TITLE: Vital Capacity in Ultrasound Guided Serratus Anterior Plane Block in Emergency Department Patients with Multiple Rib Fractures: A randomized controlled trial

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BACKGROUND

Patients with multiple rib fractures are challenging from both pulmonary and analgesia perspectives. Adequate pain management is essential in prevention of complications secondary to decreased inspiratory volume. Significant morbidity and mortality of rib fractures is secondary to severe pain that limits ribcage movement, decreases inspiratory volumes and causes inadequate cough. Decreased vital capacity predisposes patients to atelectasis, abnormal mucous clearance and pneumonia. The objective of this study is to assess the efficacy of the serratus anterior plane block (SAPB) in improvement of vital capacity in patients with multiple unilateral rib fractures when compared to conventional management with medications. Currently, evidence of efficacy of SAPB in managing pain secondary to multiple rib fractures is limited to case reports and series, none of which evaluate vital capacity.

SIGNIFICANCE

The findings of this study may indicate that SAPB is superior to pharmacological management in increasing vital capacity in patients with multiple unilateral rib fractures and suggest SAPB for first line therapy in patients with rib fractures. The findings may decrease the risk of pulmonary complications as well as the use of opiates in management of multiple rib fractures in the Emergency Department especially in patients with numerous comorbidities and contraindications to conventional treatment modalities. This study may support the need for training emergency medicine physicians in bedside SAPB in order to provide the optimal therapy for patient with multiple unilateral rib fractures.

STUDY OBJECTIVES

Our primary objectives are to evaluate whether ultrasound guided SAPB results in a greater improvement in percent predicted vital capacity compared to standard therapy with a sham injection. We will also evaluate pain scores and the safety profile of the SAPB procedure compared to those receiving standard analgesia.

HYPOTHESIS

Our primary hypothesis is that SAPB is superior to sham injection in improving the percent of predicted vital capacity. Our secondary hypothesis is that SAPB will have greater improvement in pain scores and have a superior safety profile compared to sham injection.

STUDY DESIGN

This is a single center prospective, randomized, blinded clinical trial with a convenience sample that will be conducted in the Emergency Department of an urban level I trauma center.

1. Identify and enroll all patients coming in to the ED patient with presumed or clinically apparent 2 or more unilateral rib fractures between T3 to T9, with a resting pain score of ≥5. All patients meeting exclusion criteria will be excluded.
2. Randomization procedure:
    1. Pharmacy will dispense 30mL of injectate which will be randomized in block of 10 to either the SAPB group (30mL of 0.25% bupivacaine with epinephrine) or sham group (30mL of normal saline).
3. Injection
    1. Patient consent will be obtained and time out will be performed on all patients.
    2. Patients will be placed on cardiac monitor and placed in lateral decubitus or if unable to turn, they will be supine.
    3. Under the usual sterile technique, the serratus anterior muscle overlying the 5^{th} rib at the mid-axillary line will be identified with ultrasound.
    4. A spinal needle will be introduced in-plane under ultrasound guidance and advanced until the needle tip is located in the fascial plane just above the serratus anterior muscle. The needle tip will not be advanced unless completely visualized under ultrasound.
    5. Normal saline will be injected first to determine correct location of the needle tip. Spreading of fluid along the fascial plane will confirm the correct location of the needle tip.
    6. The normal saline will then be switched to the study drug of which 30mL of either normal saline or 0.25% bupivacaine with epinephrine which will then be injected into the fascial plane as described in Blanco et al, and Hetta et al.
    7. The study drug will be injected 5mL at a time and the patient will be asked if any symptoms of Local Anesthetic Systemic Toxicity (LAST toxicity) are present (perioral numbness, tinnitus, dizziness).
    8. After injection is completed the needle will be withdrawn and patient will remain on the cardiac monitor for another 30 minutes to monitor for symptoms of LAST toxicity (Di Gregorio).
    9. This procedure was based on the serratus anterior plane block protocol from Khalil et al.
4. Slow Vital Capacity (SVC) Measurement
    1. SVC will be performed using spirometer that has been internally validated
    2. SVC will be performed by physicians trained by the respiratory therapy department and who have demonstrated validation compared to respiratory therapist obtained SVC values
    3. The patient will be sitting up when performing SVC and a script will be followed as to how to educate and coach the patient on performing appropriate incentive spirometry technique.
    4. At least 3 SVC measurements within 150mL of eachother are required to qualify for an accurate measurement.

5. The maximum of these 3 SVC values and a corresponding % predicted SVC will be obtained and considered the maximum % predicted SVC.
6. % Predicted SVC will be obtained based on the National Health and Nutrition Examination Survey (NHANES III) calculator through the CDC.

5. Pain scores
    1. Subjects will be asked to rate their maximum pain score from 0-10 with resting breathing and with deep breaths.

Subjects:

Subjects include English speaking patients 18 years of age or older with presumed or clinically apparent two or more rib fractures from T3-T9 and a pain score of ≥5/10 or above will be consented and randomized into one of two study arms: Nerve block vs. Sham injection. Patients must be able to demonstrate understanding of the informed consent, and also be able to verbalize how much pain they are having on a 10 point Numeric Rating Pain Scale.

Eligibility Criteria:

1. Inclusion Criteria:
    1. 18 years or older
    2. 2 or more acute unilateral rib fractures on radiographic imaging
    3. Pain Score ≥5
2. Exclusion Criteria:
    1. GCS<13
    2. Penetrating trauma
    3. Pregnant
    4. Unable to give consent due to dementia or altered mental status
    5. Unable to perform spirometry
    6. Requiring immediate surgical intervention
    7. Known allergy to amide-type local anesthetics
    8. Known allergy to acetaminophen
    9. Known allergy to morphine sulfate
    10. Signs of infection or laceration at injection site
    11. Systolic BP <100 mmHg
    12. History of chronic pain, chronic use of analgesics
    13. History of substance abuse
    14. Painful distracting injury (injury causing significant pain that distracts the patient from having reliable scoring of rib fracture pain, i.e. femur fracture, dislocated joint)
    15. If patient received any other pain medication besides ketamine prior to the block

Design:

1. Potential study patients will be identified through review of the emergency department (ED) electronic board, and ED physicians will also screen for potential study patients. Pain scores are assessed in triage as is standard in the ED.
2. If the patient has pain from presumed or clinically apparent 2 or more unilateral rib fractures between T3 to T9, and he/she has a resting pain score of ≥5 on the Numeric Pain Rating Scale, where 0 is no pain, 5 is moderate pain, and 10 is the worst possible pain upon initial assessment, then he/she will be eligible to participate in the study.
   The patient will then be asked to participate if he/she does not have any exclusion criteria.

3. At time of enrollment, the patient will have recorded pain scores, vital signs, and slow vital capacity measured.
4. All patients will then receive as their initial analgesic oral acetaminophen 975 mg followed by morphine sulfate 0.05 mg/kg IV rounded to the nearest milligram.
5. Each patient will then be randomized in either of two arms:
    1. Ultrasound guided serratus anterior plane block (SAPB) with 30mL 0.25% bupivacaine with epinephrine.
    2. Ultrasound guided serratus anterior plane injection with placebo injection with 30mL of normal saline.
6. Investigators will be blinded to the arm that the patient has been randomized to, as the randomization will occur through the pharmacy dispensing the medication.
7. Using an online randomizer in blocks of 10, the pharmacy will dispense either 30mL of normal saline for the sham group, or 30mL of 0.25% bupivacaine with epinephrine for the nerve block group.
8. All patients will receive either SAPB or placebo injection within an hour of receiving the initial analgesics of acetaminophen and morphine.
9. If the patient still has a pain score ≥5 thirty minutes after the injection, the treating physician will be informed and the patient will be medicated at the treating physician's discretion.
10. The patient will be followed up with up to 24 hours throughout their hospital stay.

Data Collection Procedures:

1. Demographics
    1. Age, sex, ethnicity, height
2. Past medical history
    1. Smoking status (current, prior, never smoker), diabetes, cirrhosis, chronic obstructive pulmonary disease (COPD), asthma, if patient uses home oxygen
3. Injury Mechanism
    1. Occupant in motor vehicle collision, fall from an elevation, fall down stairs, fall from standing, pedestrian or bicyclist struck by moving vehicle, bike collision or fall from bike while riding, driver or passenger in motorcycle/ATV/motorized scooter collision, assault, unknown mechanism, or other
    2. Date and time of injury

3. GCS score
4. Injury Severity Scale

4. Imaging
    1. Side of rib fractures
    2. Number of rib fractures on x-ray and on CT chest
    3. Rib fracture location: anterior, lateral, posterior, T1-12
    4. Type of imaging showing rib fractures
    5. Presence of following: atelectasis, hemothorax, infiltrate (right/left), interstitial edema, pneumothorax, pulmonary contusion
5. Medication
    1. Any medications type and dose given prior to randomization
6. At Time 0 (time of enrollment):
    1. Vital signs
    2. Resting pain score from 0-10
    3. Deep breath pain score from 0-10
    4. Slow Vital Capacity (SVC)
        1. Measured until 3 measurements are within 150mL of eachother
        2. % predicted SVC is measured based on NHANES III Calculator using age, sex, ethnicity and height. If ethnicity not included in calculator will select Caucasian.
        3. Maximum SVC and maximum % predicted SVC
    5. Symptoms after injection: sedation, dizziness, dysarthria, nausea, new cardiac rhythm (significant tachycardia or bradycardia, SVT, etc), new significantly increased shortness of breath, perioral numbness, pruritis, seizure, syncope, tinnitus, vomiting
7. At Time 30 minutes post injection
    1. Vital signs
    2. Resting pain score from 0-10
    3. Deep breath pain score from 0-10
    4. Slow Vital Capacity (SVC)
        1. Measured until 3 measurements are within 150mL of eachother
        2. % predicted SVC is measured based on NHANES III Calculator using age, sex, ethnicity and height. If ethnicity not included in calculator will select Caucasian.
        3. Maximum SVC and maximum % predicted SVC
    5. Symptoms after injection: sedation, dizziness, dysarthria, nausea, new cardiac rhythm (significant tachycardia or bradycardia, SVT, etc), new significantly increased shortness of breath, perioral numbness, pruritis, seizure, syncope, tinnitus, vomiting
8. At Time 60 minutes post injection
    1. Vital signs
    2. Resting pain score from 0-10
    3. Deep breath pain score from 0-10
    4. Slow Vital Capacity (SVC)
        1. Measured until 3 measurements are within 150mL of eachother

2. % predicted SVC is measured based on NHANES III Calculator using age, sex, ethnicity and height. If ethnicity not included in calculator will select Caucasian.
3. Maximum SVC and maximum % predicted SVC

5. Symptoms after injection: sedation, dizziness, dysarthria, nausea, new cardiac rhythm (significant tachycardia or bradycardia, SVT, etc), new significantly increased shortness of breath, perioral numbness, pruritis, seizure, syncope, tinnitus, vomiting

9. At Time 3-6 hours post injection
    1. Vital signs
    2. Resting pain score from 0-10
    3. Deep breath pain score from 0-10
    4. Slow Vital Capacity (SVC)
        1. Measured until 3 measurements are within 150mL of eachother
        2. % predicted SVC is measured based on NHANES III Calculator using age, sex, ethnicity and height. If ethnicity not included in calculator will select Caucasian.
        3. Maximum SVC and maximum % predicted SVC
    5. Symptoms after injection: sedation, dizziness, dysarthria, nausea, new cardiac rhythm (significant tachycardia or bradycardia, SVT, etc), new significantly increased shortness of breath, perioral numbness, pruritis, seizure, syncope, tinnitus, vomiting
10. At Time 12 hours post injection
    1. Vital signs
    2. Resting pain score from 0-10
    3. Deep breath pain score from 0-10
    4. Slow Vital Capacity (SVC)
        1. Measured until 3 measurements are within 150mL of eachother
        2. % predicted SVC is measured based on NHANES III Calculator using age, sex, ethnicity and height. If ethnicity not included in calculator will select Caucasian.
        3. Maximum SVC and maximum % predicted SVC
    5. Symptoms after injection: sedation, dizziness, dysarthria, nausea, new cardiac rhythm (significant tachycardia or bradycardia, SVT, etc), new significantly increased shortness of breath, perioral numbness, pruritis, seizure, syncope, tinnitus, vomiting
11. On 24 hours post injection
    1. Vital signs
    2. Resting pain score from 0-10
    3. Deep breath pain score from 0-10
    4. Slow Vital Capacity (SVC)
        1. Measured until 3 measurements are within 150mL of eachother
        2. % predicted SVC is measured based on NHANES III Calculator using age, sex, ethnicity and height. If ethnicity not included in calculator will select Caucasian.
        3. Maximum SVC and maximum % predicted SVC

5. Symptoms after injection: sedation, dizziness, dysarthria, nausea, new cardiac rhythm (significant tachycardia or bradycardia, SVT, etc), new significantly increased shortness of breath, perioral numbness, pruritis, seizure, syncope, tinnitus, vomiting

12. Slow vital capacity
    1. Researchers will be trained on appropriate incentive spirometry technique by the respiratory therapy team and their accuracy will be confirmed
    2. Patients will then be instructed to perform SVC, we will get 3 SVC measurements within 150mL of eachother and then record the maximum SVC.
    3. Percent predicted vital capacity will be calculating using NHANES III
13. Time to first rescue analgesia post injection
14. Medications during first 24 hours of hospital stay
    1. 24 hour total morphine milligram equivalent consumption
        1. Calculated based on CDC Morphine Milligram Equivalence (MME) Calculator: https://www.cdc.gov/drugoverdose/prescribing/app.html
    2. Any antimetics used after injection within 24 hours after enrollment
    3. Time to administration of first rescue analgesia post injection
15. Nerve Block performed during inpatient stay
    1. List date/time/type of any additional nerve blocks performed for rib fracture pain after the study injection during the patient's hospital stay
16. Pulmonary complications:
    1. New O2 requirement, BIPAP or intubation, transfer to ICU for respiratory issue, development of pneumonia, readmission for pulmonary issue, new need for home O2
17. Nerve Block Complications
    1. Development of cellulitis at site of block during hospital stay
    2. Pneumothorax occurring within 12 hours of injection
18. Discharge Data
    1. If cellulitis developed at the site of injection during hospital stay
    2. If a pneumothorax on the same side of the injection occurred within 12 hours of block

19. Imaging
    1. Videos of the nerve block performance will be recorded in each patient. These images will later be de-identified and reviewed by two independent reviewers not involved in the study to determine visually whether the planar spread of anesthetic was correctly placed or not correctly placed.

Data Analysis:

For the primary endpoint of increase in vital capacity at 3-6 hours and secondary outcome of change in pain score, we will be using t-tests to compare groups. Differences in complication and

side effect rates will be summarized and compared using a chi-square test or fisher exact test if applicable.

Sample Size:

III. Sample Size: 90 total (45 for each group)

1. Based on Mackersie et al, patients with epidural analgesia had a 5.1cc/kg ±6.5 increase in vital capacity before and after analgesia. Using 5.1cc/kg, we entered this value into the NHANES III calculator for a 60 kg person, with an average height of 177cm, ethnicity as caucasian, and an average age of 60. This gave us a value of 300mL or a 0.3L change in vital capacity after the nerve block which translated into a % predicted value of 6.4%. We therefore assumed that the nerve block would improve the % predicted value of vital capacity by around 6 percentage points.
2. Based on data obtained by Carver et al, the mean baseline % predicted vital capacity for 30 people in the emergency department was around 34 with SD=8. We assumed a greater variability of 10 for SD. These patients did not receive nerve blocks within the first 24 hours, had unilateral rib fractures, with GCS>13 and the ability to perform vital capacity measurements. We thus considered this group similar to our sham group receiving standard therapy. At 3 and 6 hour follow-up for this group, there was no change in the vital capacity with a range of 1-2 percentage point variation between the two values. Since within subject variations of 2.3-3.6% have been reported in the literature, we viewed the 1-2% variations as not significant (Kunzli).
3. If we expect no change in the standard group, based on measurements between 3 and 6 hours follow-up, and we expect to see a positive effect size of 6 points in the nerve block group, with 80% power and alpha of 0.05, we would need 45 people per group.

Expected Outcomes:

1. We expect that patients undergoing ultrasound guided SAPB will have a more significant improvement in percent predicted vital capacity, in pain control, and in side effect profile. We also expect that patients receiving SAPB will have significantly lower usage of opiates to treat their pain and will not have any increased rates of pulmonary complications.

Adverse Events:

Serious:	Arrhythmia, cardiac arrest/collapse, possible nerve damage, seizure, syncope
Common Side Effects:	dizziness, nausea, vomiting, weakness or fatigue, sedation, altered mental state, decrease in heart rate and blood pressure, local anesthetic systemic

	toxicity, vision change, tinnitus, shortness of breath, pruritus, numbness/tingling around the mouth or eyes (perioral & periorbital numbness), metallic taste in the mouth

SAE Reporting: Any serious adverse event, requiring intervention, will be reported to the IRB within 24 hours of discovery by the research staff. Less serious adverse events will be reported within a week of discovery.

Data Safety Monitoring Board (DSMB):

The DSMB consisting of study investigators and at least one member who is not an investigator on the study. The DSMB will meet after patient 25 is enrolled in the study. The DSMB will review the data and any adverse events and submit a report to the IRB.

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