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The CATERPILLAR study: an assessor-blinded randomized controlled trial comparing a taurolidine–citrate–heparin lock solution to a heparin-only lock solution for the prevention of central-line-associated bloodstream infections in paediatric oncology patients

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SUMMARY

Background: Taurolidine–citrate(–heparin) lock solutions (TCHL) are suggested as a promising and safe method for the prevention of central-line-associated bloodstream infections (CLABSI).

Aim: To investigate the efficacy of TCHL for the prevention of CLABSI in paediatric oncology patients.

Methods: An assessor-blinded randomized controlled trial at the Princess Máxima Centre for paediatric oncology, the Netherlands, was performed from 2020 to 2023. Paediatric oncology patients receiving a tunnelled central venous access device (CVAD) were eligible. A total of 462 patients were required to compare the TCHL to the heparin-only lock (HL). Patients were followed-up for the first 90 days after CVAD insertion. The primary outcome was the incidence of the first CLABSI from CVAD insertion until the end of follow-up. Intention-to-treat and per-protocol analyses were performed.

Findings: In total, 232 were randomized in the HL and 231 in the TCHL group. A total of 47 CLABSIs were observed. The intention-to-treat analysis showed that a CLABSI was observed in 26 (11.2%) of the HL group patients versus 21 (9.1%) of the TCHL group patients; incidence rate ratio (IRR) of 0.81 (95% confidence interval (CI): 0.46–1.45) in favour of the TCHL group. The per-protocol analysis showed that a CLABSI was observed in

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10 (7.9%) of the HL group patients versus 6 (4.8%) of the TCHL group patients; IRR of 0.59 (95% CI: 0.21—1.62) in favour of the TCHL group. Adverse events were more common in the TCHL group but rarely reported.

Conclusion: No difference was detected between the TCHL and HL in the incidence of CLABSI in paediatric oncology patients.

Introduction

Tunnelled central venous access devices (CVAD) are fundamental in the treatment of paediatric oncology patients since they provide long-term venous access. The incidence of central-line-associated bloodstream infections (CLABSI) in this patient group is high [1]. CLABSI incidence rates of 0.1—2.3 per 1000 CVAD-days have previously been reported, mostly depending on the patient population, CVAD type and infection definitions used [2]. In our hospital, the Princess Máxima Centre for paediatric oncology, a CLABSI incidence rate of 1.51 per 1000 CVAD-days has been reported; at least one CLABSI was observed in 30% of the children receiving a CVAD [3]. CLABSI episodes often result in hospital admission, postponement of anticancer treatment, early CVAD removal (15% of all CVADs inserted), and can lead to severe sepsis requiring intensive care unit admission (5% of all patients receiving a CVAD) [3]. The quality of life of children with cancer is therefore highly impacted by these CLABSIs. Furthermore, these CLABSIs result in high healthcare costs [1,4].

Taurolidine—citrate(—heparin) lock solutions (TCHL) have been suggested as a safe and promising method to prevent CLABSIs due to their anticoagulant, antimicrobial, and antibiofilm properties [5,6]. Taurolidine is a more attractive choice as compared to other antimicrobials since no antimicrobial resistance has been reported [7]. Taurolidine damages the cell wall of bacteria, inhibits bacterial pathogenicity, and constrains bacterial surface adhesion [5,7—11]. The heparin-only lock (HL) is currently the standard of care lock solution for the prevention of malfunctions in the Netherlands for paediatric oncology patients, but the HL has no antimicrobial activity, and its use is barely supported by literature [5]. We performed a meta-analysis including all randomized controlled trials (RCT) comparing the efficacy of taurolidine containing lock solutions to heparin-, saline- and citrate-only locks in haemodialysis, total parenteral nutrition, and oncology patients. According to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach, a serious risk of bias and indirectness of evidence was present in these studies [12]. However, they did show a pooled incidence rate ratio of 0.30 (95% confidence interval (CI): 0.19—0.46) in favour of the taurolidine containing lock solutions [6]. Regarding paediatric oncology patients, only two open-labelled RCTs ($N \leq 112$) and four non-RCTs have been performed investigating taurolidine containing lock solutions with/without heparin and/or citrate [13—18]. These studies did not provide enough evidence for the direct implementation of TCHLs in paediatric oncology patients due to a high risk of bias and indirectness of evidence [6,13—18].

Therefore, this assessor-blinded RCT was designed. If the TCHL appears to be safe and effective for the prevention of CLABSI, the primary goal is to decrease the number of CLABSIs and thereby increase the quality of life for children with cancer by reducing the CVAD removal rate, dispensing of antibiotics, days of hospital admission, and incidence of severe sepsis resulting in intensive care unit admission.

Methods

The CATERPILLAR study protocol has been published by *BMJ Open* in 2023 (Supplementary File 1) [19]. Patients were randomized (1:1) in either the HL or TCHL group and followed up for a maximum study period of 90 days. The locks were given at the Princess Máxima Centre for paediatric oncology after each treatment cycle, with a maximum of once weekly. The lock solution of 0.8—1.5 mL per lumen depended on the CVAD type. The locks remained *in situ* until the CVAD was used again; lock duration thereby varied per patient and was registered during the study period. No amendments were made to the protocol since this publication. One extra patient was included since his/her informed consent came in after the pre-planned 462 patients were already included. The primary analyses were performed with the intention-to-treat (ITT) principle. Additionally, a per-protocol (PP) analysis was performed, excluding patients who were not included within one week after CVAD insertion, patients who never received the intervention and patients who missed three or more of the minimum number (once every three weeks) of locks during the follow-up period. The CONSORT 2010 checklist was completed (Supplementary File 2).

Results

Between October 2020 and August 2023 (34 months of inclusion), 1034 patients were screened for eligibility. In total, 571 (55%) patients did not meet the inclusion/exclusion criteria, declined to participate, or were not included for other reasons such as advice of the oncologist not to approach certain families due to clinical or psychological circumstances. The remaining 463 (45%) patients were included, after which the recruitment was stopped since the pre-determined sample size ($N = 462$) was reached. In total, 232 patients were randomized in the HL group and 231 in the TCHL group (Figure 1). No significant difference in baseline characteristics was observed between both groups (Table I). Patients were followed-up for a total number of 36,957 CVAD-days during which they received a total number of 2544 locks (68.8 locks per 1000 CVAD-days). Of all included patients, 12 (2.6%) prematurely discontinued the intervention and 451 (97.4%) patients reached an endpoint as defined by the study protocol, i.e. 90 days of follow-up ($N = 368$, 79.5%), CLABSI occurrence ($N = 47$, 10.2%), CVAD removal

due to non-CLABSI related reasons ($N = 25$, 5.4%), and a second CVAD insertion ($N = 10$, 2.2%). One patient died ($N = 1$, 0.2%). In total, 463 patients were included in the intention-to-treat analysis and 252 patients in the per-protocol analysis.

CLABSI-related outcomes

In total, 123 episodes of bacteraemia in 105 patients were assessed by a blinded expert panel; 47 (38.2%) CLABSIs and 76 (61.8%) non-CLABSIs were scored. Reasons why a non-CLABSI instead of a CLABSI episode was scored included: mucosal-barrier injury laboratory-confirmed bloodstream infection ($N = 11$, 8.9%), <2 blood cultures obtained ($N = 14$, 11.4%), contamination ($N = 44$, 35.8%), no symptoms ($N = 3$, 2.4%), and presence of another infection source ($N = 4$, 3.3%). The intention-to-treat analysis showed that a CLABSI was observed in 26 (11.2%) of the HL group patients versus 21 (9.1%) of the TCHL group patients; IRR of 0.81 (95% CI: 0.46–1.45), in favour of the TCHL group. The per-protocol analysis showed that a CLABSI was observed in 10 (7.9%) of the HL group patients versus six (4.8%) of the TCHL group patients; IRR of 0.59 (95% CI: 0.21–1.62) in favour of the TCHL group. No other secondary outcomes differed significantly between the HL and TCHL groups (Table II).

There was no statistically significant difference in the cumulative incidence of CLABSI between the HL and TCHL groups in both the ITT and PP analyses ($P = 0.65$ and $P = 0.13$, respectively) (Figure 2). Cause-specific hazard ratios (HR_{CS}) for CLABSI were equal to 0.82 (95% CI: 0.46–1.46) and 0.80 (95% CI: 0.32–2.02) for the ITT and PP analysis, respectively. Furthermore, the insertion of a totally implantable venous access port (TIVAP) compared to a tunnelled external CVAD appeared to be a protective factor for the development of a CLABSI in the ITT analysis and ITT landmark analysis at 28 days after CVAD insertion; HR_{CS} equal to 0.26 (95% CI: 0.13–0.49) and 0.30 (95% CI: 0.13–0.69), respectively. TPN was a significant risk factor in both the ITT and PP analysis respectively; 2.84 (95% CI: 1.17–6.92) and 4.47 (95% CI: 1.21–18.98). The total number of lock-days in the first 28 days after insertion did not appear to be a significant risk factor in both the ITT and PP landmark analyses (Table III). Subgroup analyses did not show a significant effect of the TCHL for certain groups based on diagnosis, CVAD type, and TPN administration (Supplementary Table S1). In the subgroup analyses where a clinical CVAD-related infection instead of a CLABSI, as reported by the three experts, was taken as an outcome, no significant effect of the TCHL was observed (Supplementary Table S2).

Among all CLABSI episodes, 19 (40.4%) were polymicrobial, 21 (44.7%) were caused by Gram-positive bacteria only, six (12.8%) by Gram-negative bacteria only, and one (2.1%) by a *Candida* sp. There was no evidence of a difference between the HL and TCHL group in micro-organisms cultured as described in Table IV.

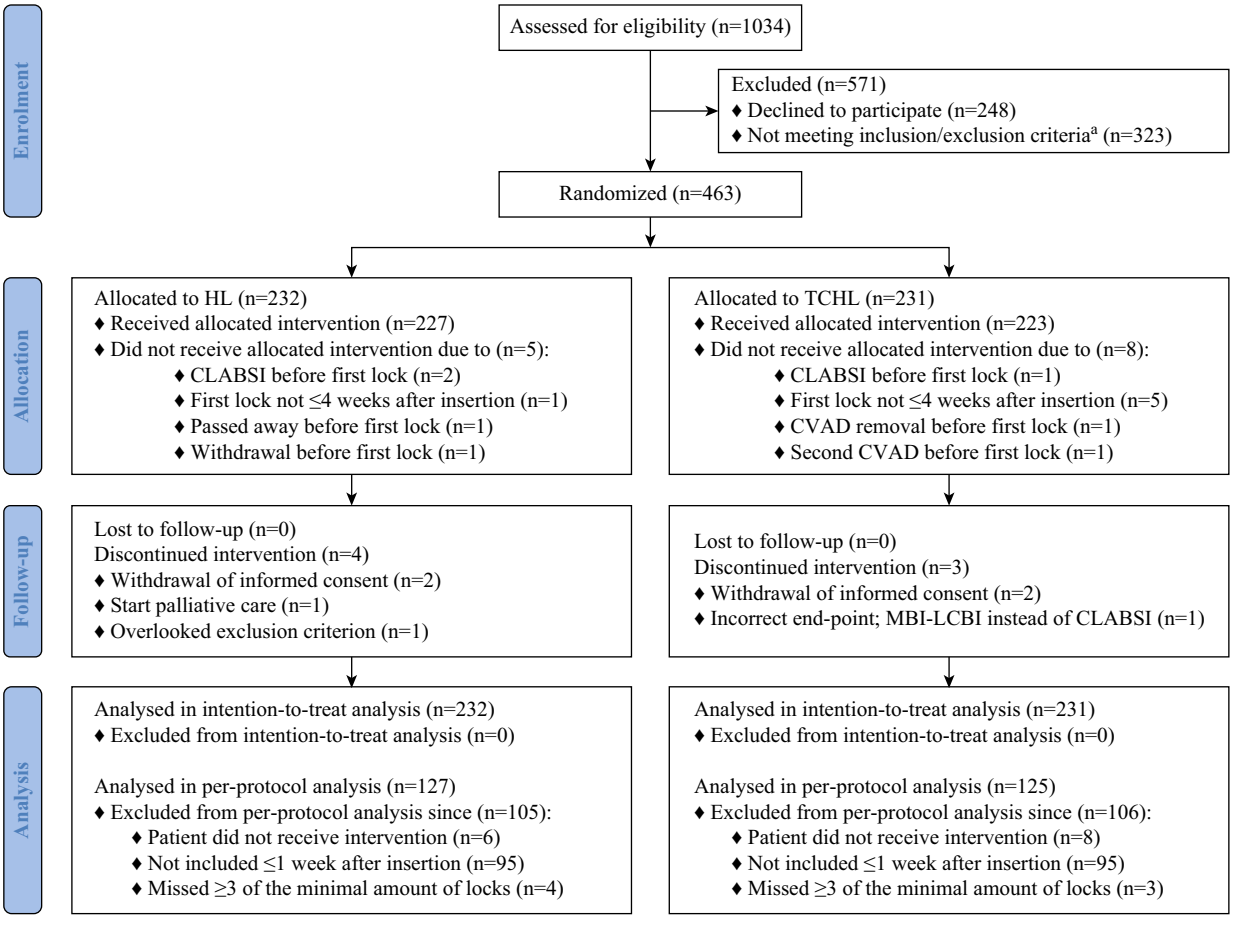

Figure 1. CONSORT 2010 flow chart. [a]Written informed consent was an inclusion criterion; however, these are counted under 'declined to participate'.

Table I
Baseline characteristics

Characteristics	HL group ($N = 232$)	TCHL group ($N = 231$)	Total ($N = 463$)	P-value[a]
Sex				
Male	134 (57.8%)	133 (57.6%)	267 (57.7%)	0.97
Female	98 (42.2%)	98 (42.4%)	196 (42.3%)	
Age (years) at inclusion, median (range)	8 (0–18)	8 (0–18)	8 (0–18)	0.94
Diagnosis				
Haemato-oncology	92 (39.7%)	94 (40.7%)	186 (40.2%)	0.34
Lymphoma	45 (19.4%)	34 (14.7%)	79 (17.1%)	
Neuro-oncology	23 (9.9%)	33 (14.3%)	56 (12.1%)	
Solid tumour	72 (31.0%)	70 (30.3%)	142 (30.7%)	
CVAD type				
Tunnelled external	36 (15.5%)	36 (15.6%)	72 (15.6%)	1.00
TIVAP	196 (84.5%)	195 (84.4%)	391 (84.4%)	
Small	8 (4.1%)	7 (3.6%)	15 (3.8%)	0.97
Medium	155 (79.1%)	155 (79.5%)	310 (79.3%)	
Large	33 (16.8%)	33 (16.9%)	66 (16.9%)	
CVAD-days, sum, median (range)	18,559, 90 (11–90)	18,398, 90 (3–90)	36,957, 90 (3–90)	0.94
Insertion method				
Ultrasound-guided	224 (96.6%)	225 (97.4%)	449 (97.0%)	0.26
Landmark-based	4 (1.7%)	2 (0.9%)	6 (1.3%)	
Open	0	2 (0.9%)	2 (0.4%)	
Missing	4 (1.7%)	2 (0.9%)	6 (1.3%)	
Lumen number				
Single	200 (86.2%)	196 (84.8%)	396 (85.5%)	0.09
Double	28 (12.1%)	35 (15.2%)	63 (13.6%)	
Triple	4 (1.7%)	0	4 (0.9%)	
Insertion vein				
Right subclavian	3 (1.3%)	5 (2.2%)	8 (1.7%)	0.73
Left subclavian	10 (4.3%)	14 (6.1%)	24 (5.2%)	
Right jugular	213 (91.8%)	203 (87.9%)	416 (89.8%)	
Left jugular	3 (1.3%)	5 (2.2%)	8 (1.7%)	
Right brachiocephalic	1 (0.4%)	0	1 (0.2%)	
Left brachiocephalic	2 (0.9%)	3 (1.3%)	5 (1.1%)	
Missing	0	1 (0.4%)	1 (0.2%)	
Complicated insertion				
No	222 (95.7%)	222 (96.1%)	444 (95.9%)	0.60
Yes	8 (3.4%)	6 (2.6%)	14 (3.0%)	
Missing	2 (0.8%)	3 (1.3%)	5 (1.1%)	
SAP[b] during study				
No	78 (33.6%)	88 (38.1%)	166 (35.9%)	0.32
Yes	154 (66.4%)	143 (61.9%)	297 (64.1%)	
IVIG during study				
No	229 (98.7%)	229 (99.1%)	458 (98.9%)	0.66
Yes	3 (1.3%)	2 (0.9%)	5 (1.1%)	
TPN during study				
No	216 (93.1%)	217 (93.9%)	433 (93.5%)	0.72
Yes	16 (6.9%)	14 (6.1%)	30 (6.5%)	
Locks given[c]: sum, median (range)	1264, 6 (0–12)	1280, 6 (0–11)	2544, 6 (0–12)	0.60
Lock days[d]: sum, median (range)	6742, 29 (0–110)	7035, 30 (0–94)	13,777, 29 (0–110)	0.30
Endpoint				
CLABSI	26 (11.2%)	21 (9.1%)	47 (10.2%)	0.74
90 days follow-up	186 (80.2%)	182 (78.8%)	368 (79.5%)	
CVAD removal (non-CLABSI related)	11 (4.7%)	14 (6.1%)	25 (5.4%)	

(*continued on next page*)

Table I (*continued*)

Characteristics	HL group ($N = 232$)	TCHL group ($N = 231$)	Total ($N = 463$)	*P*-value[a]
Second CVAD or artery line	4 (1.7%)	6 (2.6%)	10 (2.2%)	
Withdrawal[d]	1 (0.4%)	2 (0.9%)	3 (0.6%)	
Passed away	1 (0.4%)	0	1 (0.2%)	
Other[e]	3 (1.3%)	6 (2.6%)	9 (1.9%)	

HL, heparin lock; TCHL, taurolidine–citrate–heparin lock; CVAD, central venous access device; TIVAP, totally implantable venous access port; SAP, systemic antibiotic/antifungal prophylaxis; IVIG, intravenous immunoglobulin; TPN, total parenteral nutrition; Fr, French; CI, confidence interval.

[a] χ^2-Test or Mann–Whitney *U*-test, depending on the variable.

[b] SAP such as ciprofloxacin, trimethoprim/sulfamethoxazole, itraconazole, and micafungin.

[c] Fourteen (3.0%) patients never received a lock, six (42.9%) in the HL group and eight (57.1%) in the TCHL group ($P = 0.58$). For a total of 21 (4.5%) patients the total number of lock-days was missing since the removal date of one or more locks was missing, nine (42.9%) in the HL group and 12 (57.1%) in the TCHL group ($P = 0.50$).

[d] Withdrawal occurred in two cases due to adverse effects (TCHL group) and in one case due to unrest of the parents (HL group).

[e] Other reasons were: first lock instillation not possible within four weeks after CVAD insertion ($N = 6$), start palliative treatment ($N = 1$), screen failure ($N = 1$), incorrect diagnosis of CLABSI by the expert panel which incorrectly ended the follow-up ($N = 1$).

Furthermore, the days from CVAD insertion until CLABSI, the occurrence and severity of neutropenia during CLABSI, non-CLABSI related reasons, and CLABSI-related hospital and PICU admission days did not significantly differ between the HL and TCHL groups (Supplementary Table S3).

Local infections and thrombosis

In total, 63 local CVAD infection episodes with ($N = 17$) or without ($N = 46$) a positive exit-site culture were observed in 54 (11.7%) patients: 33 episodes in the HL group and 30 in the TCHL group (IRR: 0.92; 95% CI: 0.56–1.50). Six local infection episodes with a positive exit-site culture were observed in six (1.3%) patients, four episodes in the HL group and two episodes in the TCHL group (IRR: 0.50; 95% CI: 0.09–2.75). CVAD removal due to a local infection episode was necessary after eight (12.7%) of the 63 episodes, two episodes in the HL group and six in the TCHL group (IRR: 3.03; 95% CI: 0.61–15.00). In addition, during follow-up eight (1.7%) patients developed a CVAD-related central venous thrombosis (CVT), five (2.2%) patients in the HL group and three (1.3%) patients in the TCHL group (IRR: 0.61, 95% CI: 0.14–2.53). No CVADs were removed due to these CVT episodes.

Adverse events

In total, 2544 locks were instilled (1264 in the HL group and 1280 in the TCHL group). A malfunction, i.e. the inability to flush and/or aspirate the lock, during removal was observed in 54 (4.3%) and 50 (3.9%) of the HL and TCHL instillations ($P = 0.61$), respectively. In total, one (0.1%) adverse event was reported in the HL group, graded as common terminology criteria for adverse events (CTCAE) grade I. In the TCHL group 17 (1.3%) adverse events were reported during instillation, which was significantly more compared to the HL group ($P < 0.01$), and one (0.1%) adverse event was reported during lock removal. The adverse events in the TCHL group were graded following the CTCAE as grade I ($N = 15$), grade II ($N = 2$), and grade III ($N = 1$). All adverse events were observed in different patients and all of them were known side-effects. Two SAEs, one in the HL group and one in the TCHL group, were both reported to have a possible but unlikely relationship to the lock instillation, i.e. a lung embolism (Table V).

Discussion

No difference was detected between the TCHL and HL for all primary and secondary outcomes in our paediatric oncology population. Adverse events were reported more frequently in the TCHL group but were rare and mostly graded as mild. During this study, we did not identify subgroups based on diagnosis, CVAD type and TPN administration that would benefit significantly from the TCHL. The TCHL, however, might still appear to be beneficial if administered more frequently, for specific patient groups (e.g. for patients with a history of multiple CLABSIs or patients receiving TPN), or for CVAD salvage during a CLABSI in larger randomized controlled trials.

Strengths of the study are the large sample size ($N = 463$) as compared to the previously published literature in haemodialysis, total parenteral nutrition and oncology populations (14 RCTs, number per RCT $\leq$164), the inclusion of a homogeneous group (i.e. only children with a tunnelled CVAD), the assessor-blinded design using three experts, the strict use of the CLABSI criteria of the Centres for Disease Control and Prevention and that stratification was performed based on CVAD type and diagnosis [6,20].

Limitations of the study are the frequency in which locks were given as compared to other studies and/or the delay in the timing of the first lock instillation. A higher lock frequency and earlier first lock instillation might have resulted in a larger effect size. The causes for these limitations were (1) partially paediatric oncology specific, i.e. frequent and long hospital admissions as compared to other patient groups due to which fewer locks could be given and due to which, in some cases, the first lock was given one to three weeks after CVAD insertion, but are (2) presumably also caused by study-design-related factors, i.e. maximum lock frequency of once a week, lock instillation not in shared care centres, and signed informed consent required causing a delay in the timing of the first lock instillation. The per-protocol analysis, partially tackling these causes, did show a larger effect size, but the effect size was still not significant, and the number of patients included was much smaller ($N = 252$) than initially hypothesized. Also, in the per-protocol analysis, many high-risk patients (i.e. the patients receiving fewer locks due to frequent and long hospital admissions due to their severe immunocompromised state) were excluded, resulting in a lower CLABSI incidence rate in the control group than initially hypothesized. The multivariate analysis did not show a significant association

Table II
CLABSI-related outcomes for intention-to-treat ($N = 463$) and per-protocol analysis ($N = 252$)

Variable	Intention-to-treat analysis					Per-protocol analysis				
	HL group ($N = 232$, 18,559 CVAD-days)		TCHL group ($N = 231$, 18,398 CVAD-days)			HL group ($N = 127$, 10,279 CVAD-days)		TCHL group ($N = 125$, 10,502 CVAD-days)		
	No. (%) of patients	IR per 1000 CVAD-days	No. (%) of patients	IR per 1000 CVAD-days	IRR (95% CI)	No. (%) of patients	IR per 1000 CVAD-days	No. (%) of patients	IR per 1000 CVAD-days	IRR (95% CI)
CLABSI	26 (11.2%)	1.40	21 (9.1%)	1.14	0.81 (0.46–1.45)	10 (7.9%)	0.97	6 (4.8%)	0.57	0.59 (0.21–1.62)
Common commensal CLABSI[a]	11 (4.7%)	0.59	8 (3.5%)	0.43	0.73 (0.30–1.82)	4 (3.1%)	0.39	4 (3.2%)	0.38	0.98 (0.24–3.91)
Recognized pathogen CLABSI[a]	15 (6.5%)	0.81	13 (5.6%)	0.71	0.87 (0.42–1.84)	6 (4.7%)	0.58	2 (1.6%)	0.19	0.33 (0.07–1.62)
CLABSI-related hospital admission	25 10.8%)	1.35	18 (7.8%)	0.98	0.73 (0.40–1.33)	9 (7.1%)	0.88	5 (4.0%)	0.48	0.54 (0.18–1.62)
CLABSI-related removal	8 (3.4%)	0.43	8 (3.5%)	0.43	1.01 (0.38–2.69)	2 (1.6%)	0.19	3 (2.4%)	0.29	1.47 (0.25–8.79)
CLABSI-related PICU admission	3 (1.3%)	0.16	1 (0.4%)	0.05	0.34 (0.03–3.23)	0	0	0	0	NA
CLABSI-related death	0	0	0	0	NA	0	0	0	0	NA

HL, heparin lock; TCHL, taurolidine–citrate–heparin lock; CLABSI, central-line-associated bloodstream infection; CVAD, central venous access device; IR, incidence rate; IRR, incidence rate ratio; NA, not applicable.
[a] Common commensals are micro-organisms included in the National Healthcare Safety Network common commensal list (https://www.cdc.gov/nhsn/pdfs/validation/2019/2019-NHSN-Organisms-List-Validation.xlsx); recognized pathogens are micro-organisms not included in this list. If a common commensal and recognized pathogen are cultured, the CLABSI is scored as a recognized pathogen CLABSI.

between the number of lock-days and the risk of a CLABSI, suggesting that increasing the number of lock-days would probably not substantially improve the effect size to such an extent that the TCHL would reach an acceptable number needed to treat and/or be cost-effective.

Some concerns about the risk of bias due to deviations from the intended intervention might arise since patients, caregivers, and healthcare professionals were not blinded; e.g. withdrawal of informed consent due to TCHL-related adverse events. Furthermore, some concerns might arise about a risk of bias due to measurement of the outcome since the patients, caregivers, and healthcare professionals treating the patients were not blinded, which could have influenced the outcomes, e.g. clinical interpretation of symptoms, barrier for blood culture testing, or reporting of side-effects.

Compared to the previously performed RCTs, this study provided more accurate results due to the largest number of patients [6]. The effect size observed is smaller than the one used for computing the sample size, i.e. CLABSI reduction of 11.2%–9.1% instead of the initially expected reduction from 12.8% to 5.0%. As described above, this might have been caused by the lock frequency and/or the timing of the first lock instillation. The observed reduction requires a sample size of 3246 patients with 80% power, which is very challenging and time-consuming in the paediatric oncology population.

In our opinion, the results of this study are generalizable for paediatric oncology institutes with comparable CLABSI incidence rates. However, it is possible that a benefit of the TCHL might be observed in institutes and subgroups with a higher risk of CLABSI. Within the paediatric oncology population, we did not identify subgroups that would benefit from the TCHL specifically (e.g. patients at a higher risk of CLABSI such as patients diagnosed with a haemato-oncologic disease, with a tunnelled external CVAD, or receiving TPN). Furthermore, we do not know if the results of this study are generalizable to other patient populations with CVAD such as adult oncology patients, and patients receiving haemodialysis or total parenteral nutrition. These populations differ in terms of the CLABSI incidence (i.e. different risk factors such as: CVAD type, neutropenia, home treatment), CLABSI contamination routes, and lock frequency (i.e. the CVAD of paediatric oncology patients is generally locked less frequently) [6]. Additionally, other taurolidine lock solutions with various compositions exist (with/without citrate and/or heparin). The results might therefore not be generalizable for other taurolidine lock solutions. The standard of care lock in the Netherlands is the heparin lock; therefore, during this study, a taurolidine lock solution containing heparin was chosen as the investigation lock.

Handrup *et al.* ($N = 112$) and Dümichen *et al.* ($N = 71$) both performed comparable RCTs in the paediatric oncology population and described IRRs of 0.26 (95% CI: 0.09–0.61) and 0.24 (95% CI: 0.05–1.13) in favour of the taurolidine containing locks, respectively [13,14]. These authors included much smaller samples of patients and designed the trials as open-labelled, introducing bias. The high heterogeneity between the studies might be explained by the high number of haematology patients and patients with an external tunnelled CVAD, other definitions used to diagnose a bloodstream infection as CVAD-related, and frequency of lock instillations in the previously performed studies.

The TCHL might still appear to be beneficial if administered more frequently in the paediatric oncology population, for

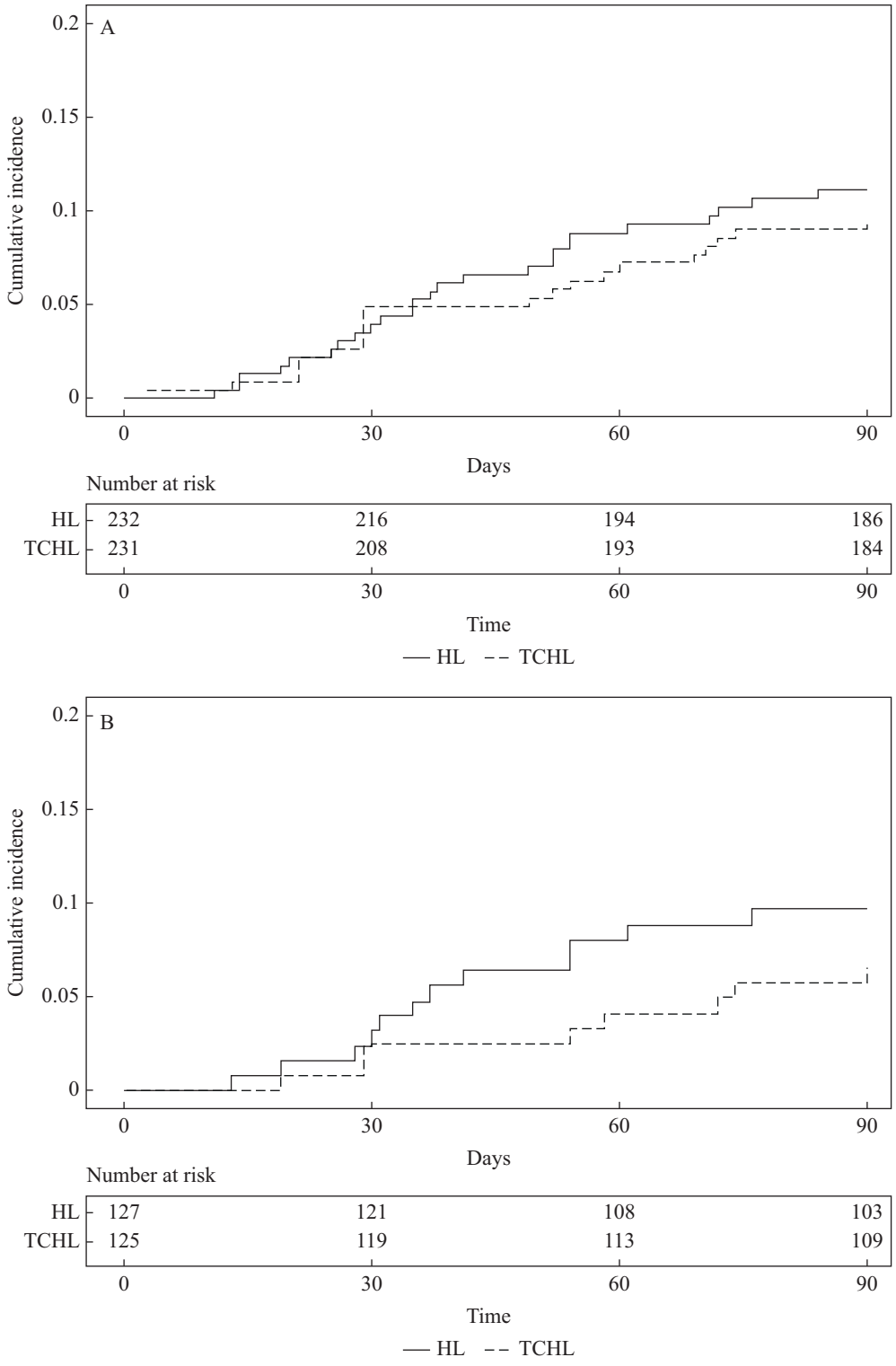

Figure 2. Competing risk analyses for central-line-associated bloodstream infection: (A) intention-to-treat analysis ($P = 0.65$), (B) per-protocol analysis ($P = 0.13$). HL, heparin lock; TCHL, taurolidine—citrate—heparin lock.

specific patient groups (e.g. for patients with a history of multiple CLABSIs or patients receiving TPN), or for CVAD salvage during a CLABSI in larger randomized controlled trials. Future research should be performed to evaluate this.

In conclusion, no difference was detected between the TCHL and HL for all primary and secondary outcomes in paediatric oncology patients. Adverse events were reported more frequently in the TCHL group but were rare and mostly graded as mild. This quality of evidence provided by this study is high, due to the assessor-blinded randomized design, stratification for two important risk factors during randomization, large patient cohort, strict use of the CLABSI criteria, and

Table III
Multivariable Cox-regression analysis: CLABSI[a]

Risk factor	Intention-to-treat analysis ($N = 463$)	Intention-to-treat landmark (28 days) analysis ($N = 435$)	Per-protocol analysis ($N = 252$)	Per-protocol landmark (28 days) analysis ($N = 243$)
Randomization group	1	1	1	1
HL				
TCHL	0.82 (0.46–1.46)	0.95 (0.46–1.95)	0.80 (0.32–2.02)	1.21 (0.41–3.37)
Diagnosis				
Haemato-oncology	1	1	1	1
Other	0.59 (0.33–1.06)	0.71 (0.34–1.50)	0.63 (0.25–1.61)	0.82 (0.26–2.62)
CVAD type				
Tunnelled external	1	1	1	1
TIVAP	0.26 (0.13–0.49)*	0.30 (0.13–0.69)*	0.40 (0.14–1.14)	0.32 (0.09–1.13)
TPN				
No	1	1	1	1
Yes	2.84 (1.17–6.92)*	2.43 (0.83–7.11)	4.47 (1.21–18.98)*	4.38 (0.98–19.24)
Lock days in first 28 days after insertion	NA	0.95 (0.88–1.02)	NA	0.95 (0.86–1.05)

HL, heparin lock; TCHL, taurolidine-citrate-heparin lock; CLABSI, central-line-associated bloodstream infection; CVAD, central venous access port; TIVAP, totally implantable venous access port; TPN, total parenteral nutrition; CI, confidence interval.
TPN is used in the model as a time-dependent covariate.
*Significant values ($P \leq 0.05$).
[a] Cox specific hazard ratio (95% confidence interval).

Table IV
Micro-organisms cultured during CLABSI

Micro-organism	HL group (CLABSI: 26; 18,559 CVAD-days)	TCHL group (CLABSI: 21; 18,398 CVAD-days)	Total (CLABSI: 47)	IRR (95% CI)
Gram-positive	13 (50.0%)	8 (38.1%)	21 (44.7%)	0.62 (0.26–1.50)
Coagulase-negative staphylococci[a]	7 (26.9%)	5 (23.8%)	12 (25.5%)	0.72 (0.23–2.27)
Staphylococcus aureus	3 (11.5%)	2 (9.5%)	5 (10.6%)	0.67 (0.11–4.02)
Viridans streptococci	0	0	0	Undefined
Streptococcus pneumoniae	0	0	0	Undefined
Enterococci	0	0	0	Undefined
Other Gram-positive[b]	3 (11.5%)	1 (4.8%)	4 (8.5%)	0.34 (0.03–3.23)
Gram-negative	3 (11.5%)	3 (14.3%)	6 (12.8%)	1.01 (0.20–5.00)
Enterobacterales[c]	1 (3.8%)	0	1 (2.1%)	Undefined
Other Gram-negative[d]	2 (7.7%)	3 (14.3%)	5 (10.6%)	1.51 (0.25–9.06)
Fungi	1 (3.8%)	0	1 (2.1%)	Undefined
Candida spp.[e]	1 (3.8%)	0	1 (2.1%)	Undefined
Polymicrobial[f]	9 (34.6%)	10(47.6%)	19 (40.4%)	1.12 (0.46–2.76)
Gram-positive polymicrobial	3 (11.5%)	1(4.8%)	4 (8.5%)	0.34 (0.03–3.23)
Gram-negative polymicrobial	1 (3.8%	0	1 (2.1%	Undefined
Mixed polymicrobial	5 (19.2%)	9 (42.9%)	11 (23.4%)	1.82 (0.61–5.42)

CLABSI, central-line-associated bloodstream infection; HL, heparin lock; TCHL, taurolidine–citrate–heparin lock; IRR, indicence rate ratio; CI, confidence interval.
[a] *S. epidermidis* (9), *S. haemolyticus* (1), *S. hominis* (1), *S. condimenti* and *S. hominis* (1).
[b] *Micrococcus luteus* (2), *Pediococcus pentasaceus* (1), *Peptoniphilus* spp. (1).
[c] *E. coli* (1).
[d] *Paracoccus yeei* (2), *Pseudomonas aeruginosa* (1), *Acinetobacter ursingii* (1), *Stenotrophomonas maltophilia* (1).
[e] *Candida parapsilosis* (1).
[f] *S. epidermidis*, *Moraxella osloensis*, and *S. hominis* (2), *S. oralis*, *Paracoccus yeei* and *Micrococcus* spp. (1), *Micrococcus luteus*, *S. hominis*, and *S. epidermidis* (1), *E. coli* and *S. epidermidis* (2), *E. coli*, *Granulicatella adiacens* and *S. epidermidis* (1), *Enterobacter cloacae*, *C. freundii*, *Klebsiella pneumoniae* (1), *Delftia acidovorans* and *S. hominis* (1), *Pseudomonas aeruginosa* and *S. mitis* (1), *Micrococcus luteus* and *S. hominis* (1), *S. epidermidis* and *Acinetobacter baumannii* (1), *S. salivarius* and *S. epidermidis* (1), *Micrococcus luteus* and *Moraxella osloensis* (1), *S. mitis*, *Granulicatella adiacens*, *Moraxella osloensis* (1), *S. hominis* and *Micrococcus luteus* (1), *Rothia mucilaginosa*, *S. hominis*, *Paracoccus yeei* (1), *S. capitis* and *Moraxella osloensis* (1), *Pseudomonas luteola* and *S. epidermidis* (1).

Table V
Malfunctions and adverse events

Malfunction/events	HL group (locks: 1264; patients: 232)			TL group (locks: 1280; patients: 231)			*P*-value[a]
	No. of events	% of locks given	No. (%) of patients	No. of events	% of locks given	No. (%) of patients	
Malfunction during lock removal[b]	54	4.3%	42 (18.1%)	50	3.9%	36 (15.6%)	0.61
Adverse events[c]							
Lock instillation	1	0.1%	1 (0.4%)	17	1.3%	17 (7.4%)	<0.01
Lock removal	0	0	0	1	0.1%	1 (0.4%)	0.33
Serious adverse events[d]	1	0.1%	1 (0.4%)	1	0.1%	1 (0.4%)	1.00

HL, heparin lock; TCHL, taurolidine—citrate—heparin lock.
[a] χ^2-Test.
[b] The inability to flush and/or aspirate the lock during study lock removal.
[c] Adverse events reported: oral dysgeusia ($N = 2$), oral dysaesthesia ($N = 2$), allergic reaction ($N = 1$), swelling of the eyelids ($N = 1$), redness ($N = 1$), chest pain ($N = 1$), rash under TIVAP ($N = 1$), pain ($N = 2$), burning sensation ($N = 1$), vasovagal reaction ($N = 1$), tingling sensation on the skin ($N = 1$), agitation/restless ($N = 1$), nausea ($N = 2$), and vomiting ($N = 2$). CTCAE grade I ($N = 16$), grade II ($N = 2$), grade III ($N = 1$).
[d] Serious adverse event reported with a possible relationship to the lock instillation: lung emboli ($N = 2$).

inclusion of a relatively homogeneous patient group. The TCHL might still appear to be beneficial if administered more frequently in the paediatric oncology population, for specific patient groups (e.g. for patients with a history of multiple CLABSIs or patients receiving TPN), or for CVAD salvage during a CLABSI in larger randomized controlled trials. Future research should be performed to evaluate this.

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Conflict of interest statement

TauroPharm and Cablon Medical supplied the TCHLs for this study. The authors declare no other conflicts of interest.

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Data availability

Data will be made available upon reasonable request to the corresponding author.

Ethics statement

The medical ethics committee NedMec, Utrecht, the Netherlands, has approved this research (number 20/370). Written informed consent for participation in this trial and publication of the trial data was obtained from all patients and/or their parents/guardians. Trial registration number: ClinicalTrials.gov NCT05740150.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2024.06.009.

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