Comparison of the Analgesic Efficacy of a Single Shot Interscalene Block With Liposomal Bupivacaine to Bupivacaine With Dexamethasone as an adjuvant-a Randomized Controlled Trial
Dr. Meg Rosenblatt
NCT03969875
Document Date: 6-25-2021

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	Principal Investigator Name/Contact Info:	MEG A. ROSENBLATT MD. YAN H. LAI MD, MPH. JUNPING CHEN MD, PHD PAUL J. CAGLE MD 212-523-6915
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Brief Summary of Research (250-400 words):

Pain management after shoulder surgeries pose a unique challenge to the surgeon as well as the anesthesiologist. Regional anesthesia in the form of interscalene approach to the brachial plexus as an adjunct to general anesthesia or as a sole primary technique comes to one's rescue. Interscalene block either as single shot or as a catheter is an established modality for effective analgesia which facilitates early mobilization helping in physical therapy and early discharge.

With the help of local anesthetic injected as a single shot, analgesia usually lasts less than 24 hours. Though catheter with a slow infusion of local anesthesia improves quality of peri-operative pain management, it adds days to hospital stay and accompanying challenges of risk of catheter migration and additional resources for post operative follow up.

Recent research in regional anesthesia is advancing towards adjuvants which will prolong the duration of local anesthesia. This has introduced the concept of "multimodal perineural analgesia (MMPNA)" whereby multiple agents with differing mechanisms of action are used with the goal of providing perineural analgesia while avoiding exposure to high and potentially toxic levels of individual agents. Some of the commonly used adjuvants in clinical studies are fentanyl, buprenorphine, morphine, tramadol, magnesium, epinephrine, ketamine, non-steroidal anti-inflammatory drug (NSAID), midazolam, parecoxib, ketorolac, clonidine, dexmedetomidine, dexamethasone, neostigmine and potassium. They find a distinct place in wide spread clinical practice as an off label use.

Steroids have a long history of safe use in epidural space for treatment of radicular pain due to nerve irritation. Dexamethasone is used routinely as a

part of anti- emetic prophylaxis and anti inflammatory effect. Methyl prednisone was the first steroid to be used as an adjuvant. Dexamethasone was first used as an adjuvant in 2003.

It has been hypothesized that steroids induce a degree of vasoconstriction, thereby reducing local anesthetic absorption, tend to have an opioid sparing effect. Another theory suggests that it increases the activity of inhibitory potassium channels on nociceptive C-fibers (via glucocorticoid receptors), thus decreasing their activity.

Several studies have demonstrated promising results with the use of 8mg of perineural dexamethasone. No neuronal injury has been reported in in vivo studies. Though there are several studies which report usage of dexamethasone in varying doses of 2mg to 8mg, the optimal effective dose of dexamethasone as an adjuvant for nerve block remains unknown. Some studies have suggested perineural is more effective than IV as an adjuvant. Hence we propose to study the lowest effective dose of dexamethasone as an adjuvant which can be used as an adjuvant to local anesthesia in interscalene block for shoulder surgeries.

Liposomal bupivacaine , a formulation where bupivacaine is encapsulated into multivesicular liposomes, making it a slow and controlled release from the liposomes, was originally indicated for wound infiltration at the surgical site to provide post surgical analgesia. Studies have demonstrated efficacy upto 24 hours in femoral nerve block in total knee arthroplasty. Recent approval of liposomal bupivacaine in interscalene block for shoulder surgeries by FDA opens an arena unexplored in the world of regional anesthesia.

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Based on the above two options in the current opioid epidemic crisis, we propose to study the analgesic efficacy of liposomal bupivacaine to bupivacaine with dexamethasone as an adjuvant in interscalene block for shoulder surgeries. Till date, there is not study comparing the two.

1) Objectives:

Research Question:

Is the analgesic efficacy of liposomal bupivacaine superior to that of bupivacaine with dexamethasone as an adjuvant in interscalene block?

Primary Outcome: The primary outcomes is the time of analgesia duration (defined as the onset of sensory discomfort that required medication) and time of motor recovery (defined as the recovery of full motor function of both wrist and elbow on the nerve block side). Time to first analgesic request, NRS at 6 hours, 12 hours, 24 hours and 48 hours, POD 3, 4, 5, 6, 7 and total narcotic consumption.

Secondary Outcome: arm weakness (0 to 24 hours, 24 to 48 hours), arm numbness (0 to 24 hours, 24 to 48 hours), nausea, vomiting, dizziness, Horner's syndrome, hoarseness, dyspnea, Intra operative narcotic consumption, PACU and hospital length of stay, pain scores as assessed by PT on POD 1, and 2.

patient's satisfaction scores(Yes- I would prefer the same analgesic technique the next time or No-I would prefer a different analgesic technique) and quality of sleep (good, moderate/average, bad) on POD 0 and 1.Patient reported outcomes measurement information system (PROMIS) baseline global assessment will be conducted prior to surgery and post operative pain assessment at first follow up visit. Each patient will be assessed by standardized assessment of shoulder function as recommnede dby American association of shoulder and elbow surgery.

2) Background

See above. There have been several studies demonstrating efficacy of dexamethasone in prolonging the analgesic effect when administered both perineurally and intra-venously as an adjuvant to local anesthesia demonstrating a dose effect relationship.

But to date there are no studies regarding the lowest effective optimal dosing as an adjuvant which can aid in analgesia and also facilitate earlier discharge from hospital avoiding nerve catheter. If an effective optimal dosing of dexamethasone as an adjuvant is deciphered, it will help in avoiding costs associated with liposomal bupivacaine facilitating earlier discharge and extending post operative analgesia avoiding narcotics.

3) Setting of the Human Research

Prospective triple blinded randomized control trial in patients undergoing elective arthroscopic shoulder surgeries. The research study will take place at Mount Sinai West hospital. The site PI is Meg Rosenblatt MD.

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4) Resources Available to Conduct the Human Research

For n=100, the feasibility of recruitment is manageable. Recruitment will be done through a coordination of the operating schedule and the surgeon's office.

The staff members on this protocol are all employees of Mount Sinai and will either be a resident or attending physicians that are included on the IRB protocol. There are four primary members of the research personnel:

a) Meg A. Rosenblatt, MD – Roles for Dr. Rosenblatt in this study include serving as primary investigator responsible for study design and planning, data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. She is certified in PPHS/IRB protocols, all Citi/IRB required training in human subject protection, and has prior clinical research experience. She is also a board certified anesthesiologist and professor and chair of anesthesiology with the Icahn School of Medicine and the Mount Sinai Health System.

b) Yan Lai, MD, MPH – Roles for Dr. Lai in this study include serving as co-primary investigator responsible for study design and planning, data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. He is certified in PPHS/IRB protocols, all Citi/IRB required training in human subject protection, and has prior clinical research experience. He is also a board certified anesthesiologist and assistant professor of anesthesiology

with the Icahn School of Medicine and the Mount Sinai Health System

Paul Cagle, MD, – Roles for Dr. Cagle in this study include serving as co-investigator responsible for study design and planning, data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. He is certified in PPHS/IRB protocols, all Citi/IRB required training in human subject protection, and has prior clinical research experience. He is also a board certified orthopedic surgeon and assistant professor of anesthesiology with the Icahn School of Medicine and the Mount Sinai Health System

b) Poonam Pai B.H MD – Roles for Dr. Pai include serving as primary research coordinator involved in data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. She has completed all of her required CITI training to be IRB certified and has experience in clinical research. In addition, she has been a resident physician in anesthesiology with the Icahn School of Medicine in good standing for the previous three years going on her fourth.

There are institutional processes to ensure that all persons assisting with the protocol will be well informed. The research personnel will conduct regular meetings and department email updates to review the results and safety data of the study. The research personnel will initiate the formation of a safety monitoring board for adverse effects, complications, or complaints from patient subjects.

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5) Study Design

Prospective triple blinded randomized control trial.
With the HIPAA waiver requested, the surgeon will provide the investigators (both of them are physicians within the Department of Anesthesiology) with information of eligible patients. Subjects will be called by the department of Anesthesiology when their surgery is scheduled, and they will be introduced about the study then. The surgeons will also introduce the study to the patients in their office. All patients will be provided with copies of the IRB protocol and consent if they wish to have it. Copy of the consent form will be sent in a secured email to the potential subject. The email will be secured by entering in [SECURE] in the e-mail subject line. All patients scheduled to undergo total shoulder repair will be approached and recruited.

On the day of the surgery, the team will finalize participation and ask the subject to sign study consent forms. The study will not be introduced to the patients on the day of the surgery.
Once the anesthesiologist team performs a thorough pre operative evaluation, an intravenous catheter will be placed for administering medications.

After placement of standard ASA monitors and 4mg of midazolam as sedation all patients will receive single shot interscalene block performed by residents under direct supervision of regional anesthesiology attending with the help of ultrasound guidance.

patients will be randomized using computer generated tables and sealed envelopes. A designated resident not involved in the study will open the sealed envelope and randomize the patient into the following groups:

Group A—Liposomal bupivacaine(133mg bupivacaine diluted normal saline total 25cc)

Group B---Dexamethasone 4mg in 0.5% Bupivacaine 25cc

The patients will be transferred to the OR to proceed with the surgery. Standard ASA monitors will be placed again and after pre oxygenation, general anesthesia will be induced with propofol and fentanyl. Laryngeal mask airway of appropriate size will be inserted and patient will be connected to the ventilator for the procedure. Maintenance of anesthesia will be achieved with sevoflurane and oxygen/air mixture. Once the procedure is completed, patients will be extubated and transferred to the recovery room(PACU) for post anesthetic care.

The patient will also receive 4mg of ondansetron intra-venous in the OR as prophylaxis for post operative nausea and vomitting.

Patients, attending anesthesiologists, surgeon and research assistant collecting the data will be blinded of the group assignment. The medication solution will be prepared by the resident physician.

Pain scores in the form of NRS (NUMERICAL RATING SCALE) will be assessed on arrival to PACU. Pain scores will also be assessed 1 hour after arrival to PACU and at the time of discharge from PACU. NRS scores will be assessed on the floors every 6 hourly during the first 24 hours, 8 hourly and then every 12 hourly during the second 24 hours. If NRS scores are more than 5 at any time a one-time dose of oxycodone 10mg and Tylenol 1000 mgwill be given.

Once the primary team discharges the patient, a telephone follow - up every day until resolution of any residual arm weakness/numbness will be done by the anesthesia resident originally involved in the surgery.

Patients will also be asked to note the time to first analgesic request in addition to onset of sensory discomfort and motor recovery.

a) Recruitment Methods

See above. With the HIPAA waiver requested, the surgeon will provide investigators (both of whom are physicians within the department of Anesthesiology) with information of eligible patients. After the operating room schedule has been reviewed for potential participants in the study the contact information will be obtained through the surgeon's office. Subjects will be called by the department of Anesthesiology when their surgery is scheduled, and they will be informed about the study then.

b) Inclusion and Exclusion Criteria

Inclusion criteria: All patients between age 18-75 years undergoing primary shoulder arthroscopic procedure. All patients who speak read and understand English will be included for follow up purposes.

Exclusion criteria included patients with patient refusal, ASA 5, presence of coagulopathy, severe lung disease, contralateral diaphragmatic palsy, insulin-dependent diabetes, hepatic disease/failure, kidney disease/failure, pregnancy, chronic opioid use (defined as opioid use for >3 months), or allergy to any of the study medications.

c) Number of Subjects

N= 100, recruit ability is manageable. Based on previous study conducted by Tandoc et al with estimated average duration of analgesia at 22 hours with dexamethasone in 0.5% bupivacaine and assumed average SD of 3 hours, they estimated that 16 patients would be needed to provide 80% power to conclude absence of effect at the significance level of 0.05 among treatment groups. To allow for 20% patient dropouts, 30 subjects per group will be targeted for enrollment.

Data will be expressed as mean ± SD or median with interquartile range as appropriate. Categorical data will be analyzed with Fisher exact test and chi-square test. The duration of analgesia and motor block will be analyzed by the Kaplan-Meier survival analysis and Cox

proportional hazards modeling. Subgroup pairwise analyses will be conducted via Kruskal-Wallis rank test with Bonferroni correction for significance. All analysis will be conducted with intent-to-treat approach to minimize the potential effects of dropout. Statistical significance will be defined as P<0 .05.

d) Study Timelines

2018-2019 and subsequent data analysis. The subject's participation will be from time of enrollment to complete resolution of arm weakness and motor strength. Estimated date of enrollment completion will be when 100 eligible subjects are enrolled in final data analysis. Estimate date for study completion will be June 2019.

e) Study Endpoints

Primary end point will be the time of first analgesic request for the first 24 hours post operatively.

Secondary end points will be NRS at 6 hours, 12 hours, 18 hours, 24 hours, 36 hours and 48 hours and oxycodone use.

f) Procedures Involved in the Human Research

Prospective randomized controlled trial and data analysis only. Ultrasound guided interscalene block with nerve catheter placement.

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g) Specimen Banking

N/A

h) Data Management and Confidentiality

Data collected in excel file to be de-identified after initial collection. Excel file be subsequently encrypted and shared only between the two above listed investigators via secure Mt. Sinai (chpnet) electronic mail.

The information included in the data will be medical record number, age, gender, ASA class, type of surgery, pain score assessments, duration of surgery, anesthesia time, time to first narcotic, total narcotic use and pain scores up to 48 hours after surgery. In case of known history of type 1 or 2 diabetes, preoperative and post operative finger stick will be recorded. Time of administration of study drug, smoking status and patient satisfaction scores will also be recorded. Only the research personnel will have access to the data. The data will be stored as a hard copy files and on a secure spreadsheet. The research personnel are responsible for the receipt of the data. The PI will keep the hard copies secure and any electronic data will be encrypted. No personal identifiers will be used. The data will undergo statistical analysis.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

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Part I: Elements of Data and Safety Monitoring Plan

MSSM Principal Monitor:

Last Name: Rosenblatt
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Academic Title: Attending Physician, Professor
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MSSM Principal Monitor:

Last Name: Lai
First Name: Yan
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Last Name: Cagle
First Name: Paul
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MSSM Additional Monitor:

Last Name: Pai B.H
First Name: Poonam
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The principal monitor is a board certified anesthesiologist thus minimizing the risk to the subjects and further optimizing their health and wellbeing. Adverse events will be monitored as a standard of care everyone receives regardless of participation in the study. The safety and data information will be reviewed on a daily basis until the desired sample size is achieved. All temporary and/or permanent suspensions will be reported.

Poonam Pai B.H MD – Roles for Dr. Pai include serving as primary research coordinator involved in data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. She has completed all of her required CITI training to be IRB certified and has experience in clinical

research. In addition, she has been a resident physician in anesthesiology with the Icahn School of Medicine in good standing for the previous three years going on her fourth.

j) Withdrawal of Subjects

Patients may withdraw from the study at any given time by contacting any member of the research study group. Data will not be collected on patients who wish to withdraw. Patient do not need to withdraw consent in writing.

6) Risks to Subjects

As with any medication, there is a possibility of an allergic reaction. Although rare, possible complications include LA toxicity, hypersensitivity reaction, bleeding or local site infection, chance of pneumothorax. All anesthesiologists involved in patient care will be prepared for the prevention and rescue for any complications involving local anesthetic injections.

7) Provisions for Research Related Injury

If patients are injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to the patient or their insurance in the ordinary manner and the patient will be

responsible for all treatment costs not covered insurance, including deductibles, co-payments and coinsurance. This does not prevent the patient from seeking payment for injury related to malpractice or negligence. Contact the investigator for more information.

8) Potential Benefits to Subjects

It is important to know that you may not get any benefit from taking part in this research. Others may not benefit either. However, possible benefits may be improved knowledge about how the addition of adjuvant to local anesthesia affects pain control in shoulder surgery. There is potential for better pain control after the surgery.

9) Provisions to Protect the Privacy Interests of Subjects

Patients will be appropriately educated about the research study. Any questions or concerns they have will be adequately addressed and patients will have the option to decline participation. Patients will be given as much time as they need to review the consent form. The study personnel will be approaching the subjects. Privacy will be maintained by not including any identifiers such as names or addresses in the data collected.

The identities of human subjects whose data is being studied will be de-identified as per HIPAA Privacy Rule.

10) Economic Impact on Subjects

Patients will not incur any additional cost for participating in the study. The medications used are part of a standard anesthetic regimen that will be billed to subject's insurance as bundled standard of anesthesia care. The cost of the procedure is overall unaffected.

11) Payment to Subjects

Patients will not be reimbursed for their participation.

12) Consent Process

Informed consent will be obtained prior to the procedure. Both the HRP-090 (SOP) Informed Consent Process for Research and the HRP-091 (SOP) Written Documentation of Consent will be followed by the study team. These documents are both available at http://icahn.mssm.edu/research/resources/program-for-the-protection-of-human-subjects/irb-members-palette.

13) Process to Document Consent in Writing

The patients will receive a paper copy of the IRB approved consent packet and will sign in the designated areas to confirm consent of participation. They will have the option of have a copy of the consent and may ask for a personal copy of the consent.

14) Vulnerable Populations

Indicate specifically whether you will include (target) or exclude each of the following populations:

Include	*Exclude*	*Vulnerable Population Type*
	X	*Adults unable to consent*
	X	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	X	*Wards of the State (e.g. foster children)*
	X	*Pregnant women*

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	X	*Prisoners*

15) Multi-Site Human Research (Coordinating Center)

This study will be performed within the Mount Sinai West and Mount Sinai Hospital. No additional centers will be involved.

16) Community-Based Participatory Research

This does not apply to our study.

17) Sharing of Results with Subjects

Results will not be shared with the patients since the study will take time to complete. Patients can request results if they contact the PI by writing.

18) External IRB Review History

This does not apply to our study.

19) Control of Drugs, Biologics, or Devices

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Not applicable. Local anesthetics and dexamethasone are routinely used in this setting.