Pediatr Blood Cancer 2013;60:1292–1298

Central Venous Catheters and Catheter Locks in Children With Cancer: A Prospective Randomized Trial of Taurolidine Versus Heparin

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Background. To determine if the catheter lock taurolidine can reduce the number of catheter-related bloodstream infections (CRBSI) in pediatric cancer patients with tunneled central venous catheters (CVC). ***Procedure.*** During a study period of 34 months, 129 newly placed tunneled CVCs in 112 patients were randomly assigned to standard lock with heparin solution or experimental lock with a taurolidine solution (ClinicalTrials.gov Identifier NCT00735813). ***Results.*** Sixty-five CVCs were included in the standard group and 64 CVCs in the experimental group. The groups were comparable regarding patients' characteristics. A total number of 72 bloodstream infections of which 33 were CRBSIs were observed during 39,127 CVC-days. A lower rate of CRBSI (0.4 per 1,000 CVC-days) was observed in the experimental arm compared with the standard arm (1.4 per 1,000 CVC-days, incidence rate ratio (IRR) = 0.26; 95% confidence interval (CI) 0.09–0.61; $P = 0.001$). A lower rate of total bloodstream infections (1.2 per 1,000 CVC-days) was also observed in the experimental arm compared with the standard arm (2.5 per 1,000 CVC-days, IRR = 0.49; 95% CI 0.29–0.82; $P = 0.004$). Median interval from catheter insertion until first CRBSI was significantly lower in the standard group (156 days, range 12–602) compared with the experimental group (300 days, range 12–1,176; $P = 0.02$). Premature removal of the CVC due to infection and overall CVC survival were similar in the two study groups. ***Conclusion.*** Locking of long-term tunneled CVC with taurolidine significantly reduces catheter-related bloodstream infections in children with cancer. Pediatr Blood Cancer 2013;60:1292–1298.

Key words: catheter lock; catheter-related bloodstream infections; central venous catheter; pediatric; taurolidine

INTRODUCTION

Central venous catheters (CVC) are an inevitable part of the treatment of children with cancer. Although many attempts have been made to reduce the risk of catheter-related infections, CVCs remain a major risk factor of bloodstream infections [1–4]. Studies have shown that biofilm develops quickly once a CVC is inserted into a patient [5]. Bacteria living in a biofilm can be very difficult to eradicate and are likely to be involved in cases of recurrent CRBSI [5,6].

Heparin is often used to lock the catheter to prevent clotting when the catheter is not in use although heparin may enhance the growth of bacteria and the biofilm formation [7]. A Cochrane review has found prophylactic antibiotic catheter-lock to be beneficial in preventing CRBSI, but it is not routinely recommended due to the risk of selecting resistant microorganisms [8,9].

Taurolidine is derived from the naturally occurring aminosulphonic acid taurinamide and formaldehyde [10]. Taurolidine and its active metabolites contain an active *N*-methylol group that cross-links with the protein part of the bacterial cell wall and thereby neutralizes endotoxins and probably also to some extent exotoxins [11,12]. Taurolidine has also been reported to have anti-adherence properties [13] and may reduce biofilm formation [14–16]. The substance has shown a broad spectrum of antimicrobial activity against both gram-positive and gram-negative bacteria as well as fungi. Taurolidine used as a catheter-lock has shown efficacy in preventing CRBSI in adult patients [17,18]. One non-randomized study of the use of taurolidine as a catheter-lock in children with cancer reduced the rate of gram-positive bloodstream infections [19]. No intrinsic microbial resistance towards taurolidine has been reported [20].

We report the result of a prospective, randomized, controlled open-label study in which CVCs locked with a taurolidine solution were compared to CVCs locked with a standard heparin solution.

DOI 10.1002/pbc.24482
Published online 15 February 2013 in Wiley Online Library (wileyonlinelibrary.com).

PATIENTS AND METHODS

Patients

The study was conducted at the Department of Pediatrics at Aarhus University Hospital Skejby, which is a tertiary referral center for pediatric hematologic and oncologic diseases in Denmark. Patients were included from April 2008 to December 2010. The follow-up data are as of August 2012.

Criteria for patient eligibility were as follows: pediatric patients, aged 0–19 years, who suffered from an oncologic disease and who required a tunneled CVC. Patients were excluded if they were transferred to another department where adherence to the protocol could not be guaranteed.

Additional Supporting Information may be found in the online version of this article.

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Grant sponsor: The Childhood Cancer Foundation, Denmark; Grant sponsor: Aarhus University, Denmark; Grant sponsor: TauroPharm GmbH, Germany.

Conflict of interest: Nothing to declare.

Author contribution: M.M.H., J.K.M., and H.S. conceived and designed the study; M.M.H. analyzed the data and wrote the manuscript; J.K.M. and H.S. contributed to writing and editing the manuscript; H.S. supervised the project.

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Received 9 October 2012; Accepted 2 January 2013

Design and Objectives

This prospective, randomized open-labeled study was approved by the Central Denmark Region Committees on Biomedical Research Ethics (ClinicalTrials.gov Identifier NCT00735813). Signed written consent was obtained from each child and/or their parents before study enrollment. Patients were randomly assigned to treatment with standard or experimental catheter-lock on 1:1 basis according to a computer-generated randomization code. The patients were randomized in blocks of twenty. No stratification was performed.

In the standard arm, catheters were locked with 250 IE heparin in 2.5 ml sterile normal saline 0.9% (Amgros I/S, Copenhagen, Denmark) and in the experimental group, catheters were locked with 2.5 ml taurolidine 1.35%/sodium citrate 4%/heparin 100 IE/ml; TauroLock^{TM} HEP100 (TauroPharm GmbH, Waldbüttelbrunn, Germany). Primary endpoint was CRBSI rate. Secondary endpoints were time to first CRBSI, overall bloodstream infection rate, CVC survival rate and premature infection related catheter removal.

CVC Insertion and Care

Using a sterile technique, the CVC was inserted in the operating theater by a trained surgeon into the superior vena cava or the right atrial junction. The patients received either a tunneled CVC with external lines (TE) or a total implantable device (TID). All CVCs were managed according to international standards. TEs were flushed once a week. A bio-occlusive dressing was applied onto the place of insertion. The dressing was changed and the skin was cleansed with chlorhexidine every third day. TIDs were flushed once a month when not in use. The TEs were used for routine blood samples as opposed to the TIDs where a peripheral vein was used for routine blood samples when the catheter was not in use for other purposes.

Definitions of CVC-Related Infections

CVC exit-site infection. This diagnosis was made when inflammation extended more than one cm around the CVC exit-side and a pathogen was isolated in culture of a skin swab [4].

Tunnel infection. We defined a tunnel infection to be present when inflammation was seen extending more than two cm along the subcutaneous tract of the CVC [2].

Catheter-related bloodstream infections (CRBSI). CRBSI were defined as growth of microbes from a blood sample drawn from a CVC at least 2 hours before microbial growth was detected in a blood sample obtained from a peripheral vein (Differential time to positivity) following the recommendations in the latest consensus statement of the Infectious Diseases Society of America [1]. We also included paired blood cultures where a recognized pathogen was found in the blood sample drawn centrally but no microorganisms were found in the blood sample obtained from a peripheral vein. If a blood culture from a peripheral vein was not available, episodes diagnosed as probable CRBSI were included. Probable CRBSI was diagnosed when one or more of the following features were present: (1) a recognized pathogen cultured from one or more blood cultures; or (2) a common skin contaminant cultured from two or more blood cultures, both drawn at separate occasions. In both cases, the cultured organism must not be related to pathogens identified at other infection sites [21].

All blood cultures were taken at the first admittance of the child to the department with a febrile episode. For all blood cultures, the first 5 ml of blood aspirated from the CVC was discarded. An automated blood culture system (BacT/Alert, Biomerieux, France) was used for detection of bacterial growth. BacT/Alert Pediatric bottles were used for children at 3 years of age or below, and BacT/Alert Aerobic standard bottles were used for children above 3 years of age. Anaerobic cultures were taken on an individual basis. Identification of microorganisms and susceptibility to antibiotics were made in accordance with international standards.

Mechanical Complications

A mechanical complication was considered to be present if the catheter was removed because it was misplaced or if a leak was found. CVCs removed due to the formation of thrombus were also included in this category.

Treatment of Infections

Fever requiring intravenous antibiotic therapy was defined as (1) $\geq$38.5°C axiliary as a single measurement or (2) 38–38.4°C axillary over 3–4 hours. Criteria for catheter removal due to infection were failure of decontaminating the catheter with intravenous antibiotics $\pm$ CVC lock therapy with antibiotics or hydrochloric acid (HCl). First line antibiotic therapy consisted of a piperacillin–tazobactam 300 mg/kg/day in three doses and gentamicin 6 mg/kg/day as one daily dose. In case of a bloodstream infection, intravenous antibiotic therapy was continued for at least 7 days and 3 days after defeverescence. In cases of fever of undetermined origin (FUO), intravenous antibiotics were given for 3–5 days or until the temperature remained below 38.0°C for 2–3 days. Antibiotic therapy was adjusted according to culture results and clinical response of the patient. After 5–6 days of neutropenic fever antifungal therapy was added, either fluconazole 6 mg/kg intravenously in one daily dose or liposomal amphotericinB (Ambisome; Gilead Sciences International Ltd., Cambrigde, England) 1–3 mg/kg intravenously in one daily dose. In case of CRBSI or CABSI, catheter lock therapy consisting of vancomycin or gentamicin was given as a supplement to intravenous antibiotics for about 7 days according to culture results or HCl was installed in the catheter lumen(s) for 2 consecutive days according to Barbaric et al. at the discretion of the attending physician [22,23].

Data Analysis

To calculate the CVC sample size we estimated that CRBSI constitutes 40% of the bacteremia in the standard group based on the results reported by other groups [24,25] and the experience from our own department [26]. We tested the hypothesis that the proportion affected of a CRBSI would be reduced to 10% in the experimental group leading to a relative risk of 0.25, based on the results of previous studies of taurolidine reported by other groups [17,18]. Considering a power of 80% and a α error of 0.05, we calculated that at least 38 patients in each treatment arm, allocated in a 1:1 ratio, were required to detect this difference. Patient characteristics in the two groups were compared with the Wilcoxon rank-sum test and the chi square statistic (or Fishers exact test as appropriate) for continuous and categorical data, respectively.

The CVC observation period started on the day of CVC placement. The CVC was observed until time of removal, death of the patient with a CVC *in situ*, transferral of the patient to another department where adherence to the protocol could not be guaranteed or end of observation period (August 2012). Patients were considered at risk of CRBSI from the day of the catheter placement. CRBSI rates were described as incidence rates (IR) and compared by incidence rate ratios (IRR). The probability of CRBSI was estimated by the Kaplan–Meier method, and differences between the experimental and standard arms were compared by log-rank test. Median time to removal, death or transferral was estimated by the Kaplan–Meier method and compared with the log rank test.

After verification of the assumption of proportional hazards, univariate and multivariate Cox regression models were performed to adjust for the effect of multiple variables and their interactions and to test which variables were associated with CRBSI and overall bloodstream infections. Hazard ratio (HR), 95% confidence intervals (CI), and two-sided P values were calculated. $P \leq 0.05$ was considered statistically significant. All analyses were performed using Stata Statistic Software (release 10.1 Stata Corp., College Station, TX).

RESULTS

During the study, 113 patients with 130 newly placed CVCs were included (Fig. 1) and of these 129 CVCs inserted in 112 patients were used for data analysis. Of these CVCs, 113 were TIDs and 16 were TEs providing 36,892 catheter days and 2,235 catheter days, respectively. Sixty-five CVCs inserted in 54 patients were assigned to the standard lock with heparin and 64 CVCs inserted in 58 patients to the experimental arm with taurolidine. Four eligible patients with a total of seven CVCs refused random assignment and were treated according to standard procedure with heparin. The majority of patients in the experimental group reported a brief, unpleasant taste when their CVC was flushed with the taurolidine solution; however, only one patient was excluded after initial assignment on patient request because of this effect. No other notable side-effects occurred. After inclusion in the study, 14 patients were censored because they were transferred to another department where adherence to the protocol could not be guaranteed. As illustrated in Table I, patient and catheter characteristics were randomly distributed except that there were more males in the experimental group.

Bacteremia

A total of 101 episodes with one or more positive blood cultures were recorded. Of these, 29 episodes were defined as contamination because only a single positive blood culture for coagulase-negative staphylococci (CoNS) or other common skin flora was found. Of the remaining 72 bacteremic, episodes 33 (46%) fulfilled the criteria for CRBSI. A lower rate of total bloodstream infections (1.2 per 1,000 CVC-days) was observed in the children whose CVCs were locked with taurolidine compared with the children whose CVCs were locked with heparin (2.5 per 1,000 CVC-days, IRR = 0.49; 95% CI 0.29–0.82; $P = 0.004$). Paired blood cultures were available in 62 out of 72 cases (86%).

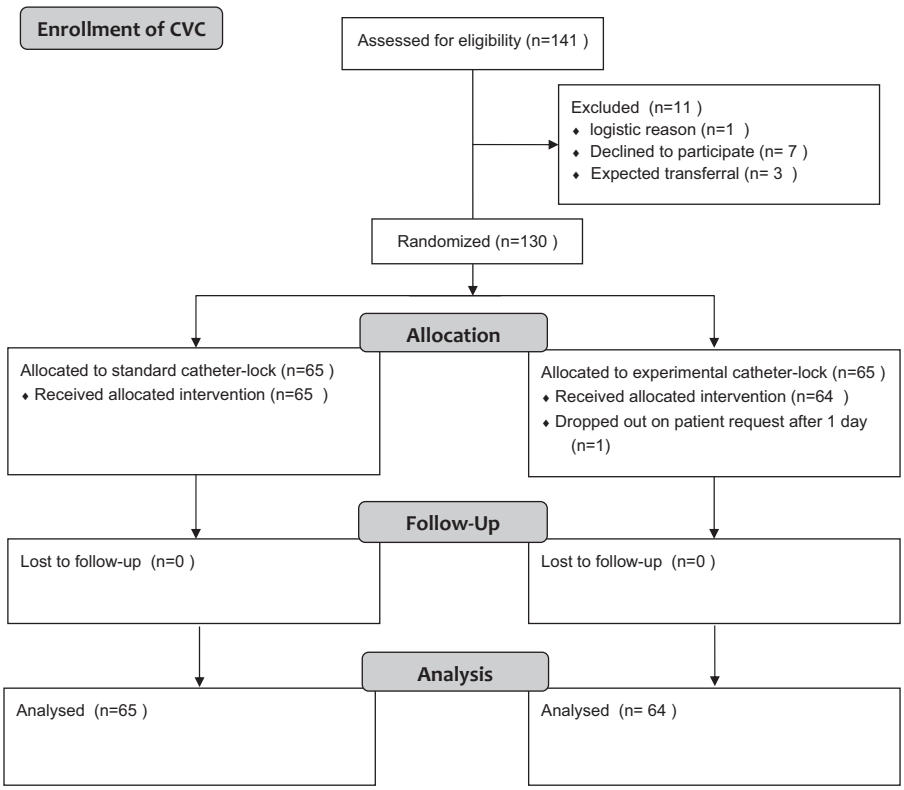

Fig. 1. CONSORT flow diagram 2010.

TABLE I. Patients and Catheter Characteristics

	Catheter lock		
	Taurolidine	Heparin	*P*-value
Number of patients	64	65	
Age (median, range)	6 (0–19)	5 (0–16)	0.83
Gender, (no. of males)	45 (70%)	33 (51%)	0.02
Underlying diagnosis			0.10
Leukemia/lymphoma	36	27	
Tumor/others	28	38	
Catheter type (n)			0.62
Total implantable device	57	56	
External lines	7	9	
Catheter lumina			0.83
Single	10	11	
Double	53	52	
Triple	1	2	
Catheter survival days (median, range)	300 (12–1,176)	236 (35–1,022)	0.19
Catheter removal (n)			0.79
End of treatment	41	39	
Infection	5	7	
Mechanical problem	4	4	
Dead with catheter *in situ*	6	6	
Censored[a]	8	10	

[a]Of the 18 patients, fourteen patients were censored because they were transferred to another department where adherence to the protocol could not be guaranteed. The remaining four patients were censored because the CVC was still in place at the end of the study period.

Catheter-Related Bloodstream Infections

Overall, there were 33 episodes of CRBSI, resulting in a rate of CRBSI of 0.8 per 1,000 CVC-days. Twenty-six CRBSI occurred in the control group locked with heparin and seven in the experimental group locked with taurolidine (Table II). In the group locked with taurolidine, six out of the seven cases of CRBSI had paired blood cultures. In the group locked with heparin, 22 out of 26 cases of CRBSI had paired blood cultures. In the majority of these cases the missing paired blood cultures were due to logistic reasons at admission. The rate of CRBSI in the experimental group was 0.4 per 1,000 CVC-days versus 1.4 per 1,000 CVC-days in the standard group (IRR = 0.26; 95% CI 0.09–0.61; $P = 0.001$). According to Kaplan-Meier analysis (Fig. 2) catheters locked with taurolidine were, over time, associated with a significantly lower risk of CRBSI ($P = 0.0001$, log rank test). In a separate Kaplan–Meier analysis including only data from the 113 TID, catheters locked with taurolidine were also associated with a significant lower risk of CRBSI ($P = 0.0001$, log rank test; see Supplementary Fig. 1).

Vancomycin was used to lock the CVC in one patient from the standard group locked with heparin. Gentamycin was used as a catheter-lock in three patients from the standard group and two patients from the experimental group locked with taurolidine. The median time interval from CVC placement to the first CRBSI was 300 days (range 12–1,176) in the experimental group and 156 (range 12–602) in the standard group ($P = 0.02$). The frequency of CRBSI caused by both gram-positive and gram-negative bacteria was reduced in the group locked with taurolidine compared with the group locked with heparin (Table III). CRBSI caused by CoNS including *Staphylococcus epidermidis* was reduced by 66% in the group locked with taurolidine compared with group locked with heparin.

As shown in Table IV, the use of taurolidine as catheter-lock was found to be independently protective against CRBSI (HR = 0.20; 95% CI 0.08–0.49; $P = 0.001$) by a multivariate Cox regression analysis. In a multivariate Cox regression analysis including only data from the 113 TID, the use of taurolidine was also independently protective of CRBSI (HR = 0.12; 95% CI 0.04–0.37; $P = 0.001$; see Supplementary Table I). The rate of CVC exit-site infections, tunnel-infections, and mechanical complications were low in both the experimental and the standard group and no difference was noted between the two groups.

CVC Non-Elective Removal and CVC Survival

Overall, premature removal was required in 21 (16%) of the inserted CVCs. The catheters were removed entirely at the discretion of the attending physician. The CVCs were removed, if the patient after 2 days of antibiotic treatment still had symptoms of sepsis with chills and spiking temperatures when using the CVC. CVC removal according to the type of complication and

TABLE II. Catheter Related Complications

	Catheter-lock						
	Taurolidine		Heparin				
	n	Rate[a]	n	Rate[a]	IRR	95% CI	*P*-value
Bacteremia							
BSI, total	25	1.3	47	2.5	0.47	0.27–0.78	0.002
CRBSI	7	0.4	26	1.4	0.26	0.09–0.61	0.0005
Non-CRBSI	18	0.9	21	1.1	0.73	0.36–1.47	0.35
Contamination	18	0.9	11	0.6	1.54	0.69–4.03	0.20
Exit site infection	5	0.3	2	0.1	2.32	0.38–24.4	0.33
Tunnel infection	0		0				

BSI, bloodstream infection; CRBSI, catheter-related bloodstream infection; IRR, incidence rate ratio; CI, confidence interval. [a]Per 1,000 catheter days.

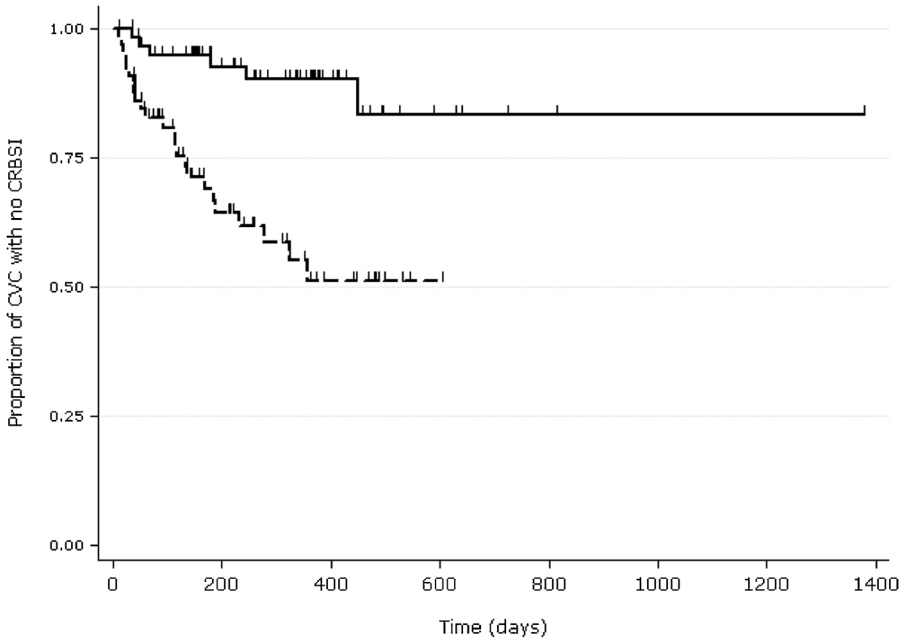

Fig. 2. Kaplan–Meier analysis of time to first catheter-related bloodstream infection (CRBSI). Catheters locked with taurolidine (solid line) were, over time, associated with a significantly lower risk of CRBSI than catheters locked with heparin (dashed line) $P = 0.001$, log rank test.

the study arm are listed in Table I. Infective complications were the most common reason for premature CVC removal in the standard group and they accounted for half of the premature CVC removal in the experimental group. There was no difference in infection related premature CVC removal between the two groups. After a median follow-up of 256 days (range 12–1,176) CVC survival was similar in the two study arms. CVCs were removed after a median of 236 days (range 35–1,022) and 300 days (range 12–1,176) in the standard and experimental group, respectively ($P = 0.19$).

TABLE III. Microorganism Involved in Catheter-Related Bloodstream Infections

	Catheter lock	
	Taurolidine	Heparin
Gram-positive		
Staphylococcus aureus	0	2
Staphylococcus epidermidis	2	2
Other coagulase-negative staphylococci	1	4
Non-hemolytic streptococci	1	2
Micrococcus sp.	0	1
Bacillus sp.	0	1
Lactococcus sp.	0	1
Rothia mucilaginosa	1	0
Total	5	13
Gram-negative		
Escherichia coli	1	1
Stenotrophomonas maltophilia	0	2
Haemophilus influenzae	1	0
Klebsiella pneumoniae	0	2
Klebsiella oxytoca	1	0
Pseudomonas spp.	0	1
Enterobacter cloacae	1	0
Acinetobacter	0	1
Citrobacter	0	1
Moraxella sp.	0	2
Aerobic gram-negative rod	0	1
Total	4	11
Candida krusei	0	1

DISCUSSION

This prospective randomized study showed that the locking of long-term CVCs with taurolidine–citrate is efficacious in preventing CRBSI in children with cancer. In this study CRBSI was classified by differential time to positivity and in most cases blood cultures were available both from the CVC and a peripheral vein. No randomized study has previously found a reduction in CRBSI using taurolidine as a catheter-lock solution. Furthermore, no difference was observed in the rate of non-CRBSI between the group locked with taurolidine–citrate and the group locked with heparin which supports the correct classification of CRBSI in this study. The use of taurolidine as a catheter-lock has not previously been shown to be independently protective against CRBSI in pediatric patients. This is also the first randomized study where the major part of the patients had a total implantable device.

In 2012 Dümichen et al. [16] reported in a small randomized study on immunocompromized pediatric patients a lower rate of BSI with taurolidine–citrate as a catheter-lock. However, in 2010 Solomon et al. [27] reported a double-blind, randomized study including 110 adult hemodialysis patients with a newly inserted tunneled CVC. In this study an experimental lock consisting of taurolidine–citrate was also compared to heparin. No difference was found in the overall rate of bacteremia, but a significant reduction of gram-negative bacteremia was seen. Simon et al. [19] published a non-randomized study in 2008 including 179 children with cancer and with newly placed tunneled CVCs. In

TABLE IV. Risk Factors for Catheter-Related Bloodstream Infection

	Catheter-related bloodstream infection					
	Unadjusted estimates			Adjusted estimates[a]		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Taurolidine versus heparin	0.20	0.08–0.49	0.001	0.20	0.08–0.49	0.001
TID versus TE	0.35	0.14–0.86	0.02	0.44	0.17–1.15	0.09
Male versus female	0.65	0.31–1.36	0.25	0.94	0.42–2.07	0.87
Leukemia and lymphoma versus solid tumor	1.51	0.73–3.12	0.27	1.63	0.78–3.41	0.20
Age $\geq$4 years versus age <4 years	0.78	0.34–1.76	0.54	0.90	0.46–2.34	0.94

TE, tunneled external line; TID, total implantable device; HR, hazard ratio. [a]Adjusted estimates are calculated using a Cox regression model adjusting for catheter-lock, catheter type, sex, diagnosis, and age.

this study taurolidine–citrate was also compared with heparin. No difference was found in the overall rate of bacteremia, but in their study a significant reduction in gram-positive bacteremia was seen in the group locked with taurolidine–citrate.

We found in our study not only a significant reduction of CRBSI but also a significant reduction in the total rate of bloodstream infections in the group of children with a CVC locked with taurolidine although this effect was influenced by the reduction in CRBSI. The discrepancy between our study and the studies by Solomon and Simon may be explained by the fact that we used CRBSI as the primary endpoint as opposed to the overall rate of bacteremia used in the other studies. Hence, the effect of taurolidine could have been masked in the Solomon and Simon studies because the use of bacteremia as a measure of CRBSI could induce a risk of over-estimating the true frequency of CRBSI [19,27,28].

Other studies of taurolidine have found a tendency towards a higher rate of catheter clotting [17]. In this study we did not analyze for the use of urokinase, but no catheters in the group locked with taurolidine were removed due to thrombosis or clotting. The majority of our patients in the group locked with taurolidine–citrate reported a brief unpleasant taste when the catheter was flushed with taurolidine–citrate and one patient dropped out of the study because of this. This effect has previously been reported by others and is most likely due to spillover of citrate from the catheter [16].

Studies have found that taurolidine works by reducing the biofilm formation [14]. A subgroup of the CVCs included in this study was also examined by scanning electron microscopy and no difference was found in the biofilm development between the two groups [29]. It is interesting, though, that in this study the number of CRBSI caused by microorganisms, for example, CoNS, known for their ability to form and live in a biofilm, was reduced in the group locked with taurolidine–citrate. These changes in the distribution of microorganisms were also found by Simon et al. [19]. Nevertheless, a reduction in both fungi, gram-negative and gram-positive bacteria was found in this study, which supports the broad anti-microbial range of taurolidine also demonstrated by others [20]. A reduction of these microorganisms living in the CVC or alternatively a reduced release of the microorganisms into the bloodstream may explain the longer median interval from CVC insertion to CRBSI in the experimental group compared to the standard group.

A limitation of this study is the open-labeled design. This design carries a risk of physician and/or caregiver bias because of an inherent desire for the patients in the experimental group to improve; a fault common to all open-label studies. However, the primary endpoint of this study was CRBSI rate. The rate of CRBSI was based on growth of microbes from blood cultures and the time to microbial growth was detected. Both of these outcomes were determined objectively by the Department of Clinical Microbiology, blinded towards the patient's catheter-lock. Furthermore, all events were systematically ascertained and data collection on events was close to complete. Another limitation of this study was the discard of the first 5 ml of blood when blood cultures were obtained. We chose this procedure to avoid a dilution of the blood culture with the catheter-lock and to avoid the potential growth-inhibiting effect of taurolidine when the blood was cultured. The procedure may have caused a reduction in the findings of microorganisms localized on the inner surface of the CVC.

In conclusion, this study found that the use of taurolidine–citrate as a catheter-lock solution in tunneled long-term CVC significantly reduced the rate of CRBSI in children with cancer.

ACKNOWLEDGMENT

We wish to thank the patients who participated in this study.

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