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Dose-Response Relationships for Hemidiaphragmatic Paresis Following Ultrasound-Guided Supraclavicular Brachial Plexus Blockade

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1.0 STUDY PROTOCOL

1.1 Background and Significance

1.1.1 Supraclavicular brachial plexus block

The brachial plexus is formed by the lower four cervical nerve roots and first thoracic nerve root (C5-C8, T1). Local anesthetic can be deposited anywhere along the course of the brachial plexus, from the neck to the axilla, depending on the desired block distribution for surgical anesthesia. Performed at the level of the brachial plexus trunks/divisions, which are located just superior to the first rib and posterior to the subclavian artery, supraclavicular blocks can provide dense surgical anesthesia for procedures below the level of the shoulder and is often called the "spinal of the arm."

The phrenic nerve, which is comprised of the anterior branches of the C3-C5 nerve roots and innervates the diaphragm, typically lies on the anterior surface of the anterior scalene muscle underneath the sternocleidomastoid muscle and enters the thorax behind the subclavian vein. Due to its close proximity to the brachial plexus, the phrenic nerve is often inadvertently blocked during supraclavicular blocks, resulting in ipsilateral hemidiaphragmatic paresis (HDP). Although this is usually well tolerated in most individuals, complications (such as insufficient ventilation) may arise in those with pre-existing pulmonary impairments.

With traditional landmark-based or nerve-stimulator techniques, the incidence of HDP following supraclavicular blocks has been reported to be 50-67%.[1] Ultrasound-guided techniques are thought to facilitate more precise deposition of local anesthetic and enable operators to use less volume to achieve a successful block. However, even with the utilization of ultrasound visualization, the incidence of HDP has been reported to be up to 60% after supraclavicular block.[1,2] Furthermore, there is no established consensus regarding what volume of local should be used to achieve a successful supraclavicular block while also minimizing HDP. Kant *et al.* estimated an ED_{95} of 27 cc of 0.5% bupivacaine for achieving a successful supraclavicular block but did not determine the level of corresponding HDP.[3] In practice, volumes of local anesthetic used for supraclavicular blocks range from 20-40cc. Proponents of using larger volumes often argue that it achieves faster onset with lower incidences of block failure. There have been no studies to date, however, determining the dose-response relationship between local anesthetic volume and the degree of HDP.

All doses used in this study are ones routinely used in our clinical practice. Lower volumes do lead to a higher likelihood of inadequate surgical anesthesia, however, which is why we have provided a mechanism with which to supplement the block if necessary.

1.1.2 Phrenic Nerve Palsy (PNP) and HDP

The left and right phrenic nerves are derived from cervical nerve roots C3-C5 to innervate the corresponding sides of the diaphragm. Phrenic nerve palsy results in hemidiaphragmatic paresis (partial loss of excursion) or paralysis. In patients without pre-existing respiratory issues who experience PNP and HDP following a supraclavicular block, the contralateral hemidiaphragm and accessory muscles of respiration are able to compensate to generate adequate negative pleural pressure necessary for inspiration. Therefore, patients are usually asymptomatic at rest but may experience dyspnea with exertion. Patients with underlying lung diseases (i.e. pneumonia, chronic obstructive pulmonary disease) or respiratory dysfunction (i.e. patients with neuromuscular disease, PNP of the contralateral side) already rely heavily on the accessory respiratory muscles for ventilation and may be susceptible to insufficient ventilation following a supraclavicular block. These patients may have dyspnea at rest and show signs of ventilatory failure (i.e. hypercapnia, hypoxemia) with HDP.

1.1.3 Diaphragmatic Motion Assessed by Ultrasonography

Motion-mode (M-mode) ultrasonography has been shown to be a reliable modality for detecting anatomical or functional diaphragmatic abnormalities by measuring diaphragmatic excursions.[4] Motion of the right hemidiaphragm is more reliably imaged than the left due to the smaller acoustic window of the spleen compared to the liver.

1.1.4 Respiratory Volumes Assessed by Spirometry

Vital capacity (VC) measured in the supine position has been shown to fall by as much as 55% in patients with diaphragm paralysis.[5] Measuring changes in VC can quantify the change in lung function resulting from unilateral diaphragmatic paresis or paralysis.

1.2 Rationale and Hypothesis

The rationale of this study is to investigate the dose-response relationship between local anesthetic volume and ipsilateral HDP in patients undergoing ultrasound-guided supraclavicular brachial plexus blocks for surgeries of the right upper extremity in an observer-blinded, prospective trial. In this study, we hypothesize that higher volumes of local anesthetic will be associated with an increased incidence of HDP. By identifying this dose response relationship, this study aims to help practitioners safely administer supraclavicular blocks, particularly in high-risk patients with underlying lung disease or respiratory dysfunction.

1.3.1 Primary Objective

To define the dose-response relationship between local anesthetic volume and ipsilateral HDP in patients undergoing ultrasound-guided supraclavicular brachial plexus blocks.

1.4 Patient Selection

30 eligible patients undergoing right upper extremity surgery and eligible for supraclavicular blocks will be recruited from the inpatient units and surgery clinics of NewYork-Presbyterian/Weill Cornell Medical Center.

1.4.1 Inclusion criteria

Each subject must meet all of the following criteria:

i. Undergoing right upper extremity surgery with supraclavicular block as the primary anesthetic
ii. Age ≥ 18 years of age
iii. American Society of Anesthesiologists (ASA) physical status 1 to 3
iv. Able to give informed consent

1.4.2 Exclusion Criteria

Subjects will not be enrolled if any of the following criteria exist:

i. Patient refusal for supraclavicular block
ii. Inability to give informed consent
iii. Allergy to local anesthetics
iv. Hemidiaphragmatic dysfunction, suspected or known PNP
v. Neuromuscular disease
vi. Obstructive or restrictive pulmonary disease
vii. Medical or anatomic contraindication to supraclavicular blockade as judged by clinician
viii. Pregnancy

1.5 Study Design

1.5.1 Preoperative Evaluation and Consent

Patients admitted to the hospital on the day of surgery will be consented for this study in advance by phone or in-person during a pre-anesthesia clinic visit. Those already admitted to the hospital as inpatients will be evaluated and consented during a preoperative workup prior to the patient being transported to the operating room.

1.5.2 Supraclavicular Blockade

All supraclavicular blocks will be performed in a dedicated regional block area or operating room suite. Prior to placement of the block, intravenous access will be established and standard ASA monitors placed. Baseline M-mode recordings of diaphragm function will be made by a skilled anesthesiologist.

At the discretion of the attending anesthesiologist, up to 0.03 mg/kg of midazolam may be given for sedation prior to the block. In cases of extreme patient anxiety unresponsive to 0.03 mg/kg of midazolam, additional midazolam may be administered up to a total dose of 0.05 mg/kg. The patient will be positioned supine with the head turned to the contralateral side, and the injection site will be disinfected with a 2% chlorhexidine and alcohol solution. The ultrasound will be placed in the supraclavicular fossa to obtain a transverse cross-sectional view of the brachial plexus and subclavian artery. The skin and subcutaneous tissues will be infiltrated lateral to the probe with 2% lidocaine. Using an in-plane technique, a 22-gauge block needle will be inserted through the skin lateral to the probe and directed medially toward the "corner pocket" at the junction of the first rib and subclavian artery.[6] Local anesthetic will be injected initially at this location. The anesthesiologist will be at liberty to redirect the needle and perform additional injections for complete coverage of the brachial plexus. The local anesthetic will be a 2:1 mix of 1.5% mepivacaine and 0.5% bupivacaine, and the volume administered will be determined per the continual reassessment method (CRM) protocol described below. Per clinical routine, all injections will be made in 5cc increments using frequent aspiration, to test for inadvertent intravascular needle placement as well as ascertaining the absence of high resistance indicative of a possible intraneural injection.

1.5.3 Intercostobrachial Nerve Blockade

Following performance of the supraclavicular block, an additional block of the ipsilateral intercostobrachial nerve will also be completed. Brachial plexus blocks do not anesthetize the intercostobrachial nerve, a branch of T2 that is responsible for sensation of the skin of the proximal medial arm.

With the patient remaining supine and with the arm abducted and externally rotated, a 1.5-inch, 25-gauge needle will be inserted at the deltoid prominence and a subcutaneous field block will be performed in a linear fashion inferiorly to the most inferior aspect of the medial arm using 10 cc of 0.5% bupivacaine. Given that this is a subcutaneous field block that does not contribute to PNP and HDP, all patients will receive the same amount of local to ensure adequate anesthesia.

1.5.4 Evaluation of HDP

M-mode tracings of right diaphragm motion will be made and recorded by a skilled anesthesiologist. Patients will be examined in the supine position and scanned from a low intercostal or subcostal approach using the liver as an acoustic window. Patients will be asked to perform a “voluntary sniff” (VS) test, for which they will be asked to forcefully inhale through the nose in a sniffing position. The above measurement will be performed immediately preceding the brachial plexus blockade, and then at 15 minute and 30 minutes after block.

The M-mode recordings will be reviewed by two blinded anesthesiologists. Diaphragmatic excursion from baseline will be measured in centimeters. Three measurements will be made, and the average will be taken. Significant hemidiaphragmatic paresis will be defined as greater than 75% reduction in diaphragmatic excursion, no movement, or paradoxical movement in the VS test. Partial paresis will be defined as a 25-75% reduction in diaphragmatic excursion. If the two reviewers come to different conclusions regarding the diagnosis of significant paresis, partial paresis, or no paresis, a third blinded anesthesiologist will review the images and serve as a “tie-breaker”.

1.5.5 Evaluation of Pulmonary Function

A bedside spirometer will be used to record Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1), and Peak Expiratory Flow (PEF) prior to the block and 30 minutes after the block.

1.5.6 Evaluation of Supraclavicular Block

At 15 and 30 minutes, we will assess sensory blockade in the axillary (lateral upper arm), musculocutaneous (lateral forearm), radial (dorsal hand), median (thenar eminenece), and ulnar (hypothenar eminence) distributions with the use of ice and a 3 point scale (0 = normal sensation of cold, 1 = perception of touch/pressure but not cold, 2 = no perception of touch/pressure, or cold).[2] Motor function will be evaluated at 15 and 30 minutes in the distribution of the axillary nerve (abduction at shoulder), musculocutaneous nerve (flexion at the elbow), radial nerve (extension at the elbow), median nerve (flexion at the wrist and opposition of the second finger and thumb), and ulnar nerve (opposition of the fifth finger and thumb). Motor block in each distribution will be graded on a 3 point scale (0 = normal strength, 1 = weakness, or 2 = no movement).[7] Failure to achieve loss of cold sensation or motor weakness at any of these dermatomes after 30 minutes will constitute an ineffective block, and the patient will receive a supplementary anesthetic block after the final M-mode ultrasound lung exam. The supplemental local anesthetic volume administered will be at the discretion of the attending anesthesiologist. During placement of the nerve block, a "catheter over needle" system will be used to place a catheter. This catheter will be dosed with additional local anesthetic if supplemental nerve blockade is needed to provide

satisfactory anesthesia. No additional procedure will be required. The patient will proceed to surgery following successful sensory blockade of the above dermatomes.

We will apply a 0-10 point verbal rating scale to assess dyspnea at 30 minutes (0 = no difference from baseline, 10 = extreme difficulty breathing). Oxygen saturation will also be measured off of supplemental oxygen 30 minutes after the block. Following the final assessment, patients will undergo surgery using the brachial plexus blockade as the primary anesthetic, with optional light sedation at the discretion of the anesthesiologist. Any instance requiring unscheduled conversion to general anesthesia intraoperatively or the need for supplementary rescue block or local infiltration by the surgeon will be recorded. Also, if the patient is brought to the operating room at any time before the 30-minute mark, the 30-minute assessments above will be performed just before the transfer.

1.5.7 Continual Reassessment Method (CRM)

The Continual Reassessment Method (CRM), developed by O'Quigley et al.[8] is a study design for dose-finding/Phase I studies. It is different from traditional dose-escalation studies in that it "learns" from information gained at earlier time points in order to limit patient exposure to non-efficacious and potentially toxic doses. The general idea behind the CRM is that an a-priori dose-response curve (DRC) is assumed and a desired effect rate chosen. The estimated DRC is updated after each subject's outcome is observed, so that the next patient's dose is based on the information about how the previous patient tolerated the intervention. As the number of subjects accumulates, the DRC becomes based on observed data instead of the a-priori assumptions. [9]

In this study we are attempting to define the dose-response curve for the degree of HDP caused by various doses of local anesthetic administered in a supraclavicular block. Based upon clinical experience and data found in the literature, we have developed the following a-priori probabilities for significant HDP after various doses of local anesthetic:

Dose Level	Volume of Local Anesthetic (mL)	Probability of HDP
1	5	0.05
2	10	0.1
3	15	0.15
4	20	0.2
5	25	0.3
6	30	0.5
7	35	0.6
8	40	0.8

CRM trials typically employ dose cohort sizes of 1,2 or 3 subjects per dose. We will use 3 subjects per cohort. The trial will begin with 3 subjects treated at a dose of 35 mL, which is a volume routinely used in clinical practice. The DRC will be re-estimated based on the HDP outcomes of the treated subjects. If, any of the patients experience significant HDP, the subsequent cohort will receive the next lowest dose of 30 mL. If none of the patients experience HDP, the subsequent cohort will instead receive the next highest dose of 40 mL. This will continue until a minimum sample of 30 subjects are enrolled, provided that the DRC has changed less than 10% after the final cohort. If the DRC changes by more than 10% after 30 subjects, additional subjects will be enrolled until the change is less than 10%.

We anticipate that some of the lower volumes used may not provide surgical anesthesia. We will overcome this by testing the subjects' blocks after US scan for diaphragm function, and if insufficient for anesthesia, we will supplement the blocks to insure complete coverage for the surgical procedure.

1.6 Statistical Analysis

Participant characteristics, such as age, sex, American Society of Anesthesiologists (ASA) score, and type of surgery will be characterized by means (standard deviations) or medians (interquartile ranges), as appropriate.

The dose-response curve of the local anesthetic on HDP, as well as sequential dose allocation, will be calculated using Stata 13 IC's CRM command (StataCorp, College Station, TX) and the BMA-CRM Simulator (MD Anderson Cancer Center, Houston, TX).

2.0 MANAGEMENT OF INTERCURRENT EVENTS

2.1 Potential Risks

2.1.1 Potential Risks of Supraclavicular Blocks

Ultrasound-guided supraclavicular blocks are widely used and safe. In addition to ipsilateral phrenic nerve palsy, potential procedure-related side effects include ipsilateral oculosympathetic palsy (Horner's syndrome) (incidence 1%) and recurrent laryngeal nerve palsy (1%), both of which are self-limited. Rare procedure-related complications include subclavian artery puncture (0.4%), and pneumothorax (<0.1%).[9] Nerve palsies are usually self-limited, and the risk of permanent neurological damage is rare (<0.01%).[9]

Supraclavicular brachial plexus blockade is the anesthetic standard of care for isolated upper extremity surgeries at our institution. Therefore, eligible subjects will incur no additional risks from participating in this study.

2.1.2 Other Potential Risks

No psychological risks to subjects are expected. In order to prevent loss of confidentiality, investigators will keep subjects' participation confidential to the extent permitted by law.

2.2 Procedure to Minimize Potential Risks

Subjects will be admitted for post-operative care to NewYork-Presbyterian Hospital. A physician from the primary surgical service and trained nursing personnel will provide continuous care for the subject during the hospital admission.

All clinicians performing supraclavicular blocks and measuring diaphragmatic excursion are board-certified anesthesiologists trained and experienced in administering regional anesthesia. The procedure will be performed using aseptic technique to minimize any potential for infection. Ultrasound guidance will be used for block placement to minimize the risk of subclavian artery and lung puncture.

Inclusion and exclusion criteria, fasting requirements, monitoring, and the clinical protocol are designed to ensure that risks are absolutely minimal. Subjects are informed that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty. Subjects will be told that in the event of a physical injury as the direct result of study procedures, they will be cared for by a member of the investigating team at no cost, within the limits of the NewYork-Presbyterian Hospital compensation plan.

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