Efficacy of ethanol locks in reducing central venous catheter infections in pediatric patients with intestinal failure

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Abstract

\textbf{Purpose:} We sought to determine whether a regimen of 70\% ethanol locks could reduce the rate of central venous catheter (CVC) infections in parenteral nutrition-dependent children with intestinal failure.

\textbf{Methods:} We performed a retrospective review of 23 parenteral nutrition-dependent children in our multidisciplinary intestinal rehabilitation clinic who started ethanol lock therapy between September 2007 and June 2009. The treatment regimen consisted of a 70\% ethanol lock instilled 3 times per week in each catheter lumen. The rate of CVC infections before and after initiation of ethanol lock therapy was compared using the Wilcoxon signed ranks test with significance set at $P < .05$.

\textbf{Results:} The most common diagnoses leading to intestinal failure were necrotizing enterocolitis (26.1\%), gastroschisis (21.7\%), and intestinal atresia (14.3\%). Ethanol locks were well tolerated with no reported adverse side effects. The infection rate decreased from 9.9 per 1000 catheter days prior to initiation of ethanol locks to 2.1 per 1000 catheter days during therapy ($P = .03$).

\textbf{Conclusions:} A regimen of ethanol lock therapy administered three days per week appears to be a safe and effective means of reducing the rate of CVC infections in parenteral nutrition–dependent children with intestinal failure.

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1. Purpose

Central venous catheter (CVC) infections are a major source of morbidity and mortality for children with intestinal failure. Parenteral nutrition (PN) remains a mainstay of therapy in the care of children with intestinal failure, and in
these patients, central venous catheters are a lifeline. Previously published reports have shown rates of catheter-related infections in children with intestinal failure ranging from 11.15 to 26.5 infections per 1000 catheter days [1, 2]. Although multidisciplinary management of intestinal failure can reduce the use of PN [3, 4], a substantial number of patients with indwelling central venous catheters continue to develop line sepsis. Catheter-associated sepsis can lead to line removal, loss of access sites, accelerated hepatic damage, hospitalization, and increased mortality.

Methods to reduce the number of infections in central venous catheters have become standard of care. These include insertion under sterile conditions, maintenance of sterile occlusive dressings, and close surveillance for signs of infection [5]. Antibiotic catheter lock solutions have also been shown to be effective in reducing catheter-related bloodstream infections in pediatric patients [6]. Concerns about the use of antibiotic lock therapy include the development of resistant bacteria strains, as well as hypersensitivity to or toxicity from the antibiotics themselves [5]. In many instances, the antibiotic-heparin combination has limited physicochemical stability which makes it impractical for homecare patients. In addition, the biofilm formed by bacteria on an indwelling catheter confers its own inherent resistance [7]. To penetrate the biofilm, antibiotic concentrations 20 to 1000 times stronger than those typically required to produce the same killing effect on planktonic (free-floating), bacteria are required [7]. Recent studies of various catheter lock solutions led to the discovery of ethanol as an effective antibacterial agent [8, 9].

Ethanol acts as a bactericidal and fungicidal agent by denaturing the cell membrane. Its wide spectrum of antimicrobial action has led to diverse uses, such as mouthwashes, hand washes, and hospital disinfectants [10]. A 4-hour exposure to a concentration of 70% ethanol has been shown to be both bactericidal and fungicidal to Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, and Candida albicans in an experimental model of plastic-adherent biofilm [11]. Ethanol has the ability to penetrate the protective biofilm, and has not been shown to pose a risk for development of resistance [12].

We recognized the potential for a reduction in catheter-related sepsis in our pediatric intestinal failure patients, and instituted an outpatient regimen of ethanol locks. Our study aim was to assess if this intervention did indeed decrease the rate of central venous catheter infections in parenteral nutrition-dependent children with intestinal failure.

2. Methods

Intestinal failure patients with a history of one or more CVC infections in the previous year were eligible for ethanol lock therapy. A regimen of 70% ethanol catheter locks was instituted on an outpatient basis, beginning in September 2007. A 70% ethanol in water solution was prepared in the Children’s Hospital Boston Pharmacy by dilution of Dehydrated Alcohol Injection, USP, which consists of not less than 98% by volume of ethanol (ethyl alcohol). The volume of lock solution delivered was determined for each patient individually, based on the volume of the catheter. Catheter volume was determined by aspirating from the catheter until blood return was noted and then using the volume of the aspirated fluid as the volume of the lock solution. For each patient, the first administration of the ethanol lock was done in a monitored inpatient setting. The ethanol lock solution was instilled into the catheter between infusions of PN, and left in place for a minimum dwell time of 4 hours. At the start of the patient’s next administration of PN, the ethanol solution was withdrawn from the catheter and discarded. Once the patient’s caregivers were instructed in the administration of ethanol locks, this process was executed three days per week on an outpatient basis (usually Monday, Wednesday, and Friday). All patients and their caregivers were questioned regarding tolerance of the ethanol locks as well as possible adverse events during outpatient clinic visits, which occurred at least every 3 months during the study period.

All patients included in this study were followed by the Center for Advanced Intestinal Rehabilitation at Children’s Hospital Boston. This is a multidisciplinary team of pediatric surgeons, gastroenterologists, nurses, pharmacists, dieticians, and social workers who specialize in the management of children with intestinal failure. This study was conducted as a retrospective review of patients’ medical records under the direction of Children’s Hospital Boston Investigational Review Board protocol M06-01-0049.

Criteria for inclusion in this study included the presence of a silicone tunneled central venous catheter or silicone peripherally inserted central catheter for administration of PN or intravenous hydration fluids to treat intestinal failure. All patients were 3 months to 18 years old and weighed at least 5 kg. All patients had at least one CVC infection in the previous year. Ethanol locks were stopped during any treatment intervals with metronidazole, due to a possible disulfiram-like reaction. In addition, ethanol locks were withheld during any inpatient admission. Documented allergies to ethanol or social or religious objections to the use of ethanol were additional criteria for exclusion from ethanol lock therapy.

Demographic data collected included the following; gender, patient age at the initiation of ethanol locks, primary diagnosis leading to intestinal failure, and serum citrulline level. Dates of catheter placement and removal were also recorded. A catheter change was defined as a confirmed removal of one catheter and replacement by another. Infection data reviewed included the number of positive blood cultures isolated from the central venous catheter and the organisms grown from those blood cultures. Central venous catheter infection was defined as at least one positive
blood culture from the CVC in the absence of another confirmed source of infection such as a positive urine or sputum culture.

Statistical analysis was done using SPSS for Windows (SPSS Inc, Chicago, Ill). CVC infection rates were expressed as number of infections per 1000 catheter days. Each patient was used as his own control, and rates of catheter infections pre- and post-ethanol lock therapy initiation were compared. Age, number of catheter days, and catheter infection rates were expressed as medians with interquartile ranges. The Wilcoxon signed ranks test was used to compare paired non-parametric data. The sign test was used to compare rate changes in non-parametric data. Significance was set at \( P < .05 \).

3. Results

A total of 31 patients started ethanol lock therapy between September 2007 and June 2009. Eight patients were excluded from analysis (2 patients left the country and were lost to follow-up, 3 patients did not meet inclusion criteria, and 3 patients were primarily managed at other institutions and did not have complete infection data). Demographic information from the 23 analyzed patients is shown in Table 1. Patients with potential motility disorders (including gastroschisis, pseudoobstruction, intestinal aganglionosis, and anal achalasia) accounted for 47.8% of all patients on ethanol lock therapy. Most patients had severe short bowel syndrome, with a mean serum citrulline (an index of intestinal mucosal mass) of 10.4 ± 6.3 \( \mu \text{mol/L} \) [13].

The rate of CVC infections and catheter changes (per 1000 catheter days) before and during ethanol lock therapy are shown in Table 2. The median rate of CVC infections prior to the initiation of ethanol lock therapy was 9.9 infections per 1000 catheter days (interquartile range [IQR], 4.4-17.3). After initiation of ethanol lock therapy, the median infection rate dropped to 2.1 infections per 1000 catheter days (IQR, 0-7.6). This statistically significant decrease (Wilcoxon signed ranks test, \( Z = -2.159, P = .03 \)) is shown in Fig. 1. Eighteen of 23 patients had a decrease in their rate of CVC infections after the initiation of ethanol lock therapy.

Fig. 1 Box plot showing decreased rate of CVC infections after starting ethanol lock therapy (median 9.9 versus 2.1 per 1000 catheter days, \( n = 23 \) patients). Grey boxes encompass IQRs, and the median is shown as a horizontal line within each grey box. Whiskers represent 95% confidence intervals, and open circles indicate outliers. The difference in infection rates before and during ethanol locks was significant (Wilcoxon signed ranks test, \( Z = -2.159, P = .03 \)).
whose rate of CVC infections increased on ethanol lock therapy had an intestinal motility disorder (Fig. 3). The change in CVC infection rate after starting ethanol lock therapy was significantly different for patients with and without motility disorders (sign test, $P = .011$). After starting ethanol lock therapy, the cohort without a motility disorder had a drop in infection rate from a median of 9.9 per 1000 catheter days (IQR, 4.8-15.8) to a median of 0 per 1000 catheter days (IQR, 0-4.9). All patients without disordered motility had a decreased catheter infection rate on ethanol lock therapy. The cohort of children with motility disorders continued to have a high rate of infections (median 7.2 per 1000 catheter days, IQR 0-13.3) after starting ethanol lock therapy, as shown in Table 3. The difference in infection rates before and after ethanol lock therapy in children with motility disorders was not significant ($P = .79$).

The entire cohort of 23 patients had a total of 122 CVC infections for the duration of the study. Ninety-three infections (76.2%) were due to a single organism; 29 (23.8%) were polymicrobial. The most frequently isolated organisms were Staphylococcus (25%), Klebsiella (23%), and Enterococcus (19%). A listing of the bacterial and fungal genera isolated from the CVC cultures is shown in Table 4.

Potential adverse events of ethanol lock therapy including dizziness, lethargy or altered mental status, and intravenous lock therapy. The cohort of children with motility disorders continued to have a high rate of infections (median 7.2 per 1000 catheter days, IQR 0-13.3) after starting ethanol lock therapy, as shown in Table 3. The difference in infection rates before and after ethanol lock therapy in children with motility disorders was not significant ($P = .79$).

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Potential adverse events of ethanol lock therapy including dizziness, lethargy or altered mental status, and intravenous

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-EtOH therapy</th>
<th>During EtOH therapy</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVC infection rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal motility</td>
<td>9.9 (4.8-15.0)</td>
<td>0.0 (0.0-4.9)</td>
<td>.002</td>
</tr>
<tr>
<td>Motility disorder</td>
<td>4.6 (4.0-17.8)</td>
<td>7.2 (0.0-13.3)</td>
<td>.79</td>
</tr>
<tr>
<td><strong>Catheter change rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal motility</td>
<td>6.5 (4.7-10.3)</td>
<td>0.0 (0.0-1.2)</td>
<td>.003</td>
</tr>
<tr>
<td>Motility disorder</td>
<td>10.2 (4.3-15.8)</td>
<td>2.2 (0.0-10.8)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Infection and change rates were calculated per 1000 catheter days.

### Table 4

<table>
<thead>
<tr>
<th>Microorganisms identified in CVC infections of the 23 patients in the cohort</th>
<th>Absolute number and percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organism genus</strong></td>
<td>Absolute number and percentage</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>37 (25%)</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>35 (23%)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>29 (19%)</td>
</tr>
<tr>
<td>Candida</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Eschericia</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Other*</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Unspeciated</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><strong>Gram-negative rods</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Type of infection</strong></td>
<td>Absolute number and percentage</td>
</tr>
<tr>
<td>Single organism</td>
<td>93 (76%)</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>29 (24%)</td>
</tr>
</tbody>
</table>

* Other organisms included: Rhodococcus, Gordonia, Corynebacterium, Clostridium, Actinomyces, Bacillus, Serratia, Bifidobacteria, Citrobacter, and Neisseria.
catheter breakage were monitored during scheduled outpatient visits. There were no adverse events reported.

4. Discussion

Although the multidisciplinary care of pediatric patients with intestinal failure continues to improve [4], CVC infections remain a major source of morbidity and mortality. In addition to the need for prolonged intravenous antibiotics and costly hospitalization related to the infection itself, recurrent CVC infections contribute directly to the progression of parenteral nutrition associated liver disease [14], and may lead to catheter removal and loss of venous access sites. These factors can lead to liver and intestinal transplantation [15], which in itself is associated with potential morbidity and mortality.

Sterile insertion technique and intensive family and caregiver education are cornerstones of CVC care in our multidisciplinary intestinal failure program. We began using a regimen of ethanol lock therapy in September 2007 with the goal of reducing the CVC infection rate in our highest-risk patients—those with at least one prior CVC infection—as these children had the greatest potential benefit from this intervention. The initiation of ethanol lock therapy was the only change in our approach to CVC care during this time period.

The use of ethanol locks to treat CVC infections was first reported by Dannenberg in 2003 [16]. Their group used ethanol locks as an adjunct to standard treatment of catheter infections in pediatric hematology/oncology patients. In 2004, Metcalf reported the first use of ethanol locks in an adult on cyclic home PN [12]. This patient had 3 infection-free years after the initiation of ethanol locks. In 2008, Mouw et al [2] reported the first use of ethanol locks in a group of pediatric intestinal failure patients with a favorable reduction in infection rates after the initiation of ethanol locks, although no statistical significance could be garnered from this study due to its small size. The aforementioned studies, while small, suggested that ethanol lock therapy may be an important factor in reducing the risk of CVC infections.

The initiation of ethanol lock therapy significantly reduced the rate of CVC infections in our cohort, from a median of 9.9 infections per 1000 catheter days prior to ethanol locks to 2.1 infections per 1000 catheter days during ethanol lock therapy ($P = .03$). The median baseline infection rate of 9.9 per 1000 catheter days was comparable to other studies in similar patient populations [1,2]. The almost 5-fold reduction in catheter infection rates seen with ethanol lock therapy supports the clinical utility of this intervention.

In order to quantify the severity of intestinal failure in our patients, we examined serum citrulline levels. Citrulline concentrations have been shown to correlate with enterocyte mass, and are predictive of the ability of a patient to achieve enteral autonomy [13,17]. The serum citrulline level of the patients in our cohort (mean ± SD) was 10.4 ± 6.3 μmol/L. Earlier studies from our group have demonstrated that patients with serum citrulline level less than 12 μmol/L are unlikely to wean from parenteral nutrition [13], indicating that the study cohort of patients did have severe intestinal failure.

An unexpected finding was that the efficacy of ethanol lock therapy was affected by the presence or absence of diagnoses associated with intestinal motility disorders. Only 5 of the 23 patients had an increased rate of infection while on ethanol lock therapy, and all 5 of these patients had an intestinal motility disorder. The one patient who had a drastically increased rate of CVC infection had a short follow-up period (41 days) on ethanol lock therapy, and had 2 infections during that time interval. Subgroup analysis revealed that 100% of patients without disordered intestinal motility had a decreased rate of CVC infection on ethanol lock therapy, whereas only 55% of children with a motility disorder had a lower rate of CVC infection. The change in infection rates after starting ethanol lock therapy for those patients with intestinal motility disorders was not statistically significant.

Previous reports have shown that some children with chronic intestinal pseudo-obstruction may have concomitant immune deficiencies, including IgG, natural killer cell, and other antibody deficiencies [18]. Since 2 of the patients in this study had a primary diagnosis of intestinal pseudo-obstruction, it is possible that an immune deficiency contributed to the increased infection rate in these patients. In addition, we hypothesize that disordered intestinal motility in these patients led to increased intestinal bacterial overgrowth and translocation of gut flora, which then caused CVC infections.

The rate of CVC changes also decreased after starting ethanol lock therapy, from a median of 8.2 (IQR, 4.6-11.7) to 0 (IQR, 0-4.7) per 1000 catheter days ($P < .001$). Only 2 of 23 patients had a higher rate of CVC changes after starting ethanol locks. The preservation of catheters associated with ethanol lock therapy is important, as previous investigations have suggested that ethanol may decrease catheter durability [19]. It is evident that this factor, if present, did not affect the overall improvement in catheter longevity.

Previous studies have reported dyspnea, dizziness, nausea, and intravenous catheter breakage with embolism of catheter fragments associated with ethanol lock therapy [16,20,21]. There were no such reported complications in this cohort of 23 patients. Some studies that have reported dizziness and altered mental status in association with ethanol locks have flushed the solution through the lumen at the end of the dwell time, rather than withdrawing it. Intravenous catheter breakage with embolization of catheter fragments with ethanol lock therapy has been described with daily therapy and use of a catheter type other than silicone [22]. It is possible that we averted these complications by using a 3 day per week ethanol lock regimen, placing only silicone catheters and withdrawing the ethanol
solution at the end of the dwell time whenever possible. We also may have reduced problems by specifying a minimum patient weight of 5 kg, to ensure that if the ethanol lock was flushed intraluminally, the patient’s blood alcohol level would theoretically not exceed a level of 0.08%. To avoid possible disulfiram-like reactions, ethanol locks were withheld from patients who were being treated with metronidazole.

The limitations of this retrospective study are recognized. For instance, clinical variables such as the reasons for central line replacement were not uniformly documented. However, its size (the largest pediatric intestinal failure cohort treated with ethanol locks reported) has allowed for some important analyses.

It is possible to conclude that ethanol lock therapy was associated with a statistically and clinically significant decrease in the rate of central venous catheter infections as well as reduced catheter replacements in a cohort of pediatric patients with severe intestinal failure. In addition, adverse reactions to the ethanol lock therapy were not seen. Based on these results, we now utilize outpatient ethanol lock therapy in all of our pediatric intestinal failure patients with a history of central venous catheter infections. Subgroup analyses indicated that the benefits of ethanol lock therapy seemed greatest in children without intestinal motility disorders. We hypothesize that this difference was due to intestinal bacterial overgrowth leading to bacterial translocation in the patients with disordered motility. Overall, ethanol lock therapy appears to be of utility in reducing central venous catheter infections in pediatric patients with intestinal failure. Further prospective investigations are warranted.

References


Discussion

Brad Warner, MD (St. Louis, Mo): Did you look at other parameters that may have contributed to sepsis, such as the presence of hepatic dysfunction?

Brian Jones, MD (Boston, Mass): We did not specifically look at these factors.

Daniel Teitelbaum, MD (Ann Arbor, Mich): We have certainly experienced a similar reduction in infections
with this method. One complication that we have noted is that our catheters become friable and have broken an increasing number of times with 70% ethanol. Have you noticed that in your series? We have not had to replace the catheters, but we have had to do a lot of repairs.

Brian Jones, MD: We attempted to look at catheter breakage in our retrospective review by examining the rate of catheter changes. No intravenous catheter breakages with embolization of catheter fragments were recorded in our patients. Because catheter repairs are not routinely documented in the patients’ electronic medical records, we could not analyze this in our study. We are designing a prospective study which will include catheter breakage and repair as an end point.

Alfred Chahine, MD (Washington, DC): There were four or five patients who you have witnessed an increase in infections. Were the ethanol locks administered by families at home or home nurses?

Brian Jones, MD: All the locks were administered with home nursing care supervision. All five of those patients had disordered intestinal motility. We hypothesize that disordered motility leads to increased bowel stasis and bacterial overgrowth with translocation into the bloodstream, leading to increased rates of CVC infections.