LIMIT Trial - Lidocaine with Intramuscular Injection of Benzathine Penicillin G for Treponema pallidum Treatment

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A Introduction

A1 Study Abstract

There is evidence to suggest that lidocaine can help reduce the pain associated with intramuscular injections of benzathine penicillin G (BPG) or Bicillin, used to treat syphilis infections. A study published in the Journal of Family Practice in 2001 compared the pain experienced during bicillin injections with and without the use of lidocaine. The study found that patients who received lidocaine injections before receiving bicillin reported significantly less pain compared to those who received bicillin injections without lidocaine. Per the International Union against Sexually Transmitted Infections (IUSTI) European Guidelines for syphilis management, lidocaine has been used as a diluent for BPG since 1998. In the United States (US), BPG often comes prepackaged and lidocaine is unable to be used as a diluent with the same ease as it is in Europe. In light of this, we propose a randomized controlled trial of benzathine penicillin G with and without lidocaine to quantify any site pain reduction with lidocaine in patients being treated for syphilis.

This study is a randomized, double blinded, placebo controlled trial. During this study, patients needing BPG treatment for syphilis will be screened for any penicillin allergies and consented to their participation. Each participant will receive 2 injections of BPG, 1.2 million units each (2x1.2 million units = 2.4 million units, the standard dose for syphilis treatment), as intramuscular injections, one in each gluteal muscle, with one of the injections randomly having 0.5ml of 1% lidocaine added while the other has 0.5 ml normal saline solution. The side of each injection will be randomized by the medical assistant (MA)/nurse filling the vials and the injecting MA will be blinded, as well as the study participant, as to which vial contains lidocaine and which contains normal saline. The participants will then be asked to rate their pain from 0-10 on each site of injection at 10 minutes post injection, then again at 24 hours after injection via email electronic survey (via RedCap). The differences in pain from the two injections will be compared and analyzed to see if lidocaine reduces pain associated with BPG injections compared to the control of normal saline added to BPG.

A2 Primary Hypothesis and Purpose of the Study

The purpose of the study is to test the question of: Does the addition of 0.5ml 1% lidocaine compared to 0.5 ml normal saline solution to 1.2 million units of benzathine penicillin G affect the pain experienced by individuals being treated for Treponema pallidum (syphilis) infections at 10 minutes and 24 hours post injection?

B Background

B1 Prior Literature and Studies, and Rationale for this Study

There is evidence to suggest that lidocaine can help reduce the pain associated with intramuscular injections of benzathine penicillin G or bicillin, used to treat syphilis

infections. A study published in the Journal of Pediatric Infectious Diseases in 1998 found that the use of lidocaine as a diluent of BPG significantly reduced the pain of injection. Another study by Estrada et al in 2019 looked at the addition of 1% mepivicaine as diluent for PGB vs PGB alone and showed that mepivicaine significantly decreased pain experienced by participants. Per the IUSTI European Guidelines for Syphilis management, lidocaine is used as a diluent for benzathine penicillin G since 1998. No studies have been performed thus far looking at prefilled benzathine penicillin G syringes and the possibility of inserting lidocaine to the injection to decrease the pain experienced by individuals being treated for syphilis infections, instead of using lidocaine as a diluent which is not possible for the BPG formulations present here in the US. in the US.

C Study Objectives

C1 Primary Aim

To see if there is any benefit of adding 0.5 ml 1% lidocaine to prepackaged Benzathine Penicillin G, with respect to pain, compared to standard of care, in the treatment of Treponema pallidum infections, both 10 minutes and 24 hours after injection.

C2 Secondary Aim

To see if there are any adverse effects of adding 0.5 ml 1% lidocaine to prepackaged Benzathine Penicillin G and to assess use of other pain medications 24 hours post injection.

D Investigational Agent

D1 Preclinical Data

1% lidocaine has been added as a solvent for BPG in other countries around the world.

D2 Clinical Data to Date

There is evidence to suggest that lidocaine can help reduce the pain associated with intramuscular injections of benzathine penicillin G (BPG) or Bicillin, used to treat syphilis infections. A study published in the Journal of Family Practice in 2001 compared the pain experienced during bicillin injections with and without the use of lidocaine. The study found that patients who received lidocaine injections before receiving bicillin reported significantly less pain compared to those who received bicillin injections without lidocaine. Per the IUSTI European Guidelines for syphilis management, lidocaine has been used as a diluent for BPG since 1998. In the US, BPG often comes prepackaged and lidocaine is unable to be used as a diluent with the same ease as it is in Europe. In light of this, we propose a randomized controlled trial of benzathine penicillin G with and without lidocaine to quantify any site pain reduction with lidocaine in patients being treated for syphilis.

D3 Dose Rationale and Risk/Benefits

Use of 0.5 ml 1% lidocaine was decided upon based off the size of the prefilled BPG syringe and the room for additional liquid within the syringe. 1% lidocaine is commonly used as a pain relief measure in clinical settings for injections and other procedures.

E Study Design

E1 Overview or Design Summary

This study is a double blinded randomized placebo control trial of addition of the effect on pain of the addition of 0.5ml 1% lidocaine solution to prepackaged benzathine Penicillin G injection, compared to addition of 0.5 ml normal saline solution, in adults being treated for syphilis (Treponema pallidum) infections, within the Infectious Diseases Clinic at Washington University in St. Louis.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

- Adults 18 years of age or above
- Confirmed syphilis diagnosis (reactive RPR with confirmatory treponemal testing)
- Receiving first injection in series if patient requires 3x weekly injections for syphilis treatment

2.a Exclusion Criteria

- Penicillin allergy (anaphylaxis)
- Lidocaine allergy (anaphylaxis)
- Second or third injection in series if patient requires 3x weekly injections for syphilis treatment
- Pregnancy

2.b Ethical Considerations

This study is comparing standard of care, of not adding lidocaine to prepackaged BPG syringes to the addition of 1% lidocaine, which may relieve pain at injection site. Individuals will receive on injection in each butt cheek, one with lidocaine and one without, and will serve as their own control population. Lidocaine is very commonly used and is quite a low risk medication, and the addition of lidocaine in now way affects the efficacy of BPG.

2.c Subject Recruitment Plans and Consent Process

Participants will be recruited from the Washington University St. Louis Oupatient Infectious Disease Clinic. Each patient who meets the inclusion criteria will be screened by clinic staff and asked if they would consider being a part of this study. They would then be referred to our clinical trials unit upstairs from the WashU Infectious Diseases clinic where they will meet with intake staff via warm handoff and be provided with

information on the study and a consent form. The consent form will be signed prior to the participant being included in the trial as well as any questions required will be answered. Individuals will have between 30-60 minutes to consider participation as they will need to receive treatment prior to them leaving clinic. Any patient will receive standard of care treatment regardless of their willingness to participate in this study and treatment will not be withheld if patients do not participate. Forms will be kept in a secure database via RedCap and treatment will be documented in the participant's chart.

Consent process:

1- Participants with confirmed syphilis (RPR and treponemal test positive) who are receiving their first treatment injection of bicillin will be screened for participation in study by infectious diseases clinicians, nurses, or Mas who interact with the patient during their injection visit. If patient is willing to participate, trial team will be notified. (15-30 minutes)
2- Trial team will assess patient for inclusion/exclusion criteria and ask if would like to be part of clinical trial. (5 minutes)
3- The participant will then be taken to a clinic room, and be shown the consent form. Study design will be explained to them including them receiving the same treatment they would normally but with one injection with 0.5 ml normal saline and one with 0.5 ml 1% lidocaine. They will then be asked if they have any questions and if they choose to consent, they will sign a physical consent form that will then be uploaded into their chart. (30-45 minutes)

2.d Randomization Method and Blinding

Both clinicians and participants will be blinded to the contents of the syringes. Only the nursing staff will know which syringe contains lidocaine and which contains normal saline as they will be drawing up the contents into the syringes, after which they will designate L and R on the syringes and in a log book which will designate which syringe had lidocaine and which had normal saline. This log book will be kept separate from clinicians and participants until study completion. Each participant will have a unique code that will be included in the log book, where the nurse who fills the syringes will state which side, left or right, contained lidocaine and which contained normal saline. This log book will then be used to cross reference injection sites and the survey results during the analysis phase, in a way that allows the data to be de-identified.

2.e Risks and Benefits

Risks
Risks are rare and mainly involve injection site pain, allergic reaction. Some risks, if severe, may cause death.

Likely / Common
Mild

- Pain at injection site (BPG)
- Headache (lidocaine)

- Transient pain (lidocaine)
- Edema (lidocaine)

Less Likely / Less Common

Mild

- Hypersensitivity Rash (BPG)
- Diarrhea (BPG)
- Agitation (lidocaine)
- Anxiety (lidocaine)
- Confusion (lidocaine)
- Dizziness (lidocaine)
- Lethargy (lidocaine)
- Tinnitus (lidocaine)

Rare

Life Threatening

- Hypersensitivity- anaphylaxis (BPG and Lidocaine)

Serious

- Neutropenia (BPG high doses)
- Hyperreflexia (BPG high doses)
- Myoclonus (BPG high doses)
- Seizure (BPG high doses)
- Acute interstitial nephritis (BPG high doses)
- Cardiac Arrhythmia (lidocaine)
- Hypotension (lidocaine)
- Seizure (lidocaine)
- Bronchospasm, dyspnea (lidocaine)

Mild

- Hyperkalemia (BPG)

There is a risk of breach of confidentiality.

Benefits

The potential benefit to the participant is that they would receive the treatment they normally would but with the potential benefit of less pain in the injection site with 1% lidocaine. As for the benefit to society, this may provide evidence that may change standard clinical practice with respect to how we perform benzathine penicillin G injections in the US and if lidocaine is shown to cause less pain, then it would become standard practice to include 1% lidocaine in each syringe of benzathine penicillin G.

2.f Early Withdrawal of Subjects, Including When and How to Withdraw Subjects

Early withdrawal of subjects will be handled by the principal investigator, with participants having the direct contact of the PI via email or phone, and through stating that they no longer would like to participate in the study. The PI also will have the right

to withdraw someone if upon evaluation of the patient, they meet certain exclusion criteria. All withdrawals will be done immediately and seeing as this study has short term of participation, withdrawal should not be difficult.

2.g Data Collection and Follow-up for Withdrawn Subjects

Individuals who withdraw from the study will be noted as lost to follow up and no further data will be obtained from them. They will continue to receive standard of care within the outpatient clinical setting.

E3 Study Drug

3.a Description

1% lidocaine solution added to prefilled 1.2 million units Benzathine penicillin G.

3.b Treatment Regimen

0.5ml 1% lidocaine solution added to prefilled 1.2 million units Benzathine Pencillin G syringe

3.c Method for Assigning Subjects to Treatment Groups

Each participant will receive 2x 1.2 million units injection, one with lidocaine and one with normal saline, therefore each participant will serve as both treatment and control group.

3.d Preparation and Administration of Study Drug

Each syringe of BPG is prefilled. A nurse/MA will then add 0.5 ml 1% lidocaine solution to one BPG syringe, and 0.5ml normal saline solution to another BPG syringe. They will randomly syringes to be injected into the left gluteal muscle vs the right gluteal muscle via random assignment program. They will log the assignment with the unique patient code into a log book.

3.e Subject Compliance Monitoring

Each log book entry will be entered into RedCap survey using the unique patient code and then the patient will fill out pain scale in RedCap using their unique code 10 minutes and 24 hours after injection through follow up email. If they do not respond to the 24 hour follow up email, a second email will be sent 48 hours after injection.

3.f Prior and Concomitant Therapy

Participants will be asked in the follow up survey about any other pain medications they have taken within the last 24 hours. They will also be asked about if this is their first treatment with respect to syphilis treatment, or if this is the second or third dose in a series of treatment. No other concomitant therapies would preclude individuals from participating in the study.

3.g Packaging

Both BPG syringes will look identical other than having one say L and one say R, based off randomization.

3.h Blinding of Study Drug

Both participants and clinicians will be blinded to the contents of the syringe. The nurse filling the syringe will assign the syringes randomly to be injected into L or R gluteal muscle and will label them accordingly, logging the designation in a log book that will remain blinded until the analysis portion of the study. The participant will be blinded as they will receive one site of injection with lidocaine and the other with normal saline, serving as their own intervention and control group.

3.i Receiving, Storage, Disposing and Return

BPG will be stored in the refrigerator in the Washington University St. Louis Infectious Diseases clinic, along with the lidocaine and normal saline solutions being kept in storage in the same clinic. All syringes will be disposed of in sharps containers, as well as used lidocaine ampules and normal saline syringes.

F Study Procedures

F1 Screening for Eligibility and Visit 1 (completed at one visit)

1- Participants with confirmed syphilis (RPR and treponemal test positive) who are receiving their first treatment injection of bicillin will be screened for participation in the study by infectious diseases clinicians, nurses, or Mas who interact with the patient during their injection visit. If patient is willing to participate, trial team will be notified. (15-30 minutes)

2- Trial team will assess patient for inclusion/exclusion criteria and ask if would like to be part of clinical trial. (5 minutes)

3- The participant will then be taken to a clinic room and be shown the consent form. Study design will be explained to them including them receiving the same treatment they would normally but with one injection with 0.5 ml normal saline and one with 0.5 ml 1% lidocaine. They will then be asked if they have any questions and if they choose to consent, they will sign a physical consent form that will then be uploaded into their chart. (30-45 minutes)

4- Trial staff will then obtain the two injections and administer them one in each gluteal muscle. The patient will then be left for 15 minutes, after which they will fill out a pain score 0-10 for each injection site at 10 minutes post injection. (15-30 minutes)
5- Patient will then be informed they will receive an email survey (via RedCap) 24 hours

from trial staff to answer the same pain scale questions at that time. Exit counseling will occur and patient is then free to go. (15 minutes)

F2 Visit 2

Participants will receive an email from trial staff 24 hours after injection site to rate their pain from 0-10 at that time via online survey (RedCap) and to ask if any other pain medication was used in the last 24 hours and if they had any other symptoms/side effects. (5 minutes)

F3 Safety and Adverse Events

3.a Safety Monitoring

Patients will be asked about other side effects/adverse events during the 24 hour follow up. Patients can also contact providers through MyChart and/or through contacting the clinic/trial team.

3.b Medical Monitoring

i Investigator only

The investigator team will be monitoring the survey results for any signs of adverse effects. The monitoring will be ongoing and there will be an internal review of combined data every 6 months.

3.c Definitions of Adverse Events

Any undesirable experience associated with the use of medical product in patient. Common adverse events are listed above.

3.d Classification of Events

i Relationship

10 minutes after injection vs. 24 hours after injection

ii Severity

Mild, Moderate, or life threatening

iii Expectedness

Rare, other than injection site pain which is common

3.e Data Collection Procedures for Adverse Events

Adverse events will be asked about in the survey given 24 hours post injection.

3.f Reporting Procedures

Participants will report adverse events via a RedCap survey emailed 24 hours post injection. Other adverse events can be reported to PI or to clinic staff.

3.g Adverse Event Reporting Period

Adverse events can be reported within 7 days post injection with participants having the ability to call for up to 7 days.

3.h Post-study Adverse Event

Any adverse event post study or the time listed above should be reported to the PI.

F4 Study Outcome Measurements and Ascertainment

The primary outcome measure will be pain rating scores from 0 (least pain) to 10 (most pain) at 10 minutes after injection in each injection site, as well as 24 hours after injection.

Secondary outcome measures will include adverse effects of lidocaine or benzathine penicillin G., such as allergic reactions or injection site reactions.

F5 Rationale for the Selection of Outcome Measures

Injection site pain is the most common adverse effect of Benzathine Penicillin G (BPG) intramuscular injections. For this reason, rating pain scales from 0-1 10 minutes and 24 hours after injection will allow us to measure immediate and longer term pain after injection, with and without lidocaine added to prefilled BPG syringes.

G Statistical Plan

G1 Sample Size Determination and Power

A sample size of 46 patients (92 injections) will be required to detect a clinically significant reduction in pain and discomfort associated with the injection of Bicillin, with a power of 80% and a significance level of 0.05.

G2 Interim Monitoring and Early Stopping

As this is a short term study with small population, it is not expected to stop early. Interim monitoring for adverse effects will occur at 6 months or after 24 participants have participated, whichever occurs first.

G3 Analysis Plan

Pain scores will be collected by trained study personnel. Data will be entered into a secure database and analyzed using statistical software. Descriptive statistics will be used to summarize the data, and t-tests or chi-squared tests will be used to compare pain scores and adverse effects between the treatment and control groups. They will also see if there any use of pain medications through descriptive statistics. Demographic data will also be collected.

G4 Statistical Methods

Descriptive statistics will be used to summarize the data, and t-tests or chi-squared tests will be used to compare pain scores and adverse effects between the treatment and control groups.

G5 Missing Outcome Data

Missing outcome data on follow up will be noted and statistical analysis will be performed on intention to treat model.

G6 Unblinding Procedures

Unblinding will occur at the analysis stage to perform analysis and designate injections as being with lidocaine or with normal saline, and assigning the proper site of injection for each. This data will then be uploaded into RedCap for further analysis.

H Data Handling and Record Keeping

H1 Confidentiality and Security

We will be using our electronic medical record as well as communicating via secure email with surveys being filled on RedCap. That survey information will be de-identified and will be saved on a secure database ensuring confidentiality.

For paper records, these will be stored in a locked area. Access will be limited to research team members only.

H2 Training

See above

H3 Records Retention

Records will be retained for the length consistent with University requirements.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

Study monitoring will occur by the investigational team, with weekly check in on data gathering and logging of information into RedCap and log book.

I2 Auditing and Inspecting

Weekly audits will occur of data obtained in log book and RedCap to ensure data safety, confidentiality, and study going according to protocol.

J Study Administration

J1 Organization and Participating Centers

Washington University St. Louis Infectious Diseases Clinic

J2 Funding Source and Conflicts of Interest

Participants insurance will be billed or they will be billed as standard of care is being provided. The cost of lidocaine and saline will be billed to insurance or patient accordingly.

J3 Subject Stipends or Payments

None

J4 Study Timetable

Ideally will complete data acquisition within 12 months

K Publication Plan

We plan to publish in academic peer reviewed journal such as Clinical Infectious Diseases or Sexually Transmitted Diseases.

L References

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