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Taurolidine-Citrate Line Locks Prevent Recurrent Central Line Associated Bloodstream Infection in Pediatric Patients

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Running title Taurolidine/Citrate in High Risk Children

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ABSTRACT

This study describes a successful, targeted intervention in central venous access device routine care, to decrease central line associated bloodstream infection (CLABSI). Taurolidine-Citrate locks significantly reduced the rate of CLABSI, particularly Gram negative organisms without adverse events.

Keywords Healthcare associated infection; central line associated bloodstream infection; catheter lock; children; taurolidine

Introduction

Central venous access devices (CVADs) are essential for the management of acutely, critically and chronically ill children[1]. CVAD-associated complications, especially infections, remain prevalent[2] and are a significant cause of morbidity and mortality for children who are reliant on their function[2]. Central line associated blood stream infection (CLABSI) develops because of intra- or extra- luminal contamination by organisms, especially *Staphylococcus aureus*. CLABSI most commonly occur because of contamination of the catheter hub, subsequently growing within a luminal biofilm layer which develops rapidly (< 24 hours) after insertion. The presence of biofilm complicates the ability of antimicrobials to completely resolve CLABSI, often resulting in premature catheter removal and treatment delays[3].

Implanted CVADs including totally implanted devices (TID; e.g., port-a-cath®) and tunneled cuffed CVADs (tc-CVAD), are used for children who require long term and sometimes lifelong vascular access[2]. Repeated catheter removal and subsequent replacement may result in venous insufficiency for future device placement, thus catheter salvage is the ultimate goal when CLABSI is suspected. Novel line salvage techniques include ethanol, antibiotic, hydrochloric acid and fibrinolytic locks[1, 4], however eliminating CLABSI continues to be challenging.

Taurolidine/citrate (Taurolock®; TauroPharm GmbH, Germany) is a catheter lock solution that may prevent biofilm formation *in vitro*[5] and has broad-spectrum bactericidal and antifungal activity [3, 5-7]. With the anti-adherence properties of taurolidine and the anti-clotting and chelator activities of both taurolidine and citrate, this lock solution is postulated to disrupt bacterial surface adherence and consequential biofilm production[3]. Contemporary pediatric literature, including a prospective cohort study[6] and two randomized controlled trials (RCTs)[8, 9] of children with cancer, and a prospective cohort study of children receiving

parenteral nutrition (PN)[7], has consistently reported a reduction in CVAD-related bloodstream infection (BSI) when using Taurolock®, in comparison to other lock solutions, without obvious adverse effects or bacterial resistance. A systematic review and meta-analysis[4] of taurolidine lock solutions (6 RCTs, 431 patients, 86,078 catheter days) reported a significant reduction in the incidence of CVAD-related BSI in comparison to heparin lock solutions (Risk ratio (RR) 0.34; 95% Confidence Interval (CI) 0.21-0.55).

In response to higher than local average CLABSI rates in a cohort of children with CVAD, and after review of the above literature, a targeted implementation of Taurolock® was initiated by an interdisciplinary collaboration of pediatric infectious disease, gastroenterology and oncology physicians, pharmacy, vascular access specialists and home healthcare nurses.

This study aimed to compare the incidence of CLABSI in children identified at high risk of CLABSI before and after the introduction of Taurolock® into routine clinical care, and to demonstrate a process by which Taurolock® can be implemented outside of a clinical trial.

Methods

This study was undertaken at the Royal Children's Hospital (Brisbane) (subsequently incorporated into Lady Cilento Children's Hospital), tertiary referral pediatric hospitals in Queensland, Australia. Taurolock® was introduced as the sole interventional change into routine clinical care in selected, high risk patients between April 2013 and September 2015. In routine care CVADs were locked intermittently with heparin with the volume based on line length; 10units/mL if less than 3 days of inactivity, 100units/mL if greater than 3 days of inactivity. Retrospective data regarding participant CLABSI results were collected from March 2011 to March 2013 to enable comparison.

Children presenting with recurrent CLABSI throughout the course of their treatment were considered for suitability of Taurolock®. Children were eligible if they met all the following

criteria: 1) had a new or previously inserted CVAD; 2) had a history of recurrent (two or more) CLABSI from a CVAD or were on home parenteral nutrition; 3) could have a Taurolock® dwell time of at least 6 hours. Children were excluded if they had a peripherally inserted central catheter (PICC), were unable to have a minimum Taurolock® dwell time of at least 6 hours or did not have a skilled or trainable carer to provide treatment.

Taurolock® (taurolidine 1.34% with citrate 4%) was administered daily with the volume / dose calculated to either the length of the line (when known) or 2mL for tc-CVAD and 4mL for TID (if line length unknown). Taurolock® was left to dwell for at least 6 hours (up to 28 days), before aspiration before the next medication administration. Clinicians, parents and caregivers were educated to administer Taurolock® or heparin. Similar aseptic non-touch technique skills had been previously taught for attaching PN and other infused medicines, including sodium chloride 0.9% flush before medication administration, and needleless connector decontamination with 2% chlorhexidine gluconate in 70% alcohol[10, 11].

The primary outcome of Taurolock® implementation was CLABSI defined in accordance with the Centers for Disease Control Device-associated Module BSI[12]. This is a laboratory confirmed BSI (LCBSI) that is not secondary to an infection at another body site (excludes Mucosal Barrier Injury LCBSI), with the CVAD in place for greater or equal to two days on the day of the BSI and on the date of the event or the day. Confirmation of CLABSI was by a pediatric infectious disease specialist using clinical and microbiological data. Whilst receiving Taurolock® calcium levels (corrected for hypoalbuminemia) were monitored to ensure safety, with values of less than 2.1mmol/L indicating an adverse event. Clinical data were collected via patient chart audit and microbiological and biochemistry data were collected from laboratory information systems.

Statistical analysis was performed with GraphPad Prism Statistical package 2017 (La Jolla, CA, USA). Descriptive statistics have been used to describe the participant cohort, including frequencies and percentages for categorical variables and mean, median, IQR and range for continuous variables. CLABSI results are expressed as rates per 1,000 catheter days, with time-to-first CLABSI between groups described using Kaplan-Meier survival curves, with comparisons made via the log-rank test. CLABSI data were compared using paired t-tests, where each patient acted as their own control. Significance was set at $P<0.05$.

Results

Nineteen children were identified who met the inclusion and exclusion criteria, and were commenced on Taurolock®. None were withdrawn from treatment. Mean age at trial commencement was 6.2 years (SD 5.5 years, range 0.3-17) with 9 (47%) males. Oncological malignancy (47%; n=9) or intestinal failure (53%; n=10) were the indication for CVADs with 15 (79%) being tunnelled, cuffed CVAD and 4 (21%) totally implanted devices. A total of 17 436 catheter days were studied across both phases: 7077 catheter days pre-Taurolock® implementation; 10 359 catheter days post-implementation.

Pre Taurolock®, 19 children had 39 episodes of CLABSI (7077 catheter days), and 5 episodes of CLABSI (10 359 catheter days) post Taurolock® . The cumulative CLABSI rate decreased from 5.5 to 0.5 per 1,000 catheter days (p=0.0001), compared with the overall hospital CLABSI rate which was 1.8 and 1.5 in the equivalent time periods. Individual mean CLABSI rates decreased from 20.39 per 1,000 catheter days (SD 23.77, range 0.76 to 71.43) to 2.26 per 1,000 catheter days (SD 4.98, range 0 to 18.2; p = 0.0001) (Table). The mean time to first CLABSI episode increased from 87 days, to 296 days after Taurolock® implementation (p=0.012). There were no episodes of hypocalcaemia observed during Taurolock® implementation.

Before Taurolock® implementation Gram-positive pathogens were identified in 62% of CLABSIs with 38% Gram-negative organisms; post Taurolock® all 5(100%) were Gram-positive (Table).

Discussion

This study describes a successful intervention into routine care for a target group of children undergoing nutritional therapy, chemotherapy and/or bone marrow transplantation. The use of Taurolock® catheter lock solution was associated with significantly reduced CLABSI, with no reported adverse events, consistent with previous pediatric studies in similar population groups [6, 8, 9] [7].

Consistent with previous literature, the pathogens resulting in CLABSI altered with the implementation of Taurolock®. In vitro work has shown that after 24 hours contact certain solutions of taurolidine-citrate were lethal for *Candida albicans, S. epidermidis, Pseudomonas aeruginosa, and Enterococcus faecalis* and after 72 hours there was no growth in the taurolidine-citrate treated devices. A systematic review reported taurolidine solutions were effective at reducing the rate of Gram negative infections (p=0.004), but were associated only with a non-significant decrease in Gram positive infections (p=0.07)[6]. Accordingly, this was demonstrated within this study, with all CLABSI identified as Gram positive after Taurolock® implementation.

With a 78% decrease in the incidence of Gram negative CLABSI per 1000 catheter days Taurolock® is promising as a viable intervention into routine care to decrease CLABSI rates in high risk groups. The results are limited in the study's retrospective comparison, lack of randomization, small sample size, and varying follow up time. However, the study provides a framework for clinicians to replicate the successful application of Taurolock® solution to reduce CLABSI in high-risk patients. Although, additional close surveillance, follow-up and more

experience is required to observe the long-term benefits of using Taurolock® CVAD locks and to test its independent effectiveness, our results suggest this could potentially reduce infectious complications, without adverse effect, resulting in improved quality of life for children with chronic illness.

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TABLE

Table: CLABSI episodes and pathogens pre- and post-implementation of Taurolock®

Children =19	**Pre-Taurolock®**	**Post-Taurolock®**
CLABSI episodes	39	5
Total catheter days	7077	10359
Participant catheter days (median, IQR, range)	186 (798; 15 -1315)	341 (499; 55 - 1584)
CLABSI rate per 1000 catheter days	5.5	0.5 (p=0.0001^)
Individual CLABSI rate per 1000 catheter days (mean, range)	20.39 (0.76 to 71.43)	2.26 (0 to 18.2) (p=0.0032^)
Staphylococcus epidermidis [N(%)]	9 (23)	1 (20)
Klebsiella pneumoniae [N(%)]	7 (18)	0
Enterobacter sp. [N(%)]	3 (8)	0
Staphylococcus aureus [N(%)]	3	1* (40)
Staphylococcus warnerii	3	0
Enterococcus faecalis	3	0
Methicillin Resistant Staphylococcus aureus (MRSA)	2	1
Pseudomonas aeruginosa	2	0
Micrococcus sp.	2	0
Streptococcus mitis [N(%)]	2	1* (20)
Acinetobacter baumanii	1	0
Pantoea sp.	1	0
Proteus mirabilis	1	0
Streptococcus parasanguinis	0	1 #(20)

CVAD= Central venous access device; CLABSI = Central line associated bloodstream infection; ^paired t-test
* Positive blood culture in hematopoietic stem cell transplant recipient and patient with acute lymphoblastic leukemia, respectively, with neutropenic sepsis. Note: at time of neutropenic sepsis patient not receiving Taurolock® due to limited CVAD access # Positive blood culture in PN dependent patient with short gut syndrome. Note: at time patient was only receiving Taurolock® via one lumen of the dual lumen CVAD. Positive blood culture was taken from the heparin only locked lumen of CVAD.