Hydrochloric acid prolongs the lifetime of central venous catheters in haematologic patients with bacteraemia

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ABSTRACT

INTRODUCTION: Bacteraemia in adult patients undergoing treatment for leukaemia is common and associated with profound morbidity and mortality. Infections related to the use of a central venous catheter (CVC) are difficult to eliminate with systemic antibiotics. Premature catheter removal is often due to retained biofilm infection. This study investigated if the additional use of hydrochloric acid (HCl) as an intraluminal lock solution may prolong the lifetime of the CVC.

METHODS: The study was performed retrospectively based on a database including patients with a tunnelled Leonard 10 F dual or triple lumen CVC implanted who received HCl instillation due to bacteraemia during a five-year period.

RESULTS: In a total of 71 cases of bacteraemia, HCl instillation was performed. Following HCl instillation, the CVC was not removed due to infection in 49 out of 71 patients (69%). Furthermore, 22 patients (31%) retained their CVC until the end of treatment. Non-infectious mortality (19/71), accidental pull (2/71) or mechanical CVC dysfunction (6/71) were other reasons for premature removal. Twenty-two catheters (31%) had to be removed due to ongoing infection. The median time from CVC placement until HCl instillation was 39 days. The median time from HCl instillation until removal of CVC was 58 days. The most common bacteriological findings were coagulase-negative staphylococci 34%, *Enterococcus* spp 14% and *Escherichia* coli 14%.

CONCLUSIONS: The study's findings indicate that a prolonged use of CVC is possible following HCl instillation in adult haematologic patients with bacteraemia.

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Patients treated for haematologic disease with a need for long-term intravenous access are highly dependent on a permanent vascular access. The use of an indwelling tunnelled central venous catheter (CVC) enables easy withdrawal of blood samples, safe and effective administration of cytotoxic and supportive antibiotic drugs, transfusions and parental nutrition. However, complications such as catheter-related blood stream infections (CRBSI), tunnel infections, thrombosis, occlusion, leakage and displacement can occur during treatment due to the CVC [1]. It is well accepted that CRBSI are often initiated from microorganisms residing in the biofilm developed on the luminal surface of the catheter [2, 3].

Due to the recalcitrant nature of biofilm-growing bacteria to antibiotic treatments, these microorganisms are generally difficult to eliminate, and inserted foreign bodies like CVCs are some of the predominant pre-disposing factors causing biofilm-related infections [4]. This combination of factors is the explanation why there is a trend towards removing CVCs if they are suspected of causing bacteraemia. CVC-derived infections may cause prolonged hospitalisation due to additional antimicrobial treatments, development of antibiotic resistance, removal of CVC, delaying of chemotherapy or mortality due to sepsis [5-7].

Local treatments with instillation of high concentrations of antibiotics in CVCs, so-called antibiotic lock therapy (ALT) have been developed to circumvent the toxicity of systemic therapy [8].

However, ALT is dependent on longer instillation times and therefore alternative non-antibiotic strategies have been developed, i.e. ethanol lock or flushing with hydrochloric acid (HCl) [9, 10]. Some studies have reported that instillation of HCl reduces CVC-associated morbidity in children [5, 6]. HCl is thought to denaturalise the protein in the biofilm and makes the embedded micro-organism more susceptible to the antimicrobial treatment. However, even after finalising antibiotic treatment, an increased risk of relapse of CRBSI remains [11]. This risk is presumably increased in severely immunocompromised patients. We retrospectively analysed the duration of CVC usage after HCl installation in adult haematologic patients with CRBSI.

METHODS

The study was conducted at the Department of Haematology, Rigshospitalet, Denmark, on consecutive patients in the 2009-2014 period. Patients with a malignant blood disorder or aplastic anaemia were enrolled if they had a tunnelled CVC and received HCl instilla-

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tion due to CRBSI. The patients were identified via a database search. The project is a retrospective, non-interventional quality control study. The regional ethics committee considered that approval was unnecessary, and informed the study that consent was not required.

All patients had tunnelled catheters of the Leonard 10 F type. Such catheters are routinely inserted at our anaesthesiologic department. Two or three lumen were used according to disease-specific treatment protocols. The catheters were inserted by anaesthetists in the operation room under sterile conditions. CRBSI was defined clinically in accordance with the guidelines of the Center for Disease Control [8]: a) one or more signs of bacteraemia (fever (> 38.0 °C)), chills or temporal hypotension, b) bacteraemia with organism(s) common to catheter-related infections and not related to an infection at another site. Paired blood cultures from peripheral vein and CVC were not performed routinely.

Patients with positive blood cultures received HCl instillations if CRBSI was suspected according to the above definition. Relevant systemic antibiotic treatment in combination with HCl lock therapy was initiated upon individual evaluation, based on results of blood cultures and clinical signs by the treating physician in conference with a microbiologist. The HCl instillation was administered by experienced nurses at a leukaemia unit according to the guideline (**Table 1**).

Data were collected on CVC type, neutrophil status at placement, bacteriological findings and antibiotic treatment. Data were also collected through the individual patient's medical record to capture complications such as sepsis, thrombosis and mortality related to CRBSI.

Categorical data are presented as frequencies and percentages. Continuous data are given as a mean ± standard deviation or median and interquartile range. All data analyses were completed using IBM SPSS software, version 22.0 (Chicago, IL).

RESULTS

During the study period, 75 adult patients received HCl instillation. Four patients were later excluded as they failed to meet the inclusion criteria. Complete medical records were available for all patients. All patients receiving HCl instillation were registered prospectively in a database.

Most patients were diagnosed with acute myeloid leukaemia (69%) or acute lymphoblastic leukaemia (24%). The mean patient age was 49.9 ± 18 years.

The median neutrophil count prior to CVC placement was 0.7 (0.5-2.5) × 10^9/l. The median time from placement of CVC to HCl instillation due to CVC-associated bacteraemia was 39 (16-132) days. The median time from HCl instillation to removal of CVC was 58 (17-193) days. No serious adverse events were observed using the HCl installation procedure.

Table 2 shows the different causes for CVC removal. In all, 22 out of 71 patients could continue the whole treatment for the underlying disease with the original CVC. Eight CVCs had to be removed due to non-infectious reasons (two accidental removals and six due to mechanical dysfunction). Nineteen patients died due to non-infectious causes.

A total of 22 CVCs were removed due to infection. Nine of the 22 patients suffered a secondary catheter-associated infection after HCl instillation. Another 13 CVCs had to be removed because of antibacterial treatment failure. In this subgroup, four patients had a tunnel infection, four infections caused severe sepsis, and five CVCs were removed with ongoing bacteraemia without another recognised focus. The tip of CVC was sent for culturing in less than 30% of cases upon removal.

Microorganisms involved in the CRBSI were Gram-positive isolates in 72% of the patients, of which coagulase-negative staphylococci were found in blood cultures in 34% and *Enterococcus* spp in 14% of all patients. Among Gram-negative isolates (25% in total), *Escherichia coli* was found in 14% of all patients. Fusarium species was demonstrated in one patient.

TABLE 1

Hydrochloric acid instillation guideline.

Procedure step	Instruction
1	Free blood flow from the CVC is ensured in each port/lumen
2	The catheter is flushed with NaCl 0.9% in each port/lumen
3	2.5 mmol/ml of HCl is installed in each port/lumen of the catheter according to the volume of dead space
4	Recap the CVC
5	Wait 10 min
6	Aspirate 5 ml of HCl/NaCl 0.9%
7	The catheter is flushed with 10 ml NaCl 0.9% in each port/lumen
8	Repeat steps 3-7 2 × to ensure that each port/lumen is flushed with HCl/NaCl 3 × each.

CVC = central venous catheter; HCl = hydrocloric acid.

TABLE 2

Removal of central venous catheters.

Cause of removal	Patients, n (%)
Concluded treatment	22 (31)
Accidental pull	2 (3)
Death	19 (27)
Dysfunction	6 (8)
Infections total	22 (31)

DISCUSSION

The treatment of catheter-associated infection with intraluminal lock solution in addition to systemic antibiotics is known to be effective in children with leukemic disease [5-7]. We report the feasibility and efficacy of the HCl lock in adult patients primarily with a malignant haematologic disease and a need for long-term intravenous access in patients suffering from a CVC-associated bacteraemia. This is the first report to describe the favourable outcome of the use of HCl lock in a large adult patient population with CRBSI. The study reflects the safety to maintain the CVC in patients with severe neutropenia due to malignant haematological diseases at placement.

We found that treatment of catheter-associated bacteraemia with HCl instillation in addition to systemic antibiotics effectively prevented preterm removal of the CVC, which would otherwise have been a consequence. Overall catheter salvage by HCl instillation was observed in 69% of the patients who had the CVC removed for other reasons than infection (Table 2). This result is in line with studies in children with leukaemia [5-7].

Patients with acute leukaemia with an expected long-term therapy are highly dependent on a permanent vascular access. Infection of a tunnelled CVC not only delays treatment but leads to significant morbidity and even mortality due to sepsis and complications following catheter removal and re-insertion of a new CVC. However, the main reason for removal of the CVC in the present study was demonstrated to be non-infectious causes. In all, 38% of the preterm removals were caused by non-infectious mortality, mechanical dysfunction of CVC and, rarely, accidental pull (Table 2). It may be speculated if HCl flushes and inability of the dacron cuff-to-bond well in the subcutaneous tunnel may add to accidental removal and mechanical dysfunction. However, the incidence of accidental pull and mechanical dysfunction together as the cause for removal in 11% of the cohort may be expected in this context. No observations in the clinic have indicated any relation to HCl instillation either during the study period or later when the principle has been used routinely. Current management at our institution remains the same in patients considered to have CRBSI as in the study, including HCl instillation.

Among patients with treatment failure by addition of HCl instillation, we observed the emergence of a new microorganism (secondary infection) in 41% (Table 2) of cases. This effect could either be the result of colonisation by a multi-bacterial biofilm or of a novel infection. The result further supports the interpretation of the efficacy of HCl in combination with systemic antibiotic treatment and that HCl instillation contributes to prolong the lifetime of the CVC after a CRBSI episode. The impact of HCl instillation on CVC-related bacteraemia may be relevant in both neutropenic and immuno-competent patients who receive treatment via a central venous access.

Neutropenia is often seen in the haematologic patient population, either as a part of the disease or presenting during treatment with chemotherapy and immunosuppressants. The circumstances at the CVC placement might have influenced the subsequent incidence of infections. Neutropenia at placement is a risk factor for early infection of CVC in paediatric patients [12]. The aim at our institution is to place the CVC within the first 48 hours of admittance in patients with acute malignant diseases and other patients who are needed to commence long-term treatments, regardless of their initial blood count. The study population with 66/71 patients (93%) suffering from acute leukaemia and overall a severe to moderate neutropenia is representative of a haematological patient in this context. Overall, the neutropenia at placement may not have been sufficiently pronounced to constitute a risk factor [12]. The time from placement of the CVC to HCl installation varied considerably: 16-132 days, which may be representative for this patient population.

The microbiological spectrum of positive blood cultures shows similarities with a report from our institution in a similar patient population published 15 years ago [13]. Coagulase-negative staphylococci, *E. coli* and enterococci remain the dominant infections, despite the increased treatment intensity and use of broad-spectrum antibiotics implemented in that period.

Our study has limitations. It is a retrospective analysis without any control group. Neither the characteristics of the study nor the number of included patients allow for a definite evaluation of the efficacy of a HCl lock solution. However, the study represents a typical clinical situation among adult haematological patients with the clinical signs of a catheter-related infection and limited possibilities of interventions, either catheter salvation under antibiotic treatment or catheter removal. As systemic antibiotic treatment alone only has limited success in catheter-related infections, especially if the patient is neutropenic, the study demonstrates a remarkably high salvation rate of CVC by concomitant systemic antibiotic treatment and intraluminal lock solution with HCl. The incidence of bacterial relapse seems to be low, even taking four cases of secondary severe sepsis into account. The clinical decision to install HCl was based on an individual assessment of each patient, the result of blood cultures, concomitant antibiotic treatment; and removal of the CVC would have been a likely alternative outcome. Paired blood cultures were not performed routinely, which is common in patients with severe pancytopenia. It also reflects a controversy in clinical practice and the translation of

applicable definitions of CRBSI when the tip of CVC was not sent to culture analysis systematically [14]. The incidence of coagulase-negative staphylococci may have been overestimated due to the risk of skin contamination from the CVC during the procedure (Table 1). In principle, this may also result in an overestimate of the effect of HCl treatment. Still, the results document that in a consecutive adult population, HCl instillation in CRBSI is safe and easy to perform and seems to hold a potential for catheter salvage in long-term neutropenic patients.

The HCl instillation procedure does not induce immediate reactions. The non-invasive procedure of HCl instillation can be performed by the nurse staff on the ward, and the training needed requires no special skills (Table 1). In this manner, HCl instillation reduces intra-hospital patient transport, removal of the CVC, painful procedures of new venous access including the risk associated with insertion, if necessary, to replace a CVC once the bacteraemia has been treated. The data collection was performed in the course of a five-year period, which adds to the representativeness of our material and underpins that the spectrum of haematologic patients included was that of a routine procedure at a leukaemia unit.

CONCLUSIONS

The HCl lock solution appears to be a good addition to the systemic treatment of CVC-related infections. The procedure represents a safe alternative to the use of intraluminal antibiotics to avoid premature removal of the catheter in the majority of simple CVC infections in neutropenic patients, occurring in a vulnerable period during the treatment course. The principle may be implemented as part of the practice in CRBSI across all age groups [8, 15]. The results justify a randomised, controlled trial assessing the HCl lock against either placebo or ALT in patients treated for conditions associated with long-term bone marrow insufficiency receiving treatment by a CVC that is complicated by CRSBI to clarify the effect of HCl instillation as an addition to systemic antibiotic therapy.

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LITERATURE

1. Boersma RS, Jie KS, Verbon A et al. Thrombotic and infectious complications of central venous catheters in patients with hematological malignancies. Ann Oncol 2008;19:433-42.
2. Lebeaux D, Chauhan A, Rendueles O et al. From in vitro to in vivo models of bacterial biofilm-related infections. Pathogens 2013;2:288-356.
3. Chatzinikolaou I, Hanna H, Hachem R et al. Differential quantitative blood cultures for the diagnosis of catheter-related bloodstream infections associated with short- and long-term catheters: a prospective study. Diagn Microbiol Infect Dis 2004;50:167-72.
4. Høiby N, Bjarnsholt T, Moser C et al. ESCMID guideline for the diagnosis and treatment of biofilm infections 2014. Clin Microbiol Infect 2015;21(suppl 1):S1-25.
5. Barbaric D, Curtin J, Pearson L et al. Role of hydrochloric acid in the treatment of central venous catheter infections in children with cancer. Cancer 2004;101:1866-72.
6. Madsen M, Rosthøj S. Impact of hydrochloric acid instillation on salvage of infected central venous catheters in children with acute lymphoblastic leukaemia. Scand J Infect Dis 2013;45:38-44.
7. Larsen LN, Malchau E, Kristensen B et al. Hydrochloric acid treatment of tunneled central venous catheter infections in children with cancer. J Pediatr Hematol Oncol 2011;33:e64-e68.
8. Mermel LA, Allon M, Bouza E et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49:1-45.
9. Metcalf SCL, Chambers ST, Pithie AD. Use of ethanol locks to prevent recurrent central line sepsis. J Infect 2004;49:20-2.
10. Takla TA, Zelenitsky SA, Vercaigne LM. Effectiveness of a 30% ethanol/4% trisodium citrate locking solution in preventing biofilm formation by organisms causing haemodialysis catheter-related infections. J Antimicrob Chemother 2008;62:1024-6.
11. Raad I, Kassar R, Ghannam D et al. Management of the catheter in documented catheter-related coagulase-negative staphylococcal bacteremia: remove or retain? Clin Infect Dis 2009;49:1187-94.
12. Shaul DB, Scheer B, Rokhsar S et al. Risk factors for early infection of central venous catheters in pediatric patients. J Am Coll Surg 1998;186:654-8.
13. Møller T, Borregaard N, Tvede M et al. Patient education – a strategy for prevention of infections caused by permanent central venous catheters in patients with haematological malignancies: a randomized clinical trial. J Hosp Infect 2005;61:330-41.
14. Tribler S, Brandt CF, Hvistendahl M et al. Catheter-related bloodstream infections in adults receiving home parenteral nutrition: substantial differences in incidence comparing a strict microbiological to a clinically based diagnosis. J Parenter Enteral Nutr 2018;42: 393-402.
15. Gominet M, Compain F, Beloin C et al. Central venous catheters and biofilms: where do we stand in 2017? APMIS 2017;125:365-75.