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Original Article

Taurolidine lock is highly effective in preventing catheter-related bloodstream infections in patients on home parenteral nutrition: A heparin-controlled prospective trial☆

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SUMMARY

Background & aims: Catheter-related bloodstream infections remain the major threat for Home Parenteral Nutrition programs. Taurolidine, a potent antimicrobial agent, holds promise as an effective catheter lock to prevent such infections. Aim of the present study was to compare taurolidine with heparin, the most frequently used lock, in this respect in these high-risk patients.

Methods: Thirty patients from one referral centre for intestinal failure were enrolled after developing a catheter-related bloodstream infection. Following adequate treatment, either with or without a new access device (tunneled catheter or subcutaneous port), these patients were randomized to continue Home Parenteral Nutrition using heparin ($n = 14$) or taurolidine ($n = 16$) as catheter lock.

Results: Whereas in controls 10 re-infections were observed, in the taurolidine group during 5370 catheter days only 1 re-infection occurred (mean infection-free survival 175 (95% CI 85–266; heparin) versus 641 (95% CI 556–727; taurolidine) days; log-rank $p < 0{\cdot}0001$). No side effects or catheter occlusions were reported in either group. Moreover, after crossing-over of 10 patients with infections on heparin to taurolidine, only 1 new infection was observed.

Conclusion: Taurolidine lock dramatically decreased catheter-related bloodstream infections when compared with heparin in this high-risk group of Home Parenteral Nutrition patients.

1. Introduction

Intravenous administration of (parenteral) nutrition in the home setting (HPN) has become the mainstay for the support of patients with chronic intestinal failure.[1,2] Infectious problems, mainly related to the presence of the vascular access device, however, remain the Achilles' heel of HPN care so far despite a nearly forty-year experience with this treatment modality.[3] Since parenteral nutrition implies that all nutrient requirements are met by a sterile, aqueous solution that is administered into a large-bore central vein, HPN requires the presence of a central venous catheter (tunneled or implantable port) to assure adequate venous access. These access devices are most frequently tunneled subcutaneously and positioned in the jugular or subclavian veins.[4] Catheter-related infectious complications are frequent and mostly concern catheter-related bloodstream infections (CRBSI) or, less frequently, local infections of the catheter exit site or –tunnel.[2,3,5] Most CRBSI originate from contamination of the catheter hub and subsequent growth of microorganisms embedded within the biofilm that rapidly (<24 h) develops on the inner catheter surface after its placement.[6] The growth of this layer is promoted by phenotypic changes in colonizing microorganisms, resulting in enrichment with exopolysaccharides, fibrin and nucleic acids.[7] Since antibiotics do not penetrate this biofilm, CRBSI are often resistant to these agents.[7,8] Given the necessity for hospital admission and the administration of intravenous antibiotics, CRBSI confer considerable morbidity and healthcare costs, and their occurrence strongly

Abbreviations: CRBSI, Catheter-related bloodstream infections; HPN, Home Parenteral Nutrition.

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determines the outcomes of HPN programs.[3,9,10] Also, repeated catheter removal and subsequent replacement eventually seriously compromises the possibilities to obtain central venous access and can necessitate small bowel transplantation in these patients with intestinal failure. Due to the fact that salvage of the central venous access is the main goal in case of a suspicion of a CRBSI, a culture of the tip cannot always be performed. As a result, the definition of a CRBSI differs between the various studies. As such, the exact incidence of CRBSI is unknown. The estimated reported frequency of CRBSI in HPN patients in the literature varies between 0.34 and 3.94 episodes per catheter year,[3,11,12] with infections being caused by Gram-positive coagulase-negative (30–40%) or –positive (15–20%) staphylococci, Gram-negative bacteria (30–40%), fungi (6–9%) or polymicrobial flora (12%).[3]

The indistinctness regarding the approach that should be taken to decrease CRBSI is reflected in the numerous therapeutic measures for this problem, ranging from meticulous training of patients to perform aseptic techniques in case of usage of the catheter for administering total parenteral nutrition (TPN), to the use of antimicrobial filters, cuffing of catheter hubs and the topical application of antimicrobial agents (e.g. povidone iodine, chlorhexidine in alcohol or mupirocin ointment) to the catheter exit site.[3,11] Treatment of CRBSI with line sterilization using fibrinolytic agents (e.g. heparin or alteplase) and systemic antibiotics has success rates, which are strongly species-dependent, ranging from over 85% for coagulase-negative staphylococci, to 50% for coagulase-positive staphylococci and Gram-negative bacteria, while fungi and polymicrobial flora are hardly ever cleared.[3] Since metallic cations, such as Mg^{2+}, Ca^{2+} and Fe^{3+} play important roles in bacterial growth, chelating agents, such as ethylenediaminetetraacetic acid (EDTA) and sodium citrate, have been applied as well as the instillation of antimicrobial lock solutions in the form of ethanol.[3,12] None of these measures, however, so far have been sufficiently effective to prevent the development of CRBSI.

Taurolidine is a potent antiseptic agent derived from the naturally occurring aminosulphonic acid taurinamide and formaldehyde, with a broad spectrum of antimicrobial activity against Gram-positive and -negative bacteria as well as fungi.[13,14] Taurolidine is non-toxic for humans[15] and is rapidly metabolized into taurine, carbon dioxide and water. Its mechanisms of action are based on the irreversible reaction of methylol taurinamide with microbial cell wall constituents resulting in the prevention of bacterial adhesion to biological surfaces.[16,17] Bacterial resistance to taurolidine has as yet not been reported.[18,19] Taurolidine has shown efficacy in the prevention of infection of indwelling central venous catheters in patients on hemodialysis[11] and chemotherapy,[14] but has as yet not been subjected to the rigorous scrutiny of a formal randomized trial in the setting of HPN.[20]

We recently reported our experiences regarding venous access-related complications and the use of arteriovenous fistulae in our 127 HPN patients between 2000 and 2006.[21] As in most institutions, we use heparin locks in our HPN centre as the standard of care to prevent catheter-related thrombosis.[22]

The present open-label prospective randomized trial was initiated at the end of this observation period and aimed to compare catheter lock therapy with taurolidine and heparin for their efficacy regarding the prevention of CRBSI in patients with proven susceptibility to such infections.

2. Methods

The present study was performed in our tertiary referral centre for intestinal failure, approximately harboring 80 out of 130 HPN patients in The Netherlands at that time. We designed an open-label, prospective, randomized trial in patients who had recently developed an episode of CRBSI and who, after the treatment of this infection, had resumed TPN administration, either with the same, or with a new access device. Patients were randomized to use taurolidine (cases) or heparin (controls) as catheter lock solution. Both heparin and taurolidine are 5 ml completely transparent solutions, which are provided in 10 ml vials. The primary endpoint of the study was the development of a subsequent episode of CRBSI. Secondary endpoint was the length of the CRBSI-free interval. The study was approved by the local Medical Ethical Committee and written informed consent was obtained from each patient before randomization.

Of our 80 patients at the start of the study, 60 used a catheter (tunneled or implantable port) for central venous access and thus would be eligible in case of development of an CRBSI. All these patient had been trained to work technically aseptic by a specialized nurse during an admittance to our hospital, before the start of home parenteral nutrition. In our centre this training has been implemented according to a standardized protocol since the mid 1970s. Apart from the switch to a taurolidine lock in the assigned patients, there was no alteration in the protocol for catheter care during the study period. In the remaining 20 patients HPN was delivered over an arteriovenous fistula and a lock solution was not applicable. Pre-study power analysis demonstrated that with an estimated incidence of 1 CRBSI per 30 months[3] and an evaluable population of 60 patients (30 cases, 30 controls), and with a power of 80% and two-sided α of 0·05, a reduction in CRBSI of 25–30% with taurolidine would thus be necessary to obtain statistical significance.

A diagnosis of CRBSI was made whenever a patient presented with clinical signs and symptoms of a bloodstream infection (temperature $> 38 \cdot 5\ ^{\circ}C$, chills, hypotension, tachycardia, elevated white blood cell count and/or CRP rise) in absence of hypovolemia and a cardiac event, without any other focus for infection than the central line. To exclude other infection foci, a urinary specimen and chest X-ray was always performed. In addition, growth of microorganisms had to be shown from at least two blood culture sets taken from the catheter or peripheral blood. Although the golden standard for diagnosing a CRBSI is a culture of the tip, this was not one of the diagnostic criteria, since we aimed to preserve the line whenever possible. Patients were randomly assigned to one of the two study-arms to receive either heparin (5 mL, 150 U/ml, controls) or taurolidine (5 ml, 2% solution, Taurocept®, Gheistlich, Wolhusen, Switzerland, cases) to lock their access device (Hickman catheter or Port-a-cath). Before onset of the study, for each study arm 30 closed envelops were prepared and randomly placed and stored in a box by a secretary. After informed consent was obtained, for each patient an envelope was drawn from this box and immediately shown to the patient. Next, patients were followed and monitored for the development of CRBSI, and, if so, there was an automatic cross-over to the other intervention arm of the study after treatment of the infection, and follow-up was continued. Patient characteristics, laboratory parameters, culture results, and clinical parameters were obtained from the medical files and put into a database.

2.1. Statistic methods

Continuous and nominal variables were evaluated by means of Man–Whitney U and Kruskall Wallis testing, incidence rates were compared by Fischer Exact test and infection-free intervals were evaluated by survival analysis according to Kaplan–Meier, respectively. The level of significance was adapted in the interim data analysis in order to preserve the $\alpha = 0.05$ in the total study. We applied the alpha spending function of O'Brien-Fleming[23] for the interim analysis, with the information time s set at 0.5. As a result, P-values$<$0.0056 are considered statistically significant in this situation.

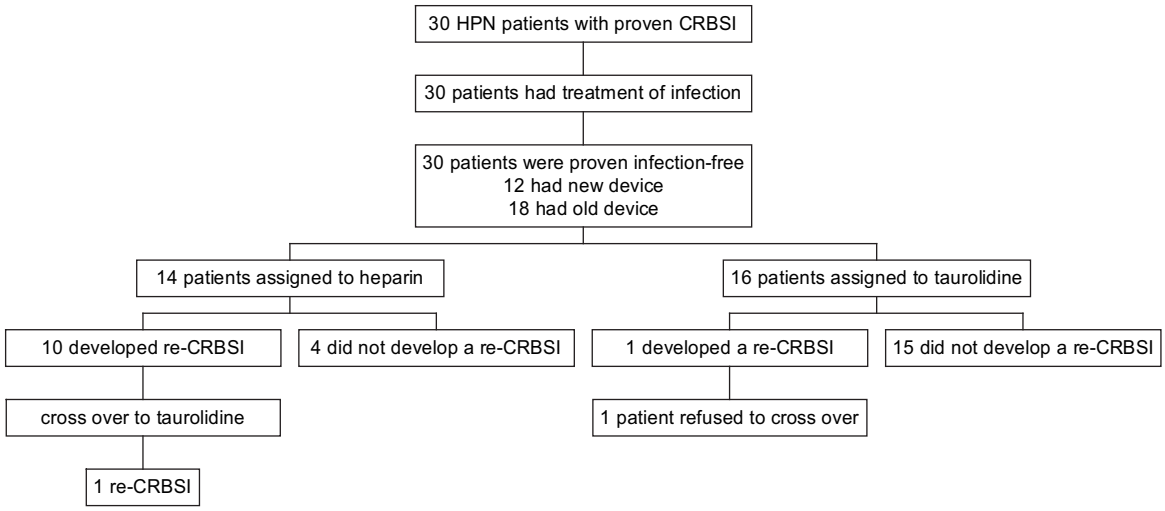

Fig. 1. Trial profile HPN = home parenteral nutrition, CRBSI = catheter-related bloodstream infection.

3. Results

We enrolled 30 patients (16 cases, 14 controls) between April 1st 2006 and March 1st 2008. Based on power analysis, our aim was to include 30 patients per arm of the protocol. After 23 months of enrolment, however, we decided to perform an interim analysis because clinical observations strongly suggested significantly lower CRBSI rates in subjects on taurolidine. Given the dramatic differences between both protocol arms, the study was terminated prematurely after obtaining consent from the ethics committee.

Patient demographics, including underlying disease and venous access characteristics were not different between groups (Table 1). CRBSI rates pre- and post-enrolment are shown in Table 2. The types of microorganism leading to CRBSI within these intervals also were not different, with three quarters of CRBSIs being caused by Gram-positive bacteria, in two third of cases *Staphylococcus* species.

The follow-up period after enrolment was 336 ± 51 (mean ± SEM) days in the taurolidin group and 353 ± 51 days in the heparin arm. In the taurolidine group, during 5370 catheter days only 1 re-infection occurred (due to *Candida albicans*), while in heparin controls during 4939 catheter days 10 re-infections were observed (Fig. 1). The mean infection-free survival according to Kaplan–Meier survival analysis was 641 (95% CI 556–727) days in the taurolidine-arm versus 176 (95% CI 85–266) days in the heparin group (log-rank test $P < 0{\cdot}0001$, see Fig. 2). After crossing-over of the 10 patients with infections on heparin to taurolidine, only 1 new infection occurred (due to *C. albicans*, see Fig. 1). Of note, neither in controls nor in the taurolidine group any catheter occlusions or side effects that could be attributed to the study medication were observed during the study period.

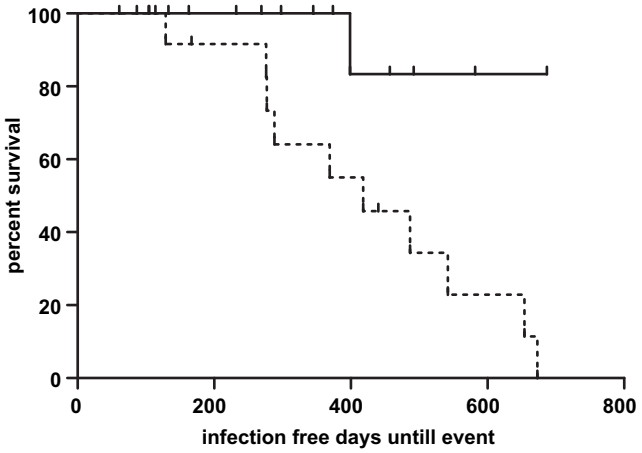

Fig. 2. Kaplan Meier survival curve presenting number of infection-free days until event with taurolidin catheter lock (continuous line) versus heparin catheter lock (interrupted line).

4. Discussion

The exciting finding of the present study is that the occurrence of CRBSI in patients on HPN with a proven susceptibility to infection, i.e. after the recent development of catheter sepsis, could be decreased from 71% to 6% by using a catheter lock with taurolidine as compared to our common practice where we use a heparin lock after cyclic PN administration. Additional evidence for this

Table 1
Patient characteristics.

		Heparin ($n = 14$)	Taurolidine ($n = 16$)	P
Female (n)		10 (71%)	12 (75%)	0.92
Age (yrs (SD)		48·6 (15.9)	55·3 (13·2)	0.75
Cause of intestinal failure (n)	Motility disorder	5 (36%)	5 (31%)	0.84
	High output stoma	1 (7%)	1 (6%)	0.93
	Short bowel syndrome	5 (36%)	6 (38%)	0.94
	Other	3 (21%)	4(25%)	0.86
Type of access	Hickman	8 (57%)	11 (69%)	0.70
	Port-a-cath	6 (43%)	5 (31%)	0.62
New device at start of study		6 (43%)	6 (38%)	0.82
Microorganism causing CRBSI at time of inclusion	Staphylococcus sp.	7 (50%)	9 (56%)	0.83
	epidermidis	5 (36%)	7 (44%)	0.74
	lugdunensis	1 (7%)	1 (6%)	0.93
	aureus	1 (7%)	1 (6%)	0.93
	Other Gram-positives	4 (29%)	2 (13%)	0.36
	Gram-negatives	3 (21%)	4 (25%)	0.86
	Other	0	1 (6%)	0.53

Patient characteristics in number (percentage), except for age; mean (SEM),.
CRBSI = catheter-related bloodstream infection.

Table 2
Catheter-related bloodstream infection characteristics pre- and post-enrolment.

		Heparin	Taurolidin	P
Infections/1000 catheter days before inclusion (n)		2.33 (1.6–3.4)	2.36 (1.8–3.1)	0.97
Infections/1000 catheter days after inclusion (n)		2.02 (1.1–3.8)	0.19 (0.03–1.3)	0.008
CRBSI-free days since inclusion (days)		129.4 (±34.3)	319.4 (±52.5)	0.004
Infection-free survival (Kaplan Meier)		175.8 (±46.1)	641.3 (±43.7)	<0.0001
Microorganism event 1	Staphylococcus	5	0	
	Other Gram-positives	2	0	
	Gram-negatives	3	0	
	Other (e.g. fungi)	0	1	

Infection/1000 catheter days in incidence (95% CI), other characteristics in mean (SEM).
CRBSI = catheter-related bloodstream infection.

protective effect of taurolidin was provided by the finding that after crossing-over of patients with a treatment failure on heparin to taurolidine only one patient (10%) developed a new episode of CRBSI. Finally, the use of taurolidine instead of the anticoagulant did not lead to any episode of catheter occlusion, vascular complications or side effects in any other respect.

The strength of our study is that it was performed in the most relevant subgroup of HPN patients, i.e. those who develop infections. As a consequence, on the other hand, the number of patients that could be enrolled was limited. We considered a single-centre investigation appropriate, however, because protocols for HPN administration and –training, as well as CRBSI treatment between centers differ significantly.

We realize that its open-label character could be considered a weakness in the design of the study (which was performed without funding). However, both solutions have the same optical appearance and the implementation of the study drug did not require any adaptation of the HPN administration protocol. In addition, the lack of any side effects in either group makes any form of bias in this respect unlikely in our opinion.

CRBSI, mainly occurring in a subset of patients, remain the major bugbear of HPN care. Apart from direct personal consequences and the strain on medical resources, the repeated loss of venous access eventually compromises the possibility to continue TPN. As mentioned, this may result in the necessity for small bowel transplantation in some patients, but may also lead to demise in those not eligible for such complex treatment. The only data on the use of taurolidine as a catheter lock in the setting of HPN so far come from a small non-controlled Canadian pilot study in 10 patients with frequent catheter sepsis and one case report.[24,25] Our results corroborate the findings of the latter pilot, where the (exceptionally high) CRBSI rate per 1000 catheter days decreased from 10·8 to 0·8 (93%) with the use of taurolidine.[25]

Besides isotonic saline lock solutions, the use of heparin lock still is the standard of care in many, if not most institutions, to prevent thrombosis.[22] Apart from the development of complications such as thrombopenia and thrombosis, the use of heparin as a catheter lock has also been subject to criticism because heparin does display antimicrobial effects at concentrations below 6000 U/ml.[26] As reviewed recently, heparin may even promote biofilm formation based on the ability of certain *Staphylococcus aureus* strains to produce a heparin-binding protein.[7] In fact, bacteria have been shown to survive and grow in heparin-locked catheters.[27] Our results suggest that compared to heparin, taurolidin, apart from its beneficial effect on the occurrence of CRBSI, may well be equally effective in preventing catheter occlusion due to thrombosis. The latter observation is supported by reports on the inhibition by taurolidine of clotting-activating substances, such as bacterial coagulase.[22,28]

Potential confounding variables of this study, might be the underlying disease and the microorganism causing the original CRBSI. As shown in Table 1, these variables do not seem to differ between the two groups. Unfortunately, the number of patients included in this study is too low to perform multivariable analysis. As such bias by these factors, although unlikely, cannot fully be excluded.

Although the present study was performed in a specific subpopulation of patients with intestinal failure, its outcome appears relevant for a broad audience given that patients with malignancies as well as renal failure encounter similar adversities in the course of their long-term dependence on a reliable venous access device.

In conclusion, the present study showed that the implementation of a catheter lock with taurolidine dramatically decreased the incidence of CRBSI as compared to heparin in patients dependent on HPN. A large multicenter, preferably multinational study supporting our findings may allow implementation of this practice as a standard of HPN care in the near future.

Conflict of interest

All authors substantially contributed to the design of this study, acquisition of de data, analysis and interpretation of the data, drafting and revising the manuscript and have seen and approved the final version. This manuscript and related data have not been published previously and are not under consideration for publication elsewhere.

Statement of authorship

The corresponding author (GW), had full access to all the data in the study and has final responsibility to the decision to submit this manuscript for publication.

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All authors disclose any financial and personal relationship with other people or organization that could inappropriately influence (bias) their work.

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