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Daptomycin lock therapy for grampositive long-term catheter-related bloodstream infections

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SUMMARY

Introduction: To evaluate the efficacy of Daptomycin (DPT) lock therapy in the treatment of Grampositive long-term catheter-related bloodstream infections (LT-CRBI). **Patients and methods:** A retrospective review of all patients receiving DPT lock therapy for the treatment of LT-CRBI from December 2009 to May 2010 was conducted. The primary endpoint used in this study was failure to cure the episode of LT-CRBI. Cure was defined as fever disappearance, negative blood cultures within 1 month after the end of treatment, and catheter salvage. **Results:** Thirteen subjects (seven men, mean age 62 years) were evaluated. There were six *Staphylococcus epidermidis*, two *Staphylococcus hominis*, one *Staphylococcus haemolyticus*, two *Enterococcus faecalis* and two polymicrobial (*S. epidermidis* and *S. hominis*) bloodstream infections. DPT lock therapy was administered for a mean of 14 days (interquartilic range 10–14). Intravenous DPT was administered in nine patients for a mean of 10 days (interquartilic range 5–11). Clinical cure and blood culture sterilisation occurred in 11 of 13 patients (85%). Two patients had fever during treatment and catheters were removed. Median length of follow-up in patients with therapeutic success was 67 days (interquartilic range 14–88). **Conclusion:** DPT lock therapy demonstrated good *in vivo* efficacy in LT-CRBI caused by coagulase negative staphylococci and *Enterococcus* species.

What's known

Antibiotic lock therapy in combination with antibiotics is recommended in guidelines as treatment for patients with coagulase negative staphylococci uncomplicated catheter-related bloodstream infections. Success rates have varied substantially among studies and even in the non-complicated patients they have not reached 100%. Vancomycin is considered the agent of choice to perform antimicrobial locks when staphylococci are involved. Daptomycin has shown high *in vitro* efficacy in eradicating staphylococcal species embedded in biofilms. Literature on efficacy of Daptomycin in this setting is limited.

What's new

To the best of our knowledge, this is the first study evaluating the activity of Daptomycin lock therapy for the treatment of long-term catheter-related bloodstream infection. In our experience, Daptomycin lock therapy appears to be an effective conservative treatment in the management of long-term catheter-related bloodstream infection especially those caused by coagulase negative staphylococci.

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Introduction

Long-term catheter use has increased over the last decade and nowadays they are commonly used in the management of haemodialysis and oncology patients. Use of long-term central venous catheters may be compromised by an increased risk of bloodstream infections, which are associated with prolonged hospitalisation, increased patient morbi-mortality and excessive hospital-related costs. Removal of a surgically implantable vascular device is often a management challenge, and it is important to determine the role of conservative approaches, trying to avoid catheter removal. The most common route of infection in long-term catheters is through the hub, and this fact supports antimicrobial lock therapy as a suitable treatment approach. The Infectious Diseases Society of America guidelines on the management of catheter-related bloodstream infections suggests the use of antibiotic lock therapy for the salvage of central venous catheters associated with catheter-related bloodstream infections (1). However, these guidelines failed to specify which antibiotics are more active in the biofilm environment and how long the antibiotic should be locked in.

Gram-positive organisms, predominantly *Staphylococcus aureus* and coagulase negative staphylococci, account for nearly 70% of catheter-related bloodstream infections. Staphylococci embed themselves in the biofilm layer in the lumen of the catheter where they are protected from antimicrobial action. Vancomycin is considered the agent of choice to perform antimicrobial locks when staphylococci are involved (1). The expanding use of central venous catheters combined with a growing concern over drug-resistant pathogens warrants study of further options

with novel lock solutions in the treatment of catheter-related bloodstream infections. Antibiotics to be used should be active against organisms embedded in biofilm. Daptomycin (DPT) is a cyclic lipopeptide antibiotic with potent activity against Grampositive microorganisms and approved for treatment of bacteremia/endocarditis caused by *S. aureus*. Time-kill studies have demonstrated that DPT is more rapidly bactericidal than vancomycin. DPT has shown high *in vitro* efficacy in eradicating staphylococcal species embedded in biofilms (2). However, literature on efficacy of DPT in this setting is limited. The aim of this study was to assess the efficacy of DPT lock therapy in the treatment of long-term catheter-related bloodstream infections (LT-CRBI) keeping the catheter in site.

Methods

The study was carried out at Clinica Universidad de Navarra, a 300-bed University Hospital in Pamplona, Spain. A retrospective review of all consecutive adult patients receiving DPT lock therapy for the treatment of LT-CRBI from December 2009 to May 2010 was conducted. Patients were diagnosed with LT-CRBI, according to accepted criteria (i.e. quantitative blood cultures positive from both sites with a concentration of microorganisms in the culture from the port at least 3-fold greater than in the peripherally drawn culture). Patients with *Staphylococcus aureus* catheter-related bloodstream infections were excluded. Catheters were aseptically removed and cultured when no longer required or when a complication developed. Catheters were processed by a vortexing-sonication technique for quantitative bacterial culture. Microbial isolates were identified using standard techniques, and susceptibility results were interpreted according to the recommendations of the Clinical and Laboratory Standards Institute guidelines. Participants gave informed consent, and Review Board and Ethics Committee approval was obtained.

Five millilitre syringes were filled with DPT (5 mg/ml) plus heparin (to achieve a final concentration of 100 UI/ml, in the case of ports and 5000 UI/ml in the case of haemodialysis catheters) and reconstituted in lactated Ringer's solution (with 0.045 mg Ca/ml). The antimicrobial locks were replaced daily or after each session in patients with haemodialysis catheters. A quantitative blood culture was withdrawn from the catheter within 1 month after end of treatment or if patient had fever during treatment. The primary endpoint used in this study was failure to cure the episode of LT-CRBI. Cure was defined as fever disappearance, negative blood cultures within 1 month after the end of treatment, and no catheter removal due to an infectious complication at the end of follow-up.

Results

During the study period, thirteen subjects (seven men, mean age 62 years) were evaluated. Table 1 presents the characteristics, aetiological agents and outcome of patients included in the study. All patients had fever when using the device. No other infectious focus was detected in any patient. DPT minimal inhibitory concentrations of all isolates remained within the susceptibility range. All isolates were susceptible to DPT (MIC_{50}, 0.5 mcg/ml, and MIC_{90}, 1 mcg/ml). DPT lock therapy was used as a rescue treatment after a previous non-DPT lock therapy failure in seven cases (54%). A successful treatment was documented in 11 (85%) episodes. The catheter had to be removed during therapy in two episodes of CNS bloodstream infection due to persistent fever. In both cases, lock therapy had been administered for a short period (1 and 5 days, respectively). One catheter culture was negative, and *Ralstonia pickettii* was isolated from the other catheter. Relapse of the bloodstream infection with the same microorganism after stopping therapy was not observed in our series.

Table 1 Characteristics and outcome of patients included in the study

Age in years, median (IQR*)	64 (53–71)
Gender (male), no. (%)	7 (54)
Underlying disease	
Solid neoplasia, no. (%)	3 (23)
Haematological neoplasia, no. (%)	3 (23)
Renal failure, no. (%)	7 (54)
Neutropenia at diagnosis, no. (%)	1 (7)
Type of catheter (port/Hickman)	6/7
Catheter life span in days until infection episode, median (IQR)	282 (53–750)
Microorganisms	
Staphylococcus epidermidis, no.	6
Staphylococcus hominis, no.	2
Staphylococcus haemolyticus, no.	1
Enterococcus faecalis, no.	2
Polymicrobial (CNS), no.	2
ALT† duration in days, median (IQR)	14 (10–14)
IV antibiotic use, no. (%)	11 (85)
IV Daptomycin use, no. (%)	9 (69)
Outcome	
Success, no. (%)	11 (85)
Relapse, no. (%)	0
Failure, no. (%)	2 (15)
Infection attributable mortality, no.	0

*Interquartilic range. †ALT, antimicrobial lock therapy.

Median length of follow-up in patients with therapeutic success was 67 days (interquartilic range 14–88 days). No DPT-resistant organisms were isolated from any source during the study period.

Discussion

To the best of our knowledge, this is the first study evaluating the activity of DPT lock therapy for the treatment of LT-CRBI. In our experience, DPT lock therapy appears to be an effective conservative treatment in the management of LT-CRBI, especially those caused by CNS.

Although some studies showed favourable results related to the use of vancomycin for antibiotic lock therapy (3), it has been recently shown that vancomycin has a limited activity against staphylococci embedded in biofilm (4,5). Other studies (6,7) have failed to demonstrate complete eradication of bacteria from endoluminal catheter surfaces even with high vancomycin concentrations. Time-kill studies have demonstrated that DPT is more rapidly bactericidal than vancomycin. *In vitro* studies have demonstrated that DPT retains significant activity on biofilm-producing *S. epidermidis*, whereas most anti-staphylococcal agents perform poorly in this setting (2,4,8). Specifically, DPT has shown high *in vitro* efficacy in eradicating staphylococcal species embedded in biofilms, in a model of silicone Hickman catheter segments infection (4). Therefore, DPT-based locks could be an attractive option for the salvage treatment of central venous catheter or venous ports infected with coagulase negative staphylococci.

Prior studies have demonstrated physical and chemical compatibility of DPT and heparin (2). Grau et al. (9) reported a case that described DPT lock therapy with successful results following a *S. aureus* port-related sepsis. However, Guimard et al. (10) reported a venous access port meticillin-resistant CNS infection that, despite prolonged DPT-based lock treatment, careful monitoring of DPT plasma concentrations and susceptibility testing, relapsed 1 week after treatment discontinuation.

Enterococci are an increasingly important cause of intravascular catheter-related bloodstream infection, but the evidence base for treating such cases is limited. We reported three out of four successfully treated patients with catheter-related enterococci bloodstream infections (11). In the present study, the two *Enterococcus faecalis* cases were successfully treated with DPT lock therapy plus intravenous DPT.

There are several limitations to our study. This is not a comparative series and includes a low number of patients, thus, removing our ability to analyse factors that might contribute to the success or failure of DPT lock therapy. On the other hand, strict inclusion criteria were used to minimise misclassification bias. The use of DPT locks could lead to the selection of resistant organisms. However, we believe that this possibility is unlikely. Using the antimicrobial lock therapy, the drug is applied locally and does not come into contact with patients' blood. It is administered at a high concentration rather than at the sub-inhibitory concentrations that seem most prone to lead to the emergence of resistance.

In spite of the limitations related to the study design, the results allow us to make a valid consideration. DPT lock therapy demonstrated good *in vivo* efficacy in LT-CRBI caused by coagulase negative staphylococci and *Enterococcus* species. Results of the present study support further investigation of DPT lock therapy in a clinical trial.

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Author contributions

All authors have contributed equally to the work (Conception or design, or analysis and interpretation of data. Providing intellectual content of critical importance to the work described. Drafting the article or revising it) and have seen and approved the manuscript.

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