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Use of 2% taurolidine lock solution for treatment and prevention of catheter-related bloodstream infections in neonates: a feasibility study

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SUMMARY

Background: Taurolidine lock, a technique used to prevent or treat catheter-related bloodstream infection (CRBSI), is effective in adult and paediatric patients but has been described rarely in neonates. The aim of this descriptive retrospective study, was to determine the feasibility and direct outcomes of prophylactic and therapeutic taurolidine locks in term and preterm neonates.

Methods: We implemented the use of therapeutic taurolidine lock in addition to antibiotic treatment with the aim of catheter salvage in critical neonates with difficult vascular access (group 1). In addition, we introduced taurolidine lock as a preventive measure in neonates with a central venous catheter (CVC) at high risk of developing CRBSI (group 2). Every 24 h (in the treatment group) a 2% taurolidine solution was injected and the catheter locked for at least 120 min, until infection clearance (group 1). In the preventive group, the catheter was locked for 30 min every 48 h until CVC removal (group 2).

Findings: Thirty-seven neonates who received taurolidine were included in this study. We did not observe any major adverse events. In group 1 (21 cases), clinical symptom disappearance and bacteraemia clearance were achieved without catheter removal in 18 cases (85.7%); in the other three neonates the catheter was removed shortly after the start of the locks as it was possible to replace the CVC. In group 2 (16 neonates), no CRBSI was observed during the duration of the catheter placement.

Conclusions: In this retrospective study, taurolidine was successfully used in neonates both for prevention and treatment of CRBSI, without major undesired effects. A larger cohort and a randomized clinical trial is warranted in order to establish its efficacy and safety in neonates.

Introduction

Newborns admitted to Neonatal Intensive Care Units (NICUs) often require the placement of central venous catheters (CVCs) for the administration of medication, parenteral nutrition, or for monitoring purposes. Neonates are, however, at risk for

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infection due to factors related to their immature developing immune systems and their complex medical needs [1].

There are two major definitions of bloodstream infections occurring in neonates in the presence of a CVC: catheter-related bloodstream infection (CRBSI) and central line-associated bloodstream infection (CLABSI). CRBSI is defined as the presence of clinical signs of sepsis in the absence of an obvious source other than CVC with one of the following: (1) simultaneous positive quantitative blood cultures (CVC vs peripheral); with a ratio of $\geq$3:1; and (2) time difference of >>2 h leading to culture positive between CVC and peripheral cultures (CVC culture positive prior to peripheral culture). A catheter-associated bloodstream infection (CLABSI) is defined as a primary bloodstream infection in a patient with a CVC *in situ;* placed at least 48 h prior, or occurring 48 h after CVC removal. For a CLABSI confirmation, the infection must also not be related to an alternative cause [2,3].

Studies have reported CLABSI rates in neonates ranging from 1.5 to 10.6 per 1000 catheter days [4]. The incidence of CLABSI in neonates varies depending on several factors, including the type of central line used, the duration of the catheter placement, the underlying medical condition of the neonate, and the adherence to infection prevention and control practices [5]. CLABSI incidence tends to be highest in very-low-birthweight infants and those with underlying medical conditions that increase the risk of infection, such as immunodeficiency. The prevention of CLABSI in neonates requires a multi-faceted approach that includes strict adherence to general infection prevention and control practices, and appropriate catheter insertion and maintenance techniques or bundles [6].

Most CRBSIs are resistant to routine systemic antibiotics due to the presence of an intraluminal bacterial biofilm. Catheter removal is therefore frequently necessary in the presence of a CRBSI. Systemic antibiotic treatment (SAT), associated with antibiotic lock therapy (ALT), is an antimicrobial therapeutic strategy that can be used to treat CRBSI when catheter removal is difficult due to the patient's critical condition [7].

Taurolidine is an antimicrobial agent that has broad-spectrum activity against bacteria and fungi. It is a derivative of the amino acid taurine, and it interacts with various components of the bacteria cell wall resulting in irreversible destruction [8]. Recently taurolidine has been introduced as an agent used in 'lock therapy' – a process consisting of injecting a small quantity of antimicrobial agent into the catheter for 30–120 min. Lock therapy using taurolidine has been proven effective in the treatment of CRBSI [9,10]. Prophylactic lock therapy with taurolidine has also been used with success, reducing the incidence of CRBSI in adults [11–13] and paediatric patients [14–16]. The use of taurolidine in neonates has, however, not been described.

The aim of our retrospective study was to describe, in a cohort of critically ill term and preterm neonates, the use of taurolidine lock therapy both in the prevention and treatment of CRBSI especially when the CVC was not able to be easily removed due to the patient's critical condition.

Methods

Study design

This retrospective study was performed in two NICUs: the Bambino Gesu Children's Hospital in Rome (Italy) and the Cliniques Universitaires Saint Luc in Brussels (Belgium). As both centres are level-III NICUs and neonatal surgical units, approximately 80% of the newborns hospitalized have a central vascular catheter placed for medical treatments, parenteral nutrition or central pressure monitoring. Approximately 200 CVCs are inserted each year in each unit (excluding umbilical venous catheters). Of these, around 64% are neonatal epicutaneo-caval catheters (ECCs), and 35% are 2 Fr or 3 Fr ultrasound-guided centrally inserted central catheters (CICCs). Only 1% are long-term tunneled CVCs.

In both units, CVC insertion and maintenance bundles for catheter procedures are used, which include adequate and continuous staff training, correct handwashing techniques, the use of 2% chlorhexidine for skin disinfection, maximum use of aseptic barriers, reduced unnecessary manipulation/access to the line, and removal of the catheter as soon as it is no longer required [6,17].

The study involved newborns hospitalized in both NICUs from the 1st January 2019 to the 31st December 2022, who received taurolidine either prophylactically or as treatment for a CRBSI. The diagnosis of a CRBSI was based on paired peripheral and central blood cultures, according to the method of 'delayed time to positivity', with a time difference of >2 h leading to culture positive between CVC and peripheral cultures (CVC culture positive prior to peripheral culture). ECCs were excluded from the study, because it is not possible to stop the infusion and perform a lock due to the high risk of occlusion of the catheter. Only CICCs were considered.

From the medical records the duration of CVC placement, infection-related data, and all possible taurolidine-related adverse events were extracted. All parents had given their consent to the use of clinical data of their children for research purposes.

Use of taurolidine locks

We used a 2% taurolidine solution both for prevention and treatment of catheter-related bloodstream infections, injecting a solution volume equal to the priming volume of the catheter + 0.2 mL.

In group 1, we included neonates with CRBSI in whom a therapeutic taurolidine lock (TTL) was added to the systemic intravenous antibiotic treatment, because removal/changing of the catheter was not feasible due to the critical condition of the neonate. Catheter removal was recommended immediately in case of a fungal infection as well as in case of *Staphylococcus aureus* or Gram-negative bacteria, if the blood culture remained positive despite 48 h of systemic intravenous antibiotic treatment. The types of organisms are listed in Table I. In the case of TTL, taurolidine was injected and locked for at least 120 min every 24 h until infection clearance.

In group 2, we included neonates who received a prophylactic taurolidine lock (PTL), neonates in the presence of a CICC or a long-term tunneled catheter, at risk for developing an infection. The characteristics of the conditions are listed in Table II. In the case of PTL, taurolidine solution was administered for at least 30 min every 48 h, from the first day of insertion until CVC removal.

In both cases, at the end of the dwell time, aspiration of the lock was performed (varying between 0.2 and 0.3 mL) and/or the CVC flushed with 0.5 mL saline (NaCl 0.9%), after which the central line was used as normal. If it was not possible to stop

Table I
Types of infections in the therapeutic group

Organism	*N*
Escherichia coli	2
Pseudomonas aeruginosa	2
Staphylococcus aureus	2
Staphylococcus epidermidis	2
Staphylococcus haemoliticus	1
Enterococcus faecium	3
Klebsiella oxytoca	3
Candida albicans	2

the infusions that were administered via the catheter (vasopressors, sedation), we inserted a peripheral line to infuse the medications that could not be stopped.

Ethical approval

Because the study was retrospective and was conducted on the existing patients' medical records, it did not require specific approval of the two Hospital's Ethics Committees, however the committees were notified, according to the respective legislation concerning retrospective scientific studies.

The patients' parents were informed of the therapeutic procedures necessary for their child upon admission to the NICU, including those related to the positioning and management of vascular catheters, and consent for the procedures and use of data was acquired.

Results

During the study period, 36 neonates who received taurolidine locks (25 in Rome and 11 in Brussels) were enrolled in this study. The median gestational age (GA) was 32 weeks (interquartile range (IQR): 23–40), while the median birthweight was 1.945 g (IQR: 600–4.200). Twenty-four neonates (65%) were born with a gestational age <35 weeks.

Forty-two CVCs were evaluated, with a median duration of vascular catheterization of 23 days (IQR: 7–105) and a total of 947 days of vascular catheterization. All the catheters were made of polyurethane and were inserted by ultrasound via the internal jugular vein, the brachiocephalic vein or the subclavian vein. Two catheters were inserted via the femoral vein.

Twenty-one catheters were therapeutically locked with taurolidine in association with SAT due to a CRBSI. Twenty neonates were included in group 1. The types of infections are listed in Table I. In all of these cases, catheter salvage, despite a CRBSI, was deliberately attempted, as conditions were too critical or not feasible to replace the existing line with a new central line. The lock was performed during the entire duration of the systemic intravenous antibiotic therapy. In three neonates the CVC was removed and replaced shortly after the start of systemic intravenous antibiotic therapy and lock therapy, due to clinical condition improvement allowing for easier replacement of the catheter. In 18 cases (85.7%) the catheter was not removed and the TTL/SAT association was effective in treating CRBSI (disappearance of clinical symptoms, normalization of laboratory values and repeated negative blood cultures).

Table II
Characteristics of neonatal diseases in the prophylactic group

Characteristic	*N*
Prematurity	11
Congenital hearth disease	3
Short bowel syndrome	6
Congenital diaphragmatic hernia	1
Oesophageal atresia	1

Sixteen neonates, who received prophylactic taurolidine locks, were included in group 2: 21 catheters were evaluated and none of these neonates developed CRBSI during this period. The characteristics of the neonates are listed in Table II.

Among the 37 neonates, 31 (81%) were treated for a surgical disease, short bowel syndrome and cardiac diseases being the most frequent surgical problem. Eighteen neonates (48.6%) were born preterm.

No cases of mechanical CVC malfunctioning were recorded and taurolidine lock was well tolerated in all infants. No cases of altered liver or renal function, heart rate and/or blood pressure nor alteration of neurological status were documented in the neonates included in the study. In one infant, as lock aspiration was not possible, the catheter was flushed and immediately after the flush, the baby presented with an episode of nausea/vomiting which quickly resolved. There was no repetition of a similar episode after subsequent locks were performed in this patient.

Discussion

Data from this retrospective study appear to support the efficacy of 2% taurolidine lock solution in the prevention and therapy of CRBSI in newborns.

In our cohort, none of the 16 patients who underwent PTL developed a CRBSI during the duration of catheter placement. In the treatment group, 18/21 patients who had developed a CRBSI, the infectious episode was resolved with lock therapy in conjunction with intravenous antibiotics, allowing the catheter to remain in place. This was an important finding in that these neonates were critically ill and were not able tolerate catheter replacement. In three cases, the use of the taurolidine 2% locks made it feasible to wait, allowing for clinical improvement of the neonate, prior to subsequent replacement of the catheter.

The presence of a CVC is one of the main risk factors for the onset of healthcare-associated infections, particularly those from *Staphylococcus spp*. infections in neonates admitted to the NICU [5]. Furthermore, the ongoing presence of the catheter itself prolongs the duration of infection, favouring persistent sepsis even under intravenous antibiotic therapy, due to an intraluminal biofilm that the bacteria, in particular *Staphylococcus* spp. strains, promote even if the primary origin of the infection is not the catheter.

Current guidelines on the management of CRBSI recommend catheter removal if the blood culture remains positive despite 48 h of systemic intravenous antibiotic treatment [18] or immediate removal in case of Candida infection [19]. Prompt catheter removal seems to improve outcome both in candidaemia infections and in Gram-negative bacteraemia [20,21].

Systemic antibiotics, however, in the context of CRBSI, have poor efficacy due to a number of factors including difficulty in achieving effective antibiotic concentrations/levels and due to the presence of the intraluminal biofilm. A catheter biofilm is a complex structure of micro-organisms that form on the surface of the catheter. It may be made up of bacteria, fungi, extracellular polymeric substances (EPSs), and other organic and inorganic materials [22,23]. EPSs are composed of polysaccharides, proteins, lipids, and other organic and inorganic substances, and create a protective environment for the micro-organisms within the biofilm. The micro-organisms within the biofilm can also produce enzymes and other factors that contribute to the formation and maintenance of the biofilm [24].

The composition of the biofilm may also change over time, as new micro-organisms colonize the biofilm and other micro-organisms die or become dormant. This can make the biofilm even more resistant to antimicrobial agents, as different micro-organisms within the biofilm may have different levels of susceptibility to antibiotics. Biofilms also protect the micro-organisms from the host's immune system, making them challenging to eliminate [22,24]. In fact, once a biofilm has formed on the surface of a catheter, due to the high resistance to antibiotics and other antimicrobial agents, it may be extremely difficult to eradicate, making them a significant challenge to treatment [25].

Preventing the formation of a biofilm is an important strategy for reducing the risk of catheter-related infections. Strategies for preventing biofilm formation include following strict evidence-based catheter insertion and maintenance bundles and adhering to infection prevention and control practices. When a CRBSI has been diagnosed, strategies that target the biofilm structure and composition, such as the use of antimicrobial lock solutions, may be more effective than traditional antibiotic therapy alone, in eradicating the micro-organisms within the biofilm [26,27].

The lock therapy consists of the instillation of the solution into the catheter lumen to fill and 'lock' the catheter between uses [7,28]. ALT consists in instilling within the lumen of the colonized catheter high concentrations of an antibiotic effective on the germ responsible for the infection and closing the catheter over time. Various types and doses of antibiotics have been used [26,27]. ALT has been proven to be effective, and can be used in difficult clinical cases, when catheter removal and replacement is not feasible, due to possible technical problems or the severity of the clinical condition of the newborn [29].

Furthermore, the routine use of ALT for CRBSI prevention is controversial and is not currently recommended as standard of practice [30]. One of the principal reasons for this is the concern over the development of antibiotic resistance. Overuse of antibiotics can lead to the emergence of antibiotic-resistant strains of bacteria, which can be difficult to treat and may limit future treatment options. Using antibiotics prophylactically also increases the likelihood of altering the intestinal microbiome, especially in preterm neonates [31].

In our case series, the organisms responsible for infection were mostly sensitive to common antibiotics. The choice to use taurolidine instead of ALT was not due to the isolation of resistant organisms, but to the higher effectiveness of taurolidine against the biofilm, compared with ALT. In fact, taurolidine has shown advantages over antibiotics and is currently the alternative of choice for lock therapy. Its use has been successfully reported in adults and children [32,33], both for preventing and treating catheter-related infections [34,35]. The mechanism of action includes the prevention of biofilm formation and its direct antimicrobial effects, disrupting the cell membrane of micro-organisms, interfering with bacterial quorum sensing and signaling, and oxidative stress induction and damage to bacterial DNA [36,37]. It works on Gram-positive, Gram-negative bacteria and fungi [38,39].

Taurolidine is a substance derived from the amino acid taurine. One of the major pathways of taurolidine metabolism is through hydrolysis [40,41]. Overall, the metabolism of taurolidine is relatively rapid, with most of the drug being eliminated from the body within 24–48 h after administration [42]. Because of its rapid metabolism and elimination, taurolidine is considered to have low potential for accumulation in the body or for long-term toxicity.

Taurolidine is generally considered to be safe and well-tolerated, with few reported side effects both in adults and in children. These may include allergic reactions, skin irritation, and transient changes in liver function tests [12].

CRBSIs are more difficult to diagnose than CLABSIs, especially in newborns, due to most of the CVCs placed in the neonatal age being ECCs. The ECCs usually placed in this age group are 1–2 French diameter, and blood sampling is strongly discouraged due to the possibility of occlusion. This makes it difficult to obtain the two simultaneous blood samples from the catheter and from a peripheral vein, a prerequisite in the diagnosis of a CRBSI. For this reason, CRBSIs are less well studied in neonates and their incidence more difficult to estimate correctly.

Our cohort of newborns included ultrasound-guided CVCs, from which blood withdrawals are feasible, allowing us to diagnose with certainty the presence of CRBSIs. We are therefore able to state with certainty that in 85.7% of the cases we describe, by associating taurolidine 2% lock therapy with SAT the CRBSI resolved, without the removal of the catheter.

In our cohort of patients, only one neonate experienced a possible short-lived adverse effect: an episode of nausea/vomiting after the saline flush of the lock solution. We believe that this reaction was due to the fact that taurolidine was flushed too quickly. After this episode the lock was flushed at a slower rate and the neonate did not have a repeat episode.

The strengths of this study include that it involves, for the first time, a cohort of neonates, managed with taurolidine locks in two different NICUs. The cohorts had the same management of central lines (same insertion and maintenance bundles) and used the same diagnostic criteria for CRBSI. All CVCs of a single patient were included and not only the first catheter placed, as most critical patients are likely to have more than one catheter during their NICU stay, making our approach more representative of clinical practice.

The retrospective nature of the study design has its inherent limitations, and we hope and plan to strengthen the pitfalls in a future multi-center randomized controlled trial.

In conclusion, our preliminary study highlighted that the use of taurolidine in neonates is safe and appears to be a promising approach in both prophylactic use as well as a treatment adjunct. Treatment with taurolidine locks could be used for treating CRBSI even in this fragile vulnerable population, however further research with a multi-center randomized controlled trial is warranted to prove its absolute efficacy in the prevention of CRBSI in term and preterm neonates, in order to reach the aim of zero CLABSI in the NICU.

Conflict of interest statement

The authors declare no competing interests.

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