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Randomized controlled trial of taurolidine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies

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SUMMARY

Background: A catheter lock solution containing 1.35% taurolidine and 4% citrate could potentially disrupt bacterial surface adherence and consecutive biofilm production due to the anti-adherence properties of taurolidine and the anticlotting and chelator activities of both compounds.

Aim: To compare the impact on microbial catheter colonization and infectious complications of heparin and taurolidine citrate as central venous catheter (CVC) lock solutions in paediatric patients with haematological malignancies.

Methods: Seventy-one patients aged 1.4–18 years were randomized to two treatment groups using either heparin ($N = 36$) or taurolidine citrate ($N = 35$). Infectious complications and clinical side-effects were prospectively monitored and microbial colonization of catheters was assessed at the time of removal.

Findings: There were two bloodstream infections in the taurolidine citrate group versus nine in the heparin group (0.3 vs 1.3 infections per 1000 catheter-days; $P = 0.03$). Fever of unknown origin and catheter occlusions were observed with a similar frequency in both groups. Microbial colonization was found in 25.4% catheters. The time of no-lock use, but not the type of lock solution or time of observation, was a significant predictor of catheter colonization ($P = 0.004$). Colonization was not observed in CVCs used immediately with taurolidine citrate lock. Seven patients in the taurolidine citrate group (20%) experienced side-effects (nausea, vomiting, abnormal taste sensations).

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Conclusion: The use of taurolidine citrate lock solution was associated with a significant reduction in bloodstream infection in immunocompromised paediatric patients. Taurolidine citrate may prevent colonization of CVCs if used from the time of insertion, but not after a period of no-lock catheter use.

Introduction

Central venous access devices constitute a significant risk for infectious complications. Prevention of catheter-related infections is a key measure to improve clinical outcomes, especially in high risk patients. Taurolidine [bis-(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)methane] is an antimicrobial agent which inhibits and kills a broad range of micro-organisms *in vitro* including multiresistant strains.[1–3] A catheter lock solution has been developed containing 1.35% taurolidine and 4% citrate. Due to the anti-adherence properties of taurolidine and the anticlotting and chelator activities of both compounds, this lock solution can disrupt bacterial surface adherence and consecutive biofilm production.[4,5]

In a previous study in paediatric cancer patients, the use of a taurolidine citrate lock solution resulted in reduction of Gram-positive infections compared with a historic control group of patients treated with a heparin lock solution.[6] However, prospective, randomized studies evaluating efficacy and safety of a taurolidine citrate lock solution have not been performed previously in a paediatric population with a high risk for infections. We hypothesized that in such patients, prolonged use of implanted central venous catheters (CVCs) and frequent handling by staff would result in a time-dependent biofilm formation and catheter colonization even in the absence of clinical symptoms. By analysing removed catheters, microbial colonization might serve as an endpoint for evaluating efficacy of catheter lock solutions. We therefore conducted a prospective randomized controlled clinical trial in paediatric patients undergoing chemotherapy for diagnosed malignancy or receiving a stem cell transplantation during 2007–2008; after allocating implanted catheters to a lock solution containing taurolidine citrate or heparin, infectious complications and clinical side-effects were prospectively monitored and microbial colonization of catheters was assessed at the time of removal.

Methods

Setting

In the Department of Paediatric Oncology/Haematology of the Charité Medical Center Berlin, each year about 90–100 children/adolescents are newly diagnosed with neoplastic disease and 20–30 with a relapse, and 40 stem cell transplantations are performed. Prior to antineoplastic treatment or stem cell transplantation, all patients receive a tunnelled single, double or triple lumen Broviac/Hickman CVC. Catheters are used immediately after placement for chemotherapy and intravenous medication/alimentation. Depending on clinical needs, the CVC is either locked after each treatment cycle (standard lock solution: heparin) or used continuously after implantation (without locking) for a limited number of days until switching to treatment cycles with intermittent locking. Treatment is started in hospital and continued in the outpatient department with continuation of locking between treatment cycles until removal of the catheter. Lock solution is only administered by experienced medical staff.

Ethical approval and informed consent

The study protocol was approved by the ethics committee of the Charité Medical Faculty Berlin and listed online as an ongoing clinical trial (ISRTCN86885538). Informed consent was given by all patients and their legal guardians. Consent forms were provided for parents and separately for children in the age groups <12 and ≥ 12 years.

Study design

Patients aged 1–18 years undergoing treatment with CVC placement with an expected duration of ≥ 4 weeks were eligible for the study. Exclusion criteria were lack of informed consent, presence of bacteraemia/sepsis at screening, presence of a secondary CVC, and known allergy to heparin or taurolidine citrate. Patients were randomized (heparin or taurolidine citrate) with stratification for age, gender and treatment facilities (oncology or stem cell transplantation unit) to two groups: group 1, heparin lock solution (5000 IU heparin/0.2 mL; Ratiopharm® Ulm, Germany, diluted to 100 IU heparin/mL sterile normal saline 0.9%); group 2, taurolidine lock solution (taurolidine 1.35%/sodium citrate 4%; TauroLock™, Tauropharm, Waldbüttelbrunn, Germany).

The catheters were locked with the appropriate filling volume. Lock solution was removed by aspiration without flushing. All catheters were tagged with a piece of colour tape to indicate group assignment. The study was performed under GCP guidelines with continuous prospective evaluation of infectious complications and side-effects by house staff and systematic follow-up during weekly visits by a study monitor (M.J.D.). In addition, external monitoring was provided by the Coordinating Centre for Clinical Studies (KKS Charité).

The primary endpoint of the study was bacterial colonization of the CVC evaluated by both qualitative and quantitative analysis after removal of the catheter. Secondary endpoints were the number of clinical infections (fever of unexplained origin: FUO), the number of primary bloodstream infections (BSIs), thrombotic occlusions, and clinical side-effects.

All patients routinely received cotrimoxazole for the prevention of *Pneumocystis jirovecii* pneumonia, but no other routine antibiotic prophylaxis. Patients were examined daily for fever (core temperature: $>38.5\ ^{\circ}C$) and signs of infection, and antibiotic broad spectrum therapy was started after drawing a blood culture from the CVC under aseptic conditions. For the latter, ≥ 2 mL of the aspirate (i.e. the catheter lock) were routinely discarded to avoid false-negative results due to dilution or antimicrobial activity of the lock solution in the case of taurolidine. Fever without a positive blood culture (FUO) was defined as clinical infection. In accordance with the