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ORIGINAL RESEARCH

Incidence of catheter-related bloodstream infections with sodium citrate lock therapy in adult patients receiving home parenteral nutrition: A descriptive cohort study

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Abstract

Background: We determined the incidence of catheter-related bloodstream infections in adult patients requiring home parenteral nutrition (HPN) while receiving sodium citrate locks.

Methods: We conducted a single-center descriptive cohort study involving 38 adults who required HPN from January 1, 2020, to August 31, 2022. The exact method, assuming a Poisson distribution, was used to estimate the incidence rate of catheter-related bloodstream infections per 1000 catheter days among patients receiving sodium citrate locks. Univariate and multivariate analyses using Poisson regression and frailty models were employed to evaluate predictive factors.

Results: Thirty-eight patients received sodium citrate locks, with 65.8% women (mean age, 50.2 ± 14.5 years). The average length of HPN was 3.6 years. Forty-six catheter-related bloodstream infections occurred during 20,085 catheter days, demonstrating an incidence rate of 2.3 (95% confidence interval, 1.7–3.1) per 1000 catheter days. Peripheral-inserted central catheters had a higher incidence rate (3.9 per 1000 catheter days) than Hickman catheters (2.2 per 1000 catheter days), with a hazard ratio of 1.27, indicating a 27% increased risk of catheter-related bloodstream infections. Univariate and multivariate Poisson regression analyses revealed that for every 1-h increase in HPN infusion duration (h/day), the incidence rate of catheter-related bloodstream infections is expected to increase by 10%.

Conclusion: Catheter-related bloodstream infections are common in adult patients requiring HPN. Sodium citrate locks may help prevent these infections. Recognizing predictive factors, such as the duration of parenteral infusion, can help healthcare providers develop more effective prevention strategies.

KEYWORDS
catheter-related bloodstream infection, ethanol lock, heparin lock, home parenteral nutrition, sodium citrate lock

INTRODUCTION

Home parenteral nutrition (HPN) is a generally safe method for delivering adequate nutrition in patients with intestinal failure and various other indications. Using the most recent 2013 data from the Centers for Medicare and Medicaid Services, the estimated prevalence of adult patients requiring HPN in the United States totaled 20,883.[1] Educating patients and caregivers on proper catheter care and aseptic technique is crucial because of the risk of infection associated with the long-term use of central venous catheters (CVCs) for HPN. CVCs, including peripherally inserted central catheters (PICCs), ports, and Hickman catheters, are most commonly used for HPN therapy. Catheter-related bloodstream infections (CRBSI) are a significant cause of morbidity, particularly in patients receiving long-term HPN, in which the recurrence rate for CRBSI is high. Overall, the documented incidence of CRBSI ranges from 0.29 to 11.5 per 1000 catheter days.[2–6] The costs attributed to CRBSIs can range from $33,000 to $75,000, depending on whether care in the intensive care unit (ICU) is required, and are associated with relatively poor reimbursement rates.[7,8] Therefore, implementing preventive measures, including locking solutions containing antibiotics, ethanol, taurolidine, and chelating agents (eg, ethylenediaminetetraacetic acid or citrate), has been proposed to prevent CRBSI and reduce the need for catheter removal. Limited evidence concerning using these locks with small samples of adult patients receiving HPN has shown benefits in preventing CRBSIs.[9–19]

Our original study, which used standard-of-care heparin locks (10–100 U/ml in prefilled syringes per home infusion policy) and 1000 U/L of heparin added to all HPN bags, revealed a high CRBSI rate.[6] Therefore, the Emory University Hospital Nutrition and Metabolic Support Team implemented new strategies to prevent CRBSI, including 70% ethanol lock therapy, which resulted in a significant 19-fold reduction in the CRBSI rate among the HPN population.[10] Other studies have consistently shown the safety and efficacy of ethanol lock therapy for adult patients receiving HPN.[10,12–14,17–19] However, with a recent patent for dehydrated alcohol for a cardiovascular procedure and the Food and Drug Administration (FDA) request to remove all unapproved dehydrated alcohol products in 2020, ethanol locks were no longer an affordable option for most patients.[20] In light of this, the team initiated the use of 4% sodium citrate lock solutions for patients with recurrent CRBSIs receiving HPN.

Sodium citrate lock therapy, also known as trisodium citrate or citrate, has been demonstrated to be a safe and cost-effective alternative for CVC care.[21–23] Although we could not obtain the cost of the compounded 4% sodium citrate locks from home infusion companies, the estimated cost was approximately $18 per week based on available data. It was a simple replacement of the patients' heparin locks. The 4% sodium citrate or 4% trisodium citrate has also been widely used as a locking solution for the interdialytic patency of CVCs for hemodialysis.[21–26] Sodium citrate has both anticoagulant and antimicrobial properties.[27] Sodium citrate exhibits antimicrobial properties via the chelation of calcium and magnesium, which are required for the growth of some microorganisms. It also alters the permeability of bacterial cell walls and decreases bacterial survival.[28] In vitro studies demonstrate that citrate in various concentrations (range from 2.2% to 30%) prevented bacterial biofilm formation, inhibited the growth of multiple types of microorganisms (eg, *Staphylococcus epidermidis*, *S. aureus*, *Candida albicans*, and *Escherichia coli*), and diminished bacterial motility.[25,28,29] There is no published data, to our knowledge, on using sodium citrate locks for CRBSI prevention in patients with long-term CVCs receiving HPN. This study aimed to assess the incidence of CRBSIs in patients requiring HPN receiving sodium citrate lock therapy after discharge from Emory University Hospital and managed by the nutrition support team.

METHODS

Study design, clinical setting, and participants

We performed a single-center descriptive cohort study involving 38 adults who received HPN from January 1, 2020, to August 31, 2022. This study was conducted at Emory University Hospital, a 791-bed and 154–ICU-bed tertiary care academic medical center in Atlanta, Georgia. Following approval by the Emory University Institutional Review Board (study 5113), which granted a full waiver for informed consent and authorization, retrospective chart reviews were conducted using the Emory Healthcare electronic medical records system. Eligible patients were at least 18 years old, were deemed to require HPN for ≥30 days, were managed by the Emory University Hospital Nutrition and Metabolic Support Team, and received daily sodium citrate lock therapy during a predefined observation period (January 1, 2020, to August 31, 2022).

Sodium citrate lock therapy

Commercial 4% sodium citrate prefilled 3- ml or 5-ml syringes were not available for use during this study. The patients' home infusion pharmacies that provided HPN only agreed to compound the lock solution as 2 ml of 4% sodium citrate solution in a syringe, based on their company protocols. Home health nurses trained the patients and/or caregivers before initiating sodium citrate locks. The sodium citrate solution was slowly instilled into all lumens of the catheter once daily during the longest period when the patient was not receiving intravenous medications and/or HPN. Lumens of CVCs were flushed with normal saline before and after each administration of intravenous medications and/or HPN. Aspirations of sodium citrate lock solutions were not required. The 4% sodium citrate locks replaced the heparin flushes and/or locks as part of the standard daily line care. All patients receiving HPN continued to receive 1000 U/L of heparin in HPN bags as the standard of practice, as per the Emory University Hospital Nutrition and Metabolic Support Team, for >30 years, unless a heparin allergy was documented.

Data collection

Information collected from medical records included patient demographic characteristics (eg, sex, age at the initiation of 4% sodium citrate locks, and past medical history), inpatient information, and HPN characteristics (eg, primary indication for HPN, duration of HPN therapy, and macronutrient concentration). Additionally, the type of CVC, the number of catheters used, the number of catheter days, and the use of sodium citrate lock were recorded. Infection-related information was also collected, including documented microbiology, dates of infections and antibiotic administration, and the total number of line infections.

Study outcome

The primary outcome was CRBSIs per 1000 catheter days for patients who received 4% sodium citrate lock therapy after discharge from Emory University Hospital and were managed by the nutrition support team. This study defined CRBSI based on several criteria: the presence of positive blood cultures, the necessity for a complete course of antibiotic treatment, the removal of central catheter lines (either through exchange over a guidewire at the same site or by placing a new catheter at a different site), and the judgment of physicians.

Statistical analysis

The exact method, assuming a Poisson distribution, was used to estimate the incidence rate of CRBSI per 1000 catheter days among patients receiving sodium citrate lock therapy. We employed a frailty model to compare the relative risk of CRBSI between patients using the Hickman catheters and those using PICCs.[30] This model accommodates the recurrent nature of CRBSI while accounting for unobserved heterogeneity across patients. Hazard ratios (HRs) were used to quantify relative risk, with an HR of 1 indicating no difference in risk relative to the reference group.

We further conducted both univariate and multivariate risk factor analyses using Poisson regressions. For the univariate analysis, we applied Poisson regressions with the total number of line infections as the outcome, catheter days as the offset, and one risk factor at a time as the predictor. This allowed us to estimate the incidence rate ratio (IRR) associated with a one-unit increase in each risk factor, where an IRR of one indicates no difference in risk relative to the reference group. For the multivariate analysis, we used a Poisson regression with the same outcome and offset while including all risk factors as predictors to evaluate the IRR for each risk factor while adjusting for all others. We applied a quasi-likelihood approach to address potential overdispersion in the count data, which provides more robust variance estimates.

To address possible violations of the Poisson distribution assumption, we also conducted univariate risk factor analyses using frailty models. Each frailty model included CRBSI occurrence as the outcome and one risk factor as the predictor, accounting for within-subject correlation. The HR was estimated to quantify the change in CRBSI risk associated with a one-unit increase in the respective risk factor.

RESULTS

Patient demographics

Table 1 summarizes participant demographics, inpatient details, HPN characteristics, central line usage, CRBSI, and sodium citrate lock usage. Among the 38 participants, 68.5% were women, with an average age of 50.2 years when starting sodium citrate lock therapy. The most common indications for HPN were short bowel syndrome (47.4%) and enterocutaneous fistula (34.2%). The average duration of HPN was 3.6 years (range, 0.12–11.7 years). The mean daily HPN calories were 23.8 kcal/kg/day, with mean daily doses of amino acids at 1.3 g/kg/day, lipid at 0.8 g/kg/day, and dextrose at 195.6 g/day. Notably, 81.6% of patients received a four-oil mixed lipid emulsion, 10.5% switched between different lipid formulations, and 7.9% received no lipid emulsion. Sixty-five percent of patients had a Hickman catheter with a mean catheter day of 528.6 days. A mean of 386 days of sodium citrate lock use was recorded during the observation period, and 36.8% of patients remained on therapy at the end of the study. A total of 18 participants (47.4%) experienced at least one CRBSI, and the mortality rate was 13.2%.

Analysis of CRBSI incidence rate

Table 2 presents the incidence rate for CRBSI among the 38 participants who received sodium citrate locks. Forty-six CRBSIs occurred during 20,085 catheter days, with an incidence rate of 2.3 (95% confidence interval [CI], 1.7–3.1) CRBSIs per 1000 catheter days. In a subgroup analysis, patients with a PICC line had a higher rate of 3.9 CRBSIs per 1000 catheter days compared with those with Hickman catheters, with an HR of 1.27 (95% CI, 0.45–3.56), suggesting a 27% increase in the hazard rate of CRBSI occurrence.

Predictive factors

Table 3 summarizes the potential risk factors we evaluated for CRBSI in adult patients receiving HPN using sodium citrate lock therapy. Both univariate and multivariate Poisson regression analyses revealed that the number of days on HPN and/or intravenous fluids weekly, HPN calories, and dextrose doses were not risk factors for CRBSI in adult patients receiving HPN using sodium citrate locks. Meanwhile, all analyses consistently showed that the HPN infusion time (h/day) demonstrated that for every 1-h increase in HPN infusion duration,

TABLE 1 Patient demographics and medical characteristics.

Variables	Summary statistics
Patient demographics ($n = 38$)	
Female sex, *n* (%)	25 (65.8)
Age at start of sodium citrate, mean (SD)	50.2 (14.5)
Age at start of sodium citrate, median (IQR)	50.0 (37.5–61.8)
Body mass index, mean (SD), kg/m^2	25.0 (6.9)
Body mass index, median (IQR), kg/m^2	23.8 (21.8–27.9)
Primary past medical histories, *n* (%)	
Short bowel syndrome	20 (52.6)
Enterocutaneous fistula	17 (44.7)
Ulcerative colitis and/or Crohn disease	8 (21.1)
Diabetes mellitus	5 (13.2)
Inpatient summary	
Number of readmissions, median (min, max)	1.5 (0.0, 14.0)
Number of admissions requiring ICU stay, median (min, max)	0.0 (0.0, 2.0)
Mortality, *n* (%), yes	5 (13.2)
HPN characteristics	
Primary HPN indications, *n* (%)	
Short bowel syndrome	18 (47.4)
Enterocutaneous fistula	13 (34.2)
Crohn disease	7 (18.4)
Gastroparesis	4 (10.5)
Duration of HPN, mean (SD), years	3.6 (2.9)
Duration of HPN, median (IQR), years	3.2 (1.1–5.3)
HPN calorie, mean (SD), kcal/kg/d	23.8 (9.5)
HPN calorie, median (IQR), kcal/kg/d	23.0 (16.6–28.4)
Amino acid, mean (SD), g/kg/d	1.3 (0.4)
Amino acid, median (IQR), g/kg/d	1.2 (1.0–1.4)
Lipid, mean (SD), g/kg/d	0.8 (0.4)
Lipid, median (IQR), g/kg/d	0.8 (0.6–1.0)
Dextrose, mean (SD), g/d	195.6 (81.4)
Dextrose, median (IQR), g/d	198.0 (137.3–240.0)
Number of days of HPN per week, mean (SD)	6.6 (1.1)
Number of days of HPN per week, median (IQR)	7.0 (7.0–7.0)
Duration of HPN infusion, mean (SD), h/d	13.5 (2.2)
Duration of HPN infusion, median (IQR), h/d	14.0 (12.0–14.0)
Receiving daily IVF, *n* (%)	9 (23.7)
Number of days of IVF per week, mean (SD)	2.1 (3.0)
Number of days of IVF per week, median (IQR)	0.0 (0.0–3.8)
Insulin added in HPN, *n* (%)	5 (13.2)
Home blood glucose level >180, *n* (%)	4 (10.5)
Central line summary	
Total number of lines, *n* (%)	
Hickman	65 (82.3)
PICC	14 (17.7)
Total catheter days for all lines, mean (SD)	528.6 (433.5)
Total catheter days for all lines, median (IQR)	469.0 (283.3–648.0)
Infection summary	
Total number of line infections, mean (SD)	1.2 (2.6)
Total number of line infections, median (IQR)	0.0 (0.0–1.8)
No infection, *n* (%)	20 (52.6)
1 infection, *n* (%)	8 (21.1)
≥2 infections, *n* (%)	10 (26.3)
Microbiology (top 3 microorganisms), *n* (%)	
Staphylococcus epidermidis	13 (23.2)
Candida parapsilosis	6 (10.7)
Klebesiella pneumoniae	6 (10.7)
Sodium citrate lock summary	
Duration of therapy, mean (SD), days	386 (217)
Duration of therapy, median (IQR), days	374 (200–600)
Remained on lock therapy at the end of the study period, *n* (%)	14 (36.8)

Abbreviations: HPN, home parenteral nutrition; ICU, intensive care unit; IQR, interquartile range; IVF, intravenous fluid; max, maximum; min, minimum; PICC, peripherally inserted central catheter; SD, standard deviation.

the incidence rate for CRBSI is expected to increase by 10%. Lipid dose as the predictive factor illustrated inconsistency. Both analyses using Poisson regressions suggested a potentially harmful effect of higher lipid doses on the risk of CRBSI. In the univariate analysis, each 1 g/kg/day increase in lipid dose was associated with a 40% higher incidence rate of CRBSI. Additionally, the multivariate analysis estimated a 230% increase; however, the 95% CI was wide, including the null value (1.0), suggesting the risk cannot be reliably estimated in this study. In contrast, the univariate frailty model showed that a higher lipid dose suggested a protective effect with an HR of 0.59 (95% CI, 0.25–1.39). After adjusting for the duration of HPN infusion (h/day), a higher lipid dose remained protective (adjusted HR, 0.55; 95% CI, 0.23–1.32).

TABLE 2 Catheter-related bloodstream infection in adult patients receiving home parental nutrition by type of catheter.

Type of catheters used for sodium citrate lock (*n* = 38)	CRBSI per 1000 catheter days (95% CI)	HR (95% CI)
Hickman and PICC	2.3 (1.7–3.1)	
Hickman (*n* = 36)	2.2 (1.6–3)	Reference
PICC (*n* = 2)	3.9 (1.3–9.1)	1.27 (0.45–3.56)

Note: Hazard ratios with 95% CIs excluding 1.0 are statistically significant.

Abbreviations: CRBSI, catheter-related bloodstream infection; CI, confidence interval; HR, hazard ratio; PICC, peripherally inserted central catheter.

TABLE 3 Risk factors for catheter-related bloodstream infection in adult patients receiving home parenteral nutrition using sodium citrate lock therapy.

Risk factors	IRR/HR (95% CI)
Univariate analysis with Poisson model	IRR
Duration of HPN infusion, h/d	1.1 (0.9–1.2)
Number of days of HPN per week	1.0 (0.9–1.3)
Number of days receiving IVF or HPN per week	1.0 (0.9–1.1)
HPN calorie, kcal/kg/d	1.01 (0.98–1.03)
Lipid, g/kg/d	1.4 (0.8–2.7)
Dextrose, g/d	1.00 (1.00–1.00)
Multivariate analysis with Poisson model	IRR
Duration of HPN infusion, h/d	1.1 (0.9–1.3)
Number of days of HPN per week	1.0 (0.8–1.4)
Number of days of IVF or HPN per week	1.0 (0.9–1.1)
HPN calorie, kcal/kg/d	1.00 (0.97–1.03)
Lipid, g/kg/d	3.3 (0.5–28.4)
Dextrose, g/d	1.00 (0.99–1.01)
Univariate analysis with frailty model	HR
Duration of HPN infusion, h/d	1.06 (0.88–1.28)
Number of days of HPN per week	1.04 (0.73–1.48)
Number of days of IVF or HPN per week	1.08 (0.97–1.19)
HPN calorie, kcal/kg/d	0.97 (0.93–1.00)
Lipid, g/kg/d	0.59 (0.25–1.39)
Dextrose, g/d	1.00 (0.99–1.00)
Multivariate analysis with frailty model	HR
Duration of HPN infusion, h/d	1.08 (0.90–1.28)
Lipid, g/kg/d	0.55 (0.23–1.32)

Note: Incidence ratios and hazard ratios with 95% CIs excluding 1.0 are statistically significant. The multivariate frailty model includes only two risk factors. Because of the relatively small sample size, the model failed to converge when adjusting for all risk factors.

Abbreviations: CI, confidence interval; HPN, home parenteral nutrition; HR, hazard ratio; IRR, incidence rate ratio; IVF, intravenous fluid.

Safety

No adverse events were reported in the 38 enrolled patients (95% CI, 0.0–9.3).

DISCUSSION

To our knowledge, this retrospective study is the first to report the use of sodium citrate locks and the incidence rate of CRBSIs in adults requiring HPN. Since its approval in March 2000, sodium citrate 4% solution has primarily been studied in patients requiring long-term CVCs on dialysis but not in patients receiving long-term HPN. Although it cannot be directly compared in this study, sodium citrate locks reduced CRBSI, with an estimated incidence rate of 2.3 (95% CI, 1.7–3.1) per 1000 catheter days, compared with our historical patients receiving HPN, from the same institution and with similar reasons for HPN who received standard heparin locks, with an estimated CRBSI rate of 8.7 per 1000 days (95% CI, 5.2–13.6).[6] A retrospective study of 307 patients who required hemodialysis via CVCs showed that 4% sodium citrate was not inferior in efficacy compared with heparin for maintaining long-term interdialytic patency of central venous hemodialysis catheters.[21] That study also resulted in an 85% cost reduction using sodium citrate locks compared with traditional heparin.[21] An in vitro study demonstrated that 4% sodium citrate significantly reduced biofilm production and bacterial motility in *Pseudomonas aeruginosa*.[25] None of our patients receiving HPN tested positive for *P. aeruginosa*. A randomized controlled trial of 78 patients in the ICU requiring hemodialysis for acute renal failure showed that citrate locks reduced CVC-related complications and extended the catheter life span by 6 days before CRBSI compared with saline locks.[24] A phase 4 study evaluating a 3 ml 4% sodium citrate lock solution as a CLABSI prophylaxis intervention for children requiring HPN will provide new insight once results become available (ClinicalTrials.gov identifier NCT04756427).

In June 2018, the FDA approved only one dehydrated alcohol, Ablysinol (a sterile, preservative-free solution of ≥99% ethyl alcohol by volume), as an orphan drug for inducing controlled cardiac septal infarction in adults, thereby granting it market exclusivity. In 2020, the FDA requested the removal of all unapproved dehydrated alcohol products, making the compounded 70% ethanol locks hard to obtain.

If ethanol lock therapy is used, it must be compounded using this costly product, ranging from $800 to $1500 per 5-ml vial, or up to $4800 weekly, with inadequate reimbursement for off-label use.[31] Planned clinical trials to further evaluate the efficacy of ethanol locks in preventing CRBSI had to be withdrawn (ClinicalTrials.gov identifiers NCT01409772 and NCT01263574) or terminated (ClinicalTrials.gov identifiers NCT02890875 and NCT02227329). Despite promising evidence for the safety and efficacy of ethanol lock therapy in reducing CRBSI, the limited availability and high cost have led to the use of sodium citrate locks as a more affordable alternative, at approximately $18 per week. Also, ethanol lock is contraindicated in polyurethane catheters because it was associated with higher occlusion rates and catheter displacement in children receiving chronic HPN,[32] whereas sodium citrate is safe for both polyurethane and silicone catheters.[29]

Other lock solutions are being evaluated to prevent CRBSIs in patients receiving HPN. Chelating agents, such as 4% tetrasodium ethylenediaminetetraacetic acid, which possess antimicrobial, antibiofilm, and anticoagulant properties, have shown promising results in reducing CRBSI in pediatric patients. It is only available in the United States for compassionate use in children. Ongoing clinical trials are evaluating 4% tetrasodium ethylenediaminetetraacetic acid lock solutions to prevent occlusions and evaluate the incidence of CRBSI in children and adults (ClinicalTrials.gov identifiers NCT05879835 and NCT04067245, respectively). Another lock solution, such as the taurolidine lock, has significantly lowered CRBSI occurrences in 30 adult patients receiving HPN compared with heparin locks.[9] A meta-analysis of nine studies (918 patients) suggested that taurolidine locks may potentially prevent CRBSI in patients in oncology and those requiring hemodialysis and PN.[33] Another meta-analysis of 34 studies (1485 patients) showed that taurolidine alone, combined with 4% citrate and/or heparin, reduced CRBSIs.[34] Taurolidine lock had been unavailable in the United States until November 2023, when the FDA approved DefenCath, a catheter lock solution with taurolidine and heparin, to reduce CRBSI in patients with kidney failure undergoing chronic hemodialysis through a CVC. A phase 3 clinical trial is underway to evaluate the efficacy and safety of a taurolidine and heparin solution compared with heparin alone in adults receiving HPN through a CVC (ClinicalTrials.gov identifier NCT06822426).

Identifying risk factors for CRBSI is crucial for clinicians in developing preventive strategies and reducing CRBSI rates. For patients receiving HPN, several known risk factors, such as catheter type, duration of catheterization, and patient-related factors, have been reported to increase the risk of developing CRBSI.[35–38] The current study suggested that patients with PICCs had a 27% increased risk of CRBSI, which is similar to a 6-year follow-up study that showed the incidence of CRBSIs per 1000 catheter days was significantly lower for Hickman catheters compared with PICCs (0.56 vs 1.63; $P < 0.05$).[35] This finding is also consistent with our original study, which found that patients with a PICC had significantly higher rates of CRBSI ($P = 0.018$).[6] The duration of catheterization (>250 days of HPN) was associated with an increased occurrence of CRBSIs (IRR, 12.8; $P < 0.001$).[37] The mean duration of HPN in the current study was 3.6 years. Patients with intestinal failure, specifically short bowel syndrome, had been associated with an increased risk of developing CRBSI ($P < 0.016$).[36] Over half of the patients receiving HPN (52.6%) in this study had short bowel syndrome, which increased the risk for CRBSI. This study shows that for every 1-h/day increase in the duration of HPN infusion (median, 14 h/day), the incidence rate for CRBSI is expected to increase by 10%. This observation is expected because a shorter HPN infusion time would allow for a longer dwelling time of any lock solutions, resulting in a reduced risk of CRBSI. The efficacy of any lock solution is related to dwell time, and the general recommendation is to dwell for at least 4 h when the catheter is not in use.

Additionally, frequent manipulation of the catheter may increase the risk for CRBSI, and proper aseptic technique should be performed to minimize this risk.[39] For patients who required more days of HPN and/or intravenous fluids necessitating more catheter manipulations, the univariate analysis with a frailty model suggested that these patients had a slightly higher risk of CRBSI (HR, 1.04 and 1.08, respectively). A prospective study involving 200 patients who received PN showed that the incidence of bloodstream infections was related to increased PN calories (36 vs 31 kcal/kg/day; $P = 0.003$).[40] In this study, PN kilocalories (mean, 23 kcal/kg/day) much lower than the studied doses, was not associated with an increased risk of CRBSI. The American Society for Parenteral and Enteral Nutrition (ASPEN) highlights that lipid injectable emulsions with a dose of ≥2.5 g/kg/day are associated with an increased risk of CRBSIs.[41] In this study, the Poisson models (both univariate and multivariate) suggested that a higher lipid dose was associated with an increased rate of CRBSI, with the association becoming stronger after adjusting for other factors (IRR rose from 1.4 to 3.3). In contrast, the frailty models (both univariate and multivariate) suggested that a higher lipid dose reduces the risk of CRBSI. This finding was reconfirmed after adjusting for the duration of HPN infusion (h/day) (HR, 0.59 and 0.55, respectively). These findings suggested a complex relationship between lipid dose and CRBSI.

The current study has several limitations. Some data were inevitably missing because of the retrospective nature of the study design. The sample size was small because commercial 4% sodium citrate locks were unavailable for prescribing to patients receiving HPN with an increased risk for recurrent CRBSI. None of the associations reached statistical significance, likely because of the limited sample size. The differing results between the Poisson and frailty models may reflect differences in underlying model assumptions and how well each model aligns with the data. Larger sample sizes in future studies may help refine these estimates. The compounded 2-ml lock solution provided a lower dose than the commercially prefilled 3- or 5-ml syringes of 4% sodium citrate locks, limiting the generalizability of the study results. There are also no comprehensive data on whether our participants received antibiotic lock therapy and/or tissue plasminogen activator therapy during the observation. Another limitation was the routine daily addition of 1000 U/L heparin to HPN bags to prevent fibrin sheath formation and maintain line

patency as the standard of practice with Emory University Hospital's Nutrition and Metabolic Support Team, which is not a common practice elsewhere. The use of sodium citrate in addition to heparin may complicate the interpretation of the isolated effects of 4% sodium citrate on CRBSI and catheter patency. As such, the generalizability of our outcomes should be interpreted with caution. Although a 4% sodium citrate lock is considered safe, the possible side effects or complications that may arise from continuous exposure as a lock solution were not adequately explored in this study.

CONCLUSIONS

It is common for adult patients requiring HPN to develop CRBSIs. This retrospective study suggests that a 4% sodium citrate lock solution may be a potentially safe alternative to prevent these infections. It is now routinely prescribed for all HPN patients in our institution. Rigorous, larger prospective clinical trials are warranted to investigate the efficacy and safety of 4% sodium citrate lock solutions in adult patients receiving HPN.

AUTHOR CONTRIBUTIONS

Rachel Leong: Conceptualization; Investigation; Writing—original draft; Methodology; Visualization; Writing—review and editing. **Nisha J. Dave**: Conceptualization. **Daniel P. Griffith**: Conceptualization. **Anna Guo**: Data curation; Writing—original draft; Writing—review and editing; Software; Formal analysis. **Kirk A. Easley**: Writing—original draft; Writing—review and editing; Software; Formal analysis; Data curation. **John R. Galloway**: Conceptualization. **Thomas R. Ziegler**: Conceptualization; Writing—original draft; Writing—review and editing; Visualization; Supervision; Resources; Validation. **Vivian M. Zhao**: Conceptualization; Investigation; Writing—original draft; Methodology; Validation; Visualization; Writing—review and editing; Formal analysis; Supervision; Resources.

CONFLICT OF INTEREST STATEMENT

None declared.

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