Protocol Title	Evaluation of diaphragm movement after an Interscalene block
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PROTOCOL COVER PAGE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
3	5/9/19	Adjusted inclusion criteria to include those who are not enrolled in the TSA study.	

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ABBREVIATIONS/DEFINITIONS

- LB liposome bupivacaine
- ISB interscalene block
- TSA total shoulder arthroplasty
- RCR rotator cuff surgery

2.0 Objectives

2.1 Purpose: To evaluate the movement of the diaphragm after an interscalene block with liposome bupivacaine (LB) compared to interscalene block (IB) with bupivacaine. This study will evaluate if there is a possible prolonged phrenic nerve paralysis when using liposome bupivacaine in an interscalene block, using ultrasound.

3.0 Background

3.1 Significance of Research Question/Purpose: To date there is no previous study looking at diaphragm movement after an Liposomal Bupivacaine Interscalene Block. It is important to see how long the phrenic nerve is affected by this block if at all.

3.2 Preliminary Data: We have not routinely examined that patient's diaphragm via ultrasound after ISB at M Health. Patients have not been readmitted for breathing problems with our current practice.

3.3 Existing Literature: There is no previous literature in LB ISB. Urmey et al. showed 100% phrenic nerve block post ISB. But others (Renes et al) have evaluated it using bupivacaine and found that lower doses resulted in less diaphragm blockade. Cuvillon showed that those with a catheter had 66% phrenic nerve paralysis at 24 hours.

4.0 Study Endpoints/Events/Outcomes

4.1 Primary Endpoint/Event/Outcome: The primary study endpoint will be diaphragm excursion (movement in cm) from rest to sigh in a sitting position.

4.2 Secondary Endpoint(s)/Event(s)/Outcome(s): The secondary endpoint will be the diaphragm excursion (movement in cm) from rest to a quick inspiratory breath.

4.3 Secondary Endpoint(s)/Event(s)/Outcome(s): Evaluation of baseline FEV1, FVC (or FEV6) and FEV1/FVC ratio via spirometry.

5.0 Study Intervention(s)/Investigational Agent(s)

5.1 Description: This study will be run concurrently with two other studies comparing bupivacaine to Liposomal Bupivacaine in shoulder surgeries. We will either use already randomized patients for our randomization process or if they are not enrolled in either RCR or TSA study we will randomize them to one of the two groups. For this study in particular we will use an ultrasound machine to scan the diaphragm of any patient who had an Interscalene Block for Total Shoulder Arthroplasy or Rotator Cuff Repair. Patients are to be scanned in an upright sitting position and scanned from a low intercostal or subcostal approach using the liver or spleen as an acoustic window. M Mode will be applied and the range of diaphragmatic movement from the resting expiratory position to deep inspiration (sigh test) will be

recorded as was the range of diaphragmatic movement from resting expiratory position when quickly inspiring through the nose (sniff test). The blocks will be done regardless of the study as they are standard of care for pain control. The only intervention is ultrasound examination of the patient's diaphragm at baseline, 3 hours post block in recovery room and on post-operative day 1, and basic spirometry to record FEV1 and FVC via a portable spirometer at the same time points. If patients did stay in hospital on postoperative day 2 we would also evaluate their diaphragm function.

5.2 Drug/Device Handling: n/a

5.3 Biosafety: n/a

5.4 Stem Cells: n/a

6.0 Procedures Involved

6.1 Study Design: This is a prospective study

Study Procedures: All patients who are enrolled in our TSA or RCR studys fit the criteria of being scheduled for overnight shoulder surgery and having an ISB with or without LB. The patients will already be randomized into either an ISB with bupivacaine or with bupivacaine and LB. If the patient is not enrolled or does not fit inclusion criteria for the RCR or TSA study they will then be randomized to either bupivacaine or liposome bupivacaine ISB. The patients will perform spirometry (one large exhale into a spirometer) and have an ultrasound examination of their diaphragm at baseline prior to the block, in PACU after their procedure, and on postoperative day 1 (24 hours after ISB). Diaphragmatic movement will be evaluated by real-time M-mode ultrasonography of the hemidiaphragm using a 17-mm 1- to 5-MHz broadband phased array US probe. Patients are to be scanned in an upright sitting position and scanned from a low intercostal or subcostal approach using the liver or spleen as an acoustic window. M Mode will be applied and the range of diaphragmatic movement from the resting expiratory position to deep inspiration (sigh test) will be recorded as well as the range of diaphragmatic movement from resting expiratory position when quickly inspiring through the nose (sniff test). This will occur three times, at baseline prior to surgery, in the recovery room, and on the ward on postoperative day 1. All nerve blocks will be confirmed to be functional via a sensory skin test prior to surgery or in the recovery room prior to the recovery room evaluation.

6.2 Study Duration: The patients will be in the study for 2 days. The duration of the study should be 3 months to enroll the 22 patients.

6.3 Individually Identifiable Health Information: PHI will be recorded but once data collection is done then the phi will be removed and replaced with unique identifier. This is just to ensure we see the correct patient for the data collection.

6.4 Use of radiation*: n/a*

6.5 Use of Center for Magnetic Resonance Research*:* n/a

7.0 Data and Specimen Banking

7.1 Storage and Access: the data will be kept in the University box. Data is kept for 7 years.

7.2 Data: The data kept will be patient demographics such as weight, BMI, age, sex. Also, block medications and volume used, time of injection, surgical procedure, range of diaphragm movement at baseline, in recovery room, and on postoperative day 1 and spirometry at baseline, in recovery and postoperative day 1.

7.3 Release/Sharing: data will be kept with the PI and co-I

8.0 Sharing of Results with Participants

8.1 No results will be shared with participants.

9.0 Study Population

9.1 Inclusion Criteria: All patients age 18 years and older who are scheduled for shoulder surgery with interscalene block and remain in the hospital for more than 24 hours that are being randomized into a bupivacaine versus LB ISB block study or those who are not enrolled in the TSA or RCR study but are having shoulder surgery with ISB and planned to spend one night in the hospital.

9.2 Exclusion Criteria: Non-English speaking patients.

9.3 Screening: On the week to day prior to surgery patients will be identified from surgical case list. Then prior to or on day of surgery patients will be asked to participate in the study and given enough time to decide to participate and ask questions.

10.0 Vulnerable Populations

10.1 Vulnerable Populations:

☐Children

☐Pregnant women/Fetuses/Neonates

☐Prisoners

☐Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders

☐Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.

☐Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare

☐Serious health condition for which there are no satisfactory standard treatments

☐Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)

☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research

☐Undervalued or disenfranchised social group

☐Members of the military

☐Non-English speakers

☐Those unable to read (illiterate)

☐Employees of the researcher

☐Students of the researcher

x None of the above

10.2 Additional Safeguards:

11.0 Local Number of Participants

11.1 Local Number of Participants to be Consented: 40 patients consented with goal of 22 patients enrolled in the study

12.0 Local Recruitment Methods

12.1 Recruitment Process: No recruitment posters. Only recruit from surgical lists. Patients will be recruited from the group of adult surgical patients at the University of Minnesota undergoing shoulder surgery and receiving an interscalene block scheduled for overnight stay that elected to participate in another ISB bupivacaine versus LB shoulder study. Patients will be approached at the preoperative assessment clinic or surgeon's clinic at the Clinic and Surgery Center if possible by a research staff member to determine their interest in participation. If they decide to be a participant they will be consented and given a copy of their consent form for their records and a consent will be scanned and placed into EPIC. These patients will have significant time to review the study with research staff as well as the physicians performing the procedure due to the fact they arrive several hours prior to their scheduled surgery. All subjects will have enough time to ask questions about the study and the potential risks involved regardless of which venue they are consented.

12.2 Identification of Potential Participants: Patients will be identified by members of the treatment team in either the surgeon's clinic, pre-assessment clinic, or preoperative area. Patients who have opted out of research will not be asked to participate in the study. Patients will be approached to consent for the study by a surgeon, anesthesiologist, or member of the research team. Patients who agree to participate in the study will sign both a study

consent and HIPAA authorization allowing the use of specified information contained in medical records for research purposes.

12.3 Recruitment Materials: n/a

12.4 Payment: n/a

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances: Subjects who have consented prior to the day of surgery and for some reason choose not to participate will be withdrawn and a notation will be made in the study records and these people will be considered screen failures. The surgeon may choose to withdraw the patient from the study prior to surgery for any medical reason or if they suffer a major life threatening adverse event.

13.2 Withdrawal Procedures: If the patient is withdrawn from study prior to the procedure, they will be noted in study records as screen failures. If they undergo the procedure and they decide they no longer want to be a part of the study or withdrawn by the physician, they will be withdrawn and no further data will be collected. This will also be noted in the study documentation.

13.3 Termination Procedures: If the study is terminated for any reason, or there is more than 5 % major adverse events the data that is already collected will be stored in a secure location only accessible to research personnel on this study. No further data will be collected if the study is terminated. Risks to Participants

13.4 Foreseeable Risks: There is a risk of loss of privacy as well as inconvenience the patient as we will ultrasound them prior to and after surgery. Otherwise this is a minimal risk study

13.5 Reproduction Risks: n/a

13.6 Risks to Others: n/a

14.0 Potential Benefits to Participants

14.1 Potential Benefits: There are no potential benefits to the patient from this study.

15.0 Statistical Considerations

15.1 Data Analysis Plan: We will use the average of the three US exams for each timed measurement as the definitive measurement. We will also use FEV1, FVC (or FEV6) and FEV1/FVC (or FEV6) ratio for each time period as a secondary measurement. This data will be be given to the statistician who will compare those in the LB ISB group to the bupivacaine ISB group to evaluate for differences (if any) between the movement of the diaphragms in each group.

15.2 Power Analysis: We assumed a 5% rate of block at 24 hours in bupivacaine and a 66% block for liposome bupivacaine. With an alpha of 0.05 and power of 80% we determined we need 9 patients in each group. Assuming we would have 20% patients drop out, screen fail, or discharge early we planned to enroll 11 per group for total of 22 patients.

15.3 Statistical Analysis: This study will be analyzed by our staff biostatistician. The data will be de-identified and shared with him in box. The statistician will be provided the protocol so they are able to analyze for primary and secondary objectives.

15.4 Data Integrity: All patients will be assigned a unique patient identifier. The data that will be sent to the statistician will be de-identified.

16.0 Confidentiality

16.1 Data Security: All paper documents and consent forms will be stored in a locked cabinet in the anesthesia research office in B573 Mayo. All study data will be stored electronically in Box and only the PI and members of the research team will have access to the data.

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

17.1 Data Integrity Monitoring.

The PI, co-investigators, and research assistants will all have access to the study data stored in the University's Box storage system. All the research assistants have experience collecting pain scores and other relevant study information. The PI of the study will periodically review the study data to ensure accuracy and completeness of study data.

1.1 Data Safety Monitoring. The Department of Anesthesiology has established a Data and Safety Monitoring Committee consisting of several staff anesthesiologists which include persons who are board certified as pain specialists. Data will be transmitted in box to persons on the board on a monthly basis for review. If there are patterns of adverse events, the board will meet as needed and provide recommendations.

All safety data will be collected on a case report form and transferred into an excel spreadsheet that will be stored in box. Also, all phone call data will be collected on a case report form and transferred into excel in box.

All data will be collected by research assistants on a daily basis. Subjects are monitored at several intervals on day of surgery and daily .

The data will be reviewed on a regular basis (weekly) by the PI and research staff. If there are consistent complications noted a meeting will be convened by the DSMB for recommendations.

The statistical tests for analyzing the safety data to determine whether harm is occurring.

The statistician uses R or SAS for analysis. Most likely a regression analysis will be performed to see which event is most likely the contributor for the complications. Also a chi-square analysis can be performed. All is very dependent on data variability.

A fatal or serious adverse event that is attributable to either the delivery or the study medication itself.

Provisions to Protect the Privacy Interests of Participants

Protecting Privacy: Patients will be asked if this is a good time to have the ultrasound study. . All patients will have the right to refuse when contacted.

Access to Participants: All patients are required to sign a consent that states their privacy of the data being collected. In addition, they are required to sign a HIPAA consent that further describes the data being collected. It also describes that all data is de-identified and stored in a secure database. They will be informed that data is stored and reviewed in box which is HIPAA compliant and that only study personnel have access. Patients are part of the PI and co I job at the University.

18.0 Compensation for Research-Related Injury

Compensation for Research-Related Injury: In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to the patient and/or insurance company.

18.1 Contract Language: n/a

19.0 Consent Process

19.1 Consent Process (when consent will be obtained):

Patients will be identified in the pre-operative time period by the block anesthesiologist or research team and if possible will be consented by the research coordinator or research assistant. If patients have more questions and do not want to sign at their clinic will be asked if it is allowable for a study staff member to contact them prior to surgery via phone to clarify if they have any questions. On the day of surgery, if the patient has not already signed consent and is still interested in participating in the study will be presented with consent and Health and Insurance Portability and Accountability Act (HIPAA) forms. The patient will review the forms with the research staff, or anesthesiologist. Subjects will be reminded that participation is completely voluntary, and that they may stop participation at any time without question or penalty. The research staff or anesthesiologist will answer any questions that the subjects may have

about the study. If the patient decides to participate, they will be asked to sign the consent and HIPAA forms. One copy will be saved for study records, and the subject will be provided with a copy of the forms for their own records. Waiver or Alteration of Consent Process (when consent will not be obtained):

Non-English Speaking Participants: n/a.

19.2 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

- n/a

19.3 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

- n/a

19.4 Adults Unable to Consent:

- Permission: n/a
- Assent: n/a
- Dissent: n/a

20.0 Setting

1.2 Research Sites: Patients will be consented in the surgeon's clinic or pre assessment clinic. The surgical procedures will take place at the Fairview riverside campus.

20.1 International Research: n/a

21.0 Multi-Site Research

- n/a

22.0 Resources Available

23.0 **Resources Available:** Research assistants are available to aid in consent and data acquisition. All research assistants will be familiar with the study protocol and have experience working with similar studies.

We plan to enroll 22 subjects. The plan is to screen 40 subjects to research this target population. This center performs approximately 500 shoulder procedures annually.

We plan to conduct this study over 3 months. Enrollment and data collection will be completed at this time. Statistical Analysis will take approximately two months to complete.

All procedures will be performed in the clinical facilities at the MHealth Clinics and Surgery Center and at the West and East Bank. Data storage and analysis will be done using desktop equipment which is available at the Research Office B573 Mayo.

23.1 References

Renes et al. Ultrasound guided low dose interscalene brachial plexus block reduces the incidence of hemidiaphragmatic paresis. Reg Anesth Pain Med. 2009;34:498-502

Urmey WF, talts Kh, Sharrock Ne: one hundred percent incidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. Anesth Analg 1991; 72:498–3