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Efficacy of 4% tetrasodium ethylenediaminetetraacetic acid (T-EDTA) catheter lock solution in home parenteral nutrition patients: A quality improvement evaluation

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Abstract

Introduction: A functioning and reliable central venous access device is fundamental for home parenteral nutrition patients to administer essential nutrition. Complications of central venous access devices including occlusion, microbial colonization, and biofilm formation are problematic and sometimes life-threatening. A novel lock solution, 4% tetrasodium ethylenediaminetetraacetic acid, has properties that may reduce such complications.

Purpose: The aim of this study was to determine the safety, efficacy, and cost implications of implementing 4% tetrasodium ethylenediaminetetraacetic acid to prevent catheter-related complications in home parenteral nutrition patients.

Methods: A pre- and post-intervention study was carried over 36 months (12 months pre; 24 months post) by the British Columbia Home Parenteral Nutrition Program in Vancouver, Canada, where 4% tetrasodium ethylenediaminetetraacetic acid was implemented for patients at high risk for central venous access device occlusion and catheter-related infection. Patients were included in the study if they had previous central venous access device complications. The outcomes evaluated were central line-associated bloodstream infection, catheter occlusion requiring thrombolytic treatment, and catheter replacements.

Results: In total, 22 out of 105 patients met the inclusion criteria. Two patients were excluded from analyses due to non-adherence and concomitant use of other lock solutions. Post intervention, 20 home parenteral nutrition patients experienced significant reduction in the central line-associated bloodstream infection rate (pre = 1.918/1000 catheter days; post = 0.563/1000 catheter days; $p = 0.04$) There were no occlusion events reported post intervention.

Conclusion: For home parenteral nutrition patients, 4% tetrasodium ethylenediaminetetraacetic acid lock solution effectively reduces the risk of central venous access device complications including occlusions and catheter-related infections.

Keywords

Lock, EDTA, vascular access, catheters, bloodstream infection, occlusion, non-antibiotic antimicrobial solution

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Introduction

Central venous access devices (CVADs) administer parenteral nutrition (PN), chemotherapy, antibiotic agents, apheresis, and hemodialysis. They provide reliable access to the bloodstream and reduce repeated, unnecessary venipuncture and pose inherent complications that can be life-threatening. Three interrelated processes that potentiate catheter-related

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complications are clot formation, microbial colonization, and biofilm formation.[1–6] These three processes, the triple threat, act as interlocking gears in a cog-like fashion. These threats must be addressed together to decrease CVAD complications.[3–8] It is insufficient, for example, to prevent clots without prophylaxis against microorganisms and their associated biofilms and vice versa.[2,6–8]

Current strategies to reduce CVAD complications include catheter design, insertion technique with ultrasound, skin decontamination,[9] and Aseptic Non-Touch Technique.[10] To complement existing strategies, an effective CVAD lock solution is integral to any multimodal preventive or catheter salvage program. To date, little focus has been placed on the interior of the catheter.[1,2,7,11] Ideally, a catheter lock solution will provide anticoagulant and broad-spectrum antimicrobial activity, the ability to penetrate and eradicate biofilm, prolonged stability, and low risk of toxicity, adverse events, and bacterial resistance.[2,7,11,12]

The British Columbia Home Parenteral Nutrition (BCHPN) Program in Vancouver, Canada, supports PN patients who frequently manipulate their CVADs and aim to prevent catheter-related complications. Prevention strategies included catheter flush (0.9% sodium chloride), anticoagulation (Heparin IV Flush Syringe; Medefil Inc., Glendale Heights, IL, USA), antimicrobial lock (Taurolin; Geistlich Pharma AG, Wolhusen, Switzerland), and a disinfectant cap as protective cover. Despite these interventions, CVAD complications persisted, so an alternative lock solution was sought.

This study aimed to evaluate the safety, efficacy, and cost implications of a 4% tetrasodium ethylenediaminetetraacetic acid (T-EDTA) lock solution in a subgroup of HPN patients at high-risk for CVAD-related complications (central line-associated bloodstream infection (CLABSI) and occlusion).

Methods

Study design

This pre- and post-Quality Improvement (QI) intervention occurred at St. Paul's Hospital, Vancouver, Canada. The 4% T-EDTA lock solution (KiteLock 4% Sterile Catheter Lock Solution; SterileCare Inc., Markham, ON, Canada), a known chelator, was introduced routinely for high risk patients (CVAD chronicity, and patient and disease complexity).

Catheter-related complication events were reviewed for 12 months pre 4% T-EDTA lock solution and 24 months post intervention to enable comparison. The Providence Health Care Research Ethics Board approved this work as meeting the local ethical requirements as a QI project.

Study population

Patients were considered for suitability if they met all the following inclusion criteria: (1) at least one CLABSI in past 12 months, (2) clinically stable and not currently being treated for a life-threatening disease unrelated to the indication for HPN and including bloodstream infection independent of the source, and (3) capable of independent CVAD maintenance at home. Patients were excluded if receiving antibiotics through the CVAD or had an infected entry site at the beginning of the study.

HPN support and training are provided at a university-affiliated, tertiary care center in Vancouver. For this evaluation, the program nurse utilized different education and training methods including in-person, 1:1 training via video link or webinar format and printed materials for patient education. Prior to instilling the 4% T-EDTA, all patients were instructed to flush with 20 mL 0.9% sodium chloride. The locking volume of 4% EDTA ranged from 2 to 3 mL per lumen. Immediately prior to HPN infusion, patients are instructed to aspirate the 4% T-EDTA and flush with 20 mL 0.9% sodium chloride before CVAD lumen access and use.

Evaluation of clinical parameters

Outcomes measured to evaluate the effectiveness of the intervention were as follows:

CLABSI: according to the Centers for Disease Control and Prevention/National Health Healthcare Safety Network (CDC/NHSN) definition;[13]

CVAD replacement (occlusions/infections or other);

CVAD occlusion[14] requiring a thrombolytic agent alteplase (Cathflo®; Hoffmann-La Roche Ltd, Basel, Switzerland);

Patient adverse events: laboratory values defined as sub-clinical alterations in electrolyte and mineral levels, and abnormal kidney and liver function. Routine laboratory testing and HPN treatment remained unchanged unless medically indicated. Patients were reporting any adverse events during the post-intervention period.

Cost implications

A return-on-investment (ROI) model calculated the cost of changing from current practice to 4% T-EDTA, considering CVAD complications pre and post intervention. The cost of 0.9% sodium chloride, heparin, taurolidine, and alteplase was based on the hospital dispensary fee, whereas the cost to treat bloodstream infection and/or catheter replacement was based on literature[15–17] and validated by a third-party, healthcare economist. The currency used was Canadian dollars (CAD), estimated as 2018 values.

Table 1. Baseline (pre-intervention) demographic data of HPN patient population using 4% T-EDTA lock solution in their CVADs for 24 months.

	Total ($N = 22$)
Mean age (years)	57 ± 15
Age range (years)	19–84
Women (%)	62
Average duration on TPN (years)	7 ± 5
Duration range on TPN (years)	0.08–40
Short bowel syndrome	17
Intestinal fistulas	3
Ileus/pseudo obstruction	2
Malabsorption	1
Gastroparesis	1
Tunneled-cuffed catheter	22
Superior vena cava	19
Inferior vena cava	3
0.9% sodium chloride lock solution	9
Heparin lock solution	6
Taurolidine lock solution	7

HPN: home parenteral nutrition; T-EDTA: tetrasodium ethylenediaminetetraacetic acid; CVAD: central venous access device; TPN: total parenteral nutrition.

Statistical analysis

Total number of incidents was recorded and rates (normalization of the number of incidents per 1000 catheter days) were reported descriptively and analyzed using the Wilcoxon matched-pairs signed rank test for non-parametric data. Statistical difference is considered significant when p-value is less than 0.05 for clinical endpoints (Statistical program: SPSS version 23).

Results

Baseline characteristics of the study population

The mean age of the 22 HPN enrolled patients was 61 ± 10.7 (range: 38–76) years with slightly more men (55%). The average number of years on the BCHPN program was 11 ± 9.3 (range: 2–27) years and most patients had a tunneled, cuffed, silicone CVAD (Table 1). Most patients (73%) had a primary diagnosis of short bowel syndrome and 32% used taurolidine with varying dwell times of 4–10 h/day. Two patients who initially met the inclusion criteria were excluded as they did not use 4% T-EDTA exclusively as instructed and were not compliant with routine use. Therefore, they were not included in the statistical analysis.

Complications

In the post-intervention period, statistically significant CLABSI reduction was observed as 71% ($p = 0.04$) with the use of 4% EDTA (Table 2). Pre intervention, CLABSI rate was 1.918/1000 catheter days compared to post-intervention at 0.563/1000 catheter days. No occlusion events requiring instillation of alteplase occurred during post-intervention. A 13% ($p = 0.88$) reduction in CVAD replacement (pre = 1.23/1000 catheter days compared to post = 1.077/1000 catheter days) was demonstrated. Although not statistically different, this has significant clinical relevance in terms of vessel health and preservation. Reasons for catheter replacements pre- and post-intervention are presented in Table 2. The one incident of repair was due to catheter wear and tear at hub connection.

Cost savings

Total catheter locks (0.9% sodium chloride, heparin, taurolidine, or 4% T-EDTA) used by 20 HPN patients in 12 and 24 months equaled 7200 and 14,400, respectively. The ROI model estimated cost savings associated with 4% T-EDTA compared to the equivalent time period during standard care (Table 3). The total expenditure pre 4% T-EDTA including the cost of a catheter lock solution, catheter replacement, and treating occlusions and CLABSI was estimated at CAD 258,573.72 for a period of 12 months and CAD 517,147.44 over a 24-month period. Similar cost parameters were used to determine the total expenditure post implementation of 4% T-EDTA. Total savings were estimated at CAD 170,225.28 for the first year and an additional savings of CAD 154.415.80 in the second year for a total of CAD 324,641.08 over the course of 2 years. This represents a 63% reduction in cost when 4% T-EDTA is used for 24 months compared to using 0.9% sodium chloride, heparin, or taurolidine.

Adverse events

Instructions were given to aspirate the lock solution (same as for previous original lock solutions) but only 50% of patients were aspirating the 4% T-EDTA before accessing their CVAD. Patients experiencing an aspiration occlusion flushed the 4% EDTA into their bloodstream due to physical limitation of partially functioning catheter without any adverse sequalae. Transient metallic taste (dysgeusia) in 11 of the 20 HPN patients was reported. This adverse event was described as mild and also experienced with the use of 0.9% sodium chloride, heparin, and taurolidine.

No change in health or hematological parameters outside of expected variations associated with the complex disease process of each patient was reported during the evaluation period.

Discussion

This landmark study describes the successful introduction of 4% T-EDTA into routine care for adult HPN patients. The use of 4% T-EDTA as the sole catheter lock solution was associated with significantly fewer CLABSI compared

Table 2. Comparison of catheter complications before and during the use of 4% T-EDTA as the sole lock solution in 20 HPN patients up to 24 months.

	Pre-intervention standard of care lock	Post-intervention 4% T-EDTA	Post-intervention 4% T-EDTA	Post-intervention 4% T-EDTA	% Reduction	*p*-value
Timeline	12 months	First 12 months	Second 12 months	Total 24 months		
Number of CLABSI	14	3	4	7	71	0.04*
CLABSI rate (per 1000 catheter days)	1.918	0.041	0.724	0.563		
CLABSI rate range	0–2.7			0–0.06		
Number of catheter replacement	9	6	6	12	13	0.88
Catheter replacement rate (per 1000 catheter days)	1.233	1.018	1.054	1.077		
Catheter replacement rate range	0–2.7			0–1.5		
Reason for catheter replacement	CLABSI (7), repair (2)	CLABSI (2), entry site infection (2), migrated out (1), collapsed valve (1)	CLABSI (2), migrated out (3), repair (1)	CLABSI (4), entry site infection (2), migrated out (4), collapsed valve (1), repair (1)		
Number of occlusion events	11	0	0	0	100	NA

HPN: home parenteral nutrition; T-EDTA: tetrasodium ethylenediaminetetraacetic acid; CLABSI: central line-associated bloodstream infection; NA: not applicable.
*Statistically significant as $p < 0.05$.

Table 3. Return-on-investment calculations for 20 HPN patients pre and post 4% T-EDTA implementation as the sole catheter lock solution (in Canadian dollars, CAD).

	Unit cost (CAD)	12 months				24 months			
		Standard of care lock solution		4% T-EDTA lock solution		Standard of care lock solution		4% T-EDTA lock solution	
		Number	Total cost	Number	Total cost	Number	Total cost	Number	Total cost
0.9% Sodium chloride	0.48	600	288.00			1200	576.00		
Heparin	0.52	3625	1885.00			7250	3770.00		
Taurolidine	10.78	3000	32,340.00			6000	64,680.00		
4% T-EDTA	5.50			7200	39,600.00			14400	79,200.00
Alteplase	68.00	11	748.00	0	–	22	1496.00	0	–
Catheter replacement	220.00	9	1980.00	6	1320.00	18	3960.00	12	2640.00
CLABSI	15,809.48	14	221,332.72	3	47,428.44	28	442,665.44	7	110,666.36
Total cost			258,573.72		88,348.44		517,147.44		192,506.36
Cost savings					**170,225.28**				**324,641.08**
Percentage cost reduction					66				63

HPN: home parenteral nutrition; T-EDTA: tetrasodium ethylenediaminetetraacetic acid; CLABSI: central line-associated bloodstream infection.

to the pre-intervention BCHPN standard of care lock solution program policy (0.9 % sodium chloride for valved catheters, heparin for non-valved catheters, and taurolidine for patients with repeated complications independent of catheter type), without reported adverse events.

Although the source of bacteria of two of the seven CLABSI events during 4% T-EDTA use was determined to be the entry site (i.e. extraluminal), they were still included in the statistical analysis. The source of remaining microorganisms cultured is unknown, but several species are commonly found in the gastrointestinal tract. It is possible that intraluminal or extraluminal spread may occur from hematogenous or exogenous contamination, respectively.

Previously, the accepted standard for CVAD flushing and locking has been 0.9% sodium chloride and heparin.[18] Recently, heparin has fallen out of favor due to potential adverse events such as heparin-induced thrombocytopenia[19,20] and for stimulating biofilm formation within CVADs.[21] For HPN patients in Canada, ethanol and taurolidine have been compounded for use as lock solutions in pediatric and adult patients.[22] Ethanol is a well-known broad-spectrum antimicrobial agent but it

lacks anticoagulant activity and can increase the risk of catheter occlusion.[23] Other adverse events including structural catheter changes, protein precipitation, clot formation, and enhancement of *Staphylococcus aureus* biofilm development within catheter lumen were reported.[24–26,41] For these reasons, compounded ethanol was never used in the BCHPN program.

Taurolidine is an amino acid with antimicrobial properties often combined with heparin and citrate but can still result in intraluminal clot formation.[27–30] Taurolidine has limited antimicrobial activity against Gram-positive bacteria, the most common microorganisms colonizing the interior of CVADs,[27,29] no effect against already-formed biofilm,[31–34] and potential for liver toxicity in mouse and rat models when used intraperitoneally.[35,36] Despite this, compounded taurolidine was the only alternative lock solution that has been for patients in the BCHPN program for many years. In this QI study, the 24-month use of 4% T-EDTA reduced the CLABSI incidence rate by 55% compared to the 12-month use of taurolidine (1.046/1000 and 2.348/1000 catheter days, respectively) but the small sample size ($n = 7$) did not allow for a statistically significant difference in this subpopulation of patients.

Overall, 11 occlusion events requiring the use of alteplase were reported pre implementation of 4% T-EDTA compared to no CVAD occlusions post implementation. This represents a 100% reduction in this expensive and laborious treatment for catheter occlusions. In addition to the cost of the drug, other hospital ancillary costs, such as supplies, clinician time, treatment delays, and increased hospital bed stays, were not calculated in this evaluation. Furthermore, patients did not miss work and/or interrupt their daily routine for CVAD occlusion management. Clinical improvements voiced by the patients including ease of flushing and use of the CVAD "as if it was brand new" after only a few months of use of the 4% T-EDTA are important patient-reported outcomes. This benefit might extend to other patient populations at high risk of catheter occlusion such as hemodialysis patients with high cost expenditures reported worldwide to treat CVAD occlusion events.[37–39]

A statistically significant reduction in CLABSI by 71% represents a clinically relevant QI in patient care and considerable cost savings. A randomized clinical trial using 4% T-EDTA as a lock for hemodialysis patients did not show a statistically significant difference in CLABSI due to the low sample size, but it did show an 87% decrease in bacterial colonization compared to heparin further supporting the antimicrobial benefit of this lock solution independent of the patient population.[6]

Although the product cost alone of 4% T-EDTA is higher (CAD 5.50 per 3 mL/lumen) compared to 0.9% sodium chloride (CAD 0.48) and heparin (CAD 0.52), it was less expensive than compounded taurolidine (CAD 10.78/lumen). This ultimately is a cost impact; even though the literature highlights variation in catheter-related infection treatment costs, it does show a value consistent with important cost savings when using 4% T-EDTA compared to standard care.[15–17]

Catheter replacement can be a source of stress for patients and hospital staff. Direct catheter replacement costs were for the catheter-only and did not consider the clinical time and resources required to insert a new catheter or the unmeasurable cost of difficult venous access and vessel depletion. These costs and implications vary from hospital to hospital and are difficult to estimate so they have not been included in this evaluation but would further enhance the cost benefit. Considering one goal of the BCHPN program is catheter salvage, the reduction in catheter complications resulted in a 13% reduction in catheter replacement over 24 months. Although this is not statistically significant, it aligns with working toward the goal of "one line for the life of the patient" and monitoring of this parameter is ongoing.

Limitations

This sample size in this study was small; however, this is relative to the rarity of intestinal failure. In addition, this was a retrospective pre–post intervention using a historical control (standard of care program policy) and did not adjust for confounding in statistical analyses given the small sample size. Reporting of outcomes was reliant on patients' self-reporting, which increased the risk of information bias.

Despite these limitations, the length of patient monitoring (24 months) provided important information to counterbalance these limitations. In addition, to the best of our abilities, we maintained a robust study by ensuring patient adherence to the recommended technique.

Conclusion

Results from this QI study suggest that 4% T-EDTA is clinically safe and effective in reducing CLABSI and lumen occlusion in adult HPN patients. These results are in line with and support previously published in vitro effectiveness of 4% T-EDTAs in preventing and eradicating biofilm formation within CVADs.[40] Use of 4% T-EDTA lock solution should be considered in any multimodal approach to decrease the risk of CVAD complications caused by the triple threat. Further studies in other patient populations will be valuable to confirm these results.

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