Tetrasodium EDTA central venous catheter lock solution in home parenteral nutrition patients: ease of use and cost analysis

Written by
Jessica Noelting MD

Principal Investigator: Johane Allard, MD, FRCPC

Department of Gastroenterology
Toronto General Hospital

Abstract:

Parenteral nutrition (PN) is a lifesaving therapy in patients with chronic intestinal failure. PN is administered via a central venous catheter (CVC), and patients are dependent on this line for ongoing nutrition. However, the presence of a CVC is associated with a risk of thrombosis and bloodstream infection. Many different types of catheter lock solutions have been used to mitigate these risks. They include solutions primarily aimed at reducing thrombosis, such as heparin and citrate, and others primarily aimed at reducing infection such as ethanol and antibiotics (for example, taurolidine). One recently developed solution, tetrasodium EDTA, aims to reduce both thrombosis and infection. This scientific review provides an overview of central venous catheter lock solutions, and an ease-of-use and cost analysis comparing heparin and tetrasodium EDTA in one home parenteral nutrition program in Toronto, Canada.

Keywords: parenteral nutrition, central venous catheter, heparin, taurolidine, citrate, ethanol, tetrasodium EDTA

Background:

Parenteral nutrition (PN) is a life-sustaining therapy required in patients who do not have a functioning gastrointestinal tract. This can be either second to surgical removal, or malfunction (such as in malabsorptive conditions and dysmotility). The intravenous provision of nutrition requires central venous access where a hyperosmolar nutrient solution can be infused. A variety of central venous catheters (CVCs) can be used, including peripherally inserted central catheters (PICC), tunneled catheters and implanted ports. The most common complication, and most frequent cause of hospitalization in patients on home PN is bloodstream infection. (8)

There are several new devices or solutions that are being developed to be used as primary prophylaxis for CRBSI. These include catheters with antibacterial and/or anti-biofilm properties and different catheter lock solutions. Antibiotic lock solutions have been used for salvage of central venous catheters in confirmed CRBSI (1). However, it is not recommended as a primary prophylaxis due to the creation of resistant organisms. (2) According to the United States Center for Disease Control (CDC), antibiotics 'should be used only to manage infection.' (3) However, one antimicrobial solution, taurolidine, has not been found to promote the emergence of resistant bacterial strains and it has been used successfully as a lock solution to prevent CRBSI. Although an antibiotic may have anti-biofilm properties in high concentrations but it does not have anticoagulant properties. Ethanol lock solutions (varying concentrations, but usually 70%) have also been used successfully to reduce CRBSI, however, there have been adverse events when they are used in polyurethane lines and it does not inherently have anticoagulant properties. Historically, citrate lock solution has also been used to maintain catheter patency, but in a meta-analysis, there was no difference between heparin and citrate lock with regards to catheter thrombosis or catheter related bloodstream infection (12).

Although its use has been evaluated in hemodialysis catheters, there are no known studies examining the use of a tetra-sodium EDTA catheter lock solution in central venous catheters of patients on home PN.

Although both hemodialysis and home PN require central venous catheters, there are many differences inherent to the different usages. First, the types of catheters that are used can differ. There is more variety in the types of catheters used for home PN. Second, most patients undergo hemodialysis on a fixed schedule, three times per week for 4 to 8 hours each time, and, for the majority of patients, this is done in-center, with the assistance of a nurse. On the other hand, home PN is usually administered five or more days per week, at home, over 12 or more hours. It can be either administered with the assistance of a home care nurse or by the patient and/or their family/partner. Furthermore, the substance infused through the catheter is different. Specifically, amino acids and fat emulsions are usually only infused in home PN, although electrolytes and fluids can be infused in both.

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RESEARCH DESIGN AND METHODS

The primary objective of this study is to evaluate patient acceptability of tetrasodium EDTA catheter lock solution in home parenteral nutrition patients.

The secondary aims are to evaluate: side effects, time for preparation and injection, cost and patient satisfaction.

This is a prospective, open-label, single-center study of the patient acceptability of using tetrasodium EDTA catheter lock solution in home parenteral nutrition patients. At study baseline, all patients will be on normal saline/heparin lock solution (which they receive normally as current standard of care) for at least 1 month before starting the study, as per inclusion criteria.

Patients will then start with one month (30 days) of their usual heparin and saline flush followed by one month (30 days) of tetrasodium EDTA solution with withdrawal (when possible), followed by one month (30 days) of tetrasodium EDTA solution. During the last week of each of the aforementioned three months, the patients will be asked to evaluate the lock and flush. Patients will be followed and treated according to usual care during the study, except for the catheter lock solution.

All patients receiving HPN at Toronto General Hospital will be invited to participate in the study. Patients will be recruited at their usually scheduled HPN appointment or by telephone. Consent will be taken by clinical fellow and nurse coordinator. Patients will be instructed on the use of the new lock solution via (1) telephone by the home TPN nurse. The patient or the other person administering the lock solution (usually caregiver or community nurse) will be responsible for filling the provided survey three times: once at the end of each month. The patients will be responsible for filling a data collection form with time of procedure, and any symptoms or side effects as they occur. The patient will receive four phone calls from the home TPN nurse in regards to this study: once at the beginning of the study and once at the end of each month. At each phone visit, the nurse will record the time to perform and any symptoms or side effects that the patient has written down in their data collection form, and administer the survey, in addition to inquiring about any interim events such as hospitalization, surgery and illness (at phone calls

2, 3 and 4) and compliance. The catheter lock solution will be distributed by Ontario Medical Supply, with home TPN solution and supplies, as per the patient's usual delivery schedule. Regular home TPN monitoring labs will be drawn at least once at the beginning of the study and once at the end of the study (3 months later), or more frequently, as clinically indicated or as per the patient's usual care.

SAMPLE SIZE

This is a pilot study; we plan to recruit 20 participants.

INCLUSION CRITERIA
Subjects who meet all of the following criteria can be enrolled in this study:

- Adult over the age of 18
- Both males and females
- Clinically stable for at least 4 weeks with no acute medical co-morbidities

EXCLUSION CRITERIA

- Inability to give informed consent
- Alcohol or drug abuse
- Pregnant and lactating women
- Clinical instability such as the following:
- Acute pulmonary edema
- Decompensated heart failure
- Decompensated chronic liver disease
- Severe post-traumatic conditions
- Uncontrolled diabetes mellitus
- Acute myocardial infarction
- Acute stroke
- Acute thromboembolism
- Metabolic acidosis
- Sepsis
- Hypotonic dehydration
- Coagulopathy with prolonged aPTT or INR
- Unstable oncology patient
- Subjects who are hypersensitive or allergic to the product ingredients of tetrasodium EDTA
- Active therapy with long-term anti-microbial, such as taurolidine (not including patients receiving intermitted antimicrobial treatment for small intestinal bacterial overgrowth)
- Active participation in another home TPN clinical trial which may interfere with the results

HPN administration:

The patients are already part of the HPN program for **at least 1 month** (the minimum time on stable HPN as part of the inclusion criteria). These patients are familiar with self-administration of HPN. The

different lock solution will affect their usual practice and does require additional training/instructions due to the need to prepare the solution from a vial, injecting the line with the solution and withdraw the solution from the line

Lock procedures:
1) Heparin and saline (standard of care), as per protocol
2) Tetrasodium EDTA lock and withdraw
3) Tetrasodium EDTA lock and flush through

Prior to disconnecting PN tubing (when infusion complete):
1) Clean work area.
2) Gather: pre-filled 10 ml saline syringe; alcohol swabs; 3 ml or 5 ml empty syringe (depending on the type of line: 3mL for PICC and Hickman and 5mL for a Port-A-Cath); and Tetrasodium EDTA lock vial or Heparin pre-filled syringe (3 ml or 5 ml)
3) Wash your hands.
4) Swab end cap properly with alcohol swab before attaching any syringes. Open clamp.

5) **For Heparin lock:**
a. Flush catheter with pre-filled saline syringe as per usual routine.
b. Flush and lock catheter with pre-filled heparin syringe as per usual routine.

6) **For Tetrasodium EDTA:**
a. Draw up 3 ml or 5 ml Tetrasodium EDTA solution in empty syringe. Set aside.
b. Flush catheter with pre-filled saline syringe as per usual routine.
c. Flush and lock catheter with Tetrasodium EDTA solution (3 or 5 ml).

7) Close clamp.

Prior to connecting to PN tubing:
1) Clean work area.
2) Gather: prefilled 10 ml saline syringe; alcohol swabs; 3 ml or 5 ml empty syringe
3) Wash hands.
4) Swab end cap properly with alcohol swab before attaching any syringes as usual. Open clamp.
5) Attach empty syringe to the catheter.
6) Pull back 3 ml (or 5 ml) Tetrasodium EDTA lock solution from the catheter. It will be mixed with some blood, this is normal. Remove the syringe.
7) Swab end cap properly with alcohol again.
8) Flush catheter with 10 mL saline syringe as per routine.
9) Connect to PN tubing as per routine.
10) Start infusion as per routine.

If flushing Tetrasodium EDTA lock solution through the catheter, repeat above steps but omit 5 - 7.

Cost analysis (this is an estimate which may be modified after the trial):

Type	Solution	Dispensing fee	SAP application	Distribution	Supplies*	Education
Saline/heparin	$2/use	0	N/A	0/contract	0/contract	0
Tetrasodium EDTA	$3.50/use	0	N/A	0/contract	10ml syringe without needle	0.5h ($40/hr)
Saline/taurolidine	$20/10ml	$11,99	2h ($55/h) Per patient		3-5ml syringe with needle	0.5h ($40/hr)

Measures:

1. Patient acceptability

See Form 2 below

2. Patient satisfaction

See Form 2 below

3. Time to prepare tetrasodium EDTA catheter lock solution

(1) From starting to prepare to infuse TPN to starting the TPN infusion (form 1)

(2) From disconnecting TPN tubing to completing catheter lock solution (form 1)

4. Symptoms and side effects

See Form 1: patient data collection form

5. Labs

Regular TPN labs, as per usual care, at the beginning and end of the study (form 4)

(1) Within 30 days of starting the study

(2) On, or up to 10 days after the last day of using the tetrasodium EDTA lock solution

Data collection forms:

-Form 1: patient data collection form:

-Record symptoms and side effects as they occur

-Record the time of the procedure on the first and last Monday of each 30-day period

-Form 2: survey on ease of use (3 per patient)

- to be filled by person administering the lock (RN, patient, family member), where possible

- to be filled three times, during the phone visit at the end of each month

- Form 3: Education time

-Nurse: over the phone

-Patient demonstration

Clinic Visits:

Clinic visits: None required

Follow up Phone call:

Each phone call will last for around 40 minutes. All participants will receive phone call at baseline and at the end of month 1,2 and 3.

Phone visits:

(1) At baseline, prior to initiation of the product

(2) At the end of month 1 (on days 27 to 30)

(3) At the end of month 2 (on days 57 to 60)

(4) At the end of month 3 (on days 87 to 90)

Follow-up phone call for the following purpose:

- **Safety**: by asking questions about side effects and tolerance to tetrasodium EDTA solution (from patient data collection form)

- **Compliance**: Recording the number of catheter lock solutions used.

- **Record times of procedure** (from patient data collection form)

- **Record events** (hospitalizations, antibiotics used, or interruption of lock solution use)

- **Record who is doing the flush** (nurse, patient or family member)

- **Perform a phone survey**

-**Review the instructions** for the next month

SUBJECT WITHDRAWAL CRITERIA

In accordance with the Declaration of Helsinki, subjects are free to stop the study at any time for any or no reason, and without prejudice to further treatment. For subjects who decide to withdraw, effort would be made to contact him/her, to obtain information about the reason for discontinuation and any adverse events (AEs). All subjects who discontinue prematurely will be evaluated for AEs that are not resolved at the time of study discontinuation and will be followed for up to 4 weeks from the date the subject stops tetrasodium EDTA or as long as is medically relevant as judged by the principle investigator. All subjects who will withdraw from the study will be maintained on appropriated standard medical care. Subjects, who decide to be discontinued, will not be replaced.

Procedures to be taken in case of an adverse event (AE):

Patients receiving PN are complex and frequently have adverse events or complications that may be related to either their PN, their underlying disease or a medical/surgical procedures. Therefore, it is

expected that during the study, some HPN patients will have some AE that are most likely not related to the tetrasodium EDTA but more to HPN overall or underlying medical/surgical conditions.

If an AE occurs:

1- The HPN team will assess whether the AE is related or not to tetrasodium EDTA solution. Depending on the nature of the AE, tetrsodium EDTA solution may be put on hold based on standard medical practice.
2- If a line infection develops, it is general practice to hold HPN for 24-48 hours while antibiotics are started. HPN can be on hold longer if a central line needs to be changed, either as a result of certain types of line infections (eg. fungi, staph aureus) or because of line malfunctions. Generally all patients are expected to resume HPN within 1 week because, otherwise, they cannot meet their nutritional requirements. Catheter lock solution will be resumed based on the types of solution the patient is receiving at that point in time whenever a central catheter is present.

Compliance with catheter locks solution

Subject compliance will be checked when they will receive a phone call every months as a follow-up asking about the number of catheter lock solution used and the amount of solution infused. In addition, they will be asked if they have taken the TPN as per the instructions provided to them about the infusion.

SAFTERY EVALUATION:

All AEs will be reported and evaluated. The research team will be responsible for detecting and documenting any AE or serious adverse event (SAE). This will help in identifying any untoward medical occurrence, thereby allowing the continuous safety of study subject and provide a greater understanding of the overall safety profile of the investigational product.

Adverse event Definition

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered medical/ pharmaceutical product. An adverse event does not necessarily have to have a causal relationship with the medical/ pharmaceutical product.

An AE can therefore be any unfavorable and unintended sign (including a clinical significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre existing illness, sign, symptom, or clinical significant laboratory test abnormality as determined by the investigator.
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration.
- Pre or post treatment events that occur as a result of protocol mandated procedures

An AE does not include:

- Expected worsening of the disease or disorder being studied or signs and symptoms associated with the disease or disorder
- A preexisting disease or condition, present at the start of the study that did not worsen
- Any overdose of the study drug or concurrent medication without any clinical sign or symptom.

Procedure for reporting adverse events

Any sign (e.g., a clinically significant abnormal laboratory finding, as determined by the investigator), symptom or disease described by the subject or noted by the research team will be recorded as an AE. If known, the diagnosis of the underlying illness or disorder will be recorded rather than its individual symptoms.

At each phone call, new AEs will be recorded on the CRF. The AE term should note the diagnosis of the event, not the individual signs of symptoms (e.g., sneezing , coughing recoded as upper respiratory tract infection).
Also, recorded are

- Start and stop date and time
- frequency (intermittent, continuous)
- Intensity (mild , moderate, sever)
    - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities
    - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activates.
    - Severe: requires vigorous therapeutic intervention and or interrupts usual activities. Hospitalization may or may not be required.
- Relationship to study drug (not related, related). An event related to drug treatment, i.e, associated with drug treatment, is considered an adverse drug reaction (ADR) . The term related includes unlikely (improbable), possibly, probably, and definitely.
- Whether or not the AE is serious (i.e, an SAE). If identified as an SAE, the AE should be reported on the SAE form and reporting guidelines followed.
- Actions taken (none; study drug dose interrupted or discontinued, other medication change, non drug therapy)
- Outcome (resolved, ongoing, fatal). If the AE has increased in severity or frequency, it should be identified as a new AE and given a new number

AE not resolved at the end of treatment will be followed for up to 4 weeks after the last dose of catheter lock solution or as long as judged medically relevant by the investigator.

Serious Adverse Events
An event that is serious must be recorded on the SAE report form and requires expeditious handling to comply with regulatory requirements.

Serious Adverse Event Definition
An adverse event is considered serious if it

- Occurs during study treatment or within 30 days of last dose of study drug (or after 30 days if considered to be a result of delayed toxicity due to administrations of study drug) and meets any of the criteria outlined below.

An SAE is any AE occurring at any dose that results in any of the following outcomes

- Death
- life threatening. A life threatening AE is any AE that place the subject in the investigator's opinion at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant disability or incapacity
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/ birth defect
- Important medical events that may not result in heath, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcome listed in this definition.

Data storage:

All data regarding the study will be stored in hospital file and UHN computer system of the clinical fellow, nurse coordinator and principal investigator for 10 years.

Statistical analysis:

Simple statistics such as mean, median and frequency will be used to initially assess the data as follows:

1. Patient acceptability will be analyzed as the proportion of participants willing to continue use of the catheter lock solution. The solution will be deemed acceptable if at least 75% of participants are willing to continue use of the solution.

2. Patient satisfaction will be analyzed as the proportion of participants overall satisfied with the catheter lock solution.

3. Ease of use will be analyzed as the proportion of participants answering that the process is easy or very easy. This will be calculated by taking the average of the answers to the 3-5 questions at the top of the questionnaire addressing the ease of the procedure (preparation of the solution, instilling, withdrawing etc). Each step will also be analyzed individually (averaged over all of the patients), to determine if one of these individual averages falls below 3 (suggesting that that procedure is difficult).
The means of patient acceptability, patient satisfaction and ease of use of the new catheter lock solution flush and the new catheter lock solution withdraw will each be compared, separately, to those of the heparin group and to each other using the chi squared test to determine if there is any difference between them.

Sample Size and Feasibility

This is a pilot study; we plan to recruit 20 participants.

Limitations:

- The expected sample size is 20 subjects and some of them live far away from TGH. This can be avoided a phone call follow-up every month.
- Some of the patients may not be compliant with the catheter lock solution or TPN infusion. Compliance will be checked by counting the number of catheter lock solutions and tpn bags delivered and used. However, compliance cannot be predicted.
- Patients may drop out after the first treatment and therefore not receive total duration of study period. Withdrawal from the study may be related to side effects or inability to accept the use of catheter lock solution. To overcome this point, treatment period provided during study is 3 months with frequent follow-up phone every month to detect any side effect and acceptability.

Significance

As yet, no current prospective data are available in Canada that assesses the use of tetrasodium EDTA catheter lock solution in hpn patients. The use of tetrasodium EDTA which is thought to have triple benefit of anti-thrombotic , anti-microbial and/or anti-biofilm may replace the use of heparin solution for ease of use and cost effectiveness. Thus, there is a need for prospective interventional study to evaluate its use in our hpn patients.

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APPENDIX

Sample size: 20 participants

Duration: 3 months

Patient will be instructed on the use of the new lock solution via:
A Telephone by HPN nurse OR
B Demonstration by company representative

Patient will receive four phone calls from HPN nurse in regards to this study:
1st- beginning of the study
2nd- end of first month
3rd- end of second month
4th- end of third month

After first phone call, the subsequent phone call is to record:
1.Time to perform the task
2.Symptom or side effects that patient has written down in their data collection
3.Survey