Preventing Catheter-Related Bacteremia with Taurolidine-Citrate Catheter Locks: A Systematic Review and Meta-Analysis

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Key Words

Intravascular catheters · Catheter-related bacteremia ·
Taurolidine-citrate · Heparin · Meta-analysis

Abstract

Background: Preliminary evidence from some studies suggests that taurolidine-citrate locks decrease catheter-related bacteremia (CRB), which is a major cause of morbidity and mortality in patients using intravascular catheters. No previous study has sought to summarize existing evidence on the use of taurolidine-citrate locks. A systematic review and meta-analysis were undertaken to determine whether taurolidine-citrate was more effective than heparin in the prevention of CRB. **Methods:** The major English (PubMed, EBSCO, Web of Science and OVID) and Chinese (CBM, CNKI, VIP and Wanfang Data) healthcare databases were searched for randomized controlled trials comparing the efficacy and safety of taurolidine-citrate lock solution (TCLS) and heparin lock solution in the prevention of CRB. **Results:** Three studies involving 236 patients with a total of 34,984 catheter days were included. The use of TCLS significantly decreased the risk of CRB (relative risk = 0.47, 95% CI: 0.25–0.89) and Gram-negative bacterial infection. There was no significant difference in Gram-positive infections and exit-site infections.

Conclusions: Catheter locking with TCLS reduced the risk of CRB and Gram-negative bacterial infection. Adverse events include thrombotic events.

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Introduction

Intravenous access is an essential lifesaving intervention in critically ill adults and children receiving parenteral alimentation, antibiotic therapy, hemodialysis, chemotherapy and hematological malignancies. The major factors limiting the long-term use of central venous catheters are catheter-related infections and poor flow, particularly catheter-related bacteremia (CRB) [1]. The prevention of CRB remains a significant challenge because of the associated high morbidity and mortality [2]. The incidence rate ranges from 0.34 to 6 CRB episodes per 1,000 catheter days in some studies [3–5], and can reach 10.8 episodes per 1,000 catheter days [6] in others.

Prevention of bacteremia is crucial. A number of strategies to reduce the incidence of CRB have been tried, including the use of strict hygienic measures, antibiotic-impregnated catheters, eradication of *Staphylococcus aureus* nasal carriage and prophylactic antibiotic ointment on

the exit site [7]. Taurolidine and heparin, which can reduce the incidence of CRB, are often used as a solution to prevent bacteremia in patients who need a central catheter, as with hemodialysis, cancer and parenteral nutrition, as well as in the ICU [8–11]. It has been suggested that heparin, the most common catheter lock in clinical practice, may be abandoned because spilling into the bloodstream may expose patients to the risk of bleeding [12]. A promising approach is to instill an antimicrobial lock solution into the lumen(s) of the catheter (lock solution) in order to prevent intraluminal colonization and the development of biofilm. Another approach is to use catheter locks containing an antibiotic. Decreased bacteremia has been reported using gentamicin and minocycline, and confirmed using meta-analysis [13–15]. However, risks include toxicity from leakage of the antibiotic into the circulation and the development of antibiotic resistance [16].

Taurolidine-citrate may be an excellent alternative. Taurolidine, a derivative of the amino acid taurine, is a potent biocompatible antimicrobial agent with broad-spectrum bactericidal activity [17–19]. In vitro taurolidine yields methylol-aurinamide components that bind to bacterial and fungal cell walls, causing irreversible damage [20]. Experiments have demonstrated its efficacy in eradicating catheter biofilm caused by a variety of Gram-positive and Gram-negative bacteria, as well as *Candida albicans* [21]. Resistance has not been reported because the mode of action resembles a disinfectant, rather than an antibiotic [22]. Moreover, preliminary observations of patients in whom a subcutaneous dialysis device or intravenous catheter is used for hemodialysis suggest that instillation of taurolidine into the catheter lumens may prevent CRB [6, 23, 24]. However, other studies have shown that it was associated with a greater need for thrombolysis to maintain catheter patency [11, 23]. Thus, a systematic review is needed to account for this controversy. In this study, we aim to perform a systematic review and meta-analysis to estimate the pooled effectiveness and safety of taurolidine-citrate locks in comparison with standard-treatment heparin locks with regard to CRB rate and thrombosis rate using intravascular catheters.

Methods

Literature Search and Study Selection

We conducted a systematic literature search of the major English (PubMed, EBSCO, Web of Science and OVID) and Chinese [CBM, CNKI, VIP (a full-text database of Chinese journals) and

Wanfang Data] healthcare databases between January and February 2013. Search terms included ‘catheter-related infections’, ‘heparin’, ‘taurolidine’, ‘citrate’, and ‘lock solutions’. References were manually inspected and relevant articles obtained.

We selected randomized controlled trials (RCTs) comparing a taurolidine-citrate lock solution (TCLS) to a standard heparin lock solution in CRB prevention. In this study, RCTs were identified by title, key words, abstract and full text with two reviewers working independently to determine which studies meet the criteria for inclusion before reaching a final consensus on which studies to include. Discrepancies would have been reviewed by the senior author. Where key information was missing from the published version, the lead author was contacted and information requested.

Inclusion Criteria

To be included in the meta-analysis, a study had to meet the following criteria: a randomized trial comparing TCLS (1.35% taurolidine and 4% citrate) with standard heparin lock solution (5,000 U/ml), report the incidence of CRB as a principal outcome with sufficient information to allow the calculation of relative risk (RR), and use a clear definition of CRB and detail the procedure followed in case CRB was suspected.

Data Extraction

After the final selection, two reviewers extracted data independently. In case of discrepancies between the two raters, disagreements were solved by consultation with the senior author. Consensus was achieved after discussion.

Data concerning size of the study sample, characteristics of patient population, type of catheters and type of CRB pathogen (Gram-positive/Gram-negative) were extracted. Randomization and blinding procedures were also evaluated.

Data Analysis

Data analysis was performed using the inverse variance fixed-effect model for generic inverse variance data. Appropriate results from individual studies were quantitatively pooled in meta-analyses using fixed- or random-effects models, depending on heterogeneity. Heterogeneity was assessed with an I^2 statistic, where 0% indicates no heterogeneity and 100% indicates the highest level of heterogeneity. If I^2 was $<50\%$, the fixed-effects model was used, and if I^2 was $>50\%$, the random-effects model was applied [25, 26]. Effect sizes were measured primarily in mean rate difference (MRD) and secondarily in RR. Effect size measure was used to increase validity of our analysis. The MRD of CRB was calculated as CRB incidence control – CRB incidence experimental. RR of CRB was calculated as the natural logarithm (CRB incidence experimental/CRB incidence control). Pooled MRDs were estimated based on the average rate per 1,000 catheter days. Data analysis was performed using Cochrane Database’s Review Manager 5.2.0 software.

Results

Search Results

A total of 58 references were retrieved from the systematic search (fig. 1). Forty studies were excluded based on the title and abstract. The other 15 studies were ex-

Fig. 1. Flow diagram followed for the selection process of studies included in the meta-analysis.

Table 1. Characteristics of the included studies

Study	Design	Period	Sample size, n	Age at heparin, years	Age at TCLS, years	Primary endpoint	Secondary endpoint	Catheter type
Betjes and van Agteren [27]	randomized prospective trial	May 2002 to June 2003	58	50.3±20.4	58.3±16.3	catheter-related sepsis	bacteremic episodes Gram-positive and Gram-negative infection	tunneled catheter and nontunneled catheter
Solomon et al. [29]	double-blind RCT	Nov. 2006 to May 2008	110	56.7±17.4	59.8±14.7	time to first bacteremia event	bacterial colonization of the catheter	tunneled cuffed intravascular catheters
Dumichen et al. [28]	randomized prospective trial	Jan. 2007 to Dec. 31, 2008	71	median: 6.3 mean: 7.9 (range: 1.7–17.1)	median: 7.5 mean: 8.5 (range: 1.4–18)	bacterial colonization of CVC	bloodstream infections, thrombotic occlusions	not reported

CVC = Central venous catheter.

cluded because of duplicates (n = 6) or due to a nonrandomized controlled study design (n = 7) or based on some other exclusion criteria (n = 2). Thus, a total of 3 studies including 236 patients with a total of 34,984 catheter days were available for analysis [27–29]. The characteristics of the included RCTs are shown in table 1.

All 3 studies included patients with long-term catheters. Two studies included adult hemodialysis patients [27, 29], one studied pediatric patients with hematologi-

cal malignancies and catheters used for chemotherapy and intravenous medication/alimentation [28]. The inclusion and exclusion criteria for each study are shown in table 2.

Concerning randomization procedures, one study used computer-generated randomization and all study personnel and participants were blinded to treatment assignment throughout the study until the database was complete [29]. The other 2 studies did not provide de-

Table 2. Inclusion and exclusion criteria in each study

Study	Inclusion criteria	Exclusion criteria
Betjes and van Agteren [27]	patients were eligible for the study if they needed a hemodialysis catheter for starting or continuing hemodialysis treatment	patients were excluded if the dialysis catheter was used in the ICU or for reasons other than hemodialysis; patients using antibiotics were also excluded
Solomon et al. [29]	adult patients aged >18 years receiving tunneled intravascular catheters for hemodialysis and able to give informed consent	not reported
Dumichen et al. [28]	patients aged 1–18 years undergoing treatment with CVC placement with an expected duration of >4 weeks	lack of informed consent, presence of bacteremia/sepsis at screening, presence of a secondary CVC, and known allergy to heparin or taurolidine-citrate.

CVC = Central venous catheter.

Table 3. The number of CRB, catheters, catheter days and thrombosis cases

Study	Lock solution	Catheters, n	Catheter days, n	CRB, n	Thrombosis, n
Betjes and van Agteren [27]	HLS	39	1,885	4	2
	TCLS	37	1,519	0	1
Solomon et al. [29]	HLS	58	9,642	23	14
	TCLS	56	8,129	11	28
Dumichen et al. [28]	HLS	NR	7,233	9	2
	TCLS	NR	6,576	2	3

HLS = Heparin lock solution; NR = not reported.

tailed information about the method used to generate the random allocation sequence [27, 28].

Some additional techniques for preventing catheter-related infections were used. In one study, an additional nasal mupirocin was used for prevention of catheter-related infections [27]. In another study, all patients routinely received cotrimoxazole for the prevention of *Pneumocystis jiroveci* pneumonia [28]. The last study did not use any antibiotics [29].

Not all studies used the same type of catheter. Two of the 3 studies only used tunneled catheters [28, 29], while the other [27] included both tunneled catheter and non-tunneled catheters.

Exit-site care is of crucial importance to patients using intravascular catheters. Only one study described exit-site care procedures [27]. Preparation and instillation of the lock solution were detailed in only 2 trials [27, 29].

The criteria used for CRB diagnosis in each study were as follows: a positive bacterial blood culture drawn from the catheter with no other apparent source of infection in a symptomatic patient [27], or the decision to obtain blood cultures was based on symptoms of infection such as fever (temperature >37.5°C) or rigors associated with dialysis. A single positive blood culture bottle defined a bacteremic episode. If the same organism was isolated in cultures <3 weeks apart, it was considered the same infection. When different organisms were identified or if cultures were >3 weeks apart, these were considered separate episodes [29]. A primary CRB had to meet the following criteria: the 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 [28]. Thus, the common criteria used for CRB diagnosis in the 3 studies was a positive bacterial blood culture drawn from the catheter without any other source of infection. However, the definition of a bacteremic episode differed slightly and the criteria of Solomon's study were stricter because the possibility of recurrent infections of the same bacteria was ruled out.

All trials evaluated the incidence of exit-site infection and some of them assessed the incidence of colonization. All trials reported catheter days, CRB episodes and thrombosis, and all the studies but one [28] reported the number of catheters (table 3).

Not all papers reported the microbiology of CRB; of those that did, 66% (n = 38) of the CRB cases were caused by Gram-positive organisms (45% were caused by *S. aureus* and 21% caused by other Gram-positive organisms) and 34% (n = 38) were caused by Gram-negative organisms. Three patients reported on in the study by Solomon

Table 4. The microbiology of CRB, CRB incidence and thrombosis rate

Study	Groups	Gram-positive		Gram-negative	CRB incidence (episodes per 1,000 catheter days)	Thrombosis rate (episodes per 1,000 catheter days)
		<i>S. aureus</i>	other			
Betjes and van Agteren [27]	TCLS	0	0	0	0 (0.5)	0.66
	HLS	3	1	0	2.12	1.06
Solomon et al. [29]	TCLS	6	3	2	1.35	3.44
	HLS	8	4	11	2.39	1.45
Dumichen et al. [28]	TCLS	NR	NR	NR	0.21	0.46
	HLS	NR	NR	NR	1.24	0.28

In order to make possible the calculation of the natural logarithm (CRB experimental/CRB control), the 0 incidence reported in the studies was arbitrarily transformed to 0.5. NR = Not reported.

et al. [29] had methicillin-resistant *S. aureus* in CRB. Multidrug-resistant Gram-negatives and fungal infections were not reported. The microbiology of CRB is detailed in table 4.

Overall Effect

Individual and pooled results are presented in figures 2–4. The incidence of CRB and thrombosis rate in all arms of each trial are listed in table 4.

The overall summary RR using the fixed-effects model was 0.47 (95% CI: 0.25–0.89), indicating a significantly reduced risk of CRB in patients randomized to receive TCLS (fig. 2.1). The meta-analysis revealed the MRD of CRB is 1.12 (95% CI: 0.45–1.8) (fig. 2.2). No difference was observed in Gram-positive infection (fig. 2.3), and its RR was 0.81 (95% CI: 0.35–1.84). The overall summary risk ratio for the Gram-negative bacterial infection rate was 0.22 (95% CI: 0.05–0.99), which pointed to a strong protective impact of TCLS (fig. 2.4).

There was a significant adverse effect of taurolidine-citrate with respect to the incidence of thrombosis (fig. 3); the pooled RR against taurolidine-citrate was 2.10 (95% CI: 1.16–3.78).

Figure 4 shows that the pooled RR of the exit-site infection rate, the overall summary RR using the fixed-effects model, was 1.03 (95% CI: 0.51–2.09), indicating that there was no difference between TCLS and heparin lock solution in exit-site infection.

Adverse Events

No serious adverse events related to the TCLS were reported in any of the 3 included trials. Only Dumichen et al. [28] reported some adverse events; the recorded

symptoms were discomfort in the chest and neck, perioral dysaesthesia, abnormal taste sensations, nausea and vomiting. There were no adverse events or side effects reported in the study by Betjes and van Agteren [27], and Solomon et al. [29] did not report information on side effects.

Discussion

Different types of antimicrobial agents have been investigated to prevent CRB, and taurolidine-citrate may be an excellent agent. Our analysis showed that TCLS significantly reduced the risks of CRB and Gram-negative infections, but there was a greater need for thrombolytic therapy compared to heparin catheter locks.

Given that CRB is associated with high morbidity, mortality and cost in patients using intravascular catheters, the use of TCLS may offer a promising way to prevent this complication. It has been reported that the use of a taurolidine-citrate locking agent in patients using intravascular catheters has significantly reduced the sepsis rate and exerted positive impact on morbidity, mortality and cost [30]. In the USA, approximately 80,000 CRBs occur in ICUs each year [31]. The attributable cost per infection is an estimated USD 34,508–56,000 [32] and the annual cost of caring for patients with CRBs ranges from USD 296 million to 2.3 billion [31, 33]. The introduction of the taurolidine-citrate locks reduced the total costs of line infections in 6 months by EUR 19,200 (GBP 15,000) [30]. Though most studies reported 4–6 episodes per 1,000 catheter days [13], the incidence of CRB involved in our meta-analysis ranged from 0 to 2.39 episodes per 1,000 catheter days (table 4), and the meta-analysis indi-

Fig. 2. Pooled RR of CRB rate and its bacterial infection rate. **1** Pooled RR of CRB rate. **2** MRD of CRB. **3** Pooled RR of the Gram-positive bacterial infection rate. **4** Pooled RR of the Gram-negative bacterial infection rate.

Fig. 3. Pooled RR of the thrombosis rate.

Fig. 4. Pooled RR of the exit-site infection rate.

cated that the use of TCLS decreased the risk of CRB by approximately a factor of 1.12 episodes per 1,000 catheter days (fig. 2.2).

The main disadvantage of taurolidine-citrate was a greater need for thrombolytic therapy to maintain catheter patency, indicating a less effective anticoagulant activity of 4% sodium citrate compared with heparin. Observational evidence suggested that the addition of a small amount of heparin solved this problem [11]. A further study to determine the optimum amount of heparin is needed.

Formation of an intraluminal microbial biofilm has been noted to play a significant role in the development of catheter-related infections [34]. Microbial colonization and development of biofilms, which are known to be recalcitrant to antibiotic therapy, often lead to the loss of vascular access system patency. The use of catheter lock solutions has been recognized as an effective way to pre-

vent CRB, probably by reducing biofilm formation [20]. However, one study included in our meta-analysis [29] only found accumulation of fibrin, erythrocytes and platelets at the tip of all catheters in both groups using transmission electron microscopy; they failed to manifest bacterial biofilms in any catheter. However, other studies have revealed that most central vein catheters develop a bacterial biofilm on their inner surface as early as 24 h after their placement [35, 36]. Therefore, it may be hard to determine whether taurolidine-citrate destroys established bacterial biofilm or not. Although host factors such as humoral, cellular response and leukocyte function are important defense mechanisms against CRB, a taurolidine-citrate-heparin lock solution has effectively eradicated pathogens from the catheter biofilm in hemodialysis patients [37]. Therefore, larger in vivo studies are needed to explore the association between biofilm formation and CRB.

There was no significant difference in the incidence of Gram-positive organisms including *S. aureus* in our meta-analysis. Most of organisms isolated from patients in 3 trials [27–29] were *S. aureus*. In vitro studies have indicated that the concentration of taurolidine was sufficient to kill *S. aureus* [21, 38]. One possibility is that *S. aureus* enters by a different portal, such as the exit site. It is said that TCLS significantly reduced central venous access device-associated Gram-positive infections (coagulase-negative staphylococci and methicillin-resistant *S. epidermidis*) in pediatric cancer patients [10]. This point might need further study. However, it is proven to significantly reduce risk of Gram-negative infections in patients randomized to receive TCLS. Likewise, a recent study observed similar results [22, 23].

Exit-site infections may also contribute to the pathogenesis of CRB [39]. In studies included in our meta-analysis, a low incidence of exit-site infections was observed with, as expected, no difference between the heparin- and citrate-taurolidine-filling groups, indicating that exit-site infections may have a different pathogenesis. Optimal catheter care by an experienced nursing team reduced the rate of CRB by up to 8 times [39], which implies meticulous nursing techniques might be of particular importance. We were unable to display a difference in bacterial colonization incidence for catheters filled with taurolidine-citrate or heparin. Bacterial infections related to catheters can develop through extra- and intraluminal routes [40]. This may require different measures.

Conclusions

Our analysis indicated that catheter locking with taurolidine-citrate reduced the incidence of CRB and Gram-negative bacterial infection, whereas it was associated with an increased need for thrombolysis. We believe TCLS would be preferable to heparin or antibiotic locks if the need for thrombolysis can be decreased.

Limitations

Some possible limitations of this meta-analysis have to be considered in explaining the results. Firstly, publication bias may have occurred because only published researches were included in this study. A funnel plot was not performed to assess the publication bias because there were only 3 studies in this meta-analysis. Secondly, as with other meta-analyses, limitations come from heterogeneity of the study populations, protocols and outcome definitions. Thus, in the future, more RCTs are needed to confirm these results.

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Disclosure Statement

The authors certify that no conflict of interest exists.

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