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ORIGINAL ARTICLE

Efficacy of ethanol locks to reduce the incidence of catheter-related bloodstream infections for home parenteral nutrition pediatric patients: comparison of therapeutic treatment with prophylactic treatment

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Abstract
Purpose Children with intestinal failure (IF) requiring central venous catheters (CVCs) often experience frequent catheter-related bloodstream infections (CRBSIs), which is a serious and life-threatening complication. To reduce the incidence of CRBSI, prophylactic ethanol lock therapy (ELT) was initiated.
Methods Patients with IF received home parenteral nutrition via a silicone tunneled CVC. All of them had received therapeutic ELT from January 2009 (first period) and prophylactic ELT from December 2012 (second period). Prophylactic ELT refers to ethanol lock for 2 h during the monthly hospital visit. We compared the CRBSI rate and number of CVC replacements between both periods.
Results Four patients received 19 CVCs for a total of 5623 catheter days. In the first period, there were 12 CRBSIs in 1823 catheter days (rate 6.77 per 1000 catheter days). In the second period, there were 9 CRBSIs in 3800 catheter days (rate 3.13 per 1000 catheter days). Overall, the rate of CVC replacement decreased from 4.92 to 1.72 per 1000 catheter days ($p = 0.04$). No adverse reactions were experienced during ethanol instillation.
Conclusion Monthly prophylactic ELT for IF patients is considered to be a safe and effective modality for reducing the replacement of CVCs due to CRBSIs.

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Keywords Ethanol lock therapy · Catheter-related bloodstream infection · Pediatric patients · Intestinal failure

Introduction

Central venous catheters (CVCs) are necessary for the treatment of children with intestinal failure (IF), such as short bowel syndrome and intestinal dysmotility disorder. The children require CVCs to maintain an adequate hydration and nutritional status. For these patients, the ultimate treatment goal is to achieve intestinal autonomy and independence from parenteral nutrition (PN), if possible, as the intestine undergoes adaptation. However, adaptation may require months to years, and during this period, patients are either partially or completely dependent upon PN.

Long-term indwelling, tunneled silicon CVCs are widely used in the treatment of such pediatric patients with IF. However, patients with CVCs are always at a risk of catheter-related bloodstream infection (CRBSI), which is a serious and life-threatening complication. CRBSI is reported to be a significant cause of morbidity and mortality in pediatric patients with IF who are PN dependent [1–3]. If CRBSI occurs, almost all CVCs must be removed to prevent advanced to severe sepsis. In addition, repeated CVC insertion can cause the loss of a venous access site for CVC insertion. The loss of vascular access sites is an indication for intestinal transplantation. Although CVC removal is the best treatment for CRBSI, it can be fatal for PN dependent patients. The prevention of CRBSI in patients with IF could reduce morbidity and hospital readmission and improve the patients' quality of life. Therefore, effective therapy against CRBSI to reduce the rate of CRBSI occurrence and to prevent catheter removal is necessary.

To salvage infected CVCs, several methods of prophylaxis or treatment have been developed and reported, such as antibiotic locks with or without anticoagulation, with variable success. However, the long-term use or frequent use of antibiotics can induce bacterial resistance.

Ethanol is used an antiseptic that may be used to sterilize the catheter and is not known to have any associated bacterial resistance. Dannenberg et al. were the first to report the use of ethanol locks in pediatric patients with CRBSIs in conjunction with systemic antibiotics [4–6]. In addition, Opilla et al. used ethanol locks in patients with home parenteral nutrition and reported the reduction of CRBSI occurrence and catheter replacement for the first time [7]. Therefore, in addition to ethanol lock therapy (ELT) against CRBSI, we utilized periodic ELT during regular hospital visits, as prophylactic ELT, to reduce the rate of CRBSI occurrence.

The aim of this study was to evaluate the efficacy of prophylactic ELT for IF patients.

Methods

Four patients with IF were analyzed. All enrolled pediatric patients with IF dependent on PN were managed at Kagoshima University Hospital. A tunneled silicon catheter was inserted in all patients. In our institution, therapeutic ELT was initiated from January 2009 (first period). Prophylactic ELT to prevent recurrent CRBSI was introduced from December 2012 for the same home PN patients, and the patients were followed-up through December 31, 2015 (second period).

Patients were excluded from ELT if there was a known hypersensitivity, allergy or reaction to ethanol, temporary CVC, or failure to obtain consent from the patient; however, no patients were excluded in this study.

CRBSI was defined as a positive blood culture from the CVC and/or peripheral blood. 70 % ethanol was prepared by mixing 3.5-ml 98 % dehydrated ethanol with 1.5-ml saline. Therapeutic ELT was performed as follows: 70 % ethanol was instilled into the CVC (0.8 ml) every 12 h. The exact volume was determined according to the previous reports [5]. After this period, the ethanol was withdrawn and discarded, followed by a saline flush. This procedure was repeated for 5 consecutive days, which means that we performed 12 h ELT for 10 times. A separate peripheral line was placed for intravenous antibiotics and maintenance transfusion. Prophylactic ELT was performed as follows: patients had a 70 % ethanol solution instilled into the CVC (0.8 mL) for 2 h. The exact volume was determined according to the previous reports [5]. Thereafter, the entire ethanol solution was withdrawn from the catheter and discarded, the central line was flushed with 5–10 mL of normal saline, and PN administration was restarted.

Prophylactic ELT was performed once or twice a month when the patient came to our outpatient clinic. If the patient was diagnosed with a CRBSI during this period, he/she was admitted to our institution and treated using therapeutic ELT. Data collection included patient demographics, diagnosis, number of CRBSIs, and rate of CVC replacement. Infection rates and catheter replacements were reported per 1000 catheter days.

Statistical analysis was performed using the Mann–Whitney *U* test for the CRBSI rates and the rate of CVC replacement. A p value less than 0.05 was considered to be significant. The indwelling catheter survival rates, which did not require replacements, was estimated using Kaplan–Meier analyses, and differences between the control and treatment population were determined by the log-rank test, with a p value less than 0.05 considered to be significant.

This clinical study was performed according to the ethical guidelines of clinical research from the Japanese Ministry of Health, Labour and Welfare. The Research Ethics Committee of Kagoshima University Hospital approved this clinical study (registration number: 27-133). All patients provided their informed consent.

Results

The patient demographics are summarized in Table 1. There were three girls and one boy with a median age of 67 months (range 1–131 months) at the start of therapy. The primary disease was as follows: 1 short bowel syndrome (SBS) due to midgut volvulus extended to the proximal jejunum, 1 hypoganglionosis, 1 extensive aganglionosis, and 1 chronic intestinal pseudo-obstruction.

The residual small bowel length in the patient with SBS was 12 cm, and the other three patients had a stoma in the jejunum. No patients had significant intestinal failure-associated liver disease (D-Bil >2.0 mg/dl). The mean age of patients in the first and second periods was 37 months (range 1–131 months) and 49 months (range 11–149 months), respectively. The follow-up periods of the first and second periods were 185–849 and 699–1524 days, respectively.

In the first period, there were 12 CRBSIs in 1823 catheter days with a mean rate of infection of 6.77 ± 2.48 per 1000 catheter days, and the rate of CVC replacement was 4.92 ± 1.30 per 1000 catheter days (Table 2). In the second period, patients had received prophylactic ELT for 3800 catheter days with nine CRBSIs. The CRBSI rate was 3.13 ± 3.2 per 1000 catheter days ($p = 0.014$) and the rate of CVC replacement was 1.72 ± 1.17 per 1000 catheter days (Table 2). The CRBSI rates tended to decrease, but were not significantly different between the

Table 1 Patient demographics and follow-up period

Patient no.	1		2		3		4	
Sex	Male		Female		Female		Female	
Primary disease	Short bowel syndrome		Hypoganglionosis		Extensive aganglionosis		Chronic intestinal pseudo-obstruction	
Stoma site	(—)		Jejunum		Jejunum		Jejunum	
Period	First	Second	First	Second	First	Second	First	Second
ELT	tELT only	pELT and tELT	tELT only	pELT and tELT	tELT only	pELT and tELT	tELT only	pELT and tELT
Age at beginning (months)	13	24	1	16	5	11	131	149
Follow-up period (days)	335	699	454	770	185	1524	849	807

mo months, *ELT* ethanol lock therapy, *tELT* therapeutic ethanol lock therapy, *pELT* prophylactic ethanol lock therapy

Table 2 Summary of the rate of CRBSI and catheter replacements

Patient no.	CRBSI rate per 1000 catheter days		Rate of CVC replacements per 1000 catheter days	
	First (tELT only)	Second (pELT and tELT)	First (tELT only)	Second (pELT and tELT)
1	5.97	2.86	3.00	2.98
2	11.01	7.79	6.60	2.60
3	5.40	0.65	5.41	1.31
4	4.71	1.24	4.71	0.00
Average rate	6.77 ± 2.48	3.13 ± 2.80	4.92 ± 1.30	1.72 ± 1.17
p value	$p = 0.14$		$p = 0.02$	

The data were analyzed using the Mann–Whitney *U* test, and a *p* value less than 0.05 was considered to be significant

CVC central venous catheter, *CRBSI* catheter-related bloodstream infections

two periods. The rate of CVC replacement was significantly decreased in the first period compared with that in the second period ($p = 0.02$) (Table 2). Figure 1 shows the catheter insertion period using Kaplan–Meier analyses. The catheter insertion period in the first period was significantly prolonged after prophylactic ELT ($p = 0.04$) (Fig. 1). In the second period, there were ten infections. Three patients had only one or two episodes of CRBSIs, which were all improved by therapeutic ELT. Although patient 2 had six infections due to recurrent CVC site infections that spread to the bloodstream, all catheters were removed due to uncontrollable local CVC site infection. No complications of ELT were experienced in either period.

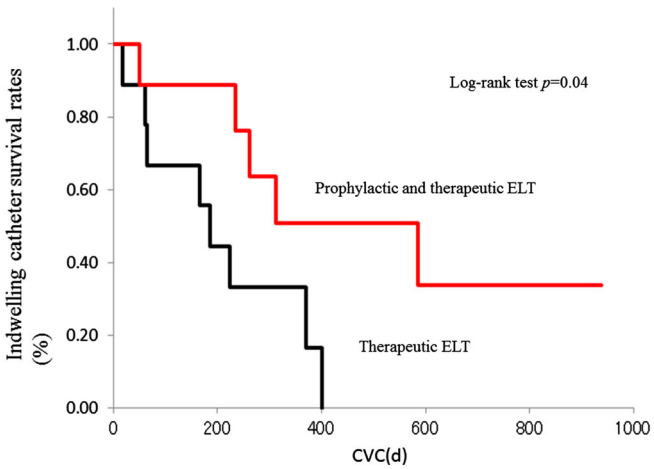

Fig. 1 Indwelling catheter survival rates. Kaplan–Meier survival curves to compare the first period with the second period

Discussion

CRBSIs are widely recognized as a major factor of morbidity and mortality in pediatric patients with IF. The prevention of CRBSI is of utmost importance, because of a limited number of available vascular access sites, and the development of systemic infections can impact the liver function and patients' quality-of-life.

Several therapies against CRBSIs, including antibiotics, were presented. Various anti-infective locks, including vancomycin, ciprofloxacin, gentamicin, and amphotericin B, have been studied for the prevention of CRBSIs with variable efficacy ranging from 30 to 100 % [4]. The use of antibiotic lock therapy for CRBSI prevention has a theoretical disadvantage of increased antibiotic resistance. Therefore, the main advantage of an ethanol lock is that resistance is not a concern, because ethanol denatures proteins and is bactericidal and fungicidal, including organisms in established biofilms, at concentrations ranging from 40 to 100 % [8].

Therefore, we utilized periodic ELT during regular hospital visits, as prophylactic ELT, in addition to ELT against CRBSIs to reduce the rate of CRBSI occurrence.

In this study, the rate of CVC replacement and the period of catheter insertion per one catheter in prophylactic ELT (second period) improved with significantly different.(Table 2; Fig. 1). However, the CRBSI rate was not improved with significant difference ($p = 0.14$) (Table 2). This lack of significant difference was because patient 2 experienced repeated CVC site infections that were difficult to control and developed into CRBSIs repeatedly. Taken together, our strategy of prophylactic ELT showed acceptable results.

Most CVCs was salvaged by therapeutic ELT even in the first period. A previous study showed that the CRBSI rate varied according to the disease of the patients and type of CVCs inserted. The CRBSI rate in tunneled CVCs inserted in pediatric cases was previously shown to range from 1.7 to 2.9 per 1000 catheter days when CVCs were used for non-PN purposes, such as in oncologic patients [9]. However, regarding CVCs for IF patients, the CRBSI rate was reported to range from 8.0 to 11.2 per 1000 catheter days [1, 10]. In the first period, the rate was 6.77 per 1000 catheter days and the rate of catheter replacement was 4.92 per 1000 catheter days. Thus, the CRBSI rates in our first period were not higher than previously reported. However, the rate of CVCs replacement, which directly contributed to mortality, was not satisfactory. Therefore, we utilized periodic ELT during regular hospital visits, as prophylactic ELT, in addition to ELT against CRBSIs to reduce the CRBSI rates.

A meta-analysis of prophylactic ELT showed a reduction of the CRBSI rate per 1000 catheter days by 7.67 events and catheter replacements by 5.07 [11]. The relative risk of CRBSI was 0.16 (95 % CI 0.05–0.52) and 0.16 (95 % CI 0.05–0.57) in the studies by Wales et al. [10] and Mouw et al. [1], respectively, which indicated that prophylactic ELT reduced the frequency of CRBSI. Sanders et al. achieved a significantly different CRBSI rate by administering 3 ml of 70 % ethanol for 2 h daily and subsequent heparin lock (HL) when compared with HL alone ($p = 0.008$, $n = 60$) [12]. However, Slobbe et al. did not detect a significant CRBSI rate reduction after daily 15-min exposure to 3 ml of 70 % ethanol compared with normal saline ($n = 376$) [13]. Mokha et al. reported that in 13 children who had a pre-ELT and post-ELT period, 2-h ELT was associated with a decrease in the rate of CVC replacement due to infection (0.36 vs 4.74 per 1000 catheter days). These clinical consequences suggest that the duration of ELT is crucial its effect; hence, 15-min ELT is likely too short.

Ethanol is a very effective disinfectant against a broad range of microorganisms, including bacteria and fungi even in biofilms. In an experimental study, all microorganisms, including fungi, incubated for 16 h were killed by 1-h exposure to 70 % ethanol. After incubation for 40 h, 4-h exposure to ethanol was required to kill two of four strains of *Candida albicans* in vitro [9]. This indicates that the concentration of microorganisms likely has an impact on the effect of ethanol. However, when patients visit our regular outpatient clinic, they do not have CRBSIs. This experimental study and previous clinical studies suggested that the duration of ethanol lock as prophylactic ELT should be administered for no more than 2 h.

With the widespread use of ELT, concerns have been raised, regarding mechanical complications, such as CVC occlusion and breakage, and the subsequent increase in the rate of CVC replacement [14]. It was reported that ethanol locks could lead to plasma protein precipitation [15]. As protein precipitation forms in the inner lumen, it is possible that it creates obstruction upon aspirating and flushing. Mokha et al. reported that in 13 children with IF who had a pre-prophylactic ELT and post-daily prophylactic ELT period, ELT was associated with a decrease in the rate of CVC replacement due to infection, but an increase in the rate of CVC replacement due to mechanical problems (5.05 vs 0 per 1000 catheter days) [14]. This is a major concern which might be caused by daily prophylactic ELT; however, in our regimen, no such adverse effect was noted. A previous study reported that weekly ELT may also lead to a decrease in CRBSI without mechanical complications [16]. We speculate that monthly prophylactic ELT is adequate to prevent CRBSI, very safe, and can improve the patients' quality-of-life.

There are some limitations associated with this study. This was a retrospective study and the condition of the

patients changed with age. Despite the limitations of this retrospective study, our results suggested that administering monthly prophylactic ELT is safe and effective in our series of four patients with IF. A large, randomized, controlled trial is warranted to determine the overall efficacy and safety of ELT for CRBSI prevention in children. An effective method for CRBSI prevention in children with PN-dependent IF could significantly improve the outcome and patients' quality of life.

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Compliance with ethical standards

Conflict of interest No competing financial interests exist.

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