Adjunctive management of central line-associated bloodstream infections with 70% ethanol-lock therapy

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Received 19 June 2013; returned 23 September 2013; revised 16 January 2014; accepted 17 January 2014

Objectives: Ethanol is bactericidal against most pathogens implicated in central line-associated bloodstream infections (CLABSIs) and biofilms. Current Infectious Diseases Society of America guidelines cite insufficient evidence to support adjunctive ethanol-lock therapy (ELT) for central venous catheter (CVC) salvage in patients with CLABSI in combination with systemic antimicrobial treatment. We evaluated the safety and potential efficacy of 70% ELT for CLABSI at our institution after implementation of a hospital ELT protocol.

Methods: We collected data on all patients treated with adjunctive 70% ELT for catheter salvage from September 2009 to September 2011 and assessed clinical outcomes and adverse events associated with ELT.

Results: Sixty-eight hospitalized patients received 70% ELT for CVC salvage: 45 (66%) met the criteria for CLABSI. Five (11%) had persistent or recurrent bacteraemia triggering CVC removal; 28 (62%) preserved their CVC long term. There were no documented adverse events associated with ELT.

Discussion: Adjunctive 70% ELT is an inexpensive, well-tolerated option for CVC salvage in patients with CLABSI and warrants further investigation.

Keywords: catheter-related infections, biofilms, salvage therapy

Introduction

In 2011, the US CDC estimated that 41 000 central line-associated bloodstream infections (CLABSIs) occur in hospitalized patients across the USA annually, with an excess cost of up to $56 000 per episode.1, 2

Current Infectious Diseases Society of America (IDSA) guidelines recommend antimicrobial lock therapy as an option for central venous catheter (CVC) salvage in patients with CLABSI.3 There are drawbacks to antibiotic lock therapy, however, including poor biofilm penetration, with partial killing of microbial populations embedded in an extracellular polymeric substance matrix, selection of antibiotic resistance and recrudescence of bacterial growth after cessation of antibiotic therapy.4, 5

Ethanol is an inexpensive, readily available antiseptic agent that exerts its broad-spectrum bactericidal and fungicidal activity by non-specific denaturing of proteins and dissolution of lipids.6 Ethanol is effective at eradicating biofilm-embedded bacteria.7 Prolonged exposure to 70% ethanol solutions does not appreciably alter the integrity or mechanical properties of polyurethane and silicone intravascular catheters.8

Ethanol-lock therapy (ELT) is safe and effective in CLABSI prophylaxis in oncology patients and total parenteral nutrition recipients but clinical data supporting the use of ELT for CVC salvage in CLABSI are sparse and limited to paediatric populations.9– 12 Current IDSA guidelines do not endorse the use of adjunctive ELT for CVC salvage in CLABSI, citing insufficient evidence.1

In September 2009, we implemented an institutional ELT protocol for CVC salvage in CLABSI. We sought to evaluate the safety and outcomes associated with the use of ELT for CVC salvage at our institution.

Patients and methods

Patient population

We reviewed the medical records of patients with a bloodstream infection who received ELT for CVC salvage at our institution from September 2009 through September 2011. All patients prescribed ELT over this period were identified through electronic pharmacy records. The decision to initiate ELT was at the discretion of each patient’s clinical care team.

ELT protocol

For CVC salvage in patients with long-term CVCs and suspected CLABSI, our institutional ELT protocol (available as Supplementary data at JAC Online) recommends the instillation of up to 2 mL of a 70% ethanol
Data collection

Demographics and details of each bloodstream infection were recorded, including the aetiological organism, duration of bacteraemia or fungaemia, concomitant systemic antibiotics and CVC type and site. The frequency and duration of repeat blood cultures after the initiation of ELT was determined at the discretion of clinical care teams.

We collected details of ELT, including ELT duration and adverse events potentially related to ELT administration (CNS depression, headaches, light-headedness, dizziness, arrhythmias, fatigue, nausea, local venous irritation or flushing requiring premature cessation of ELT). Data were censored on 1 November 2011.

CLABSI adjudication

We evaluated each bloodstream infection episode according to CDC/National Healthcare Safety Network (NHSN) CLABSI criteria and classified each episode as CLABSI or secondary bloodstream infection from another anatomical site.13

Outcome measures

CVCs were removed at the discretion of each patient’s clinical care team. We recorded the duration of CVC retention following the initiation of ELT and the reasons for CVC removal. The Partners Healthcare Human Research Committee approved this study.

Results

We identified 68 first bloodstream infection episodes in patients treated with adjunctive ELT for CVC salvage. Forty-five (66%) of these episodes met CDC/NHSN criteria for CLABSI.13 These patients had a median age of 53 years and most had an underlying malignancy (Table 1). Administration of chemotherapy (56%) and total parenteral nutrition (20%) were the most common CVC indications. Most patients (67%) received ELT for CLABSI associated with a tunnelled catheter. Coagulase-negative Staphylococcus (44%) was the most commonly implicated aetiological organism, followed by Gram-negative bacilli (22%) and Enterococcus faecium (7%).

Patients were bacteraemic or fungaemic for a median of 3 days (IQR 2–4; range 0–7) prior to the initiation of ELT. Patients received a median of 5 days (IQR 3–6; range 1–21) of adjunctive ELT with systemic antimicrobial therapy.

In 35 (78%) patients, blood cultures became sterile prior to ELT initiation; in 4 patients, blood cultures became sterile on the date of ELT initiation; and for 1 patient each, blood cultures became sterile 1, 2 and 3 days after ELT initiation. The remaining three patients were bacteraemic for 4, 6 and 7 days, respectively, after initiation of ELT, with sterilization of blood cultures after CVC removal. Two patients had recurrent bacteraemia after ELT treatment.

Sixteen (36%) CLABSI patients underwent removal of their infected CVCs within 7 days of ELT treatment, 3 due to persistent bacteraemia (2 coagulase-negative Staphylococcus and 1 Bacillus cereus) and the remainder because the CVC was no longer clinically necessary (7), not functioning well (3) or clinician preference despite the absence of persistent CLABSI (3). One patient died of complications of an underlying malignancy 7 days after initiation of ELT without evidence of persistent CLABSI.

The remaining 28 (62%) CLABSI patients retained their CVCs for a median of 71 days (IQR 34–162; range 11–569), for a total of 3274 additional patient CVC-days after ELT treatment. One patient with Stenotrophomonas malophilia CLABSI had recurrent St. malophilia bacteraemia 51 days after her initial CLABSI. A second patient with S. malophilia CLABSI developed Candida parapsilosis fungaemia 115 days after the initial CLABSI and 50 colonies of S. malophilia grew from cultures of the CVC tip. No other patients had evidence of recurrent CLABSI after ELT.

Of 45 CLABSI patients, 9 (20%) had a CVC for administration of total parenteral nutrition. One patient’s CVC was removed due to persistent bacteraemia with B. cereus despite 6 days of ELT. Three

| Table 1. Patient, CVC and bloodstream infection characteristics of patients with CLABSI who received adjuvant 70% ELT |
|---------------------------------|-----------------|
| **Characteristic**              | **n**           |
| Patients, n                      | 45              |
| Age (years), median (IQR; range) | 53 (41–65; 21–90) |
| Female, n (%)                    | 23 (51)         |
| Malignancy, n (%)                | 34 (76)         |
| Primary CVC indication, n (%)    |                 |
| chemotherapy                     | 25 (56)         |
| total parenteral nutrition       | 9 (20)          |
| other parenteral medications     | 6 (13)          |
| blood product transfusions       | 3 (7)           |
| haemodialysis                    | 2 (4)           |
| Type of CVC, n (%)               |                 |
| tunneled CVC (silicone)          | 30 (67)         |
| implanted port (polyurethane)    | 10 (22)         |
| PICC (polyurethane)              | 4 (9)           |
| both implanted port and PICC     | 1 (2)           |
| Causative pathogen, n (%)        |                 |
| coagulase-negative staphylococci | 20 (44)         |
| Gram-negative bacilli            | 10 (22)         |
| E. faecium                       | 3 (7)           |
| Streptococcus mitis              | 1 (2)           |
| S. aureus                       | 1 (2)           |
| Candida spp.                     | 2 (4)           |
| B. cereus                       | 1 (2)           |
| Corynebacterium jeikeium         | 1 (2)           |
| polymicrobial bacteraemia        | 6 (13)          |

PICC, peripherally inserted central catheter.

aThree Escherichia coli, two S. maltophilia, two Pantoaea agglomerans, one Pseudomonas aeruginosa, one Enterobacter aerogenes and one Citrobacter freundii.

bOne C. albicans and one C. parapsilosis.

cTwo S. mitis and coagulase-negative staphylococci (CoNS), two CoNS and methicillin-resistant S. aureus, one CoNS and methicillin-resistant S. aureus and one CoNS and Enterococcus faecalis.
of these patients had their catheters removed after 2 days of ELT, one because the CVC was no longer clinically necessary for the patient’s nutrition and two because the CVC was not functioning well despite the absence of persistent CLABSI. The remaining five patients had sterilization of blood cultures and retained their CVCs for a median of 82 days.

Safety and adverse events

There were no documented adverse events potentially associated with ELT in the 45 CLABSI patients. Two of the 23 patients treated with ELT for secondary bloodstream infection discontinued ELT therapy after 3 and 5 days, respectively, because of recurrent CVC lumen occlusion. No patients were reported to have experienced CNS depression, arrhythmias, fatigue, headaches, dizziness, nausea, light-headedness, local venous irritation or flushing, attributed clinically to ELT.

Discussion

The use of 70% ELT for adjunctive therapy of CLABSI appeared to be well tolerated and potentially effective in a cohort comprised predominantly of cancer patients requiring long-term indwelling CVCs for chemotherapy and supportive care. Only five (11%) patients had persistent or recurrent bacteraemia triggering CVC removal after ELT: three patients had persistent bacteraemia with coagulase-negative Staphylococcus or B. cereus during the initial CLABSI episode, while two patients had evidence of recurrent S. maltophilia infection several weeks after the initial CLABSI episode. While 36% of CVCs were removed within 1 week of ELT initiation, mostly in patients whose CVCs were no longer clinically necessary, 28 of 45 (62%) patients retained their CVCs for a median of 71 additional CVC-days without recrudescence of bloodstream infection.

While this study is relatively small in size and retrospective in nature, with substantial heterogeneity in the length of bacteremia prior to ELT, the duration of ELT exposure and each clinician’s threshold for CVC removal, it is the largest and most comprehensive assessment of the clinical safety and efficacy of ELT in adult CLABSI patients to date, with a relatively long duration of follow-up after ELT exposure.

Our findings should be interpreted cautiously: prior to initiation of this ELT protocol, the majority of patients with CLABSI at our institution had prompt removal of their CVCs, so it was not possible to define a comparable control group where CVC salvage was attempted with systemic antimicrobial therapy alone, making it challenging to draw definitive conclusions about the efficacy and safety of exposure to adjunctive ELT. Also, due to the retrospective nature of this analysis, the assessment of adverse events associated with ELT depended on the quality of physician and nursing clinical documentation, which was variable. However, no patients in this cohort were reported to have any symptoms theoretically associated with ethanol toxicity, namely CNS depression, arrhythmias, fatigue, headaches, dizziness, nausea, light-headedness, local venous irritation or flushing, that triggered discontinuation of ELT. Additionally, there were no documented reports of CVC malfunction or diminished integrity attributed to ELT.

Ethanol is comparable or superior to antibiotic agents in sterilizing catheter-associated biofilms in vitro. Sherertz et al. examined the efficacy of ethanol and various antibiotic agents (vancomycin, ciprofloxacin, minocycline and rifampicin) in sterilizing S. aureus biofilms incubated on silicone CVCs. At concentrations of ≥ 30%, ethanol was superior to all other agents tested, with 3.6–3.9 log units of killing at 2, 4 and 24 h. At concentrations of ≥ 35%, ethanol has been shown to reduce the metabolic activity of mature Candida albicans biofilms by ≥ 99%.

Despite these in vitro studies demonstrating the effectiveness of ethanol in sterilizing biofilms, clinical data on the efficacy of ELT for CVC salvage are sparse and most analyses have included patients who did not clearly meet CLABSI criteria. In a retrospective analysis of 28 children with 39 discrete bloodstream infections, 16 of 24 (67%) patients treated with adjunctive ELT and only 7 of 15 (47%) treated with systemic antibiotics alone were free of recurrent bloodstream infection at 4 weeks. Another study of 70% ELT in 51 bloodstream infection episodes in 40 children found no recurrent bloodstream infection at 30 days in 45 of 51 (88%) episodes. Another study prospectively examined the effects of ELT in conjunction with systemic antibiotics in 19 paediatric and adult patients with bloodstream infection, predominantly due to Gram-negative pathogens. Of 17 patients who completed 5 days of ELT, all had sterile blood cultures 6 days after completion of ELT and 12 (71%) retained their CVCs for > 14 days without recrudescence of bacteraemia.

One patient in our study had persistent B. cereus CLABSI and two patients developed late recrudescent S. maltophilia infections associated with their salvaged catheters despite appropriate antimicrobial therapy and ≥ 5 days of adjunctive ELT. B. cereus and S. maltophilia are known to form highly tenacious biofilms in vitro that may be refractory to sterilization by even relatively high concentrations of ethanol. CLABSI due to these organisms should probably not be considered for 70% ELT.

It is difficult to assess and capture all potential adverse events associated with ELT in a retrospective analysis. The amount of ethanol that may reach the systemic circulation with our ELT protocol is miniscule, as it is mostly aspirated after the dwell period, and generally well-tolerated by our study population. Whenever possible, the ethanol-lock solution instilled in the CVC should be aspirated and not flushed into the systemic circulation. Although unlikely, clinicians should monitor patients receiving ELT closely for adverse effects that may be associated with ELT, including CNS depression, cardiac arrhythmias, excessive fatigue, prolonged headaches, dizziness, severe nausea, light-headedness, local venous irritation or flushing. The development of these or other symptoms potentially attributable to ELT should warrant reconsideration of ELT therapy for CVC salvage.

The removal and replacement of long-term CVCs is burdensome and costly. Further controlled studies into the effects of adjunctive ELT, an inexpensive, well-tolerated and potentially effective method for CVC salvage in CLABSI, are warranted.

Acknowledgements

Results from this study were presented in part at the Forty-ninth Annual Meeting of the Infectious Diseases Society of America, Boston, MA, USA, 2011 (Abstract 670).
Funding
The work was carried out in part with support from the National Institutes of Health (AI097225 to S. K.).

Transparency declarations
None to declare.

Supplementary data
Our institutional ELT protocol is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References