Official Title: Single Injection Interscalene Brachial Plexus Nerve Block With Adjuvants vs. Liposomal Bupivacaine Interscalene Brachial Plexus Nerve Block for Total Shoulder Arthroplasty
NCT03845894
Document Date: 6/9/2020

Single Injection interscalene brachial plexus nerve block with adjuvants vs. Liposomal bupivacaine interscalene brachial plexus nerve block for total shoulder arthroplasty

Principal Investigator:
J. Douglas Jaffe, DO
Department of Anesthesiology
Wake Forest School of Medicine
Winston-Salem, NC 27157
jjaffe@wakehealth.edu
336-716-5855

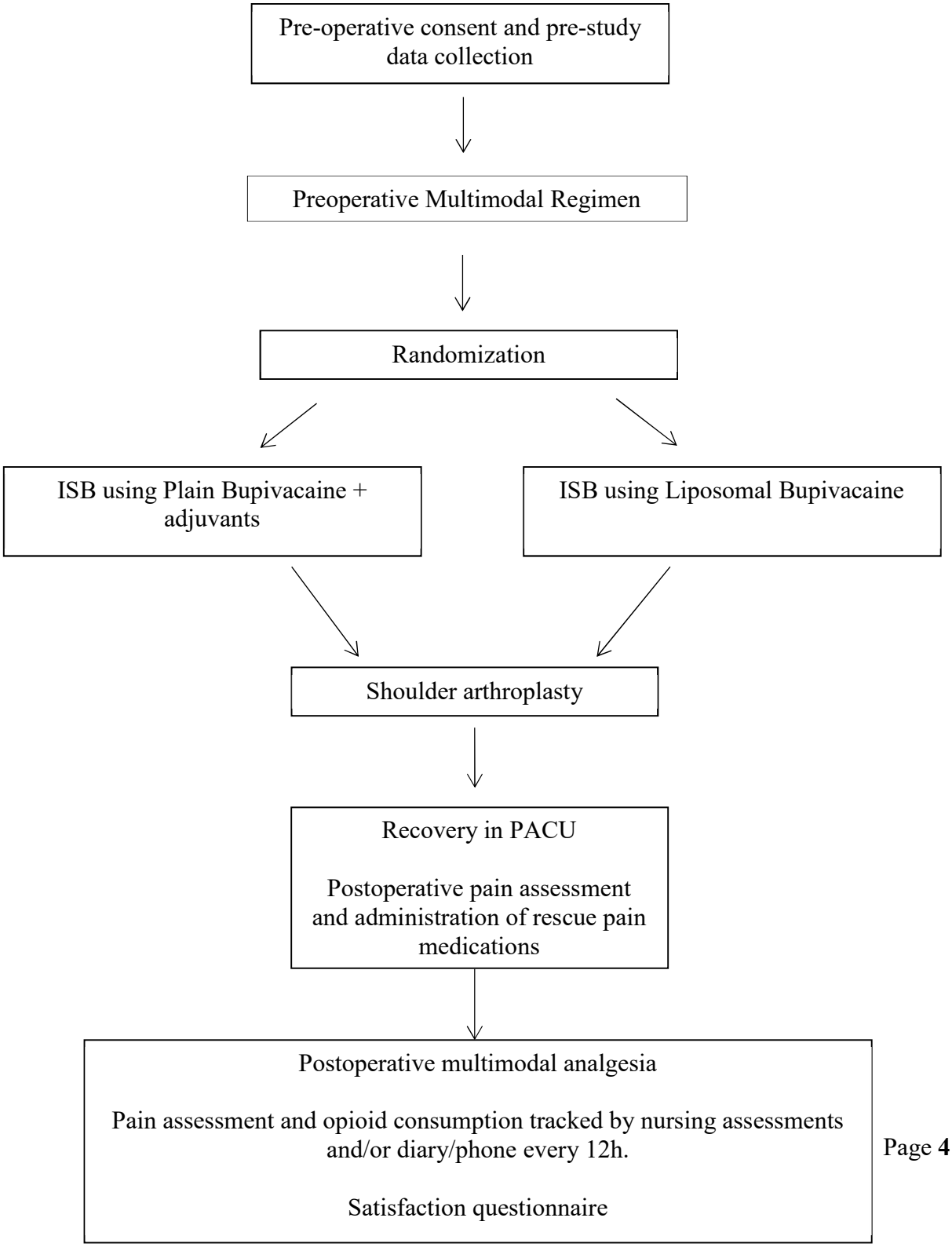
Co-Principal Investigator(s):
Michael D Font, MD
Department of Anesthesiology
Wake Forest School of Medicine
Winston-Salem, NC 27157
mfont@wakehealth.edu
336-716-5855

James D Turner, MD
Department of Anesthesiology
Wake Forest School of Medicine
Winston-Salem, NC 27157
jturner@wakehealth.edu
336-716-5855

Biostatistician:
Hiaying Chen
Department of Biostatistical Sciences
Division of Public Health Sciences
hchen@wakehealth.edu
336-716-4431

Table of Contents

SCHEMA


Pre-operative consent and pre-study data collection
Preoperative Multimodal Regimen
Randomization
ISB using Plain Bupivacaine + adjuvants
ISB using Liposomal Bupivacaine
Shoulder arthroplasty
Recovery in PACU
Postoperative pain assessment and administration of rescue pain medications
Postoperative multimodal analgesia
Pain assessment and opioid consumption tracked by nursing assessments and/or diary/phone every 12h.
Satisfaction questionnaire

1.0 Introduction and Background

In 2011, liposomal bupivacaine received FDA approval for the use of local surgical site infiltration, and its use has become common for a variety of abdominal, gynecological, and orthopedic surgeries, with varying efficacy.[1,2,3]Studies evaluating the efficacy of liposomal bupivacaine for regional procedures have also displayed mixed results.[4]

Liposomal bupivacaine has recently been approved by the FDA for use in brachial plexus blocks for patients undergoing major shoulder surgery.[5] Per the manufacturer's data, ISB using liposomal bupivacaine provided significant pain reduction in the first 48 hours after surgery compared to ISB using placebo, establishing that liposomal bupivacaine has an opioid sparing effect in this patient population without significant risk.

A recent study compared the addition of liposomal bupivacaine to plain bupivacaine for interscalene blocks in patients undergoing shoulder surgery, and found a modest improvement in pain.[6]

At a cost of about $300 per administration for liposomal bupivacaine, there are significant economic impacts to be considered, given that plain bupivacaine is significantly less expensive. Data from future studies are required to perform a cost-benefit analysis for this new drug.

Common and relatively inexpensive adjuvants have been shown to extend the duration of analgesia provided by interscalene nerve blocks (ISB) using plain bupivacaine, with a significant analgesic effect extending up to 48 hours postoperatively.[7–9]

To date, there has been no study comparing the efficacy of ISB using liposomal bupivacaine vs plain bupivacaine with these common adjuvants, such as epinephrine, dexamethasone, clonidine, and buprenorphine.

The purpose of this study is to determine whether the use of plain bupivacaine with common adjuvants for ISB provides non-inferior analgesic results compared to the use of liposomal bupivacaine for ISB, in patients undergoing primary total shoulder arthroplasty.

LB= Liposomal bupivacaine
PBA= Plain bupivacaine + adjuvants
ISB= Interscalene peripheral nerve block

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 The primary objective of this clinical study is to evaluate the comparative efficacy of ISB using plain bupivacaine with adjuvants vs. liposomal bupivacaine on mean postoperative pain levels in patients who have undergone shoulder arthroplasty within the first 48 hours. We hypothesize that ISB using plain bupivacaine with adjuvants will provide similar pain relief as ISB using liposomal bupivacaine.

2.2 Secondary Objective(s)

2.2.1 To evaluate the effect of ISB using plain bupivacaine with adjuvants vs. liposomal bupivacaine on pain control at the single time point of 48 hours post-surgery.

2.2.2 To evaluate the effect of ISB using plain bupivacaine with adjuvants vs. liposomal bupivacaine on cumulative postoperative opioid consumption within the first 48 hours after shoulder arthroplasty.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 All patients undergoing primary total shoulder arthroplasty
3.1.2 Age ≥ 18 years
3.1.3 Ability to understand and the willingness to sign an IRB-approved informed consent document.
3.1.4 ASA patient status I-III patients
3.1.5 Weight Greater than or equal to 50 kg

3.2 Exclusion Criteria

3.2.1 No contraindications to an interscalene block or phrenic blockade.
3.2.2 Infection at injection site.
3.2.3 Pre-existing neurological dysfunction affecting the operative extremity.
3.2.4 Chronic pain diagnosis or opioid use >40mg oxycodone daily equivalents or use of long-acting opioids.
3.2.5 BMI >40
3.2.6 Uncontrolled diabetes (A1c >8.0)
3.2.7 Concurrent painful physical condition requiring analgesic treatment (eg, NSAID or opioid) in the postsurgical period for pain not strictly related to the surgery
3.2.8 Contraindications to any pain-control agents planned for surgical or postsurgical use (i.e., bupivacaine, hydromorphone, etc.)
3.2.9 Patients who are wards of the state
3.2.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to bupivacaine or liposomal bupivacaine.
3.2.11 Patients with moderate-severe hepatic or renal impairment because of the increased risk of toxicity.
3.2.12 Patients who are pregnant.
3.2.13 Patients who are lactating.
3.2.14 Patients with hypersensitivity to any of the study drugs, including dexamethasone, clonidine, and buprenorphine.
3.2.15 Patients with labeled contraindications for the study drugs, such as systemic fungal infections.
3.2.16 Patients undergoing repeat shoulder arthroplasty or reverse total shoulder arthroplasty.

4.0 Study Outcomes and Study Measures

4.1 Primary Outcome

4.1.1 The primary outcome of this study is the area-under-the-curve (AUC) of the mean visual analog scores numerical rating system (VAS-NRS) within the first 48 hours postoperatively. Pain levels (with shoulder movement) will be measured upon arrival to the PACU, at 6 hours, 12 hours, 24 hours, 36 hours, and 48 hours after surgery.

4.1.1.1 The mean AUC48 of the liposomal bupivacaine ISB group was 136.4 with a standard error of 12.09. [10]

4.1.1.2 There are no existing data to predict the mean AUC48 for ISB using plain bupivacaine +adjuvants, but we predict that this value will be within 20% of the mean AUC48 of the liposomal bupivacaine group, for a value of ~163.0.

4.2 Secondary Outcomes

4.2.1 Mean VAS-NRS pain score at 48 hours.

4.2.1.1 For patients undergoing ISB with liposomal bupivacaine, the mean VAS pain score at 48 hours was 3.39 with a standard error of 0.37.[10]

4.2.1.2 There are no existing data to predict the mean VAS pain score at 48 hours for patients undergoing ISB with plain bupivacaine + adjuvants, however a similar study using plain bupivacaine alone demonstrated a mean NRS (similar to VAS) pain score of 5.5 with standard error +/-0.5[6]. We expect the mean pain score to be slightly below this value, approximately 4.5.

4.2.2 Postoperative opioid consumption

4.2.2.1 The mean rescue opioid consumption (in IV morphine equivalents) in the first 48 hours after receiving ISB using liposomal bupivacaine was 12.0 +/- 2.3 in a previous study.[10]

4.2.2.2 We expect the patients treated with plain bupivacaine and adjuvants to use a similar average of 12.0 intravenous morphine equivalents in the first 48-hours following surgery. For the purpose of this study, we will convert IV morphine equivalents to oral codeine equivalents.

4.2.3 Satisfaction with surgical experience

4.2.3.1 At the 48 hour mark, the patient's satisfaction with the surgical experience, satisfaction with pain control, and willingness to recommend the procedure to another patient will be assessed via Likert scale. Adverse events will also be evaluated.

5.0 Treatment Plan

Table 1- Protocol stages

	Day of Surgery- Pre-op	Intraoperative	15 departure from PACU	6 hours postop	12 hours postop	24 hours postop	36 hours postop	48 hours postop
Pre-operative pain score	X							
Preoperative multimodal regimen unless contraindicated	X							
Receive ISB with Exparel or plain bupivacaine + adjuvants	X							
Receive short-acting IV opioids if needed		X						
Rescue opioids if needed			X	X	X	X	X	X
Postoperative multimodal regimen				X	X	X	X	X
Pain score assessment in diary			X	X	X	X	X	X
Patent diary of narcotic use			X	X	X	X	X	X
Study coordinator contact via phone call						X		X
Patient satisfaction assessed via Likert scale. Review of potential adverse events								X

5.1 Study-Related Activities

Patients will be recruited from 2 sites- Wake Forest Baptist Health (Main Campus) and WFBH Davie. Patient involvement in the study will be initiated upon scheduling of their surgery with the Anesthesiology team. Eligible subjects will be identified via eligibility checklist (Appendix A) and contacted via phone call to inform them of the study and give them a brief overview. On the day of surgery, the consent for the study will be obtained after a pre-operative assessment and prior to initiating the regional block by the RAAPM team.

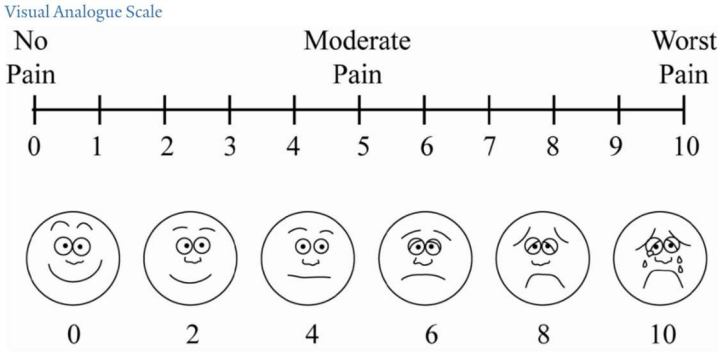
The study coordinator will then assign the patients will receive a study number, and the patient will be randomized by computer software algorithm to one of the study arms:

1. ISB using liposomal bupivacaine
2. ISB using plain bupivacaine with adjuvants

The study will be double blinded to patients, the perioperative nurses, the surgeon, and the study coordinators contacting the patient post-surgery.

To monitor our primary outcomes, patients will be asked to rate their pain level on a visual analog scale (Table 2, Appendix D) upon discharge from the PACU. Following discharge, they will continue to get every 12-hour pain assessments performed by research staff in person and/or over the phone (if they are discharged) until 48 hours have passed.

Table 2: Visual Analog Scale



Additionally, upon discharge, patients will be given a sheet to record the amount of narcotics and the time that they were used (Appendix G). At the 48-hour mark, patient's will be asked to rate their satisfaction with the procedure, and their willingness to recommend it, via Likert scale (Appendix E).

5.2 Treatment Administration

Patients assigned to the ISB with liposomal bupivacaine group will receive a 20cc solution of 133mg liposomal bupivacaine (10mL expanded with 10mL 0.25% plain bupivacaine) in an interscalene block, conducted via Ultrasound guidance.

Patients assigned to the ISB with plain bupivacaine and adjuvants group will receive a 20cc solution of plain bupivacaine 0.25% with adjuvants (clonidine 1.6mcg/mL, epinephrine

2.5mcg/mL, dexamethasone 0.1mg/mL, and buprenorphine 150mcg) in an interscalene block, conducted via Ultrasound guidance.

The absolute dosages of medications will be as follows: either 133mg liposomal bupivacaine with 25mg plain bupivacaine OR 50mg plain bupivacaine with adjunct medicines: 32mcg clonidine, 50mcg epinephrine, 2mg dexamethasone and 150mcg buprenorphine.

The treatment will be administered by either an attending anesthesiologist, or a resident anesthesiologist under the supervision of an attending.

5.3 General Concomitant Medication and Supportive Care Guidelines

This local anesthetic will get delivered at the time of surgery by an attending or resident anesthesiologist. Standardized anesthetic criteria will be applied to all patients enrolled in the study. Pre-operatively, all patients will receive multi-modal therapy, such as acetaminophen 1000 mg PO, celecoxib 200 mg PO, and gabapentin 300 mg PO or pregabalin 150 mg PO unless contraindicated based on past medical history.

Intraoperatively, patients will only receive short acting opioids for analgesia, such as fentanyl as needed. Intraoperative ketamine and dexamethasone will be avoided. Postoperative non-opioid medications will supplement as needed opioid mediations for analgesic management. Postoperative pain management for breakthrough pain will include the following options: IV fentanyl, IV hydromorphone, or PO oxycodone.

Patients will receive full supportive care as medically necessary, including transfusions of blood and blood products, antibiotics, antiemetics, etc. Medications considered necessary for the patient's well-being may be given as long as they are considered safe in the postoperative period and clinically indicated. The reason(s) for treatment, dosage, and dates of treatment will be recorded on the flow sheets.

Anesthesia monitoring for the study procedure will following institutional guidelines. It includes the following: vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation) will be initiated in the regional anesthesia holding room at the time of procedure time out, and includes parameters measured every 5 minutes until subject goes to the operating room. At that time routine anesthesia monitoring continues with vital signs every 3 minutes. Once the subject enters the post anesthesia care unit the vital sign monitoring is every 15 minutes until discharge.

5.4 Duration of Follow Up

Patients will be followed by research personnel upon arrival to the PACU, again 6 hours postoperatively, and then at 12, 24, 36 and 48 hours after surgery both in the hospital and at home via phone call.

5.5 Safety Monitoring Plan

Any adverse safety events occurring in the perioperative period (pre-op, intra-op, or PACU) will be reported by the attending anesthesiologist to the PI and the study coordinator. The PI will record these events and contact the patient to determine the result of these events and arrange any follow-up care that is necessary.

Patients will be instructed to contact the research team to report any adverse events that occur in the postoperative period (after discharge). Patients will be given daytime and evening contact numbers for the PI and the Regional Anesthesia team (on call 24/7) via telephone. These events will be reported to the PI and the study coordinator. The PI will record these events and contact the patient to determine the result of these events and arrange any follow-up care that is necessary.

Serious adverse events will be reviewed by the PI and reported to the IRB promptly within 48 hours. Adverse events of special interest include the following: local anesthetic systemic toxicity, chest pain, shortness of breath, altered sensorium, tinnitus, visual disturbance, and severe dizziness.

6 Statistical Considerations

6.1 Analysis of Primary Objective

6.1.1 The VAS-NRS scale is an 11-point scale that assesses pain from 0- “No pain” to 10- “Worst possible pain”. For this study, a difference of >=2 points will be considered to be clinically significant. Pain scores will be taken measured on departure from the PACU and at each 12-hour interval, and average pain scores for each cohort will be calculated. The area under the curve (AUC) for each cohort will be calculated using the least squares method. The inferiority threshold will be set as >=2 points over 48 hours, which would result in an AUC difference of 96 point-hours.

Prior studies have found an AUC48 for ISB using liposomal bupivacaine to be 136.4 with a standard error of 12.09.[10] There are no data evaluating the AUC48 for ISB using plain bupivacaine with adjuvants; however we estimate that the

pain scores will be within 20% of that of liposomal bupivacaine, resulting in an AUC48 of 163.0 or below, and a similar standard error of 12.09.

With a 2-sample t test using $\alpha = 0.05$ and $\beta = 0.1$, the study will be powered to detect a difference of 96 point-hours between the 2 groups with 36 subjects per arm.

To test for differences in these AUC between the 2 arms, an independent t-test will be used; if the observed p-value is <0.05, statistical significance will be assumed. Two-sided t-test will be performed for statistical analysis once data collection is complete.

6.2 Analysis of Secondary Objectives

6.2.1 For the mean VAS-NRS score at 48 hours, prior studies have found an average score of 3.8 with a standard deviation of 2.88 (standard error of 0.36) for ISB using liposomal bupivacaine.[10] There have been no studies to evaluate the pain scores after ISB using plain bupivacaine with adjuvants. This study will be powered to detect a difference of at least 0.4 on the VAS-NRS scale. We will define the threshold for inferiority as a difference of >=2 points on the VAS scale. Analysis will be conducted using a two-sample t test with $\alpha = 0.05$ and $\beta = 0.1$.

6.2.2 For the comparison of post-operative opioid consumption, each patient's total post-operative opioid usage during the first 48 hours will be converted to oxycodone equivalents. The geometric mean opioid consumption for each cohort will be calculated, and the two cohorts will be compared for statistical difference using a two-sample t test, with $\alpha = 0.05$ and $\beta = 0.1$.

6.2.3 Patient satisfaction will be assessed on POD#2 by 5-point Likert rating scale, and via a binary question of "would you recommend this pain relief regiment to the next patient". The results of these questions will be compared with a Fisher's Exact Test, with $\alpha = 0.05$.

6.3 Power and Sample Size

We will have a power of 80%, as described in 10.1.1, with a sample size of 36 patients in each arm for a total of 72 patients, plus 8 patients to allow for attrition, for a total of 80 patients.

6.4 Accrual Rate

We plan on accruing 10 new patients per month until the goal of 80 total patients is reached.

6.5 Estimated Study Length

Estimated study length will be approximately 1 year.

6.6 Interim Analysis Plan

We will plan on performing an interim analysis for the primary outcome and secondary outcomes after there are at least 10 patients in each treatment group in order to detect the evidence of severe side effects in either group.

7.0 Adverse Event Reporting

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.
Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in

the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The investigator will assess the relationship/causality of the AE to study drug after careful medical consideration on a case-by-case basis. General guidelines for determining the causality of an AE to the study drug are provided as follows:

Unrelated: A causal relationship between the study drug and the AE can be easily ruled out(e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).

Unlikely: A clinical event with a temporal relationship to study drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide a plausible explanation.

Possible: A clinical event with a reasonable time sequence to administration of the study drug but which could also be explained by a concurrent disease or other drugs or chemicals.

Probable: A clinical event with a reasonable time sequence to administration of the study drug unlikely to be attributed to a concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (dechallenge).

Definite: The pharmacological properties of the study drug(s) or of the substance class, and the course of the AE after dechallenge and, if applicable, after rechallenge, and/or specific test indicate involvement of the study drug(s) in the occurrence/worsening of the AE, and no indication of other causes exists.

The investigator will assess the outcome of the AE after careful medical consideration, on a case-by-case basis. General guidelines are provided below:

Recovered/Resolved: The event resolved and the subject recovered from the AE.
Recovered/Resolved with Sequelae: The initial event resolved, but has a continuing abnormal condition as a result of the AE.
Not Recovered/Not Resolved: At the time of the last assessment, the event was ongoing, with an undetermined outcome.

Recovering/Resolving: At the time of the last assessment, the event was decreasing in frequency, severity, etc., and a resolution was expected.
Fatal: The AE directly caused death.
Unknown: There was an inability to access the subject or the subject's records to determine the outcome (e.g., subject withdrew consent or was lost to follow-up).

The subject will receive adequate medical care by the medical provider for any adverse events related to the clinical trial. The investigator will provide any actions taken regarding the subject (e.g., treatment, diagnostic tests, laboratory tests, or therapy) for each reported AE. These include the following options:

- None.
- Medication.
- Non-pharmaceutical therapy. (The specific therapy used must be recorded in the data collection sheet)
- Discontinued from study.
- Other-document specific action taken

Serious and unexpected suspected adverse reaction: The investigator will report any suspected adverse reaction that is both serious and unexpected. The investigator will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as if the study participation meets one of the following criteria:
(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;
(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug;
(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

In case a cardiac or neurological AE of special interest (AESI) or serious AE (SAE) occurs during the study, if the investigator considers that the event may be related to study treatment or suggests the possible occurrence of local anesthetic systemic toxicity (LAST; with or without the need for treatment [e.g., intralipids]), or if a plausible etiology for the event cannot be found, vital signs, and clinical laboratory tests will be performed per institutional standard of care of such occurrence. Cardiac AESIs include chest pain, abnormal/irregular heart rate, and shortness of breath requiring intervention.

Neurologic AESIs include seizure, altered mental status/altered sensorium, tinnitus, visual disturbance, and severe dizziness.

This study involves a single administration of the study drug for the analgesic block; therefore, subjects should not be withdrawn from the ongoing study assessments as long as they are willing and able to continue with the follow-up schedule according to the protocol in order to obtain analgesic and safety data. Any subject exhibiting undesirable AESIs will receive appropriate treatment at the discretion of the investigator.

Subjects will be monitored for the occurrence of all potential adverse events by research personnel. This clinical research study will be paused after one death where a clear alternate cause is not readily apparent. The study will be paused after 2 non-fatal SAEs where a clear alternate cause is not readily apparent; the study will be paused after 3 moderate or severe adverse events of special interest. The adverse event(s) will be assessed by all investigators for causality and relationship prior to the study enrollment being resumed. Assessment of adverse event severity will be assessed and graded as per the definitions noted in Appendix I.

8.0 Study Costs

The funding for the medications used in this study is supplied by an internal departmental research grant from the WFBH Department of Anesthesiology. The research participants will not experience any additional fees or costs for participation in this study outside of the usual anesthesiologist's fee for surgery. The research participant will still incur the cost of the actual procedure as it is done as standard of care.

References

1. Sakamoto B, Keiser S, Meldrum R, Harker G, Freese A. Efficacy of liposomal bupivacaine infiltration on the management of total knee arthroplasty. *JAMA Surg*. 2017;152(1):90-95. doi:10.1001/jamasurg.2016.3474
2. Hamilton TW, Athanassoglou V, Mellon S, et al. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. *Cochrane Database Syst Rev*. 2017;2017(2). doi:10.1002/14651858.CD011419.pub2
3. Pichler L, Poeran J, Zubizarreta N, et al. Liposomal Bupivacaine Does Not Reduce Inpatient Opioid Prescription or Related Complications after Knee Arthroplasty: A Database Analysis. *Anesthesiology*. 2018;(October). doi:https://dx.doi.org/10.1097/ALN.0000000000002267
4. Hamilton TW, Athanassoglou V, Trivella M, et al. Liposomal bupivacaine peripheral nerve block for the management of postoperative pain. *Cochrane Database Syst Rev*. 2016;2016(8). doi:10.1002/14651858.CD011476.pub2
5. Rabin T. FDA In Brief: FDA approves new use of Exparel for nerve block pain relief following shoulder surgeries. https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm604021.htm. Published 2018.
6. Vandepitte C, Kuroda M, Witvrouw R, et al. Addition of liposome bupivacaine to bupivacaine HCl versus bupivacaine HCl alone for interscalene brachial plexus block in patients having major shoulder surgery. *Reg Anesth Pain Med*. 2017;42(3):334-341. doi:10.1097/AAP.0000000000000560
7. Vieira PA, Pulai I, Tsao GC, Manikantan P, Kelle B, Connelly NR. Dexamethasone with bupivacaine increases duration of analgesia in ultrasound-guided interscalene brachial plexus blockade. *Eur J Anaesthesiol*. 2010;27(3):285-288. doi:10.1097/EJA.0b013e3283350c38
8. Baeriswyl M, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: A systematic review and meta-analysis. *Br J Anaesth*. 2017;119(2):183-191. doi:10.1093/bja/aex191
9. Candido KD, Winnie AP, Ghaleb AH, Fattouh MW, Franco CD. Buprenorphine added to the local anesthetic for axillary brachial plexus block prolongs postoperative analgesia. *Reg Anesth Pain Med*. 2002;27(2):162-167. doi:10.1053/rapm.2002.30671
10. Patel M, Gadsen J, Bao X, Bendsten T. Brachial Plexus Block With Liposomal Bupivacaine for Total Shoulder Arthroplasty or Rotator Cuff Repair: Results from a Randomized Controlled Trial. *Poster Present NYSORA 16th Annu Symp*. 2016:31-32. https://nysorasymposium.com/wp-content/uploads/2016/02/NYSORA-Sep-2017-all-Abstracts-2017.08.16-revised-1.pdf.
11. *US Food and Drug Administration. Indications and Usage of Liposomal Bupivacaine.* Silver Spring, MD; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022496s9lbl.pdf.
12. *US Food and Drug Administration. Indications and Usage of Bupivacaine Hydrochloride and Epinephrine Injection.* Vol 000. Silver Spring, MD https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018692s015lbl.pdf.

Single Injection interscalene brachial plexus nerve block with adjuvants vs. Liposomal bupivacaine interscalene brachial plexus nerve block for total shoulder arthroplasty

Appendix A- Eligibility Checklist

IRB Protocol No. _00055981__	**SUBJECT ID:**
Study Title: SINGLE INJECTION INTERSCALENE BRACHIAL PLEXUS NERVE BLOCK WITH ADJUVANTS VS. LIPOSOMAL BUPIVACAINE INTERSCALENE BRACHIAL PLEXUS NERVE BLOCK FOR TOTAL SHOULDER ARTHROPLASTY	
Principal Investigator: Doug Jaffe, D.O.	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
All patients who are undergoing total shoulder arthroplasty	☐	☐	
Age >18 years	☐	☐	
Ability to understand and willingness to sign IRB-approved informed consent document	☐	☐	
Weight Greater than or equal to 50 kg	☐	☐	
ASA patient status I-III	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
No contraindications to an interscalene block or phrenic blockade.	☐	☐	
Infection at injection site.	☐	☐	
Pre-existing neurological dysfunction affecting the operative extremity.	☐	☐	
Patients who abuse narcotics or have chronic pain (using greater than 40 mg equivalents of oxycodone per day)	☐	☐	
Patients who are wards of the state	☐	☐	
BMI >40	☐	☐	
Uncontrolled diabetes (HbA1c >8.0)	☐	☐	
Contraindications to any pain-control agents planned for surgical or postsurgical use (ie, bupivacaine, hydromorphone, etc.)	☐	☐	

Single Injection interscalene brachial plexus nerve block with adjuvants vs. Liposomal bupivacaine interscalene brachial plexus nerve block for total shoulder arthroplasty

History of allergic reactions attributed to compounds of similar chemical or biologic composition to bupivacaine or liposomal bupivacaine or its adjuncts (dexamethasone, buprenorphine, or clonidine).	☐	☐	
Patients with moderate-severe hepatic or renal impairment.	☐	☐	
Patient is pregnant or lactating	☐	☐	
Patient has a labeled contraindication for the study drug, such as a systemic fungal infection	☐	☐	
Patients undergoing repeat shoulder arthroplasty or reverse total shoulder arthroplasty.	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

REDCap Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Treating Physician: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Principal Investigator**: _____

Date: ___ ___ / ___ ___ / ___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, physical exam, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: Pathology report, 01/01/14" or "Clinic note, 01/01/14"

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by REDCap): ___ ___ ___ ___ ___ ___ ___ ___

Appendix C – Pain Assessment Form

Subject Number:___ ___ ___ ___ ___ ___ ___ ___ DATE: __ __/__ __/__ __TIME: __ __:__ __AM/PM

1 - Rate the intensity of your worst pain in the past 12 hours related to your operated shoulder

0 1 2 3 4 5 6 7 8 9 10

2 - Did you take prescription pain pills in the past 24 hours? YES NO

If yes please circle the medication below

2a1 – Oxycodone (Roxicodone)

2a2 - Hydromorphone (Dilaudid)

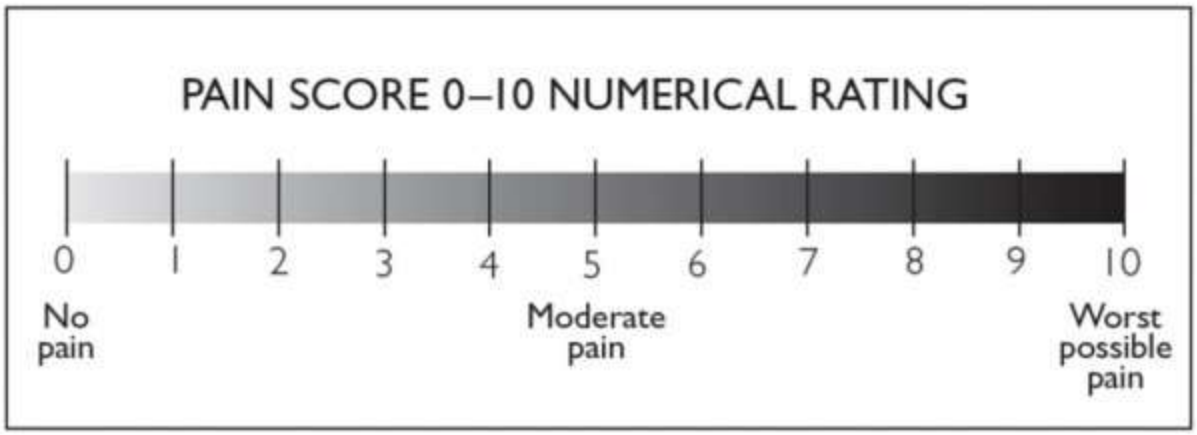
2a3 - Hydrocodone + acetaminophen (Vicodin, Norco)

2a4- Oxycodone + acetaminophen (Percocet)

2a5 -Diazepam (Valium)

2a6- Alprazolam (Xanax)

Appendix D- Verbal Numerical Rating Scale



https://www.physio-pedia.com/images/4/47/NRS_pain.jpg

Appendix E – Satisfaction Questionnaire

Subject Number:___ ___ ___ ___ ___ ___ ___ _DATE: __ __/__ __/__ __TIME: __ __:__ __AM/PM

*Instructions: On the **second day** (48 hours) after surgery, please review the following questions, and choose the answer that best corresponds to each question regarding your experience.*

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I believe my pain was well-controlled during after surgery.					
I would recommend this pain-control treatment to another patient.					
Have you had any itching since your surgery in your shoulder area?	YES	NO			
Have you had any nausea and/or vomiting since your surgery?	YES	NO			

Appendix F – Off-Study Form

Study Number: __ __ __ __ __	PID: ___ ___ ___ ___ ___ ___ ___ ___
Investigator: J. Doug Jaffe, DO	Date: __ __/__ __/__ __

Name of Person Competing form_____

Did the subject meet eligibility criteria for study enrollment? Yes ☐ No ☐

Was the subject withdrawn from the study? Yes ☐ No ☐

Reason(s) for withdrawal:

1. ☐ Patient exhibited progression of disease

2. ☐ Unacceptable toxicity /adverse event of special interest: if so, list event/submit as adverse event on case report form

   If Yes, Please specify whether the toxicity was:
   ☐ From Bupivacaine
   ☐ From Liposomal Bupivacaine
   ☐ From BOTH
   ☐ Other _____

   Adverse event of special interest and reportable to the IRB?
   If so, date reported: _____

3. ☐ Patient withdraw
   If Yes, Please specify what portion of the study the subject wishes to withdraw from:

   ☐ For just the Drug A administration only
   ☐ For just the Drug B administration only
   ☐ For both
   ☐ For all components of the research study (including follow up in the medical record)

4. ☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest (*Describe below)

5. ☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible (*Describe below)

6. ☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment (*Describe below)

7. ☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits (*Describe below)

8. ☐ Termination of the clinical trial by the principal investigator

Comment:

If reason for withdrawal includes #4, 5, 6, or 7 then please add comments clarifying this information)_____

_____

_____

_____

Appendix G- Pain Medication Diary.

Assists patients in recording the amount and time of narcotic and benzodiazepine use.

	Date	Pain Medication Used (Include dose)	Number of pills taken	Time
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				

28				
29				
30				
31				
32				
33				

Appendix H- Data Collection Form

Demographics	**Assigned Study Number:**
	WakeOne MRN
	Age
	Sex
	Procedure
Medical Hx	**Comorbidities**
	Pre-surgical analgesics **Preop pain score**
Pre-Op	**Pre-op multimodal analgesics** **Post-Block assessment**
Intraop	**Intra-op Narcotics (PO oxy equivalents)**
PACU	**Pain score in PACU p/t discharge** **PACU block assessment** **PACU opioids (PO oxy equivalents)**
	+6hr worst pain score (VAS)

Post OP	**+12h worst pain score (VAS)** **+24h worst pain score (VAS)** **+36h worst pain score (VAS)** **+48h worst pain score (VAS)** **+6hr opioid use (PO oxy eq)** **+12h opioid use (PO oxy eq)** **+24h opioid use (PO oxy eq)** **+36h opioid use (PO oxy eq)** **+48h opioid use (PO oxy eq)** **Likert Satisfaction #1** **Likert satisfaction #2** **Nonopioid Analgesics Used** **Side effect evaluation (Itching, Nausea/vomiting)**
Off study	**("OFF" if applicable)** **Reasons:**

Date of study completion:

Evaluable subject?

Protocol deviations?

APPENDIX I: ADVERSE EVENT GRADING SCALES

LOCAL REACTION TO INJECTABLE PRODUCT	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potential life threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/Redness	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	necrosis
VITAL SIGNS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life threatening (Grade 4)**
Fever-*F	100.4-101.1	101.2-102.0	102.1-104	>104
Tachycardia	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia	50-54	45-49	<45	ER visit or hospitalization for arrhythmia
Hypertension-systolic	141-150	151-155	>155	ER visit or hospitalization for malignant hypertension
Hypertension-diastolic	91-95	96-100	>100	ER visit or hospitalization for malignant hypertension
Hypotension	85-89	80-84	<80	ER visit or hospitalization for hypotensive shock
Respiratory rate	17-20	21-25	>25	Intubation
SYSTEMIC (GENERAL)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools	4 – 5 stools	6 or more watery stools or requires IV hydration	ER visit or hospitalization

Headache	No interference with activity	Repeated use of nonnarcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization