Sodium Citrate 4% Locking Solution for Children Requiring Home Parenteral Nutrition

NCT04756427

January 25, 2022

Date: ___1/25/22_____
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Application Number: __ IRB00264457
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1. Abstract

Children with intestinal failure require long-term central venous catheters for home parenteral nutrition and are at high risk for central line-associated blood stream infections (CLABSI). Ethanol 70% locks are no longer available to use as prophylaxis as recent manufacturer price changes have made them cost-prohibitive for home health companies, and ethanol is not compatible with all tunneled catheters used for home parenteral nutrition. Another FDA-approved product does not exist; therefore, the standard of care is to use heparin locks, which prevent thrombus but have no antimicrobial activity. Sodium citrate 4% has been safe and effective for use in children with dialysis catheters, which are very similar to the central catheters used for home parenteral nutrition, to both prevent thrombus and CLABSI. Our hypothesis is that sodium citrate 4% prophylaxis locks will also be safe and effective for use in central lines for children requiring home parenteral nutrition. Reducing the risk of CLABSI with have a significant impact on the health and quality of life of our pediatric patients. Children with CLABSI require intravenous antibiotic treatment and frequent hospitalization, which includes risk of septic shock and death. Frequent hospitalization negatively impacts the quality of life for both the child with intestinal failure and their family.

2. **Objectives** (include all primary and secondary objectives)

Our objectives are 1) to determine if the safety of sodium citrate prophylaxis 4% locks is different from the standard of care using heparin locks in children with central lines for long-term home parenteral nutrition, and 2) to determine the efficacy of sodium citrate 4% locks in preventing central line-associated blood stream infections in children with central lines for long-term home parenteral nutrition.

3. **Background** (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Among our pediatric intestinal failure population on home parenteral nutrition, our CLABSI rate ranges from 4-7 infections/1,000 line days, which is similar to other sites.(1, 2) Our current standard of care is to use daily heparin locks in the central line for anti-coagulation, and if recurrent CLABSI occurs, we previously used 70% ethanol locks 3 days per week as a means of infection prophylaxis. However, there are several problems with ethanol: 1) ethanol is not compatible with polyurethane catheters, which are occasionally used in our population 2) manufacturing has recently changed and this product is now cost prohibitive and no longer available to most of our home care companies, and 3) our CLABSI rate has not noticeably improved with its use.

There is not another FDA approved infection prophylaxis lock available in the US. Other products are available in Canada and Europe, including sodium citrate. Through quality improvement initiatives, some centers have transitioned from heparin to sodium citrate 4% locks as standard of care for dialysis catheters.(3, 4) A recent international evidence based review also recommended citrate as a locking solution for non-hemodialysis catheters.(5)

Potential Benefits. Sodium citrate has both anti-coagulant and anti-microbial activity and is indicated for use a as a daily lock. The antimicrobial/anti-biofilm properties are likely related to citrate's chelation of ions, such as calcium, which destabilizes bacterial cell walls, whereas heparin may actually facilitate biofilm formation.(6) Sodium citrate (4%) is FDA approved for

hemodialysis and apheresis catheters, and it has been used in both adults and children. Similar to our indwelling catheters, hemodialysis catheters are also made of both silicon and polyurethane, and sodium citrate is not contraindicated with either material. Sodium citrate is also compatible with antibiotic locks that are commonly used to help treat CLABSI when it does occur.(7, 8)

Potential Risks. While locking solution are intended to dwell in the catheter and then be redrawn, there is a potential for systemic leak. When used as a 4% locking solution in dialysis and apheresis catheters, sodium citrate has been well tolerated. If a small amount of sodium citrate enters the blood stream, it is rapidly metabolized with sodium bicarbonate without deleterious effects.(9) When compared to heparin, 4% sodium citrate has had either similar or fewer adverse bleeding events.(3, 4, 10) A prospective study of patients in the intensive care found no clinically significant difference in ionized calcium using sodium citrate 4% locks.(11) In a randomized trial of nearly 300 subjects, the use of trisodium acetate 30% resulted in significantly fewer CLABSI events and bleeding events compared to heparin without any serious adverse events. At high concentrations (46%) and in the setting of citrate use with continuous renal replacement therapy and extra-corporeal membrane oxygenation, hypocalcemia leading to cardiac arrhythmia has been reported.(12) There is also risk protein precipitate causing line occlusion, particularly with sodium citrate concentrations >12%. Our protocol will only include a 4% lock solution.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This is a prospective observational cohort study of pediatric patients requiring home parenteral nutrition using daily sodium citrate 4% catheter locking solution for CLABSI prophylaxis instead of heparin. Subjects will be monitored for 12 months for adverse events, including CLABSI. Subjects will have the same routine laboratory schedule and monthly outpatient follow up. After 12 months, subjects will be given the option to continue to use sodium citrate 4% locks after the initial study period if no serious adverse events have occurred. We anticipate enrolling 10-15 subjects per year. We anticipate enrollment to continue for 3-5 years.

Sodium citrate locks – 3 ml syringes of locking solution will be prepared by the infusion pharmacy using commercially available 4% sodium citrate IV fluid (available in 500 ml bags). The sodium citrate locks will be instilled into the central catheter daily during the period that parenteral nutrition is not infusing, and will be withdrawn and disposed of prior to resuming infusion of parenteral nutrition. If subjects are hospitalized, sodium citrate locks will be temporarily held during the duration of the inpatient stay, and will be resumed once the subject is discharged home.

Metrics - The primary outcome will be CLABSI rate, defined as a positive central line culture in the absence of other known primary infection per 1,000 line days. Secondary outcomes will be frequency of central catheter thrombus, any serious adverse event (hospitalization for any reason or death), or catheter removal per 1,000 line days.
Other variables – Demographics, age, underlying gastrointestinal disorder, comorbidities, catheter type, and catheter insertion date will also be recorded

b. If your study involves data/biospecimens from participants enrolled under other research studies with a written consent or under a waiver of consent, please list the IRB application numbers for those studies. Please note: Certificate of Confidentiality (CoC) protections applied to the data in source studies funded by NIH or CDC will extend to this new study if the funding was active in 2016. If this situation applies, Section 36, question 4 in the application will need to be answered "Yes" and "Hopkins Faculty" should be selected in question 7. No other documents are required.

Our intestinal failure patients are also enrolled in our prospective database IRB00077416 with overlapping clinical data which can be used for comparison to historical adverse events, including CLABSI.

c. Study duration and number of study visits required of research participants.

The study period will be twelve month. Subject will continue their routine monthly outpatient visits, as well as urgent visits for fever.

d. Blinding, including justification for blinding or not blinding the trial, if applicable.
Not applicable

e. Justification of why participants will not receive routine care or will have current therapy stopped.
Routine care with heparin provides insufficient CLABSI prophylaxis. No other therapy will be changed.

f. Justification for inclusion of a placebo or non-treatment group.
Not applicable

g. Definition of treatment failure or participant removal criteria.
Significant adverse event due to sodium citrate 4%, such as recurrent central line thrombus, significant bleeding, significant electrolyte instability not due to other etiologies, or cardiac arrythmia

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
If the subject withdraws from the study, they will resume standard of care heparin locks. Once the study is completed, if there have been no adverse events due to sodium citrate 4%, we propose continuing to use sodium citrate 4% as the daily locking solution.

5. Inclusion/Exclusion Criteria

Inclusion criteria - Pediatric patients (<22 years) requiring long-term (>3 months) home parenteral nutrition who have had at least one central line-associated blood stream infection. Parenteral nutrition must be cycled to 22 hours or less (>2 hours per day where parenteral nutrition is not infusing).
Exclusion criteria – patients with known cardiac arrhythmias, hypersensitivity to citrate, pregnancy, or receiving continuous parenteral nutrition (infusing over 24 hours).

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
See background. This drug and dose has been safe and effective when used in similar dialysis catheters

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
The drug is FDA approved for similar dialysis catheters.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

7. Study Statistics

a. Primary outcome variable.
The primary outcome will be CLABSI rate, defined as a positive central line culture in the absence of other known primary infection per 1,000 line days.

b. Secondary outcome variables.
Secondary outcomes will be frequency of central catheter thrombus, any serious adverse event (hospitalization for any reason or death), or catheter removal per 1,000 line days

c. Statistical plan including sample size justification and interim data analysis.
A predetermined sample size will not be used. All eligible, consented subjects will be enrolled. The frequency and proportion of adverse events will be compared to our historical control population of home parenteral nutrition subjects who used either heparin or ethanol locks, who are already enrolled in a prospective observational cohort to monitor outcomes (IRB00077416) using descriptive statistics

d. Early stopping rules.
Based on the safety of previous studies, we do not anticipate the need for early stopping. Given our small population, adverse events will be monitored quarterly. If there is a significant change in frequency of events that appear to be directly related to sodium citrate 4%, the study will be stopped early.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
Please see the Background for additional information. Bleeding risk is low and similar to heparin. At high concentration, other risks have been reported: sodium citrate 12% has been associated with protein precipitate, and sodium 46% has been associated with hypocalcemia and arrhythmia

b. Steps taken to minimize the risks.
To minimize risk, we are using the previously well tolerated 4% sodium citrate solution. The lock withdrawn and discarded after dwelling in the catheter to prevent systemic circulation. If the sodium citrate enters systemic circulation, the most likely outcome is metabolism to bicarbonate.

c. Plan for reporting unanticipated problems or study deviations.
The data will be monitored quarterly and unanticipated problems or deviations will be reported to the IRB

d. Legal risks such as the risks that would be associated with breach of confidentiality.
We do not anticipate greater risk of breach of confidentiality by participation in this study. Only minimal data is recorded, and it is stored in a secure, HIPAA compliant online database, only accessible by study members.

e. Financial risks to the participants.
There will be no direct costs to the subjects. We will request insurance coverage of the sodium citrate locks to be included in the per diem parenteral nutrition charge, similar to the way heparin locks are already included as standard of care. Clinic visits and laboratory tests are scheduled as standard of care. If insurance declines to cover the cost of the locks, we will not enroll the subject in the study.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Subjects may directly benefit from study participation by reducing risk of CLABSI. Determining if sodium citrate is safe and effective will benefit the vulnerable intestinal failure population in general.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.
Subjects will not be compensated financially for participating in the study.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

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Sodium citrate locks can be compounded and shipped out by the Johns Hopkins pharmacy in a 14-day supply. The cost of a 14-day supply of sodium citrate locks is $182 ($7/day x 14 days for drug, $34 for compounding session, $50 delivery fee). The cost of 1 year of participation would be $4,732 ($182 x 26 weeks) per subject. We will request insurance coverage for the cost. If we are unable to get insurance coverage, the subject will not be enrolled.