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Randomized controlled trial of taurolidine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies

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SUMMARY

Background: A catheter lock solution containing 1.35% taurolidine and 4% citrate could potentially disrupt bacterial surface adherence and consecutive biofilm production due to the anti-adherence properties of taurolidine and the anticlotting and chelator activities of both compounds.

Aim: To compare the impact on microbial catheter colonization and infectious complications of heparin and taurolidine citrate as central venous catheter (CVC) lock solutions in paediatric patients with haematological malignancies.

Methods: Seventy-one patients aged 1.4–18 years were randomized to two treatment groups using either heparin ($N = 36$) or taurolidine citrate ($N = 35$). Infectious complications and clinical side-effects were prospectively monitored and microbial colonization of catheters was assessed at the time of removal.

Findings: There were two bloodstream infections in the taurolidine citrate group versus nine in the heparin group (0.3 vs 1.3 infections per 1000 catheter-days; $P = 0.03$). Fever of unknown origin and catheter occlusions were observed with a similar frequency in both groups. Microbial colonization was found in 25.4% catheters. The time of no-lock use, but not the type of lock solution or time of observation, was a significant predictor of catheter colonization ($P = 0.004$). Colonization was not observed in CVCs used immediately with taurolidine citrate lock. Seven patients in the taurolidine citrate group (20%) experienced side-effects (nausea, vomiting, abnormal taste sensations).

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Conclusion: The use of taurolidine citrate lock solution was associated with a significant reduction in bloodstream infection in immunocompromised paediatric patients. Taurolidine citrate may prevent colonization of CVCs if used from the time of insertion, but not after a period of no-lock catheter use.

Introduction

Central venous access devices constitute a significant risk for infectious complications. Prevention of catheter-related infections is a key measure to improve clinical outcomes, especially in high risk patients. Taurolidine [bis-(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)methane] is an antimicrobial agent which inhibits and kills a broad range of micro-organisms *in vitro* including multiresistant strains.[1–3] A catheter lock solution has been developed containing 1.35% taurolidine and 4% citrate. Due to the anti-adherence properties of taurolidine and the anticlotting and chelator activities of both compounds, this lock solution can disrupt bacterial surface adherence and consecutive biofilm production.[4,5]

In a previous study in paediatric cancer patients, the use of a taurolidine citrate lock solution resulted in reduction of Gram-positive infections compared with a historic control group of patients treated with a heparin lock solution.[6] However, prospective, randomized studies evaluating efficacy and safety of a taurolidine citrate lock solution have not been performed previously in a paediatric population with a high risk for infections. We hypothesized that in such patients, prolonged use of implanted central venous catheters (CVCs) and frequent handling by staff would result in a time-dependent biofilm formation and catheter colonization even in the absence of clinical symptoms. By analysing removed catheters, microbial colonization might serve as an endpoint for evaluating efficacy of catheter lock solutions. We therefore conducted a prospective randomized controlled clinical trial in paediatric patients undergoing chemotherapy for diagnosed malignancy or receiving a stem cell transplantation during 2007–2008; after allocating implanted catheters to a lock solution containing taurolidine citrate or heparin, infectious complications and clinical side-effects were prospectively monitored and microbial colonization of catheters was assessed at the time of removal.

Methods

Setting

In the Department of Paediatric Oncology/Haematology of the Charité Medical Center Berlin, each year about 90–100 children/adolescents are newly diagnosed with neoplastic disease and 20–30 with a relapse, and 40 stem cell transplantations are performed. Prior to antineoplastic treatment or stem cell transplantation, all patients receive a tunnelled single, double or triple lumen Broviac/Hickman CVC. Catheters are used immediately after placement for chemotherapy and intravenous medication/alimentation. Depending on clinical needs, the CVC is either locked after each treatment cycle (standard lock solution: heparin) or used continuously after implantation (without locking) for a limited number of days until switching to treatment cycles with intermittent locking. Treatment is started in hospital and continued in the outpatient department with continuation of locking between treatment cycles until removal of the catheter. Lock solution is only administered by experienced medical staff.

Ethical approval and informed consent

The study protocol was approved by the ethics committee of the Charité Medical Faculty Berlin and listed online as an ongoing clinical trial (ISRTCN86885538). Informed consent was given by all patients and their legal guardians. Consent forms were provided for parents and separately for children in the age groups <12 and ≥ 12 years.

Study design

Patients aged 1–18 years undergoing treatment with CVC placement with an expected duration of ≥ 4 weeks were eligible for the study. Exclusion criteria were lack of informed consent, presence of bacteraemia/sepsis at screening, presence of a secondary CVC, and known allergy to heparin or taurolidine citrate. Patients were randomized (heparin or taurolidine citrate) with stratification for age, gender and treatment facilities (oncology or stem cell transplantation unit) to two groups: group 1, heparin lock solution (5000 IU heparin/0.2 mL; Ratiopharm® Ulm, Germany, diluted to 100 IU heparin/mL sterile normal saline 0.9%); group 2, taurolidine lock solution (taurolidine 1.35%/sodium citrate 4%; TauroLock™, Tauropharm, Waldbüttelbrunn, Germany).

The catheters were locked with the appropriate filling volume. Lock solution was removed by aspiration without flushing. All catheters were tagged with a piece of colour tape to indicate group assignment. The study was performed under GCP guidelines with continuous prospective evaluation of infectious complications and side-effects by house staff and systematic follow-up during weekly visits by a study monitor (M.J.D.). In addition, external monitoring was provided by the Coordinating Centre for Clinical Studies (KKS Charité).

The primary endpoint of the study was bacterial colonization of the CVC evaluated by both qualitative and quantitative analysis after removal of the catheter. Secondary endpoints were the number of clinical infections (fever of unexplained origin: FUO), the number of primary bloodstream infections (BSIs), thrombotic occlusions, and clinical side-effects.

All patients routinely received cotrimoxazole for the prevention of *Pneumocystis jirovecii* pneumonia, but no other routine antibiotic prophylaxis. Patients were examined daily for fever (core temperature: $>38.5\ ^{\circ}C$) and signs of infection, and antibiotic broad spectrum therapy was started after drawing a blood culture from the CVC under aseptic conditions. For the latter, ≥ 2 mL of the aspirate (i.e. the catheter lock) were routinely discarded to avoid false-negative results due to dilution or antimicrobial activity of the lock solution in the case of taurolidine. Fever without a positive blood culture (FUO) was defined as clinical infection. In accordance with the

Centers for Disease Control and Prevention definition for the laboratory-confirmed BSI, a primary BSI had to meet the following criteria: patient has a recognized pathogen cultured from one or more blood cultures, and the organism cultured from blood is not related to an infection at another site. Catheter occlusion by thrombosis was diagnosed by the use of antithrombolytic therapy by staff (urokinase).

Statistical analysis

The incidence of bacterial colonization of indwelling catheters is not known for this patient group and no previous studies have been performed on the efficacy of taurolidine citrate on bacterial colonization *in vivo*. Therefore, sample size calculation was only possible for the secondary endpoint, catheter-related BSI. Estimating an incidence of 1.7 per 1000 catheter-days it was calculated (two-arm normal test) that a minimum of 25 patients in each group would be needed to show a decrease in the incidence of bacteraemia by 50% in the taurolidine group with a power of 0.8 at $P < 0.05$ (two-sided test).[7] PASW statistical software was used for data analysis of differences between groups.

Patients

All patients undergoing catheter implantation for treatment with antineoplastic chemotherapy or stem cell transplantation during the period of 1 January 2007 until 31 December 2008 were screened for the study.

Of a total of 252 children, 177 refused participation, 75 patients were willing to participate, but 4 did not meet inclusion criteria for age. Thus, 71 patients with malignancies (Table I) were enrolled in the study; 56 patients were treated in the oncology unit and 15 in the stem cell transplantation unit. These patients were randomized to receive either heparin ($N = 36$) or taurolidine citrate ($N = 35$) as lock solution (Table II).

A total of 9 (12.7 %) of the enrolled patients dropped out of the study; reasons were: death (2), loss to follow-up (2), discontinuation due to side-effects (dysaesthesia, nausea, vomiting, 3) and thrombotic occlusion (1), self-removal of CVC (1). Catheters removed from the remaining 62 patients were sent for microbiological testing, but 10 catheters were lost during transport and 1 not examined according to protocol. Thus, only 51 CVCs were included in the final analysis of the primary endpoint, bacterial CVC contamination (26 from the heparin and 25 from the taurolidine citrate group).

Table I
Malignancies

Clinical diagnosis	*N*	%
Leukaemia	44	62
Acute lymphoblastic leukaemia	35	49.3
Acute myeloblastic leukaemia	8	11.3
As part of myelodysplastic syndrome	1	1.4
Myelodysplastic syndrome	1	1.4
Thalassaemia	1	1.4
Fanconi anaemia	2	2.8
Lymphoma	4	5.6
Peripheral T-cell	1	1.4
Burkitt	1	1.4
Non-Hodgkin	2	2.8
Neuroblastoma	6	8.5
Sarcoma of bone	6	8.5
Ewing sarcoma	5	7
Osteosarcoma	1	1.4
Germ cell tumour	2	2.8
Seminoma	1	1.4
Germinoma	1	1.4
Rhabdomyosarcoma	2	2.8
Brain tumour	1	1.4
Medulloblastoma	1	1.4
Metachromatic leucodystrophy	1	1.4
Adrenoleucodystrophy	1	1.4
Total	71	100

Table II
Patients and treatment groups

	Group 1 (heparin)	Group 2 (TauroLock™)
No. of patients	36	35
Male (proportion in %)	23 (32%)	19 (27%)
Female (proportion in %)	13 (18%)	16 (23%)
Age (years)		
Mean	7.9	8.5
Median	6.3	7.5
Range	1.7–17.1	1.4–18
Duration of catheter use (days)[a]	200.9 ± 74.1	187.9 ± 119.7
Duration of locking (days)[a]	187.4 ± 86.5	172.6 ± 127.7
Catheter use without lock (days)[a]	13.4 ± 26.8	20.6 ± 41.6
No. of lumina		
1	16	12
2	14	17
3	6	6
Total	80	82
Treatment in:		
Oncology	29	27
Bone marrow unit	7	8
Duration of catheter use (days)[a]		
Oncology	219.7 ± 68.6	196.4 ± 112
Bone marrow unit	123.3 ± 37	159.1 ± 147.3
Duration of locking (days)[a]		
Oncology	215.7 ± 66.6	201.0 ± 121.3
Bone marrow unit	70 ± 41.6	77 ± 104.7
Catheter use without lock (days)[a]		
Oncology	1.7 ± 1.8	2.9 ± 3.2
Bone marrow unit	61.7 ± 28.2	80.5 ± 55.3
Cumulative no. of days of observation (catheter-days)		
Sum	7233	6576
Range	91–368	19–510
Mean ± SD	201 ± 74	188 ± 120
Cumulative no. of days of locking		
Sum	6747	6041
Range	20–365	19–442
Mean ± SD	187 ± 87	173 ± 128

[a] Mean ± SD.

Laboratory methods

To assess the quantity of micro-organism growth on the internal and external surface of the catheter tip, the sonication method described by Sherertz *et al.* was used.[8] The first 6 cm of each catheter was placed in 10 mL of tryptic soy broth, sonicated for 1 min, and then vortexed for 15 s. A 0.1 mL sample of the broth was added to 9.9 mL (1:100 dilution) of saline and vortexed. Then, 0.1 mL of these dilutions and 0.1 mL of the sonicated broth were surface-plated by using a wire loop on Columbia Agar with 5% sheep blood. The plates and the original broth containing the catheter were incubated for 48 h at 37 °C, and then the number of organisms was quantified. Accurate colony-forming unit (cfu) counts could be made for cfu between 10^2 and 10^7 (1:100 dilution). Counts below this range (growth in broth only) were classified as $<10^2$ cfu. Organisms were then identified by routine microbiological techniques by using the API® (bioMérieux).

Results

The observation period (duration of catheter use), the locking period (duration of catheter locking) and the days without lock prior to the locking period (no lock use) were similar in both groups of patients (Table II). Seven patients in group 1 (heparin lock) and 8 patients in group 2 (taurolidine citrate lock) were treated in the bone marrow unit and all other patients in the oncology unit, without a significant difference in duration of catheter use or duration of locking (Table II). However, due to differences in standard procedures, catheters were used unlocked for a longer period in the bone marrow unit than in the oncology unit. There were no significant differences between patient groups 1 or 2 within these units (Table II).

Clinical infections (FUOs) were observed with a similar frequency in both groups of patients. Eleven patients in the heparin group and 13 patients in the taurolidine citrate group were without clinical infections throughout the study. The other patients experienced from 1 to 6 infections per patient. FUOs were not significantly different in both groups if calculated either for the time of observation or the time of locking (Table III). The total number of infections was positively correlated with the time of observation ($r = 0.445$, $P < 0.0001$) and the time of locking ($r = 0.390$, $P < 0.001$). After the start of the locking period, there was no significant difference in the time until the first clinical infection in both groups, either for the whole population or calculated separately for the two treatment units. In line with these observations, there was no significant difference in the duration of intravenous antibiotic use in both patient groups.

A total of 202 blood cultures were drawn from 56 of the 71 patients enrolled in the study, and there were 9/27 patients in the heparin group and 4/29 patients in the taurolidine citrate group with at least 1 positive culture ($P = 0.084$). A total of 151 blood cultures were drawn from 39 of the 51 patients completing the study, and there were 8/20 with positive cultures in the heparin group and 2/19 with positive cultures in the taurolidine citrate group ($P = 0.035$).

There were 9 patients in the heparin group and 2 patients in the taurolidine group with BSI ($P = 0.018$, chi-squared test). BSI was significantly ($P = 0.03$) more frequent in the heparin group than in the taurolidine citrate group, whether calculated for the time of observation or the time of locking (Table III).

The occurrence of BSI was not associated with observation time, locking time, days without lock, number of implanted lumina, or the presence of catheter occlusions.

Catheter occlusion due to suspected thrombosis was diagnosed in 11 patients, and a thrombus formation was confirmed in 5 patients (2 in the heparin, 3 in the taurolidine citrate group). The study was discontinued in 1 case; in the other patients urokinase administration was successful in establishing catheter flow.

Microbiological analysis

Altogether, 51 CVCs were studied for bacterial growth. Seven CVCs (2 in the heparin, 5 in the taurolidine citrate group) were removed for suspected infections, and six of these were without colonization; the other CVCs were removed electively at the end of therapy. Both for the CVCs removed early and for the CVCs removed at the end of therapy, there were no differences between patient groups in observation time, locking time or days without lock during the use of these catheters (Table IV).

Table III
Infections and complications in patient groups

	Group 1 (heparin)	Group 2 (TauroLock™)	*P*-value
No. of patients	36	35	
Clinical infections (FUOs)	25 (69%)	22 (63%)	NS
Time until first infection after start of locking (days)	41.2 ± 49.4	35.6 ± 31.8	NS
Use of intravenous antibiotics (days)	25.3 ± 25	18.1 ± 24.7	NS
Clinical infections per 1000 catheter-days	9.5 ± 10	10.3 ± 11.6	0.916
Clinical infections per 1000 locking-days	9.9 ± 10.3	10.7 ± 11.8	0.981
BSI			
Patients without BSI	27	33	0.032
With BSI	9	2	
No. of BSIs per 1000 catheter-days	1.3 ± 2.5	0.3 ± 1.2	0.03[a]
No. of BSIs per 1000 locking-days	1.3 ± 2.6	0.3 ± 1.3	0.03[a]

FUO, fever of unexplained origin; BSI, bloodstream infection; NS, non-significant.
[a] Mann–Whitney *U*-test.

Table IV
Catheters at removal ($N = 51$)

	Group 1 (heparin) ($N = 26$)	Group 2 (TauroLock™) ($N = 25$)
Observation time (days) until study end	203.2 ± 75.6	217.2 ± 107.4
Locking time (days)	191.2 ± 91	189.2 ± 112.9
Days without lock	14.3 ± 29.8	27.5 ± 47.7
Removal site		
Operating room	19	14
Outpatient department	7	11
Catheter removal due to suspected infection	2	5
No bacterial growth	2	4
Significant bacterial growth	0	1

Nine of 51 catheters (17.6%) showed non-significant bacterial colonization. These were caused by *S. epidermidis* (4 in the heparin, 1 in the taurolidine citrate group) and *S. aureus* (1 in each group). Four of 51 catheters (7.8%) showed significant bacterial colonization amounting to a total incidence of 13 (25.4%) colonized catheters. These were caused by *Bacillus pumilus* (1 in the heparin group) and *S. epidermidis* (1 in the heparin, 2 in the taurolidine citrate group).

Whereas there was no apparent benefit of heparin lock, colonization-free catheter survival was longer in the taurolidine citrate group in CVCs never used without lock ($N = 17$), but this difference did not reach statistical significance; colonization occurred in no catheter in the taurolidine citrate group but did occur in two catheters in the heparin group (Figure 1).

If all colonized CVCs were analysed (7 in heparin group, 6 in the taurolidine citrate group), the time without lock was not significantly different (median: 45.7 and 76 days) between patient groups. Six colonized catheters were from oncology patients and 7 from bone marrow transplant patients. In a multivariate logistic regression model, time without lock but not the type of lock solution was the only significant predictor of overall catheter colonization ($P = 0.004$).

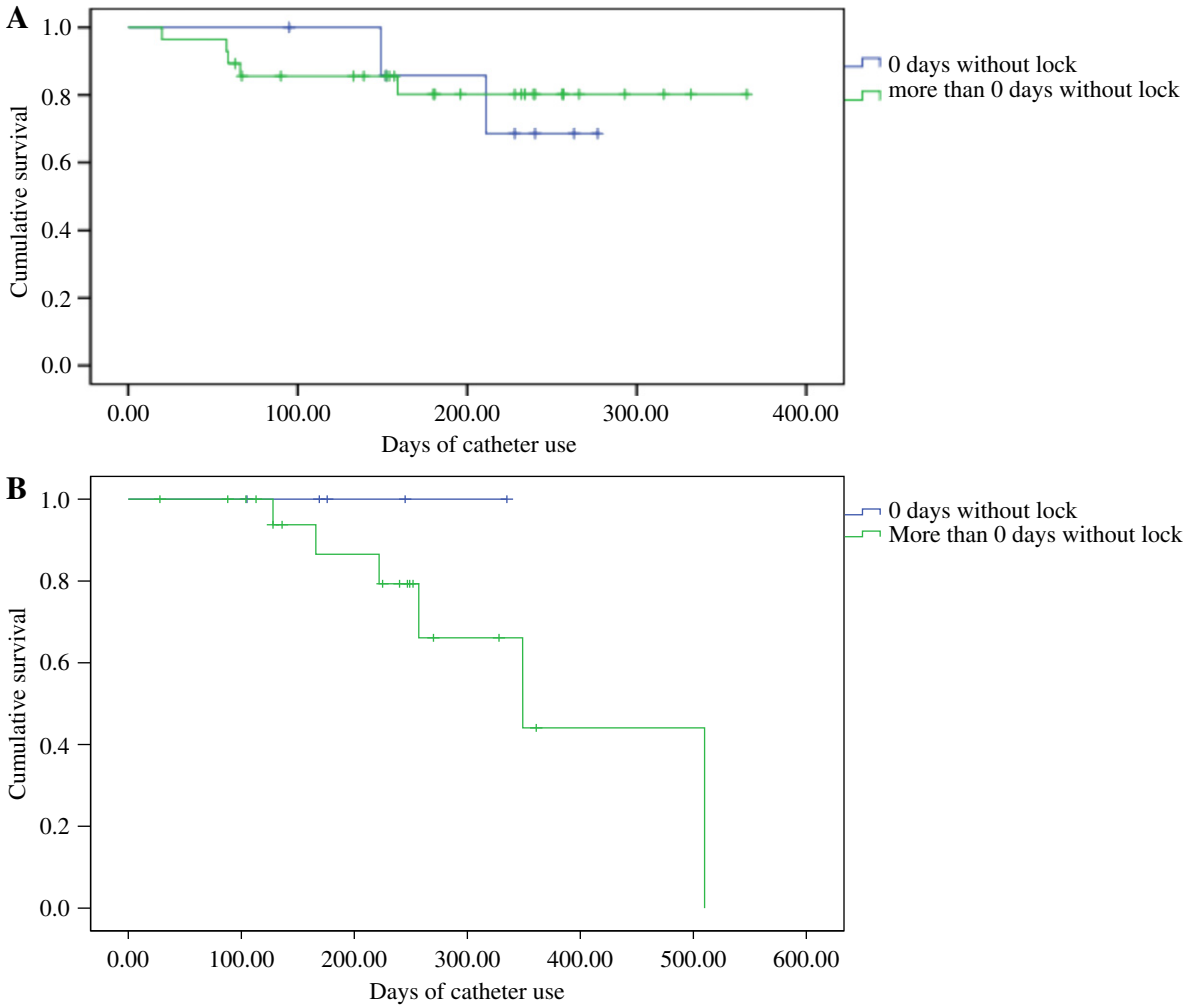

Figure 1. Colonization-free catheter survival: (A) heparin (group 1) or (B) taurolidine citrate (group 2) locking solution. Log rank test for group 2: not significant.

Side-effects

Seven patients with a mean age of 9.3 years in the taurolidine citrate group (20%) experienced side-effects that were unique to this group and attributed to the locking solution; three of these discontinued the study. Recorded symptoms were: discomfort in chest and neck (1), perioral dysaesthesia (1), abnormal taste sensations (2), nausea (2), and vomiting (1).

Discussion

In this first prospective randomized trial in paediatric patients undergoing chemotherapy or bone marrow transplantation, the use of taurolidine citrate lock solution was associated with significantly fewer primary BSI. The rate of BSI observed in the heparin lock group (1.3 per 1000 catheter-days) was similar to a previous report in paediatric patients and to the mean rate observed in adults with surgically implanted long term CVCs (1.6 per 1000 catheter-days).[7,9] If calculated for 1000 days of locking, the mean BSI rate was more than fourfold higher with the use of heparin lock in the present study.

There were similar rates of FUOs and thrombotic occlusions in both groups. These latter complications, however, may not be related to the use of a particular lock solution, but could be due to multiple other factors during the course of chemotherapy.

About 25% of removed catheters were colonized by bacteria, without a significant difference between lock solutions for both non-significant and significant colonization. Thus, taurolidine citrate had no effect on the primary outcome of this study. However, the duration of catheter use without lock solution was the only significant predictor of bacterial colonization. These data indicate that using a CVC for prolonged periods without locking results in time-dependent bacterial colonization, independent of the lock solution used. It is therefore apparent that no-lock use of catheters was a confounding variable in this study, preventing the detection of differences between lock solutions by affecting bacterial colonization. In catheters used immediately with lock solutions, no positive cultures were found in the taurolidine citrate group but two were found in the heparin group; thus, colonization-free catheter survival was longer in the taurolidine citrate group, but due to the small number of cases this difference did not reach statistical significance (Figure 1).

Biofilm formation is almost universal in long-term indwelling CVCs, and the risk of catheter-related BSI increases with duration of catheterization.[10,11] It is therefore of interest that in our study, the duration of no-lock use — but neither the time of catheter use nor the time of application of lock solutions — was associated with bacterial colonization. Thus, regular locking of catheters with effective lock solutions might be beneficial only if used from the time of insertion.

One limitation of this study is that many eligible patients refused participation. Further, only few catheters were immediately locked after implantation. Thus, the study was underpowered to detect significant differences between lock solutions in preventing bacterial colonization.

Side-effects were observed in a considerable percentage (20%) of patients. Uncommon taste sensation associated with taurolidine citrate lock have been previously described in paediatric patients — and are probably due to spillover of citrate from the catheter, resulting in a temporary drop in plasma calcium and magnesium concentrations.[6,12] There was no apparent explanation for the occurrence of the other observed side-effects. Further controlled studies are needed to evaluate the unique side-effects of taurolidine citrate, which could potentially limit the clinical use in children.

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Conflict of interest statement
None declared.

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