50, 1.60)	0.49 (0.13, 1.25)	1.58 (0.72, 3.0)	0.0719[5]
CVC MCs, n	13	6	7	
Time to first MC,[3] d	206 (27–442)	212.5 (28–442)	206 (27–286)	
Defect CVC (no CVC defects in patients experiencing a CRBSI)	8	3	5	
Infusion problem or long infusion time	3	2	1	
Reporting resistance when flushing the study lock	2	1	1	
MC incidence rate	0.93 (0.49, 1.58)	0.74 (0.27, 1.6)	1.18 (0.47, 2.44)	0.395[5]
CVC replacement/removal, n	15/2	4/1	11/1	
Time to CVC removal from baseline,[3] d	194 (25–454)	159 (62–454)	194 (25–386)	
Mechanical problems/accidental autoremoval of CVC, n	5/3	2/2	3/1	
CRBSI	4	0	4	
Tunnel infection	2	0	2	
Sustained exit-site infection	1	0	1	
Deaths	2	1	1	
CVC removal incidence rate	1.02 (0.60, 1.64)	0.52 (0.17, 1.21)	1.72 (0.89, 3.0)	0.0611[5]
Patients with side effects, n (%)	13 (31.7)	11 (55)	2 (9.5)	
Abnormal or metallic taste sensation	8	8	0	
Nausea, vomiting, or anorexia	2	2	0	
Heartburn or acid reflux	1	0	1	
Paresthesia or tingling sensation (oropharyngeal region, hands, or chest)	4	3	1	
Dizziness or feeling that low blood glucose was provoked by study start	1	0	1	
Patients who withdrew consent because of reported side effects, n (%)	3 (7.3)	2	1	
Total admission time under the study, d	577	374	203	0.15[2]
Admission time per patient[3]	5 (0–98)	11 (0–98)	2 (0–96)	
25th−75th percentile	0–14	0–23	0–12	

(Continued)

TABLE 2 (*Continued*)

	Total	Taurolidine-citrate-heparin	Heparin 100 IU/mL	P value
Total antimicrobial treatment time during the study, d	299	208	91	0.16[2]
Antimicrobial treatment time per patient[3]	0 (0–68)	1.5 (0–68)	0 (0–45)	
25th−75th percentile	1–10	0–16	0–1	

[1] Incidence rates are presented as episodes/1000 CVC days (95% Poisson confidence limits) unless otherwise indicated. Exit-site infection was defined by erythema, induration, purulent drainage, and/or tenderness within 2 cm of the catheter exit site. Tunnel-infection was defined by symptoms >2 cm from the exit site and along the subcutaneous tunnel. *P* values testing the null hypothesis, no difference between groups, 2-sided $P < 0.05$ was considered statistically significant. The log-rank exact permutation tests were used to test difference in incidence rates between the 2 groups. Nonparametric statistics with Wilcoxon's rank-sum test were used to test difference for continuous variables. BC, blood culture; CoNS, coagulase-negative *Staphylococci*; CRBSI, catheter-related bloodstream infections; CVC, central venous catheter; ESBL, extended spectrum beta-lactamase producing; MC, mechanical complication.

[2] Determined by Wilcoxon's rank-sum test.

[3] Median; minimum–maximum in parentheses (all such values).

[4] Indicates the number of positive blood cultures flasks out of the number of flasks performed at the described location.

[5] Determined by log-rank exact permutation test.

receiving long-term HPS. This makes performance of large-scale, well-designed, randomized, and placebo-controlled prospective trials a challenge (2). The current single-center study design presents greater methodologic strength but is still subject to a small sample size and a low number of events. According to the exact test, there is a 0.5% probability of experiencing the present CRBSI outcome if taurolidine-citrate-heparin had no preventive effect on the CRBSI occurrence. Furthermore, the *P* values of the log-rank and exact tests were of the same magnitude. This indicates that the sample size was sufficiently large to draw statistically valid conclusions with the use of asymptotic assumptions.

We observed 15 episodes with positive blood cultures during the study: 7 assessed as contaminants and colonization and 1 with another primary focus of infection than the CVC. These 8 episodes occurred in the taurolidine-citrate-heparin arm. However, the categorization of all positive blood culture episodes was decided with full consensus in the study group at a meeting before unblinding. This skewed distribution of episodes assessed as blood culture contamination or colonization is difficult to explain. Whether these episodes represent mere contamination of blood cultures or represent intraluminal CVC colonization without systemic symptoms of infection is speculative. The observed microbial species and patterns are typical findings at blood culture contamination (34, 35), but common skin commensal microorganisms also have great ability to colonize and form biofilm on CVCs (26). Most participants were enrolled with an old tunneled CVC with high probability of an intraluminal biofilm independent of systemic symptoms of infection (37). In pediatric cancer patients, Handrup et al. (38) found 44 of 48 long-term CVCs to be ultrastructural colonized when evaluated by scanning electron microscopy, with no significant differences between catheters locked with taurolidine-citrate-heparin and heparin. Despite an even distribution of bacteremias, they also found a significant reduction of CRBSIs in the taurolidine-citrate-heparin arm (18, 38). The CRBSI preventive mechanism of taurolidine is perhaps not only related to a reduction or inhibition of biofilm formation (38). Although in vitro studies have demonstrated a substantial reduction of biofilm-formation with taurolidine, this has mainly been investigated in young and mono-species biofilms, which perhaps do not illustrate in vivo circumstances well (39–42). Thus, the mechanism by which taurolidine prevents CRBSI in long-term CVCs is still not fully elucidated. The biofilm formation

may be reduced or the detached microorganisms from the biofilm into the bloodstream may be less viable with loss of virulence due to the taurolidine effect. The distribution of potential CRBSI risk factors in baseline characteristics (4, 43) (i.e., the use of opioids and immune suppressants, the HPS administration form, frequency of PS infusions, and presence of an ostomy) were balanced between the 2 groups. An interesting finding was the uneven distribution with higher PS requirements in the taurolidine-citrate-heparin arm. In IF populations, it has been reported that a higher dose of lipid infusion is a risk factor for CRBSI (4, 44). It is assumed that the infusion of energy-rich nutrients could facilitate microbial growth and intraluminal biofilm formation, with subsequent increased risk of CRBSI (45, 46). The higher PS energy and volume in the taurolidine-citrate-heparin arm did not result in CRBSI occurrence.

When considering the mode of action, the high frequency of local infections is most likely to be random and unrelated to the catheter locks, because these only exert an intraluminal effect. However, the presence of a local infection with a disrupted cuff barrier could increase the risk of extraluminal migration of microorganisms and possibly bacteremia, illustrated specifically in one CRBSI episode potentially originating from an extraluminal source (extended spectrum beta-lactamase producing *E. coli* in an exit-site swab and blood cultures).
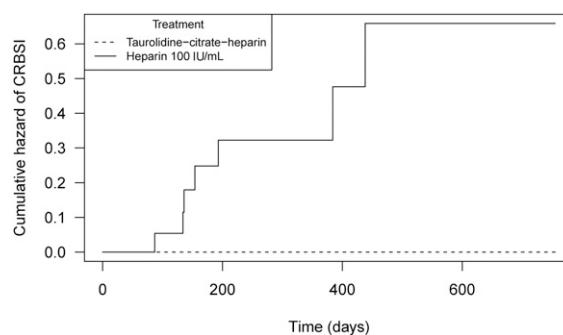

FIGURE 1 Cumulative hazards curves for CRBSI events. The log-rank exact permutation test indicated no difference in the distribution of time to a CRBSI ($P = 0.0052$). Taurolidine-citrate-heparin arm, at baseline ($n = 20$) and active at end of treatment ($n = 11$), and for heparin 100 IU/mL arm, at baseline ($n = 21$) and active at end of treatment ($n = 5$). CRBSI, catheter-related bloodstream infection.
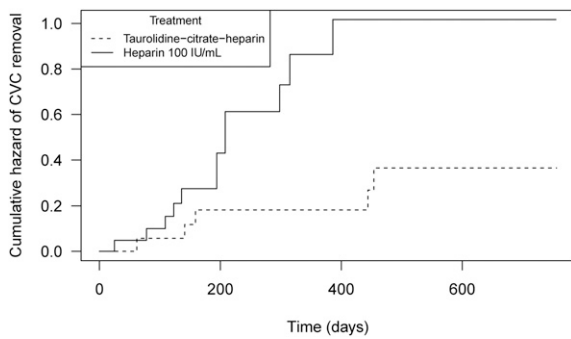
FIGURE 2 Cumulative hazard curves for time to CVC removal due to all causes. The log-rank exact permutation test was used to test difference in the distribution of time to CVC removal ($P = 0.0611$). Taurolidine-citrate-heparin arm, at baseline ($n = 20$) and active at end of treatment ($n = 11$), and for heparin 100 IU/mL arm, at baseline ($n = 21$) and active at end of treatment ($n = 5$). CVC, central venous catheter.

In the patients randomly assigned to the heparin arm, the CRBSI incidence rate decreased from 2.2 CRBSIs/1000 CVC days (95% Poisson CLs: 1.8, 2.6 CRBSIs/1000 CVC days) before enrollment to 1.0 CRBSIs/1000 CVC days (95% Poisson CLs: 0.4, 2.07 CRBSIs/1000 CVC days) during the study. Based on the recommendation from the taurolidine-citrate-heparin manufacturer (TauroPharm GmbH), a single catheter care procedure was changed for all study participants, with implementation of a saline flush on both side of the lock instillation. Theoretically, the additional 0.9% saline flush could have reduced intraluminal deposits of PS residues and/or fibrin for microorganisms to adhere to and, by this mechanism,

could have contributed to a decreased colonization and CRBSI risk (47).

It is important to be aware of possible altered participant behavior with propensity to higher compliance with hygiene and catheter care procedures when participating in a clinical trial. This Hawthorne effect (48), a potential subconscious change in behavior by participants, could have attributed in some extent to an overall decrease in CRBSI incidence best illustrated in the control arm. This potential effect merely highlights the need for a continuously high focus on the primary preventive strategies (aseptic nontouch catheter care technique), with attention to proper education of patients and health care staff.

In the taurolidine-citrate-heparin arm, 55% of the patients experienced side effects, with the majority describing a metallic taste sensation or short-lasting paraesthesia in the oropharyngeal region, but none of the patients regarded these side effects as a discomfort that would make them stop using the assigned lock. According to the protocol, the lock volume was 2–4 mL with a spill-over volume, where the citrate 4% content, with its calcium-ion binding capacity, is known to potentially trigger short-lasting paraesthesia (17, 19). Four patients received decreased catheter lock volume ($\sim$1.5 mL) with resolution of symptoms. Two patients in the taurolidine-citrate-heparin arm withdrew consent because of reported side effects such as nausea, vomiting, and anorexia; these side effects have been reported previously but are not clearly understood (19, 21).

In conclusion, the catheter lock solution, taurolidine-citrate-heparin, resulted in a significant and clinically relevant reduction in CRBSI occurrence compared with heparin without increased risk

TABLE 3

Associated costs of catheter locks and treatment costs for catheter-related complications[1]

Description of costs	Taurolidine-citrate-heparin	Heparin 100 IU/mL
Treatment days in the study (treatment years)	9622 (26.3)	6956 (19)
Ampoules, n	9038	6341
Unit price, €	5	3.5
Ampoule cost, €	45,190[2]	22,193
CRBSI admissions, n	0	7
CRBSI admission-days,[3] n (cost, €)	0	103 (82,400)
Antimicrobial days to treat CRBSI,[4] n	0	97
Admissions due to other (non-CRBSI) CVC complications, n	4	7
Admission-days to treat other CVC complications (non-CRBSIs), n	20	28
Admission cost,[3] €	16,000	22,400
Antimicrobial days to treat non-CRBSI CVC complications,[4] n	13	2
Tunneled CVC replacements, n	4	11
CVC cost (insertion procedure[4]),[5] €	284	781
Short-term CVCs in relation to CVC complication,[4] n	0	3
CVC repairs, n	3	4
Cost of CVC repairs,[6] €	270	360
Total costs, €	61,744	128,134
Costs per treatment day	6.4	18.4
Costs per treatment year	2347.7	6743.9

[1] CRBSI, catheter-related bloodstream infections; CVC, central venous catheter; IF, intestinal failure.
[2] TaurolockHep100 (TauroPharm GmbH) unit price.
[3] Our IF unit's price for an admission day = $\sim$€800
[4] The costs are included in the cost per admission day according to hospital pricing.
[5] Hospital purchase price for CVC (Broviac; BARD Medical) = €71.
[6] Cost of Broviac repair kit = €90

of other secondary CVC complications. In general, treatment was associated with mild and tolerable side effects and high patient satisfaction. A simplified cost analysis demonstrated a clear health care–associated cost benefit with the introduction of the taurolidine-citrate-heparin catheter lock to high-risk patients receiving HPS, with a one-third reduction in the overall treatment costs. As illustrated by the estimated costs in our IF unit, admission-related costs are the largest economic burden. By preventing just one CRBSI equaling a reduction in admission days (e.g., 10–14 d, ∼€9600), it would be possible to treat ∼5 patients with a taurolidine-citrate-heparin catheter lock for a year. Clearly, the CRBSI preventive efficacy and cost-benefit analysis of taurolidine-citrate-heparin from this study is not fully applicable to a population receiving HPS with a lower CRBSI risk. Thus, different clinical criteria and risk factors for selection of patients receiving HPS to initiate on a taurolidine-containing catheter lock need to be investigated and validated in future studies. The cornerstone in CRBSI prevention will always be a high focus on primary preventive strategies. However, we do recommend that antimicrobial taurolidine-containing locks should be used as an additive preventive measure for high-risk patients receiving HPS.

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