

Local Anesthesia for Ultrasound
Guided Hip Joint Injections: A
Double-Blind Randomized
Controlled Trial of
Bacteriostatic Saline versus
Buffered Lidocaine

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Title: Local Anesthesia for Ultrasound Guided Hip Joint Injections: A Double-Blind Randomized Controlled Trial of Bacteriostatic Saline versus Buffered Lidocaine

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Abstract:

Local anesthesia is commonly used to reduce pain during joint injections, particularly for deep joints like the hip. Lidocaine is the most commonly used local anesthetic in most medical practices. It is well known that lidocaine infiltration itself is painful. Many strategies have been studied to minimize pain associated with lidocaine administration, including buffering, warming, and slowing infiltration rate. Bacteriostatic saline (BS) is an alternative local anesthetic that has been shown to be less painful when injected into subcutaneous tissues compared with lidocaine. However, BS use has not been widely implemented for local anesthesia, and it has not been studied in the context of joint injections. The purpose of this study is to compare infiltration pain and anesthetic efficacy between lidocaine and BS for ultrasound (US) guided intraarticular hip injections.

Primary Aims:

1. To compare subcutaneous/intramuscular infiltration pain of BS versus buffered 1% lidocaine *prior to* US guided intraarticular hip injections.
2. To compare local anesthesia efficacy of BS versus buffered 1% lidocaine *during* US guided intraarticular hip injections.

Hypotheses:

1. BS infiltration into subcutaneous and intramuscular tissue is significantly less painful than buffered 1% lidocaine.
2. US guided intraarticular hip injections are equally or less painful after local anesthesia with BS versus buffered 1% lidocaine infiltration.

Background and Significance:

Local anesthesia has been shown to significantly reduce pain associated with needle procedures (6). The most commonly used local anesthetic is lidocaine. It is well known that lidocaine infiltration into tissues is painful. Numerous strategies have been studied and utilized to attempt to minimize the pain of lidocaine infiltration.

Much of the pain associated with lidocaine infiltration is thought to be due its acidic pH. Physiologic pH is between 7.35 and 7.45, whereas lidocaine formulations currently available on the market range from pH 3.5 to 7.0. Therefore, buffering lidocaine with sodium bicarbonate increases the pH to values more similar to physiologic pH, resulting in reduction of pain upon infiltration (3,4,7). Additionally, slowing the administration rate has been shown to reduce infiltrative discomfort (7). Warming local anesthetics to body temperature is another simple and inexpensive way to reduce discomfort of administration (5), though this is not a widespread practice.

Ultrasound (US) guidance for peripheral musculoskeletal procedures has become increasingly popular over recent years. US allows clinicians to avoid important neurovascular structures when advancing a needle toward a given target, which may improve procedure safety. Furthermore, US guidance improves accuracy of needle placement and medication deposition as the needle tip and target may be easily visualized to ensure proper needle positioning prior to agent administration. However, procedure length inevitably increases when the proceduralist takes time to make fine adjustments in needle placement prior to injecting. The potential for patient discomfort likely increases with the length of time the needle is within tissues. Therefore, local anesthesia is commonly used during US guided procedures, particularly deep injections such as the hip joint, to minimize discomfort and improve patient experience.

Lidocaine has historically been the local anesthetic of choice. However, several alternative agents are available. In particular, bacteriostatic saline (BS, 0.9% benzyl alcohol) has been found to be efficacious for local anesthesia during subcutaneous suturing and needle procedures. BS has low systemic toxicity, low allergic potential, low cost, and ready availability (8,9). BS manufacturer indications include subcutaneous and intramuscular injection. Animal studies have shown that intramuscular and perineural BS (0.75% benzyl alcohol) injections concentrated to 0.75% benzyl alcohol cause no histological tissue damage (14,15). Clinical studies have demonstrated that subcutaneous BS infiltration is significantly less painful than lidocaine (1,2). Furthermore, BS anesthetic efficacy is comparable to that of lidocaine. Although BS seems to have a shorter anesthetic duration than lidocaine, this is likely not relevant given the brevity of US guided hip injections (2).

BS is a safe alternative local anesthetic with several potential advantages over lidocaine, including lower cost, less painful infiltration, and similar efficacy. The primary aim of this study is to compare infiltrative pain and anesthetic efficacy of lidocaine versus BS for US guided intraarticular hip injections. We hypothesize that BS administration will be less painful and equally or more effective than lidocaine, making it an appealing alternative local anesthetic for US guided intraarticular hip injections.

Progress Report and Preliminary Studies:

There are no prior studies examining BS as a local anesthetic for musculoskeletal joint or soft tissue injections.

Research Design and Methods:

Study Design

The senior authors (JLS, JS, and SJW) will complete US guided intraarticular hip injections on patients referred to the Mayo Sports Medicine Center, Mayo-14 PM&R Clinic, or Gonda Musculoskeletal Clinic.

The non-injecting author (BJK) will contact patients scheduled for hip injections in the above clinics ahead of time to inform them about the study and assess interest in participating (Appendix A). This author will then contact the respective injecting authors to notify them of potential study subjects.

On the day of the procedure, the injectionist will confirm interest in the study (Appendix B) and obtain formal consent.

All patients will receive two separate injections: (1) US guided local anesthetic infiltration using a 25-gauge, 2-inch stainless steel needle, followed by (2) US guided hip joint injection using a 22-gauge, 3.5-inch stainless steel needle. The local anesthetic used, either buffered 1% lidocaine [1:9 sodium bicarbonate (8.4%):lidocaine(1%)] or BS (normal saline with 0.9% benzyl alcohol), will be administered based on computer randomization on a Microsoft Excel® data table. The study subjects and injecting authors (JLS, JS, and SJW) will be blinded to the type of anesthetic administered. All medications will be prepared by a non-injecting physician to maintain blinding.

For all injections, 3 mL of anesthetic will be administered over 5-15 seconds. Anesthetic infiltration duration will be measured using a timer on the US machine. The subsequent hip joint injection will then be performed in the same manner for both groups as per a standard approach (anterior femoral head in an oblique-sagittal plane, in-plane with the transducer, distal to proximal).

The Visual Analog Scale (VAS) for Pain will be used for outcome measurements (Appendix C). This validated tool is a 100 mm horizontal line anchored by “no pain” (score of 0) and “pain as bad as it could be” (score of 100). The patient will be asked to mark the line to indicate pain level at 3 times during the encounter: (1) rating of baseline hip pain prior to the procedure, (2) rating of local anesthetic infiltration pain immediately after administration, and (3) rating of hip joint injection pain immediately after the procedure. An assistant will administer the VAS for Pain, and it will not be visible to the injectionist.

Immediately after the procedure, both the patient and injectionist will be given a questionnaire asking which local anesthetic they believe was used during the procedure (Appendices C/D).

Two weeks after the procedure the non-injecting author (BJK) will contact each patient to assess whether there were any adverse effects after the procedure (Appendix E).

Equipment

All US-guided hip injections will be completed using a cart-based Philips ultrasound machine in either the Sports Medicine Center, Mayo-14 PM&R Clinic, or Gonda Musculoskeletal Clinic. US-guided local anesthetic administration will be completed using a 25-gauge, 2-inch stainless steel needle. US-guided hip injections will be completed using a 22-gauge, 3.5-inch stainless steel needle. The equipment for this study is available in each respective clinic and will be used at no additional cost.

Study Subjects

Mayo Clinic patients 18-75 years old referred for US-guided intraarticular hip injections in the Sports Medicine Center, Mayo-14 PM&R Clinic, or Gonda-14 Musculoskeletal Clinic.

Exclusion criteria will include: (1) chronic opioid use, (2) opioid use on day of procedure, (3) history of fibromyalgia or other diffuse chronic pain syndrome, (4) pain behavior during the clinical encounter as judged by the injectionist, or (5) anesthetic administration time outside the designated 5-15 second time frame.

Sample Size

The primary outcome will be the VAS for Pain score during local anesthesia infiltration. We will use two-sample t-tests to compare the mean VAS for Pain scores between the two groups at each of the three time points. Based on prior studies assessing the VAS for Pain, 14 can be considered the minimal clinically important difference when assessing moderate pain levels (10-12). At test significance level (α) = 0.05 with 80% power, a difference in means ($\mu_1 - \mu_2$) = 14 with common standard deviation (σ) = 20, i.e. an effect size ($\delta = |\mu_1 - \mu_2|/\sigma$) = 0.70, can be detected when the sample size (n) per group is 34 (68 total subjects). Since data will be collected at a single point of care, we anticipate a low dropout rate of approximately 10%. Therefore, total sample size for the study will be 76 patients after adjusting for dropouts.

Data Collection

Data collection is described above in *Study Design*. The non-injecting author (BJK) will collect and collate the data.

Data Handling/Processing

The data will be compiled on an Excel® file for data analysis. The computer files will be stored in the primary investigator's H-drive of Mayo Clinic's computer network.

Data Analysis

Patient demographic characteristics data will be summarized and compared between the two treatment arms. Mean \pm SD for continuous variables and frequency (% percentage) for categorical variables will be given. Differences between arms will be tested using Wilcoxon tests for continuous variables and chi-square tests for categorical variables. Differences in adverse events between arms will be tested using chi-square tests. The mean VAS for Pain score prior to and during local anesthesia infiltration will be compared between the 2 groups by two-sample t-tests or Wilcoxon Rank sum tests when appropriate. Changes in pain from baseline will also be compared between arms using t-tests or Wilcoxon tests as appropriate. A generalized linear model (GLM) will be used to compare the two groups after adjusting for age, gender and baseline VAS pain score. Mixed effects models will be fit to model the longitudinal VAS pain scores. The primary analysis will be based on patients with anesthetic administered within the targeted 5-15 second infiltration window. However, an intent-to-treat analysis will also be performed, including patients that had anesthetic administered outside of the 5-15 second window. For all analyses, two-sided tests will be used and p-values less than 0.05 will be considered as statistically significant. All statistical analyses will be performed by SAS 9.3 version software (SAS institute Inc., Cary NC).

Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatments under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. CTCAE v4.0, a grading system for adverse event severity, will be used to determine grading for these stopping rules.

Study accrual will be temporarily suspended if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

- if 5 or more patients in the first 20 treated patients (or 25% of all patients after 20 are accrued) experience a grade 2 (moderate) or higher adverse event, and the adverse event incidence rate is higher in the BS arm than the lidocaine arm.

We note that we will review grade 4 (life-threatening) and 5 (death) adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

After the first 20 patients are treated, accrual will also be temporarily suspended if there is significantly more pain after baseline on the BS arm.

Feasibility and Time Frame

Over 5,000 US guided injections are performed yearly in these three clinics combined, and a significant portion are intraarticular hip injections. We estimate it will take 6-12 months to recruit the patients. Patients will not need to be referred specifically for the study, as they will be recruited at the time of presentation for routine US guided hip injection. The study will likely add about 5-10 minutes to the typical US guided hip injection visit.

Strengths

There are several reasons this study has the potential to change the widespread practice of lidocaine local anesthesia prior to US guided hip joint injections. BS is a safe alternative local anesthetic with several potential advantages over lidocaine, including lower cost, less painful infiltration, and similar efficacy. Patients would be subjected to no additional risk or cost over routine US guided injections. Lower cost of BS would decrease health care costs. Less painful anesthetic infiltration and similar efficacy would minimize patient discomfort and improve patient experience.

Limitations

A limitation of this study design is that it will be specific to the hip joint, which is likely the US guided injection for which local anesthesia is most commonly used. Although similar efficacy would be expected in other body regions, the comparison of BS versus lidocaine may not be valid for other musculoskeletal injections.

Human Subjects:

Detailed Description and Population

For subject details and inclusion/exclusion criteria, see *Study Subjects* section above.

Research Materials

As noted above, pain will be assessed using a VAS for Pain scale.

Recruitment of Subjects

All recruitment will occur directly with patients via a telephone call prior to their scheduled hip injection or at the point of care. An email will be sent to our PM&R and Sports Medicine colleagues to increase awareness and encourage internal referral for US guided intraarticular hip injections.

Potential Risks

The control group will receive the same treatment as is currently being provided with US guided hip joint injections. The BS group will be subjected to no increased risks relative to routine US guided hip joint injection. BS manufacturer indications include

subcutaneous and intramuscular injection. Animal studies have shown that 0.75% BS intramuscular and perineural injections cause no histological tissue damage (14,15). Furthermore, the BS manufacturer literature states “adverse reactions to intravenous, intramuscular, or subcutaneous injection of 0.9% benzyl alcohol are not known to occur in man... preparations containing 0.9% benzyl alcohol in several species of animals have indicated that an estimated intravenous dose of up to 30 mL may be safely given to an adult without toxic effects.” In this study, only 3 mL will be administered (subcutaneous/intramuscular) in each BS group subject.

Protection

Subjects will be provided with a contact number to call if any concerns arise. In the event of an adverse reaction or complication, the patient will be handled no differently than he/she would be following routine injections. Full evaluation and management will be provided as indicated.

As noted above in *Study Design*, subjects will be contacted 2 weeks post-procedure to assess for adverse events. After the first 20 patients have been completed, the non-injecting author (BJK) will assess the data for concerning trends in pain scores and adverse events in the BS group. If there are significantly elevated pain scores or more adverse events in the BS group, the study will be stopped.

Benefits

As noted above, preliminary studies have shown BS to be a safe alternative local anesthetic with potential advantages over lidocaine, including less painful infiltration and similar efficacy. BS has potential to minimize patient discomfort and improve patient experience associated with US guided injections without increasing procedural risks or cost.

Gender/Minority Mix:

This study will be available to all eligible patients, regardless of race or ethnic origin. There is no information currently available regarding differential effects of BS in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist. Nonetheless, the planned analyses will, as always, look for differences in treatment effect based on racial groupings.

Based on current treatment practice, we expect about 10% of patients will be classified as minorities by race and 50% of patients will be women in the study accrual. Expected sizes of racial subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	1	1	2

Not Hispanic or Latino	37	37	74
Ethnic Category: Total of all subjects	38	38	76
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	3	3	6
Native Hawaiian or other Pacific Islander	0	0	0
White	34	34	68
Racial Category: Total of all subjects	38	38	76

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino**Racial Categories:**

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

References:

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Budget:

For budget details, see attached “Budget” and “Statement of Work” documents.