

Treatment of long-term catheter-related bloodstream infections with a taurolidine block: a single cancer center experience

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ABSTRACT

Purpose: Catheter-related bloodstream infections (CRBSIs) are a common problem in cancer patients with long-term catheters. The effectiveness of taurolidine, a new antimicrobial solution, in the management of CRBSIs is still unknown. A retrospective analysis of patients with proven CRBSIs treated with a taurolidine block in combination with systemic antibiotic treatment was performed to define its role in the management of CRBSIs.

Methods: Twenty-four episodes of CRBSIs in 23 cancer patients with permanent use of the long-term catheter were treated with a taurolidine block for 3 consecutive days in combination with systemic antibiotic treatment.

Results: Treatment was successful in 16 of 24 events (67%). Explantation was performed in 8 cases (33%): in 3 patients due to a second positive blood culture, and in 1 patient due to recurrent fever after the conservative treatment. In 4 patients, the conservative approach was prematurely stopped due to persisting fever.

Conclusion: Taurolidine-based treatment may be a promising, noninvasive therapeutical approach in the management of long-term catheter-related bloodstream infections in cancer patients.

Key words: Catheter, Infection, Taurolidine, Cancer, CRBSI

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INTRODUCTION

The use of long-term central venous catheter systems in oncological patients has significantly increased during recent decades due to the widespread use of intravenous chemotherapy and parental nutrition (1). Long-term catheters such as the port-catheter system or Hickman-catheter system have facilitated this vascular access. However, severe complications such as infections or thrombosis can occur associated with the use of permanent central venous catheters (1). Catheter-related bloodstream infections (CRBSIs) are a common problem in oncological patients with permanent use of a long-term intravascular catheter. The rate of catheter-related infections ranges from 0.6% to 27%, depending on the catheter type and location and the patient's constitution (2). CRBSIs are the third most frequent type of nosocomial infection (3, 4). Management of suspected or proven CRBSIs includes antibiotic treatment alone or in combination with antibiotic locking techniques, or the immediate explantation of the indwelling catheter (5). To date, there are scarce data concerning conservative treatment approaches. The antibiotic lock technique has been first described in 1988 (6) and was greeted with great expectations. However, the experience supporting the antibiotic lock technique is still limited with only a few randomized trials and very variable

success rates (7, 8). The optimal duration of the lock, the optimal antibiotic medication, and the optimal concentration remain unknown (5). Furthermore, concerns have been raised about the emergence of antimicrobial resistance and fungal superinfection, though they have neither been proved nor disproved. On the other hand, the immediate explantation of an indwelling catheter system causes morbidity, additional costs and discomfort for the patients, which might be avoidable if conservative management of CRBSIs was more effective.

Taurolock Hep 100® (1.4% cyclo-taurolidine, 0.4 % citrate solution, heparin 100 IU/ml) is a commercially available antimicrobial catheter lock solution approved for prophylaxis against CRBSIs in dialysis, oncology, and parenteral nutrition. The antiseptic agent taurolidine is a derivative of taurinamide. Taurolidine has a broad spectrum of antimicrobial activity including activity against gram-negative and gram-positive bacteria and fungi (9). Simon et al showed a significant reduction of long-term CRBSIs in pediatric cancer patients who received a prophylaxis with taurolidine (10). In patients requiring permanent parenteral nutrition, a significant reduction in the number of CRBSIs was observed with a taurolidine-based secondary prophylaxis in a recently published randomized trial (11).

To date, the role of taurolidine in the treatment of CRBSIs is largely unclear. An observational study of Kolde-

hoff et al described a cure rate of 100% in 11 patients with CRBSIs in an inpatient setting. However, 3 patients developed a recurrent bloodstream infection, 1 of them with the same bacterial species (12).

PATIENTS AND METHODS

In this retrospective analysis, we report on a case series of 24 episodes of CRBSIs in 23 patients with permanent use of a port- or Hickman-catheter system. Patients received palliative chemotherapy for advanced cancer diseases (Tab. I). Their long-term central venous catheter system was used daily for parenteral nutrition or other intravenous medication.

Routine management included obtaining paired blood cultures (aerobic and anaerobic) from a peripheral vein and the central long-term catheter in patients with a suspected CRBSI.

A CRBSI was defined as follows: first, by a positive blood culture taken from the long-term catheter in combination with second, clinical signs such as fever or chills, in the absence of other sources of infection. The time of growth detected in the central/peripheral blood cultures was documented in the microbial report, helping the clinician to distinguish a CRBSI from another sources of infection by using the differential time to positivity (DTTP), which refers to growth detected from the catheter sample at least 2 hours before growth detected from the peripheral vein sample (13).

In all patients in this analysis, the long-term catheter was blocked with Taurolock Hep 100® for 3 to 4 consecutive days. All intravenous medication was applied via a newly inserted peripheral or central venous access. Calculated antibiotic treatment was started at the discretion

of the responsible physician and was adapted to antibio-gram-guided treatment, if necessary. After 3 to 4 days of taurolidine blockade, it was recommended to take a second blood culture from the indwelling catheter.

In case of persisting fever or signs of systemic inflammatory response syndrome (SIRS) during the taurolidine treatment, immediate explantation of the long-term catheter was performed. Patients without medical need for hospitalization were treated in an outpatient setting.

RESULTS

During the observation period (October 2008-July 2010) 24 CRBSIs in 23 patients occurred. The median patient age was 58 years (Tab. I), and the most common cancer diseases were pancreatic carcinoma and gastroesophageal cancer. All patients had daily parenteral nutrition or other intravenous medication via long-term catheter. Eight out of 24 episodes of CRBSI were diagnosed in an outpatient setting, and 11 episodes in an inpatient setting. Five patients had to be hospitalized during the CRBSI for antiinfective treatment. Blood culture analysis revealed coagulase-negative staphylococci as the most frequent bacterium (Tab. II). Neither multiresistant pathogens such as methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus faecium* nor fungi or mycobacteria were detected in our cohort. Initial calculated antibiotic treatment consisted mostly of quinolones or beta-lactam antibiotics, and secondary antibiotic treatment was mainly based on vancomycin in combination with antibiotics targeting gram-negative bacteria (Tabs. III and IV). In 2 patients, no concurrent systemic antibiotics were given at the discretion of the responsible physician due to the disappearance of systemic infection signs after interruption of the port usage.

The conservative treatment with taurolidine and antibiotic treatment was successful in 16 cases of CRBSI (67%); in 8 cases explantation of the long-term catheter was performed (33%): Explantation was performed in 3 patients after the taurolidine treatment due to a second positive

TABLE I - PATIENT CHARACTERISTICS

Median age (range)	58 years (36-75)
<i>Treatment setting</i>	
Inpatient setting	11 (46%)
Outpatient setting	8 (33%)
Hospitalization during the CRBSI episode	5 (21%)
<i>Tumor diagnosis</i>	
Pancreatic cancer	6 (26%)
Gastroesophageal cancer	5 (22%)
Head and neck cancer	3 (13%)
Colorectal cancer	2 (9%)
Cholangiocellular carcinoma	2 (9%)
Gastrointestinal neuroendocrine carcinoma	1 (4%)
Renal cell cancer	1 (4%)
Germ cell cancer	1 (4%)
Lung cancer	1 (4%)
Urothelial cancer	1 (4%)

CRBSI = catheter-related bloodstream infection

TABLE II - MICROBIAL ISOLATES FROM THE CATHETER-RELATED BLOOD CULTURES

Species	Number of isolates
Coagulase-negative <i>Staphylococcus</i> spp.	18 (75%)
<i>Escherichia coli</i>	1 (4%)
<i>Stenotrophomonas maltophilia</i>	1 (4%)
<i>Klebsiella</i> spp.	1 (4%)
<i>Kocuria kristinae</i>	1 (4%)
<i>Enterobacter cloacae</i>	1 (4%)
<i>Staphylococcus aureus</i> (MRSA)	1 (4%)

blood culture taken from the indwelling catheter after the taurolidine treatment. In 1 patient, catheter explantation was performed after the conservative treatment approach due to recurrent fever. In 4 patients, conservative treatment was prematurely stopped and immediate explantation was performed due to persistent fever, at the discretion of the treating physician. A second catheter-related infection occurred in 1 patient with a different pathogen (Tab. V).

During the conservative treatment, no taurolidine-related adverse effects were observed, especially no symptomatic hypocalcemia (citrate-containing blocking solution) or allergic reaction to taurolidine.

Furthermore no episode of septic complication such as SIRS, endocarditis, septic embolism, or septic osteomyelitis occurred. None of the patients became hemodynamically unstable or had to be transferred to the intensive care unit. None of the patients died during the treatment of the CRBSI, all patients recovered completely. Furthermore, no thrombosis, catheter occlusion, or other catheter malfunction occurred.

TABLE III - INITIAL CALCULATED ANTIBIOTIC MEDICATION

Quinolones (ciprofloxacin, moxifloxacin, levofloxacin)	8 (33%)
Amoxicillin ± clavulanic acid	4 (17%)
Ceftazidime	2 (8%)
Imipenem/cilastatin	2 (8%)
Vancomycin + sec. gram-negative antibiotic	2 (8%)
Piperacillin/tazobactam	2 (8%)
Other	2 (8%)
None	2 (8%)

TABLE IV - ANTIBIOGRAM-GUIDED ANTIBIOTIC MEDICATION

Vancomycin + sec. gram-negative antibiotic	8 (33%)
Amoxicillin ± clavulanic acid	3 (13%)
Quinolones (ciprofloxacin, moxifloxacin, levofloxacin)	3 (13%)
Co-trimoxazole	2 (8%)
1st/2nd generation cephalosporins	2 (8%)
Others	4 (17%)
None	2 (8%)

TABLE V - RECURRENT CATHETER-RELATED INFECTIONS

Patient ID	Primary isolate	Secondary isolate	Interval between CRBSI episodes
1	Coagulase-negative <i>Staphylococcus</i> spp.	<i>Kocuria kristinae</i>	11.9 weeks

CRBSI = catheter-related bloodstream infection

DISCUSSION

Only a few randomized studies exist concerning the optimal management of CRBSIs in tumor patients with indwelling catheters. Possible treatment options include noninvasive approaches as antibiotic treatment alone or in combination with the antibiotic lock technique or immediate explantation. According to the Infectious Diseases Society of America (IDSA) guidelines, conservative management in combination with antibiotic lock technique may be performed in patients with CRBSI without any sign of complications such as endocarditis or osteomyelitis (5). Immediate explantation is recommended if the patient is hemodynamically unstable or *Staphylococcus aureus*, *Pseudomonas aeruginosa*, fungi or mycobacteria are involved in the CRBSI due to the high pathogenic potential of these germs. An optimal antibiotic lock technique requires the identification of the relevant pathogen, since the choice of an effective antibiotic for the lock is essential for a success. Until the results of the microbial identification are available, an empirically chosen combination of antibiotics can be used for initial systemic treatment of the CRBSI. Since many different species can be found in CRBSIs besides coagulase-negative staphylococci, it is difficult to start the antibiotic lock treatment without having the identification of the bacteria being involved, whereas taurolidine can also be used for CRBSIs without microbial identification of the pathogen.

Taurolidine is approved for the prevention of CRBSIs. Significant reduction of events was shown in a cohort study with pediatric patients in an oncological unit and in a recently published randomized trial in patients with home parenteral nutrition (10, 11).

The data for treatment with a taurolidine lock and concurrent antibiotic treatment seems comparable to the data published for an antibiotic lock technique, by Rijnders et al, who describe a failure rate of 33% with the antibiotic lock technique in a randomized trial (7). A high success rate of 84% with antibiotic lock technique was reported by Fortun et al (8), although the success rates with antibiotic treatment alone or in combination with antibiotic lock technique did not differ significantly in this trial.

With conservative approaches in CRBSIs becoming more effective, a substantial proportion of explantations of the long-term catheters can be avoided. At present, immediate explantation of the long-term catheter after diagnosis of a CRBSI is still often performed, although guidelines

suggest that a conservative approach is an alternative, depending on the pathogens being identified.

The combination of antibiotic treatment in combination with taurolidine in our patients was safe. There were no episodes of SIRS or sepsis or complications such as endocarditis, septic osteomyelitis, or death during treatment. In any case, patients were intensely monitored, and the catheter was explanted at any sign of persisting systemic inflammation. The rate of recurrence was low and seems to be comparable to that for patients with no earlier catheter-related infection.

Defining the failure rate is difficult. Explantation was performed in 33% of patients; however, in half of these patients (4 of 8 patients) the conservative treatment was prematurely interrupted. Failure is clear in those patients with a second positive blood culture. However, the true rate of persistent catheter infection could be higher due to false negative blood cultures with concurrent antibiotic treatment.

Of those patients with the catheter being removed, more than 50% had persistent fever despite catheter removal and antibiogram-guided antibiotic treatment, showing the difficulties in distinguishing a CRBSI from other sources of infection or tumor-related inflammation in patients with advanced tumor diseases.

The optimal regimen and duration of taurolidine treat-

ment as well as the optimal combination of antibiotic treatment and local treatment are still unknown. Furthermore, it is still unclear if the combination of taurolidine with systemic antibiotic treatment is superior to antibiotic treatment alone.

Based on our results highlighting the chance of avoiding invasive and painful procedures in patients with a general reduced condition in a palliative setting, we consider a conservative approach for oncological patients with CRBSIs to be a treatment option worthy of discussion. Further randomized trials are needed to generate reliable data on the optimal management of catheter-related bloodstream infections in oncological patients.

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