



Short report

Effects of prophylactic use of taurolidine-citrate lock on the number of catheter-related infections in children under 2 years of age undergoing surgery

M. Łyszkowska*, G. Kowalewski, M. Szymczak, D. Polnik, A. Mikołajczyk, P. Kaliciński

Department of Paediatric Surgery and Organ Transplantation, Children's Memorial Health Institute, Warsaw, Poland

ARTICLE INFO

Article history:

Received 25 January 2019

Accepted 26 April 2019

Available online 2 May 2019

Keywords:

Central venous catheter
Catheter-related infection
Septicaemia
Parenteral nutrition
Taurolidine-citrate lock
Children



SUMMARY

Central venous access poses a risk for the development of catheter-related infections (CRIs). The aim of this study was to evaluate prophylactic use of taurolidine-citrate (T-C) solution on the number of CRIs. Ninety-seven catheters, used in 86 children, were divided at random into two groups: Group T(-) ($N=49$) underwent standard aseptic procedures, and Group T(+) ($N=48$) received additional filling of the lines with T-C solution during intervals in cycles of parenteral nutrition or drug supply. Sixteen CRIs occurred in Group T(-) and one CRI occurred in Group T(+); this difference was significant ($P<0.05$). Use of T-C appears to be a safe and effective method for the prevention of CRIs.

© 2019 The Healthcare Infection Society. Published by Elsevier Ltd. All rights reserved.

Introduction

Central venous catheters (CVCs) are associated with increased risk of bloodstream infection [1]. The main source of infection is micro-organisms on the skin of medical personnel using CVCs for therapeutic procedures [1]. Another source of infection is colonization of the patient's skin in the area of the external CVC output, as well as infection of fluids during their preparation [1]. Infection is one of the most commonly

described complications in patients treated using CVCs. It occurs regardless of underlying disease, treatment or age of the patient. Direct insertion into the central veins, peripherally inserted central catheters (PICC) and implantable venous ports have a similar risk of catheter-related infections (CRIs). Staphylococci are the most common cause of CRIs [1]. The long dwell time of the CVC is another factor increasing the risk of infection [2]. Many authors have reported a reduction in the number of bacterial [3,4] and fungal [5] CRIs after the use of taurolidine lock in the catheter lumen, but there is no general agreement on the efficacy of this intervention.

Taurolidine-citrate (T-C) is a chemically modified antimicrobial amino acid (taurine). No antimicrobial resistance to T-C has been found to date. The prophylactic use of T-C stems

* Corresponding author. Address: Department of Paediatric Surgery and Organ Transplantation, Children's Memorial Health Institute, 04-736 Warsaw, Aleja Dzieci Polskich 20, Poland. Tel.: +48 22 8151431.

E-mail address: mlyszkowska@interia.pl (M. Łyszkowska).

from its broad antibacterial spectrum, which includes both Gram-positive and -negative bacteria, including antibiotic-resistant strains such as methicillin-resistant *Staphylococcus aureus* and coagulase-staphylococci and vancomycin-resistant enterococci [1]. T-C has rarely been reported to be toxic. Single reports of transient adverse reactions concerned less than 8% of patients receiving this product [4]. Hypertransaminasaemia has been described in in-vitro and in-vivo studies conducted in rats treated with very high doses of T-C. T-C has also been found to prevent thrombotic complications by affecting the complement system and fibrinolysis [6].

The primary objective of the study was to assess the influence of 4% T-C solution on the number of CRIs in children aged <2 years undergoing surgery. The secondary objective was to assess the safety and tolerability of T-C.

Methods

This randomized, prospective, observational cohort study was conducted for 44 months.

Inclusion criteria were: written informed consent by parents/guardians for child's participation in the study; age of child <2 years; surgical treatment with observation; and CVC inserted in perioperative period.

Exclusion criteria were: lack of consent for the child's participation in the study; age of child >2 years; no indications for surgical treatment; and CVC implantation.

The analysis covered 97 CVCs implanted in 86 children hospitalized in the Department of Paediatric Surgery and Organ Transplantation at the Children's Memorial Health Institute. Based on randomization, the CVCs were assigned to two groups: 49 CVCs were in Group T(-) and 48 CVCs were in Group T(+). The care of all central lines included standard aseptic procedures. Additionally, in Group T(+), the lines were filled with manufactured T-C solution (2 mL) during intervals in the cycles of parenteral nutrition (PN) or intravenous drug supply for at least 2 h/day. According to the manufacturer's description, most microbes are killed by T-C solution within 2 h of application. T-C lock was used until the removal of the CVC due to its infection, lack of indications for its maintenance, or the patient's discharge from hospital with a tunnelled CVC for PN at home.

CRI was suspected in the case of deterioration of the patient's condition, an increase or decrease in the number of white blood cells, thrombocytopenia, anaemia and exclusion of other sources of infection. A positive blood culture result confirmed CRI. CVC colonization was diagnosed by a positive microbiological culture of the catheter tip after withdrawal in the absence of clinical and laboratory signs of infection.

The average cost of T-C administration in Group T(+) and the average cost of treatment of patients with CRI were taken into consideration for this comparison. Direct costs of treatment associated with CRI included: extended hospital stay; use of drugs resulting from CRI; catheter removal/replacement; general anaesthesia; and laboratory and microbiological tests. The cost of a single T-C solution application, using pre-prepared, manufactured product, was €18.5.

The Bioethical Commission of the Children's Memorial Health Institute approved this study (No. 110/KBE/2013).

Table 1

Comparison of the number of complications related to central venous access (infections, colonizations, thrombosis) between Groups T(-) and T(+)

Complications	Group T(-) N=49	Group T(+) N=48	P-values
Number of catheter-related infections	14	1	<0.05
Catheter infection rate (number of infections/1000 catheter-days)	14.3	1.06	<0.05
Number of catheter colonizations	2	0	NS
Catheter colonization rate (number of colonizations/1000 catheter-days)	2.05	0	NS
Urgent catheter removal due to infection	11	1	<0.05
Number of catheter-related thromboses	1	1	NS
Thrombosis rate (number of thromboses/1000 catheter-days)	1.02	1.06	NS

NS, not significant.

The Mann–Whitney test was used to compare dependent variables, and Chi-squared test was used to compare independent variables. Odds ratios were calculated using the logistics regression module. $P < 0.05$ was considered to indicate statistical significance.

Results

The age of children ranged from 1 to 586 days. Neonates, infants (<1 year) and children aged 12–19 months accounted for 45.4% ($N=39$), 48.8% ($N=42$) and 5.8% ($N=5$) of the study population, respectively. The most common indications for surgery were congenital defects of the abdominal wall ($N=20$; 23.3%), necrotizing enterocolitis ($N=17$; 19.8%) and congenital stenosis or atresia of the small intestine ($N=13$; 15.1%).

All children received antibiotics as standard perioperative prophylaxis or for treatment of co-existing bacterial infection.

The CVCs were inserted mainly through the internal jugular vein ($N=68$; 70.1%), and less frequently through the femoral vein ($N=24$; 24.7%). Other accesses were used occasionally: through the subclavian vein ($N=2$; 2.1%) or PICC via the basilica vein ($N=3$; 3.1%). Most catheters were short term and non-tunnelled ($N=81$; 83.5%). The remaining catheters were tunnelled Broviac accesses ($N=16$; 16.5%), mainly provided to children requiring long-term PN. Random selection of central lines for particular groups resulted in a significantly higher number of tunnelled CVCs of Broviac type in Group T(+) compared with Group T(-) (13 vs 4; $P < 0.05$.)

CVCs were used mainly for PN, and were also used periodically for the supply of drugs and blood products ($N=95$; 97.9%). Only two catheters (2.1%) were used exclusively for drug supply.

During observation in Group T(+), T-C was locked in the CVC lumen from 2 to 24 h/day (median 5 h) for a period of 1–18 days (median 6 days). No adverse reactions resulting from T-C use were found.

The dwell time of the central catheter in the vein was comparable in both groups: 5–62 days in Group T(-) (median 19.9 days) and 3–86 days (median 19.9 days) in Group T(+).

Table II
Aetiology of catheter-related infections and catheter colonizations in Groups T(-) and T(+).

Aetiology of infections	Group T(-) N=49	Group T(+) N=48
Catheter-related infections	14	1
Coagulase-negative staphylococci	8	1
<i>Staphylococcus aureus</i>	3	0
<i>Klebsiella pneumoniae</i>	1	0
<i>Escherichia coli</i> and <i>Enterococcus faecalis</i>	1	0
False-negative result	1	0
Catheter colonizations	2	0
Coagulase-negative staphylococci	2	0
Total bacterial complications related to central venous line	16	1

The total number of days of observation of all catheters was 976 in Group T(-) and 942 in Group T(+).

Overall, there were 15 cases of catheter-related bloodstream infection and two cases of catheter colonization. More than half of the infections occurred 15–28 days after CVC implantation ($N=9$; 60%). Fourteen CRIs occurred in Group T(-), compared with one CRI in Group T(+) [odds ratio (OR) 4.98, 95% confidence interval (CI) 1.45–17.06; $P=0.011$] (Table I). Staphylococci caused 88.2% of all bacterial infections (CRIs and colonizations) in the two groups (Table II). No fungal infections were found. There was one case of culture-negative, clinically diagnosed CRI in Group T (-). Catheter-related thrombosis occurred twice (Table I). None of the patients died of infection or thrombotic complication.

There were no significant differences between the analysed groups in terms of gestational age, birth weight, Apgar score, duration of PN or catheter dwell time. The average cost of treatment resulting from the CRI was €3304 per patient. The average cost of prophylactic use of T-C was €113 per patient.

Discussion

Prevention of CRIs is an important issue in hospital care. The bacteria causing CRIs are localized on the catheter surface in free (planktonic) form or in a biofilm layer. T-C inhibits the formation of bacterial biofilm on the internal surface of the central access and in the connection sockets in the ports [1]. While the elimination of free micro-organisms is fairly easy, the eradication of micro-organisms in the biofilm layer is problematic.

Studies from various centres treating very young children have shown that the rate of CRI exceeds 10 per 1000 catheter-days [7,8], and CRIs increase mortality and treatment costs [9].

According to Rafferty *et al.*, the prophylactic use of a T-C lock in adult patients with intestinal failure significantly reduced the number of CRIs, with an annual cost saving of £138,760 [9]. The present study found that the average cost of treatment of a child due to a CRI was 28.7 times higher than the average cost of prophylactic use of T-C.

A study undertaken in neonates with PICC demonstrated that the risk of infection increased during the first 2 weeks after implantation of the catheter, and remained relatively

stable over the next observation period [2]. The present study also found the highest number of central line infections (53%) between 15 and 28 days after introduction of the CVC. Recognizing all CRIs in the perioperative period during the systemic supply of antibiotics constitutes an important therapeutic premise.

The preferred vessel for implantation of a central catheter is the internal jugular vein. There is no uniform opinion on the site of introduction for CVCs and the frequency of CRIs. Patients in the present study were much more likely to have a central catheter implanted via the internal jugular vein. The low number of CVCs inserted in other veins and the low number of long-term, tunnelled CVCs makes it difficult to compare associations between CRI occurrence and catheter entry site, and CRI occurrence and type of CVC.

Most previous studies have described adult patients with CVCs and were not randomized. A randomized paediatric study in 113 children undergoing anti-tumour treatment was reported by Handrup *et al.* This study showed a significantly lower number of CRIs in the T-C group compared with patients who received standard CVC care with heparin lock [10]. A series reported by Simon *et al.* also found a significant reduction in the number of CRIs caused by coagulase-negative and meticillin-resistant staphylococci in children undergoing anti-tumour treatment with T-C [1]. Reports of home PN of children with T-C also indicate a significant reduction in the number of CRIs. In the present study, significantly fewer CRIs occurred in Group T(+) compared with the reference group. Similar to other studies, this study found that staphylococci were the most common aetiological agents of CRIs.

In conclusion, T-C lock is a safe and cost-effective method for the prevention of CRIs in very young children.

Conflict of interest statement

None declared.

Funding sources

None.

References

- [1] Simon A, Ammann RA, Wiszniewsky G, Bode U, Fleischhack G, Besuden MM. Taurolidyne-citrate lock solution (TauroLock) significantly reduces CVAD-associated grampositive infections in pediatric cancer patients. *BMC Infect Dis* 2008;8:102–9.
- [2] Milstone AM, Reich NG, Advani S, Yuan G, Bryant K, Coffin SE, et al. Catheter dwell time and CLABSIs in neonates with PICCs: a multicenter cohort study. *Pediatrics* 2013;132:1609–15.
- [3] Jurewitsch B, Lee T, Park J, Jeejeebhoy K. Taurolidine 2% as an antimicrobial lock solution for prevention of recurrent catheter-related bloodstream infections. *JPEN* 1998;22:242–4.
- [4] Olthof ED, Versleijen MW, Huisman-de Waal G, Feuth T, Kievit W, Wanten GJA. Taurolidine lock is superior to heparin lock in the prevention of catheter related bloodstream infections and occlusions. *PLoS One* 2014;e111216.
- [5] Diamanti A, Iacono A. Recurrent catheter related bloodstream infections by *Candida glabrata*: successful treatment with taurolidine. *Clin Nutr* 2014;33:367.
- [6] Reinmuller J. The influence of taurolidine on physiological and pathological blood coagulation and implications for its use. *Zentralbl Chir* 1999;124:13–8.

- [7] Mobley RE, Bizzarro MJ. Central line-associated bloodstream infections in the NICU: successes and controversies in the quest for zero. *Semin Perinatol* 2017;41:166–74.
- [8] Sanderson E, Yeo KT, Wang AY, Gallander I, Bajuk B, Bolisetty S, et al. Dwell time and risk of central-line-associated bloodstream infection in neonates. *J Hosp Infect* 2017;97:267–74.
- [9] Rafferty GP, Nightingale J, Small M, Eastwood J, UgarteCano C, Gabe S. The targeted use of Taurolock to reduce central venous catheter sepsis in a home parenteral nutrition cohort. *Gut* 2010;59:A35.
- [10] Handrup MM, Møller JK, Schrøder H. Central venous catheters and catheter locks in children with cancer: a prospective randomized trial of taurolidine versus heparin. *Pediatr Blood Cancer* 2013;60:1292–8.