NCT: 03028012

TITLE: Double-blind, prospective comparison of medications used in trigger point injections – ketorolac, lidocaine, or dexamethasone

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Protocol Summary

IRB Approval Date of Current Version:	4/5/2017
University of Utah IRB #:	IRB_00098370
Sponsor:	
Principal Investigator:	Daniel Cushman
Internal Staff and Sub-Investigators:	Nathan Clements Tera Grant Masaru Teramoto Stuart Willick
External Sub-Investigators:	

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Background and Introduction

Background

Trigger point injections (TPIs) are a commonly-performed procedures by physicians for the treatment of myofascial pain, specifically targeting myofascial trigger points (MTrPs). Commonly injected substances include local anesthetic[1-10], botulinum toxin[11-19], or corticosteroid (CS)[2,3,9,20,21], though non-steroidal anti-inflammatory drugs (NSAIDs)[20,22-24] and other substances[25,26] have been reported. A Cochrane review[27] found that intramuscular injection of local anesthetic demonstrated moderate evidence of benefit for mechanical neck disorders; no other treatment demonstrated greater benefit.

Great variation is seen in how TPIs are performed, however. The standard method was described by Simons and Travell[28], and is often cited. Hong et al.[1] demonstrated that, similar to the technique described by Simons and Travell, obtaining a local twitch response (LTR) was the most important factor in producing pain relief. Further research by Shah et al.[29], which demonstrated an inflammatory component to MTrPs, also showed a decrease in inflammatory cytokines following trigger point injections that obtained a LTR. Despite these findings, most studies do not use the LTR method in their TPI techniques.

Prior studies[2,3,9,20] demonstrated that most patients obtain significant relief from TPI, but did not identify differences between injection of CS or other substances. However, none of these studies identified LTRs in their injection techniques.

As can be learned from a review of the published literature on muscular trigger points, the cause of this condition is unknown, and no single treatment approach has been established as a clearly accepted gold standard treatment. There is evidence, however, that there is an inflammatory component associated with trigger points and that obtaining a local twitch response is associated with a decrease in local inflammation at the site of a trigger point. The combination of injecting an anti-inflammatory medication and obtaining a local twitch response has never been studied. The purpose of this study is to examine the comparative effectiveness of injectable substances on patient outcome after a TPI with LTR identified, namely a CS (dexamethasone), a NSAID (ketorolac), or only a local anesthetic (lidocaine).

Purpose and Objectives

Hypothesis

The main hypothesis of this study is that anti-inflammatory medications (ketorolac or dexamethasone) will provide longer-lasting and greater pain relief than just lidocaine in trigger point injections where a local twitch response is evoked at the time of the injection.

Purpose/Specific Aims

The primary objective of this study is to compare the efficacy of three substances used in TPIs with a LTR identified at the time of the injection: a CS (dexamethasone), a NSAID (ketorolac), or only a local anesthetic (lidocaine).

Study Population

Age of Participants: 18-100

Sample Size:

At Utah:	60
All Centers:	60

Inclusion Criteria:

1. Men or women age 18 or over
2. At least one active trigger point, as defined by Simons and Travell

Exclusion Criteria:

1. Allergy or contraindication to any NSAID, CS, or local anesthetic
2. Receiving anticoagulant medication
3. History of bleeding disorder
4. Pregnant or breast feeding women
5. Gastrointestinal ulceration
6. Pre-existing renal disease
7. Pre-existing congestive heart failure
8. Diabetes mellitus
9. Prior myocardial infarction or stroke
10. Fibromyalgia

Design

Observational Research
Double Blind
Randomized

Study Procedures

Recruitment/Participant Identification Process:

Subject recruitment

Subjects will be recruited from the University of Utah Orthopaedic Center, Farmington Health Center, and South Jordan Health Center during an existing appointment. Participation in this study will not require any additional study-specific visits. Subjects requiring a TPI for treatment will be approached by a study team member who will provide a basic description of the study and review inclusion and exclusion criteria with the patient. If the patient is interested in participating, a member of the study team will obtain written informed consent. University of Utah physical therapists and physicians will be notified about this study and asked to help recruit appropriate subjects.

Informed Consent:

Description of location(s) where consent will be obtained:

University of Utah Orthopaedic Center, Farmington Health Center, and South Jordan Health Center

Description of the consent process(es), including the timing of consent:

Informed written consent will be obtained from all participants. The researcher will provide an explanation of the consent form and study details to these individuals. One of the investigators will always be available to speak with prospective participants that have questions. The potential participants can take as much time as they like until they choose to consent and do not have to consent on the same day the study is presented.

Procedures:

Consent process

Consent: Written informed consent will be obtained from all participants. The researcher will provide an explanation of the consent form and study details to each participant. One of the investigators will always be available to speak with prospective participants that have questions. Institutional Review Board approval will be granted through the University of Utah.

Study procedures

TPIs are a standard procedure performed by physicians. Regardless of participation in the research study, the procedure will be performed in the same manner. Participants will undergo TPIs by the following method. A 3mL syringe with any of the three medications listed below would be drawn by an assigned, unbiased, and unblinded health care professional (e.g. medical

assistant, nurse, etc.), leaving its contents unknown to the physician doing the injection. A 25g, 1.5" needle will be used for all injections. The needle will be inserted into the trigger point with the goal of eliciting a LTR. When a LTR is obtained, 0.1mL will be injected into that location within the muscle. This will be repeated until LTRs disappear, or 1.0mL has been injected, whichever comes first. This can be performed in a similar manner for all affected muscles, up to a maximum of 2mL.

Blinding: Both the physician performing the injection and the participant will be blinded to the medication injected. Only the assigned health care professional will be unblinded. Each substance is clear and cannot be distinguished from the other. The blinding procedure has been fully discussed and approved by the medical staff at all sites (UUOC, FHC, SJHC).

Study Drug Ordering: A study team member (with IDS assistance), will create a blinded study drug order in the medical record (Epic). This blinded study drug order will have a title similar to "study blinded ketorolac/dexamethasone/lidocaine injection, 2mL." When a participant enrolls, the blinded PI will place an order for the study drug. The assigned health care professional will access the participant's medical record to ensure the PI has placed and signed an order for study drug.

Randomization: A randomization schema will be created in Excel (with IDS assistance) by an unblinded study team member that will ensure even accrual numbers across the three different cohorts. Neither the blinded physician, nor the participant will have access to this document. A health care professional at each of the three participating sites will be unblinded and assigned to have access to this shared drive for purposes of randomizing newly enrolled participants and unblinding a participant in the event of an adverse reaction. This randomization document will be kept and maintained on uBOX (a secure shared drive). Once the assigned health care professional has confirmed that an order has been placed and signed by the blinded PI for study drug, they will access the randomization schema to obtain a randomization number. This randomization number will be either a 1, 2, or 3 and each number will correlate to a different study drug combination. The health care professional will draw up the randomly assigned study drug outside of the participant's room and hand-off the syringe to the PI for injection.

Medical Record Documentation: After the medication has been administered, the blinded PI or the physician who completed the injection will document the process in the medical record, specifying how much of the 2mL study drug was used for the injection.

Medication Inventory: Each of the three participating sites will have the same medications for use and they will be stored in locked cabinets and labeled for investigational use only. IDS will provide each site with a drug inventory log to document study drug usage. This drug inventory log will be monitored by the Data and Safety Monitoring Board at intervals specified in this application.

Unfortunately, the use of the local pharmacy (e.g. UUOC pharmacy or FHC pharmacy) will not be a feasible option. This will take at least 30 minutes extra to obtain the medication, for

which will be too time-intensive for most patients to tolerate. Additionally, this will interrupt regular clinic flow to a large degree.

All three medications used in this study have been shown to be safe, and are already used in a standard fashion for intramuscular injections; therefore, these medications will not pose undue risk to the participant. Furthermore, as lidocaine will be included in all injections, the participant will unlikely be able to differentiate which medication they received based off the presence or absence of short-term numbness.

The PI has successfully administered these drugs in the below mentioned dosages and combinations. From past experience, the PI does not express any safety concerns regarding the administration of these drug combinations.

Subsequent injections

Participants will be allowed to have subsequent injections, which is standard practice[39-43]. They may receive up to four injections, spaced at least 1 week apart. The assigned health care professional will access the randomization schema at each subsequent visit to identify which substance was injected at their previous visit and use that same substance for all subsequent injections. The primary time point will be maintained, and questionnaires will be administered.

Medications:

1. 1mL of 1% lidocaine + 1mL of 4mg/mL dexamethasone
2. 1mL of 1% lidocaine + 1mL of 30mg/mL ketorolac
3. 2mL of 1% lidocaine

Outcomes:

1. Pre- and post-injection numeric rating scale (NRS) from 0-10 with regards to the trigger point(s).
2. Survey questions

Primary outcome measure

1. Responder (>50% NRS relief)

Secondary outcome measures

1. NRS improvement
2. Brief pain inventory (BPI) improvement

Time points:

Participants will fill out a pre-injection survey that contains demographic information and pain- and function-related questions. Participants will also complete a survey at the following time points:

1. Immediately post-injection
2. 1 week post-injection
3. 2 weeks post-injection
4. 4 weeks post-injection
5. 3 months post-injection

Procedures performed for research purposes only:

TPIs are a standard procedure performed by physicians. Regardless of participation in the research study, the procedure will be performed in the same manner.

The research component of this study is to compare the efficacy of three substances used i TPIs with a LTR identified at the time of the injection: a CS (dexamethasone), a NSAID (ketorolac), or only a local anesthetic (lidocaine).

Statistical Methods, Data Analysis and Interpretation

Statistical plan:

Chi-square analysis will be used to identify differences in responders between groups. Repeated-measures ANOVA testing will be used to identify changes in pain scores.

Power Analysis:

Similar to the study by Gerber et al.[41], if 5% of patients spontaneously improve their MTrP status without intervention and aiming for detection of 10% responders, a sample size of 90 subjects would be required. However, in their study, they found that this was substantially overpowered due to a much higher percentage of responders. We have identified a sample size of 60 subjects (20 per group) as being sufficient, based on the prior work being overpowered. As they had a much larger response rate in their actual cohort, we feel that a conservative estimate of 15% responders would be appropriate (as opposed to 10%), which yields a sample size around 60 total subjects.

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Type of Report: Informed Consent Form 4-5-2017

Consent and Authorization Document

BACKGROUND

Trigger point injections (TPIs) are a commonly-performed procedures by physicians for the treatment of myofascial pain. Myofascial pain is a chronic pain disorder that presents in the form of pressure on sensitive points in muscles (trigger points). This pressure results in pain in seemingly unrelated parts of the body and the discomfort generally persists or worsens with no treatment. Commonly injected substances include local anesthetic, botulinum toxin (Botox), or corticosteroid (CS), though non-steroidal anti-inflammatory drugs (NSAIDs), and other substances have been reported. Prior studies have demonstrated that most patients obtain significant relief from TPI, but did not identify differences between injection of CS or other substances.

No single treatment approach has been established as a clearly accepted gold standard treatment, and practitioners are quite variable in what they use for these injections. There is evidence, however, that there is an inflammatory component associated with trigger points. The combination of injecting an anti-inflammatory medication and obtaining a local twitch response has never been studied. The purpose of this study is to examine the comparative effectiveness of injectable substances on patient outcome after a TPI, namely a CS (dexamethasone), a NSAID (ketorolac), or only a local anesthetic (lidocaine).

STUDY PROCEDURES

TPIs are a standard procedure performed by physicians. Regardless of participation in the research study, the procedure will be performed in the same manner. You will undergo TPIs by the following method. A 3mL syringe with any of the three medications listed below would be drawn by an unbiased health care professional (e.g. medical assistant, nurse, etc.), leaving its contents unknown to the physician doing the injection and to you, the participant.

Blinding: Both the physician performing the injection and you will be blinded to the medication injected. Each substance is clear and cannot be distinguished from the other. The health care professional drawing up the medication will draw it up outside of the room. The order will be signed by the blinded PI using a blinded study drug order. . All three medications used in this study have been shown to be safe, and are already used in a standard fashion for intramuscular injections; therefore, these medications will not pose undue risk to the participant. Furthermore, as lidocaine will be included in all injections, the participant will unlikely be able to differentiate which medication they received based off the presence or absence of short-term numbness.

Randomization: You will be randomly assigned to one of the three study medications listed below.

Subsequent injections

You will be allowed to have subsequent injections, which is standard practice. You may receive up to four injections, spaced at least 1 week apart. The health care professional will use the same substance the patient received on their previous injections.

Medications:
1. 1mL of 1% lidocaine + 1mL of 4mg/mL dexamethasone
2. 1mL of 1% lidocaine + 1mL of 30mg/mL ketorolac
3. 2mL of 1% lidocaine

Time points:
You will fill out a pre-injection survey that contains demographic information and pain- and function-related questions. You will also complete a survey at the following time points:
1. Immediately post-injection
2. 1 week post-injection
3. 2 weeks post-injection
4. 4 weeks post-injection
5. 3 months post-injection

RISKS
Common adverse effects from trigger point injections include soreness, hematoma, bruising, and medication allergy. If you have an adverse effect, you will be instructed to call the Principal Investigator (PI). If the PI deems this may be related to the medication, they will be unblinded for the purposes of proper medical triage. For all intents and purposes, the participant will have received the standard treatment for their trigger point, but will be unaware of which medication they have received.

UNFORESEEABLE RISKS
In addition to the risks listed above, you may experience a previously unknown risk or side effect.

BENEFITS
TPIs are a standard procedure performed by physicians, so there are no added benefits to participation in this study, however the goal is to compare the efficacy of the three substances studied to possibly change standard of care for future patients.

ALTERNATIVE PROCEDURES
You may choose not to participate in this study and receive the standard of care trigger point injection your doctor and you decide on instead.

PERSON TO CONTACT
If you have questions, complaints, or concerns about this study, or feel you have been injured or become ill from being in this study, please contact Dr. Cushman or his research team at 801-581-5328 during regular business hours. If this is after hours, please contact the hospital operator at 801-581-2121 and ask for the physical medicine & rehabilitation resident on call. Let them know that you received a trigger point injection containing lidocaine and possibly dexamethasone or ketorolac.

If you have inquiries regarding a serious (life-threatening) research-related injury, illness, or adverse effect, please seek immediate medical attention from your local hospital.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY
If you are injured from being in the study, medical care is available to you at the University of Utah Hospital, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or its doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G-7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION
Research studies include only people who choose to take part. You can tell us that you do not want to be in this study. You can start the study and then choose to stop the study later. Your decision will not affect your relationship with the study team in any way.

RIGHT OF INVESTIGATOR TO WITHDRAW PARTICIPANTS
The investigator can withdraw you without your approval. Possible reasons for withdrawal include if the investigator feels the study procedures place you at an unexpected risk.

COSTS AND COMPENSATION TO PARTICIPANTS
There are no additional costs to you for participating in this study. The Trigger Point Injections would normally be done as standard treatment, so they will be billed to you or your insurance company. You will not be paid for participating in this study.

NEW INFORMATION
Sometimes during the course of a research project, new information becomes available about the drugs that are being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study.

If you decide to withdraw at that time, your research doctor will make arrangements for your medical care to continue. If you decide to continue in the study, you may be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your medical care to continue.

NUMBER OF PARTICIPANTS

We expect to enroll 90 participants at the University of Utah Orthopaedic Center, the Farmington Health Center, and the South Jordan Health Center.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION

Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, email address, date of birth
- Related medical information about you like concurrent health issues, past procedures, medical history
- All tests and procedures that will be done in the study

How we will protect and share your information:

- We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

- In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:
  - Members of the research team and University of Utah Health Sciences Center;
  - The University of Utah Institutional Review Board (IRB), which reviews research involving people to make sure the study protects your rights;

- If we share your information with groups outside of University of Utah Health Sciences Center, we will not share your name or identifying information. We will label your information with a code number, so they will not know your identity.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

CONSENT

I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date