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Opinion paper

Taurolidine lock solution in the secondary prevention of central venous catheter-associated bloodstream infection in home parenteral nutrition patients

Abdoulaye Touré [a,*], Madeleine Lauverjat [b], Catherine Peraldi [b], Michèle Boncompain-Gerard [b], Patrick Gelas [b], Didier Barnoud [c], Cécile Chambrier [a,b,c]

[a] Inserm Unit 1060/Inra 1235, University of Lyon, Lyon, France
[b] Approved Centre for Home Parenteral Nutrition in Adults in Lyon, Hospices Civils of Lyon, France
[c] Transversal Unit of Clinical Nutrition, Hospices Civils of Lyon, France

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SUMMARY

Background & aims: Central venous catheter-associated bloodstream infection (CBSI) is a serious complication in patients on home parenteral nutrition (HPN). The aim was to analyze the impact of taurolidine–citrate lock solution (TLS) on CBSI rate in HPN patients with a high risk of catheter infection.
Methods: This retrospective study compared CBSI rates 12 months before and 12 months after implementation of TLS. In the first period, only standardized strategies were used to reduce the CBSI rate. In the second period, TLS was injected into the catheter at the end of parenteral nutrition. The CBSI rate with a confident interval was calculated as Poisson event rates, and compared by testing for homogeneity of rates.
Results: 15 patients were included. During the 24 months, the CBSI rate was 6.58/1000 catheter-days in the first period and 1.09/1000 catheter-days in the second period ($p < 0.001$). In patients with TLS once a week ($n = 8$), the CBSI rate decreased from 4.8/1000 catheter-days to 1.37/1000 catheter-days ($p = 0.02$) and in patients with TLS after each TPN ($n = 7$), the CBSI rate decreased from 8.61/1000 catheter-days to 0.78/1000 catheter-days ($p = 0.001$).
Conclusion: In HPN patients, TLS associated with standardized precautions significantly reduced the CBSI rate.

1. Introduction

Home parenteral nutrition (HPN) has become the mainstay for the support of patients with severe chronic intestinal failure. The use of central venous catheters is essential for administration of HPN in these patients. However, numerous complications including thrombosis and catheter-related infections can occur. Central venous catheter-associated bloodstream infection (CBSI) contributes to high patient morbidity and mortality, increasing hospital costs and length of stay.[1–3] Some patients are prone to repetitive CBSI without apparent reason. These infections can lead to many complications such as venous thrombosis, endocarditis infections, spondylodiscitis, and hepatopathy. Management with repeated courses of antibiotics and occasional catheter removals in these patients suffering from multiple CBSI often fails in preventing recurrence.[3]

Despite standardized protocols,[4,5] CBSI remains one of the main challenges in the management of HPN patients. CBSI incidence ranges from 3 to 52% with an incidence rate from 0.34 to 6 infections per 1000 catheter-days.[6–11] This can reach 10.8/1000 catheter-days in some patients.[3] Many studies have been performed on the prevention of CBSI by antibiotic, alcohol, or heparin lock,[11,12] but no consensus is currently available for clinical practice.

An in vitro study has suggested that taurolidine–citrate solution could prevent colonization of catheter surfaces by a broad range of microbial pathogens and prevent life-threatening CBSI during clinical use.[2] Taurolidine's mechanism of action is attributed to biologically active methylol taurinamide which reacts with cell wall constituents of bacteria and fungi via methylene iminium ions.[16] The emergence of bacterial resistance to taurolidine has not been demonstrated. Taurolidine is non-toxic and is metabolized to taurine, carbon dioxide and water.[24] Sodium citrate provides local anticoagulation by binding Ca^{2+}, and the chelation of Mg^{2+} can interfere with cellular integrity by degradation of the bacterial cell

* Corresponding author. Unité de Nutrition Clinique Intensive, 103 Grande Rue de la Croix Rousse, 69004 Lyon, France. Tel.: +33 (0) 472 001 526; fax: +33 (0) 472 001 536.
E-mail addresses: abdoulayek2002@yahoo.fr (A. Touré), cecile.chambrier@chu-lyon.fr (C. Chambrier).

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wall membrane.[23] Given the efficacy of the Taurolidine lock in some studies,[2,3] we decided to use taurolidine 1.35%/Sodium citrate 4% lock solution (TLS) as secondary prevention in patients on HPN for intestinal failure who had recurrence of CBSI. We report a retrospective analysis of the CBSI rates 12 months before and 12 months during TLS in these patients.

2. Methods

2.1. Setting

Our unit is an approved French center for HPN. We take care of approximately 190 HPN patients per year. Our active patient line is from 120 to 130 patients-day. All central venous catheters are implanted in an operating room under strict aseptic conditions according to French guidelines.

2.2. Patients and design

This 24-month retrospective cohort study focused on the prevention of CBSI in 15 patients receiving PN from September 2005 to May 2011. Each patient acted as his or her own control over two periods in which CBSI episodes were recorded during the pre and the per-intervention period. In the first period, only standardized strategies such as appropriate choice of insertion site of catheter, maximal barrier precautions during insertion, proper education and specific training of the staff, adequate policy of hand washing, appropriate dressing of the exit site, disinfection of hubs, stopcocks and needle-free connectors, and regular change of administration sets[5] were used to reduce the incidence of CBSI. At the end of parenteral nutrition infusion, catheters were locked with 10 ml of saline solution to avoid catheter obstruction. In the second period, TLS was used and replaced saline solution to reduce CBSI. TLS was injected as bolus into the catheter at the end of PN (just the catheter volume, approximately 3 ml) and aspirated before the next intravenous treatment. As these patients received only parenteral nutrition, TLS remained approximately 12 h in the catheter. Serum saline locks were stopped during this period. In our practice, without official guidelines on TLS, depending on the physician' habits and prescription, some patients received TLS at the end of each parenteral nutrition and others received TLS once a week. We also evaluated this difference of practice.

Inclusion criteria were patients on long-term HPN for at least 2 years and at high risk of CBSI and who received taurolidine 1.35%/Sodium citrate 4% (TauroLock™, Théradial S.A.S., France) within the last 12 months as secondary prophylaxis of CBSI. High risk of infection was defined by the occurrence of at least one episode of CBSI in 12 months. Data from patient characteristics were collected 12 months prior and when TLS started. CBSI events and cause-active germs were collected in the both consecutive periods.

2.3. Definition of CBSI

Peripheral and central catheter blood samples were performed when patients presented with symptoms of bloodstream infection: temperature >38.5 °C, chills, elevated leukocyte cell count, or an increase in CRP level. CBSI was defined as a positive blood culture from the central venous catheter and a simultaneous blood culture positive from the peripheral vein for the same organism, with no other focus for infection than the central line.[1,15]

2.4. Statistical analysis

Because of the non-normal distribution, median (min-max) was used to summarize data. The Fischer's test was used to compare categorical variables. Continuous variables were compared using the Wilcoxon–Mann–Whitney test. CBSI rate with a 95% confident interval was calculated as Poisson event rates, and compared by testing for homogeneity of rates. *P*-values <0.05 were considered as statistically significant. Statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

A total of 15 patients (8 men, 7 women) were included in this study. Indications of HPN were short gut syndrome ($n = 11$), short gut associated with chronic pseudo-obstruction ($n = 1$), chronic pseudo-obstruction ($n = 1$), chronic diarrhea ($n = 1$), and villous atrophy ($n = 1$). The co-morbidities were solid cancer ($n = 1$), and leukemia ($n = 1$). Ten patients had an ileostomy. Before TLS, they received PN 6 (2–7) times per week. On inclusion, patient characteristics were: age: 47.0 years (18.5–79.6), body mass index: 20.0 (15.2–46.2), albumin: 38.1 gL^{-1} (26.0–49.0), and duration of HPN: 62.5 months (9.6–235.7). During the study period, 23 central venous catheters included 21 tunneled central venous catheters with a cuff (Broviac®) and 2 totally implantable venous access ports (Port-a-cath®). Patient characteristics were comparable in both periods.

In the second period, 3 ml of TLS were instilled in the catheter once a week in 8/15 patients, and after each TPN in 7/15 patients. None of our patients revealed local, laboratory, or organ toxicities for TLS. Some patients complained about a quick sensation of tingling after the injection of TLS owing to citrate which is known to induce a brief gap in calcemia. None of the patients received other antimicrobial lock as prophylaxis for CBSI during the two study periods.

3.2. CBSI

During the entire study period, the 15 patients experienced a total of 42 episodes of CBSI: 36 in the 12 months before TLS and 6 in the 12 months during TLS. CBSI rate was 6.58 [4.61–9.12]/1000 catheter-days during the first period without TLS and 1.09 [0.40–2.39]/1000 catheter-days in the second period with TLS ($p < 0.001$).

Figure 1 shows a significant decrease in both patients with TLS once a week ($P = 0.02$) and with TLS after each administration of PN ($P = 0.001$). Details of the number of CBSI episodes before and after TLS are described in Table 1.

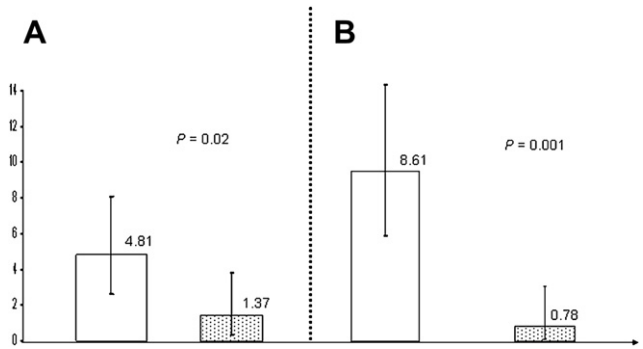

Fig. 1. Incidence density in 12 months without TauroLock™ and in 12 months with TauroLock™. A. Patients who instilled TauroLock™ in their catheters once a week. B. Patients who instilled TauroLock™ in their catheters after each administration of parenteral nutrition.

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Table 1
Incidence of central venous catheter-associated bloodstream infections according to pre and post-TauroLock™ in home parenteral nutrition patients.

No.	TPN/ week	Pre-TauroLock™	Post-TauroLock™	
		Number of CBSI[a] ($N = 36$)	TauroLock™/week	Number of CBSI[a] ($N = 6$)
1	7	1	1	1
2	4	1	1	1
3	7	1	1	0
4	7	1	1	0
5	7	1	1	1
6	6	2	1	0
7	7	3	1	0
8	4	4	1	1
9	4	1	4	1
10	4	3	4	0
11	4	3	4	0
12	4	1	5	0
13	6	4	6	1
14	7	4	7	0
15	7	6	7	0

[a] CNS = Coagulase negative *Staphylococci*.

3.3. Microorganisms

In the pre-intervention period, coagulase negative *Staphylococci* (CNS) and other Gram-negative bacilli groups (Fig. 2) responsible for the numerous CBSI episodes were mainly caused by *Staphylococcus epidermidis* ($n = 12$), and *Klebsiella pneumoniae* ($n = 5$) respectively. In the post-intervention period, CBSI were caused by *Staphylococcus hominis* ($n = 2$), *Escherichia coli* ($n = 1$), and *Enterobacter cloacae* ($n = 1$).

3.4. CBSI treatment

CBSI treatment did not change during the study. Treatment was initiated immediately after the results of blood cultures. Intravenous systemic antibiotic or antifungal (fluconazole, caspofungine) and lock antibiotic (vancomycin, gentamicin, or amikacin) treatment was performed according to the results of blood cultures. PN, intravenous systemic antibiotic and the use of central lines except for antibiotic lock were suspended during the first 48 h.

Catheters were withdrawn in 6 cases in the first period and in 2 cases in the second period. In the first period, the microorganisms responsible for catheter removal were *Citrobacter freundii, Pseudomonas aeruginosa, Stenotrophomonas maltophila*, fungi, relapse of *Klebsiella pneumoniae*, and relapse of *S. epidermidis*. In the second period, polymicrobial including *K. pneumoniae* and fungi, and *E. cloacae* led to catheter removal.

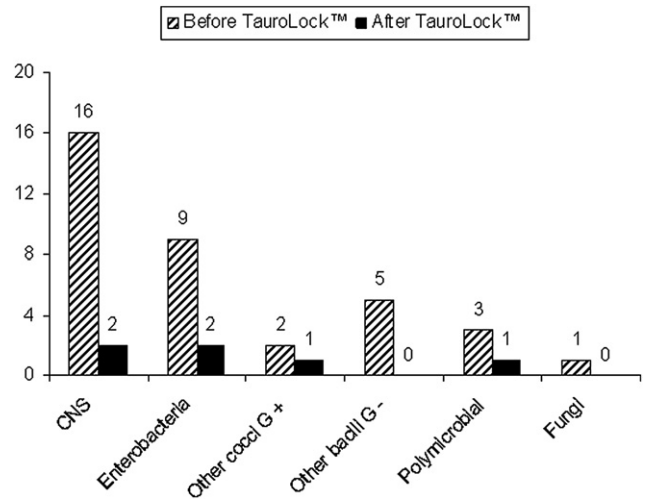

Fig. 2. Microorganisms isolated in the 42 central venous catheter-associated bloodstream infections in home parenteral nutrition patients CNS = Coagulase negative *Staphylococci*.

In both periods, CBSI required transfer to an intensive care unit in only 2 patients. There were no cases of organ failure.

4. Discussion

Despite prevention strategies including antisepsis, maximal sterile barriers for insertion, and tunneling of catheters, HPN patients remain at high risk for infection. This retrospective study was performed to evaluate the impact of the use of TLS on CBSI rate in a specific group of adult HPN patients with a high risk of CBSI. We report a dramatic reduction in CBSI rate from 6.58 during the first period without TLS to 1.09 per 1000 catheter-days in the second period with TLS ($p < 0.001$).

The first study of taurolidine lock solution used for prevention of recurrent CBSI in HPN patients was a case report.[16] The results showed that in a 29-year-old male with short bowel syndrome, the rate of catheter-associated bloodstream infections decreased from 8.5 per 1000 catheter-days before taurolidine to 1.5 with taurolidine. Since then, nonrandomized studies have been performed that report the effectiveness of taurolidine for the prevention of CBSI in HPN patients.[3,14] The only randomized trial performed included 30 HPN comparing taurolidine 2%/Povidone 5% (TauroSept™) with heparin.[12] The authors showed that TauroSept™ dramatically decreased the CBSI incidence rate when compared with heparin (2.02 vs. 0.19/1000 catheter-days; $p = 0.008$). In pediatric cancer patients, the rate of CBSI owing to CNS was higher in patients with heparin than patients with TauroLock™ (2.30 vs. 0.45/1000 catheter-days; $p = 0.004$).[13] In the literature, the majority of studies showing the effectiveness of taurolidine on the prevention of catheter infections were performed in patients requiring hemodialysis.[17–21]

The effectiveness of TLS could be explained by the fact that taurolidine is a potent antiseptic agent derived from naturally occurring aminosulphonic acid taurinamide and formaldehyde which is effective at killing a diverse group of bacteria within biofilms as well as fungi.[12,20] In an in vitro study, C.B. Shah et al reported in an in vitro study that after 24 h of contact, a 13,500 mg/L taurolidine–citrate solution was lethal for *Candida albicans*, *S. epidermidis*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*.[2] Their results also showed that after 72 h, there was no growth in the taurolidine–citrate treated devices. In another in vitro study, investigators reported that there was no evidence of resistance to taurolidine when it was tested against a broad range of microbial pathogens.[22]

TLS was effective both in patients who instilled once a week and those who instilled after each PN. However, the decrease in the incidence was dramatic in those who received TLS after each TPN. These patients experienced 22 episodes of CBSI during the pre-intervention period and only 2 episodes after the introduction of TLS. Among the six episodes of CBSI that occurred with TLS, four were diagnosed in the patients who received TLS once a week. In hemodialysis, taurolidine lock solution is usually used three times a week after each dialysis. In HPN, the frequency of TLS was never discussed in previous studies. Until now, TLS has been used after each PN. Thus, further investigations are necessary to determine the optimum frequency of TLS administration according the number of PN per week.

Our study has some limitations. This was a retrospective study with a small size. However, we performed a special kind of matching where the patient served as his or her own match. Despite the small size, the power of this retrospective study can be considered as sufficient ($1\text{-}\beta = 91\%$). However, care must be taken

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in the comparison of practices owing to the small number of patients and obviously requires a specific study. The before-and-after study design precludes establishing causation but demonstrates the practical adoption of a new infection-control method.[25] Our CBSI rates were high but did not represent the rate of our general population. They may have been overestimated, because TLS was used only in patients with recurrent CBSIs. Moreover, we used a simple definition owing to the unavailability of quantitative methods. The differential time to positivity or quantification of blood cultures from peripheral and central lines was not recorded because some blood samples were not performed in the laboratories of University of Lyon Hospital. In non-hospital laboratories, differential time to positivity is not performed.

In conclusion, this 24-month retrospective cohort study showed that TLS associated with standardized precautions significantly reduces the CBSI rate. This lock is of interest in such patients in order to reduce infectious complications, improve the quality of life and decrease the cost of HPN. The use of this lock for primary prevention of CBSI in HPN patients and the frequency of instillations require further discussion.

Statement of authorship

TA, CP, ML, MBG, PG, DB and CC. Study concept and design and acquisition of data. TA. Statistical analysis. TA, ML, CP, MBG, PG, DB and CC interpretation of data. TA and ML drafting of the manuscript. CP, MBG, PG, DB and CC. Critical revision of the manuscript. CC. Study supervision. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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