PAIN-RELIEF ALTERNATIVE FOR SHOULDER SURGERY

(PASS TRIAL)

The Novel Anterior Suprascapular Nerve Block vs. Conventional Interscalene Brachial Plexus Block for Pain-Relief Following Arthroscopic Shoulder Surgery: A Multi-centre Randomized, Patient and Assessor Blinded, Non-inferiority Trial

by

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Abstract

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Introduction

Interscalene nerve block (ISB) is the pain relief standard for shoulder surgery. But ISB is invasive and associated with complications. Suprascapular nerve block (SSNB) may be an alternative; but evidence of comparative efficacy is sparse. We examine whether SSNB is non-inferior to ISB for pain after shoulder surgery.

Methods

140 shoulder surgery patients were enrolled into this multi-centre non-inferiority trial. Patients were randomized to ISB or SSNB. Pain at 6 hours (Numerical Rating Scale, NRS) was designated as primary outcome. A difference of -1.3 units was set as non-inferiority margin.

Results

The mean difference (90% confidence interval) in pain for the (ISB-SSNB) comparison was -0.40 (-1.10, 0.30), less than the non-inferiority margin (P=0.016), suggesting non-inferiority of SSNB for pain at six hours.

Conclusion

SSNB is an effective alternative to ISB for pain after shoulder surgery. SSNB can be considered for patients at high risk for complications with ISB.

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List of Abbreviations

AHRC: Applied Health Research Center

ASA: American Society of Anesthesiologists

ASRA: American Society of Regional Anesthesia and Pain Medicine

AUC: area under the curve

CI: confidence interval

CRF: case report form

DSMB: data safety monitoring board

ISB: interscalene block

LMA: laryngeal mask airway

MCID: minimal clinically important difference

NRS: numerical rating scale

NYGH: North York General Hospital

PAC: pre-admission clinic

PACU: post-anesthesia care unit

QoR: quality of recovery

REB: research ethics board

SD: standard deviation

SLAP: superior labrum anterior posterior repair

SSNB: suprascapular nerve block

TWH: Toronto Western Hospital

US: ultrasound

WCH: Women's College Hospital

Δ: non-inferiority margin-

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Chapter 1: Introduction and Background

1.1 Pain relief following shoulder surgery using interscalene block

Up to 70%[1] of patients undergoing shoulder surgery experience severe postoperative (acute) pain that is poorly controlled by opioids alone and which lasts over 48 hours[2] following their surgical intervention. Introduced in 1970, the interscalene block (ISB), whereby local anesthetics are injected pre-surgically in the neck around the brachial plexus nerves that transmit pain from the shoulder area, has been used to produce effective pain relief (analgesia) lasting 6-8 hours following shoulder surgery.[3] The established benefits of the ISB include a reduction in acute pain severity, opioid analgesic requirement, and incidence of postoperative nausea and vomiting triggered by opioid consumption in the first 24 hours post-surgery.[4] ISB can also expedite postoperative recovery and allow the performance of arthroscopic shoulder surgery on an ambulatory (same day) basis.[5] Not surprisingly, it is currently considered the gold standard of pain relief following shoulder surgery,[6] and has become the standard of care for arthroscopic shoulder procedures in many centres worldwide.[7] Indeed, 82% of patients having shoulder surgery receive ISB for postoperative analgesia.[8] The recent integration of ultrasound (US) imaging with the ISB[9] allowed the technique to be refined, by reducing the incidence of ISB complications (e.g. unintentional vascular puncture), the number of attempts (needle passes), the volume of local anesthetics required, and has increased ISB success rates.[10]

1.2 Complications and limitations of ISB block

Despite its benefits and wide-spread use, a growing body of evidence suggests that ISB, by virtue of its invasiveness and associated complications, is not the ideal pain relief modality for shoulder surgery, and suggests that its current role as the principal component of postoperative

multimodal analgesia is mainly for lack of alternatives that are as effective.[4,11,12] While ISB does provide effective pain relief for shoulder procedures,[6] several well-recognized and important limitations of this analgesic technique exist because of the anatomic properties of the targeted nerves and the neck, a region packed with neural and vascular structures. These limitations are described below.

1.2.1 Catastrophic complications

Although ISB of the brachial plexus is considered an intermediate skill block[13] that is frequently performed by anesthesia trainees,[14] the anatomical proximity of this plexus to the lung pleura, vertebral artery and other vasculature, and the spinal cord results in an ISB-specific risk of rare, yet very serious, complications despite the use of US guidance. While we do not have an estimate of the frequency of such complications, published case reports indicate that they are not theoretical. These complications include pneumothorax,[15] local anesthetic systemic toxicity,[16,17] as well as undesirable neuraxial local anesthetic spread.[18] For the latter, at least four distinct routes of spread of the injected local anesthetics to the neuraxis have been identified, namely injection through the vertebral foramens,[19] along the prevertebral fascia,[20] into dural root sleeves,[19] and subepineural injection.[21] The outcome of such spread is deleterious; a handful of case reports describing acute and permanent quadriplegia[22-26] underscore the potential of catastrophic neurologic deficits resulting from either direct intra-cord local anesthetic injection[24] or retrograde intraneural dissection of local anesthetics.[27] Importantly, safe-guarding against such complications seems challenging, as they may occur even when US guidance is used,[25] without noticing increased resistance or eliciting pain during injection, a common “red flag” when injecting local anesthetics around nerves.[24,25]

1.2.2 Transient and long-term neurologic symptoms

The structural complexity of the brachial plexus anatomy at the interscalene level and the poor demarcation of the boundaries between the neural tissue and its surrounding connective tissue[28] render the sonographic guidance of a needle to a safe location during ISB challenging. This may explain the concerning risk profile associated with ISB, specifically, the high incidence (19.2[29]-50[21]%) of unintentional intraneural injection associated with US-guided ISB; fortunately, only a minority of these result in nerve injury. The complexity, compounded with the relatively high proportion (45%) of neural to connective tissue in the proximal brachial plexus,[28] makes the ISB more invasive than other peripheral nerve blocks. Not surprisingly, it is associated with a much higher incidence (8[30]-14%[31]) of transient neurologic symptoms (pain, paresthesia, dysesthesia, sensory loss, motor power weakness lasting a few days or weeks), ***3-fold more common*** than all other peripheral nerve blocks combined.[4] Similarly, the long-term neurologic symptoms lasting for a few months associated with ISB (0.31%) are ***6-fold more common*** than all other peripheral nerve blocks combined.[17]

1.2.3 Damage to neighbouring nerves

The ideal US-guided ISB technique that minimizes the risk of damage to surrounding nerves remains elusive. The brachial plexus in the neck region is surrounded by numerous small nerves that are difficult to safe-guard, even when US imaging is used, such as the phrenic nerve, long thoracic nerve, dorsal scapular nerve, and the superficial cervical plexus. For example, injury to the phrenic nerve (0.1%)[32] resulting in long-term dysfunction (paralysis) and unilateral diaphragmatic paralysis[33-35] is more common in patients with pre-existing inflammation,[34] new inflammation triggered by local anesthetics injection during the block,[32] and cervical spine

disease,[35] regardless of the ISB technique used. Furthermore, all approaches to the block can cause injury to neighbouring nerves. For example, injury to the superficial cervical plexus (8%)[36] is reported with the lateral modified[37] and the medial-to-lateral ISB techniques;[38] while injury to the long thoracic[39] and dorsal scapular[40] nerves are reported with posterior and lateral-to-medial ISB techniques.

1.2.4 Respiratory complications

Performing ISB deposits local anesthetics in the vicinity of the phrenic nerve; thus injected local anesthetic spread to this nerve results in a 100% incidence of transient ipsilateral phrenic nerve block, hemidiaphragmatic paresis, and temporarily impaired pulmonary function[41] (25% reduction).[42] The latter, an extremely common respiratory complication of the ISB, limits its use in patients recognized to have compromised respiratory function.[43] Though a few studies propose that reducing the ISB local anesthetic volume injected decreases the risk of hemidiaphragmatic paresis,[44-46] other studies contradict this finding and indicate that this risk remains unchanged, even with small local anesthetic volumes (e.g. 5 milliliters).[47-49] Practically, the ISB is generally avoided in some patient populations who would benefit most from its opioid-sparing capacity; this includes patients with morbid obesity,[50] obstructive sleep apnea,[51] and severe chronic obstructive pulmonary disease.[41,42]

1.2.5 Hemodynamic complications

Performing shoulder surgery in the sitting (beach chair) position is associated with the common incidence (13.3%)[52] of bradycardia and hypotension due to the pooling of blood in lower extremities and activation of the Bezold-Jarisch's physiologic reflex,[53]which may result in

serious complications such as cardiac arrest, ischemic brain injury, and visual loss.[54-56] ISB deposits local anesthetics in the vicinity to the stellate cervical sympathetic ganglion commonly (up to 75%)[57] blocking it, resulting in predominance of the parasympathetic (vagal) tone to the heart and reducing its variability and responsiveness to hypotension and bradycardia.[58] Consequently, it is believed that a stellate ganglion block produced by an ISB,[53,59] particularly if right-sided,[60] can aggravate the hemodynamic risks associated with shoulder surgery performed in the sitting position, leading to clinically important hypotension,[61] and even some rare cases of cardiac asystole.[56,62]

1.2.6 Overall safety profile

With all of the potential risks associated with the ISB, it is not surprizing that this block, on its own, accounts for 42%[63] of all American Society of Anesthesiologists' (ASA) closed claims analysis related to nerve blocks. These claims represent complications occurring after peripheral nerve blocks that were the subject of complaints against anesthesiologists. The remaining closed claims are associated with eight other peripheral nerve blocks combined. Consequently, the American Society of Regional Anesthesia (ASRA) has singled-out this specific block with a high degree of suggested precautions unlike any other block. Attempting to reduce the associated risks of nerve injury, ASRA guidelines recommend that ISB be administered to conscious patients only, and that the block "*should not be performed in anesthetized or heavily sedated adult or pediatric patients*".[64] That said, it is important to note that the serious complications associated with ISB are actually rare, which accounts for its role as the mainstay of postoperative analgesia following shoulder surgery.

1.3 Shoulder innervation and potential ISB alternatives

The nerves relevant to shoulder surgery include the suprascapular nerve, innervating the superior and posterior portions of the shoulder joint and overlying skin, and the axillary nerve as well as branches of the subscapular and lateral pectoral nerves, innervating the anterior and inferior portions of the joint and overlying skin.[65] Although these nerves are collectively blocked proximally, before they branch from the brachial plexus, by an ISB injection in the neck, they may also be blocked distally, after branching from the brachial plexus.[66] This is thought to improve safety by reducing the risk of nerve damage caused by needles during nerve blocks, as the ratio of neural: connective tissue in each nerve decreases as nerves depart the neck.[28]

To that end, the suprascapular nerve alone accounts for the majority (>70%) of the sensory innervation of the shoulder joint.[67] Furthermore, a recently described anterior approach to blocking this nerve in the supraclavicular fossa (behind the collar bone) permits clear visualization of the nerve and facilitates blocking it away from the neck.[68] These two important factors provide the anatomical rationale for a potential ISB alternative.

Predictably, by virtue of increased distance away from the phrenic nerve, the novel suprascapular block (SSNB) has not been associated with respiratory complications.[69] Furthermore, a distal block of the individual nerves spares the neck the risks of needle trauma, and is also expected to further reduce neurologic, respiratory, and hemodynamic risks while still providing effective pain relief for shoulder surgery. In fact, the success and effectiveness of the suprascapular nerve blocks in providing pain relief following shoulder surgery, compared to control, has already been described in a few reports.[70-74] It is noteworthy that a portion of the shoulder joint (<30%)

limited to the subscapularis tendon and anterior glenohumeral capsule, which may be of surgical relevance and contribute to postoperative pain, is not anesthetized by the SSNB technique.[69]

1.4 Limitations of evidence supporting interscalene block alternatives

While the ISB is an established technique with benefits supported by several systematic reviews,[4,8] the quality of evidence supporting the comparative analgesic efficacy of the SSNB relative to the ISB is very limited. Conceivably, this paucity of evidence is the reason there has been slow incorporation of the SSNB technique into clinical practice. At the outset of this project, only two reports had attempted such a comparison;[74,75] but their results were promising and in agreement. Both trials suggested that the analgesic effect, namely pain relief, reduction in opioid analgesic consumption, and satisfaction with pain management, associated with SSNB was similar to that of ISB in patients undergoing shoulder surgery.[74,75] However, this evidence had significant design and methodological limitations. The work of Lee and colleagues[74] was a prospective study of 30 patients that was not randomized or blinded; it designated postoperative pain at six time points in the first 24 hours as a first primary outcome, and the proportion of patients requiring opioid supplementation as a second primary outcome. The sample size calculation was not presented; and the authors did not test for non-inferiority, yet inappropriately concluded that lack of statistical difference is indicative of equivalence of the two analgesic interventions. The report by Pitombo and colleagues[75] was an unblinded randomized controlled trial of 68 patients that did not specify a primary outcome or present a sample size calculation. This study advocated for SSNB based on the inability to detect a statistically significant difference in cumulative postoperative analgesic consumption at 24 hours as well as in pain scores between six and 12 hours. Furthermore, both studies deviated from contemporary practice

standards by not including multi-modal non-opioid analgesics as the first line of managing postoperative pain, and relied on nerve stimulation for nerve localization instead of US guidance. Consequently, the question of whether SSNB provides analgesia that is as efficacious as that of ISB was still unanswered.

Chapter 2: Rationale, Hypothesis and Objectives

2.1 Noninferiority rationale and design

Noninferiority trials employ a one-sided statistical comparison test to determine if a novel intervention is no worse than a standard intervention.[76] Such trials are generally chosen when placebo-controlled or superiority trials are not feasible, or there is no biological rationale to suggest that the treatment being studied could be superior. These conditions apply to the population of interest for the PASS trial. In patients having shoulder surgery, ISB has been established as an analgesic gold standard for pain control,[4] rendering a placebo arm in any future trials investigating postoperative analgesia an unethical choice. Consequently, analgesic strategies have to be compared against ISB, or, alternatively, examined as an addition to ISB. Furthermore, from an anatomical perspective, the proposed alternative nerve block, SSNB, may provide comparable postoperative analgesia following shoulder surgery; but it is highly unlikely to provide superior analgesia.[77]

The noninferiority design is also chosen when the new treatment offers an advantage in safety, convenience, or cost.[78] An important assumption with this design is that both interventions being compared are effective compared to placebo. Again, both of these requirements are applicable to this trial. Because the SSNB is performed away from the neck, it carries a lower risk of complications than ISB. As such, it would be an acceptable alternative to ISB if it is worse than the standard of care for postoperative analgesia by, at most, a small pre-specified non-clinically important difference. Furthermore, both ISB[79] and SSNB[80] have demonstrated efficacy against placebo in earlier studies. The lack of a control arm entails additional assumptions in the noninferiority design. These include i) assay sensitivity, or the ability of the trial to detect a

difference if this difference exists (i.e. adequate study design and good conduct to maximize that compliance and minimize deviations), and ii) constancy, or the preservation of the treatment effect observed previously in trials of ISB vs. control, and the ability to detect this effect in our trial, had a placebo group been included in the design of this study (i.e. similar patient characteristics, treatment, and design).[81]

Therefore, to demonstrate that SSNB is not worse than ISB, a noninferiority trial was undertaken,[76] with the primary outcome being pain intensity measured by the Numerical Rating Scale (NRS, where higher values indicate more pain). This trial design allows testing the null hypothesis that the NRS pain intensity of ISB – SSNB $\geq \Delta$ (alternative hypothesis ISB – SSNB $< \Delta$), where Δ is a non-clinically important difference in pain intensity, or non-inferiority margin. Stated otherwise, the null hypothesis is that the NRS pain intensity associated with SSNB exceeds that of ISB by at least a pre-specified difference (i.e., Δ). When the null hypothesis is rejected, one can conclude that the NRS pain intensity associated with SSNB does ***not*** exceed that of ISB by this difference. In general, a greater treatment effect (ISB – SSNB) means that ISB is better; but in the case of NRS values, where higher values mean worse pain, Δ has to be assigned a negative value. In our scenario, the value of Δ is anticipated to be ≤ 0, as SSNB, unlike ISB, does not block the entire innervation of the shoulder (hence NRS pain intensity scores are unlikely to be lower in the SSNB arm compared to the ISB arm).[82]

2.1.1 Type-I and type-II error estimates

To test for noninferiority, the difference in treatment effect ISB – SSNB is compared against the pre-specified Δ. For this comparison, we are willing to accept a type-I error margin equivalent to

5% for the one-sided test of noninferiority of SSNB compared to ISB. This error margin corresponds to using a 90% confidence interval for this test. In order to achieve power no less than 80%, we chose a type-II error margin of 20%.

2.1.2 Testing for noninferiority

To declare noninferiority, the 90% confidence interval for the difference in pain scores (primary outcome) should include zero; but its lower margin should not cross Δ.[78] For the purpose of noninferiority studies, a confidence interval that crosses Δ is interpreted as inconclusive. A confidence interval less than the noninferiority margin indicates-inferiority; while a confidence interval greater than zero is indicative of superiority.

2.1.3 Choice of noninferiority margin

The treatment effect of interest in this trial was measured using postoperative pain scores. Selecting the noninferiority margin of this treatment effect has major implications on the validity of findings. While there is no gold standard criterion for determining an appropriate margin, this margin should be smaller than the minimum clinically important difference.[83] To that end, choosing an unreasonably small difference in pains scores as a noninferiority margin will unnecessarily bolster the sample size required, and increase the risk of having inconclusive findings.[84] In contrast, an unreasonably large noninferiority margin bolsters the risk of type-I error or rejecting a true null hypothesis, and might inappropriately label an inferior treatment as non-inferior.

2.1.4 Common pitfalls of noninferiority trials

In the conduct of this study, we aimed to avoid the most common pitfalls of noninferiority trials that limit their clinical utility.[85] The first is choosing a treatment that does not offer any additional benefits; in our case, the performance of the SSNB behind the clavicle, away from the neck, was considered to entail safety advantages. The second is using an intention-to-treat analysis, which biases towards absence of a difference; in our case, we choose to perform a per-protocol analysis for the primary analysis. The third is using composite outcomes whereby the shortcomings of one outcome are compensated by another; in our case, we designated pain severity scores as a simple primary outcome. Fourth, using an unreasonably high noninferiority margin; in our case, we chose a conservative margin based on published meta-analysis of clinical trials[79] examining the effect of ISB on postoperative pain scores following shoulder surgery. This margin was chosen to be smaller than the minimum clinically important difference in postoperative pain following arthroscopic shoulder surgery, as determined in recent studies examining this specific surgical procedure.[86,87]. Fifth, not including the noninferiority margin in the sample size calculations; in our case, the sample size calculation incorporates the pre-specified noninferiority margin.

2.2 PASS Trial rationale

The cumulative evidence of ISB invasiveness and associated complications suggests that the time is ripe to study alternatives to this block. This is corroborated by several recent calls in regional anesthesia literature to seek alternatives to ISB.[43,44,66,88] While demonstrating improved safety in a randomized trial is not feasible due to the large numbers of patients required, establishing that the SSNB is *as efficacious as* (non-inferior) ISB in treating acute pain following shoulder surgery will help support recommendations for a change in provision of anesthesia for shoulder surgery to include SSNB as an

alternative to ISB. Since SSNB blocks most but not all of the sensory innervation of the shoulder joint and surrounding tissues, it may provide pain control that is not worse than that provided by the ISB, but it is very unlikely that pain relief will be superior.

I therefore conducted a multicentre, randomized, patient- and assessor-blind, parallel-group, non-inferiority trial to determine whether the combination of suprascapular and axillary nerve blocks is non-inferior to ISB in providing pain relief during the first postoperative day in healthy adult patients (age > 18) undergoing ambulatory shoulder surgery. Given the risks and complications associated with the ISB, I believed that establishing non-inferiority of analgesic effectiveness will encourage clinicians to adopt the new SSNB technique.

2.3 Study hypothesis

The pain relief provided by suprascapular nerve block is non-inferior to that produced by conventional interscalene block at six hours postoperatively in adult patients undergoing ambulatory shoulder surgery.

2.4 Study objectives

2.4.1 Primary study objective

Demonstrate non-inferiority of pain relief produced by SSNB treatment compared to ISB.

2.4.2 Secondary study objectives

2.4.2.1 Rest pain at other time points:

Compare the effect of the two interventions on rest pain severity using the NRS at 0, 12, 18, and 24 hours postoperatively, measured from time of arrival to the post-anesthesia care unit (PACU I).

2.4.2.2 Quality of recovery:

Compare the postoperative quality of recovery (QoR) in patients receiving SSNB, as measured by the QoR-15 questionnaire,[89] to the ISB. The QoR-15 is a validated tool that quantifies the impact of anesthetic interventions on perioperative health status by examining the effects on physical and mental well-being. Pain affecting the shoulder joint is associated with deterioration of perioperative quality of life.[90-94]

2.4.3 Other study objectives

2.4.3.1 Safety:

Compare the impact of SSNB and ISB on the risk of intraoperative hemodynamic complications (bradycardia and hypotension), postoperative hypoxemia, and short-term block-related neurologic symptoms in the brachial plexus distribution at one week postoperatively.

2.4.3.2 Other pain relief indicators:

Examine additional pain relief parameters that are routinely evaluated for completing the assessment of pain relief, including consumption of opioid analgesics in the first 24 hours following surgery and opioid-related side effects (nausea/vomiting, sedation, pruritus, urinary retention).

Chapter 3: Methods

3.1 Study design and overview

This was a multi-centre, prospective, randomized, patient and assessor blinded, two-arm, parallel-group, 1:1 allocation ratio, placebo-controlled, non-inferiority clinical trial comparing the effect of SSNB to ISB on pain relief during the first postoperative 24 hours in patients undergoing ambulatory shoulder surgery under general anesthesia. **Appendix I** details the study structure.

3.2 Study participants

The target population was adult patients (age>18) presenting for outpatient (same day hospital discharge) unilateral arthroscopic shoulder surgery. The surgeries included were:

- Shoulder arthroscopy
- Rotator cuff repair
- Acromioplasty
- Bankart repair
- Superior labrum anterior posterior repair (SLAP)

3.3 Study eligibility

The ambulatory nature of surgeries studied dictated excluding patients with serious comorbidities.

3.3.1 Inclusion criteria:

- English speaking adult patients (age>18)
- American Society of Anesthesiologists (ASA) Physical Status classification I-III

- BMI≤38 kg/m^2 (quality of US imaging deteriorates significantly with increasing depth of structures visualized)
- Ambulatory unilateral arthroscopic shoulder surgery

3.3.2 Exclusion criteria:

- Total shoulder arthroplasty (different care standard: continuous catheter based block)
- Severe bronchopulmonary disease compromising respiratory function and precluding ISB
- Known phrenic nerve pathology
- Contra-indication to nerve blocks (e.g. infection, bleeding diathesis, allergy to local anesthetics)
- Existing chronic pain disorders or daily opioid consumption≥30 mg oxycodone or equivalent
- Pre-existing neurological deficits or peripheral neuropathy involving the brachial plexus on the surgical side
- Contraindication to any component of multi-modal analgesia (acetaminophen, non-steroidal anti-inflammatory medications, opioid analgesics)
- History of significant psychiatric conditions that may affect patient assessment
- Pregnancy
- Inability to provide informed consent

3.4 Study centres

The trial was conducted at three medical centres in Toronto where ambulatory arthroscopic shoulder surgery is routinely performed: Women's College Hospital (WCH), Toronto Western

Hospital (TWH), and North York General Hospital (NYGH). All three centres have dedicated block rooms where nerve blocks are administered prior to surgery, employ anesthesiologists adept in US-guided blocks, and routinely perform these blocks for shoulder surgeries.

3.5 Study investigators identification and training

Administration of blocks as part of the study procedures was limited to anesthesiologists who had training in regional anesthesia and had performed successful ISB (indicated by presence of sensory block) without serious complications on at least 80 patients.[14] By reviewing healthcare quality databases that document serious complications, we identified 15 anesthesiologists (5 / centre) who met this condition, and who were interested in participating in the study.

All study investigators completed a structured preparatory training phase prior to the trial. This phase trained anesthesiologists at multiple centres on the performance of SSNB and ensured competency before participation in the trial. First, the 15 anesthesiologists from the three participating centres were invited to receive standardized training on performing US-guided SSNB on a weekend. The training module included didactic and practical training sessions. The didactic session described the SSNB and related anatomy, while the practical training session allowed scanning of the relevant SSNB anatomy in live volunteer models. Ultrasound scanning is a popular approach in learning basic ultrasound-guided blocks of the upper extremity.[95] Second, the principal investigator traveled to the participating centers to observe investigators perform both ISB and SSNB on actual patients, and ensured consistency of technique. Anesthesiologists who completed the training and demonstrated competency in performing the blocks were invited to participate in the PASS trial.

3.6 Study procedures

3.6.1 Preliminary participant identification

An information leaflet briefly describing the study was provided at the clinics of surgeons collaborating in the study to potential study candidates when they had their preoperative surgical appointment, at least 2 weeks before surgery. Patients were informed that a research coordinator would further discuss the study with them when they arrived for their preoperative anesthesia consult.

3.6.2 Obtaining informed consent

Patients scheduled for ambulatory shoulder surgery are routinely booked for a preoperative anesthesia consultation and evaluation in a Pre-Admission Clinic (PAC) at least two days prior to the scheduled surgery. All patients who met the inclusion criteria were identified from individual surgeons' booking schedules, and the timing of their PAC appointment was noted by the research coordinator. The anesthesiologists performing the assessment introduced the research coordinator at the end of their anesthesia consult. The coordinator met with the patients immediately after their consult to elaborate on the study, respond to questions, obtain informed consent, and perform a baseline assessment. The coordinator's phone number was also provided in case patients had further questions after they left the clinic. Please refer to the Recruitment section for a detailed description of the recruitment process.

3.6.3 Preoperative management

On the day of surgery, and unless allergic to acetaminophen or celecoxib (an exclusion criterion), all patients received acetaminophen 1 g and celecoxib 400 mg orally with small sips of water one

hour before the actual procedure, while waiting in the holding area. The anesthesiologist performing the blocks checked if participants had any study-related questions. Subsequently, all blocks were performed one hour before surgery in the block room. In accordance with routine pre-block management, non-invasive blood pressure, electrocardiogram and pulse oximetry were applied and intravenous access secured on the non-operative side for infusion of a 0.9% saline or lactated ringer's solution. Prior to block performance, all patients received intravenous midazolam 1-4 mg IV and/or fentanyl 25 µg IV for anxiolysis and analgesia, respectively, as needed, while avoiding deep sedation.

3.6.4 Suprascapular block (SSNB group)

Patients allocated to the SSNB group received that block in the supine position, with the shoulder in the neutral position. The suprascapular nerve was blocked as it branched from the superior trunk, in the supraclavicular fossa, as described by Siegenthaler et al.[96] After sterile skin preparation with chlorhexidine, a linear array transducer (6-13 MHz, Sonosite M-Turbo) probe protected by a 3M Tegaderm® dressing or a sterile sheath was placed in the transverse plane to visualize the superior trunk in the short axis, beneath the inferior belly of the omohyoid muscle. After infiltration with 1 mL of 1% lidocaine, a 5 cm 22 G insulated needle (B. Braun Medical Inc., Bethlehem, PA, USA) was then inserted in line with the probe in a medial-to-lateral orientation towards the suprascapular nerve. Local anesthetic solution (15 mL of 0.5% ropivacaine) was then injected in 5 mL aliquots after negative aspiration for blood to achieve circumferential spread around the neurovascular bundle.

To maintain patient blinding, sham ISB block was performed in the supine position. This was done at the designated site using a 25G needle to inject 1 mL of lidocaine 1% subcutaneously. Skin sterilization, scanning with US, US probe pressure on the skin, and the duration of scanning matched an actual ISB block.

Figure 1 illustrates the US-guided SSNB technique.

3.6.5 Interscalene block (ISB group)

Patients allocated to the ISB group had the ISB performed in the supine position with the neck tilted away from the shoulder blocked. After sterile skin preparation with chlorhexidine and infiltration with 1 mL of 1% lidocaine, a linear array transducer (6-13 MHz, Sonosite M-Turbo) probe protected by a 3M Tegaderm® dressing or a sterile sheath was placed in the transverse plane to visualize the brachial plexus. The interscalene trunks/roots were identified between the anterior and middle scalene muscles. A 5 cm 22 G insulated needle (B. Braun Medical Inc., Bethlehem, PA, USA) was then inserted in line with the probe in a medial-to-lateral or lateral-to-medial needle orientation. Local anesthetic solution (30 mL of 0.5% ropivacaine) was then injected in 5 mL aliquots after negative aspiration for blood to achieve spread posterior to or between the C5 and C6 nerve roots. Additional needle adjustments were made to ensure this local anesthetic spread pattern.

Subsequently, patients received sham SSNB. This was done at the designated site using a 25G needle to inject 1 mL of lidocaine 1% subcutaneously. Skin sterilization, scanning with US, US probe pressure on the skin, and the duration of scanning matched an actual SSNB block.

3.6.6 Assessment of block success

Assessment of sensory block onset was performed to confirm block success. Sensory block onset was tested by the anesthesiologist performing the blocks every five minutes for the subsequent 30 minutes using a blunt 22G needle applied to the skin, in comparison to the contralateral upper extremity. Block success was defined as complete sensory loss to pinprick at 30 minutes. Sensory testing for the ISB and SSNB blocks was performed over the posterior and superior deltoid area. Block success was scored on a 3-point scale as follows: (2) normal sensation; (1) reduced sensation; and (0) no sensation.

With patients for whom block success was not achieved after 30 minutes, failure of blocks was documented; such patients proceeded to surgery and relied on oral and IV analgesics for postoperative pain relief.

3.6.7 Intraoperative anesthetic management

All patients received a standardized general anesthesia regimen. General anesthesia was induced using fentanyl 0.5-2 μg kg^{-1} IV and propofol 2-4 mg kg^{-1} IV. Patients who require endotracheal intubation were paralyzed using rocuronium, a muscle relaxant, with a dose of 0.6 mg kg^{-1}. A laryngeal mask airway (LMA) or an endotracheal tube was inserted, as necessary. General anesthesia was maintained using 2 - 6% of desflurane or 0.8 – 2.8% sevoflurane inhalational gas, in a 50:50 mixture of oxygen and air. Patients were allowed to breathe spontaneously if a LMA was used. Supplemental analgesia was provided by morphine 2.5-5 mg IV boluses, as needed, to a maximum of 15 mg, or hydromorphone 0.2-0.4 mg IV boluses, as needed, to a maximum of 2.4 mg, to treat hemodynamic increases (heart rate or blood pressure) of more than 15% above

pre-induction baseline values. Desflurane or sevoflurane was discontinued at completion of surgery and muscle relaxation were antagonized with neostigmine 50 μg kg^{-1} and glycopyrrolate 5-10 μg kg^{-1}, if necessary. Patients also received standardized doses of ondansetron 4 mg as an anti-emetic following induction of anesthesia.

3.6.8 Postoperative management

During the stay in PACU I, postoperative pain at rest was assessed using an NRS score. Patients with a score≥4 or patients requesting additional analgesia were treated with intravenous fentanyl 25 μg increments every 5 minutes, as needed, up to a total of 100 μg, followed by intravenous morphine 5 mg increments every 10 minutes up to a total of 20 mg or hydromorphone 0.2 mg increments every 10 minutes up to a total of 3 mg. Pain in the same-day surgery unit (PACU II) was treated with oral Tylenol #3® every 4 hours, as needed, followed by oral Oxycodone 5-10 mg every 4 hours, as needed. Pain NRS scores at 0, 30, 60, and 90 minutes since PACU I admission, as well as time to first analgesic request were documented. All doses of postoperative analgesics administered in PACU I and II were also documented. The site of nerve blocks was assessed for any block-related complications (bleeding, hematoma) prior to discharge.

Discharged patients received a prescription for Tylenol #3®, as needed, or Percocet® if intolerant to codeine. Discharged patients were also given a home diary (**Appendix II**) to complete and return to the study team using a stamped, return-addressed envelope. Patients were asked to record their NRS pain severity scores at 6, 12, 18, and 24 hours following surgery, as well as their cumulative oral analgesic consumption since discharge from hospital, and their satisfaction with the pain relief they received reported on an NRS. Using this patient diary for

postoperative data collection has been validated in a previous study, and has been shown to minimize the rates of non-response and missing data.[16]

3.6.9 Follow-up

A study follow-up phone call was arranged at two weeks following surgery to specifically assess any potential block-related neurologic symptoms such as pain, paresthesia, dysesthesia, sensory loss, or motor power weakness. The research coordinator telephoned patients, and any participants found to have such symptoms were offered a referral to the chronic pain clinic at WCH for assessment and management.

3.7 Outcomes assessed

3.7.1 Primary outcome (pain at six hours)

The primary outcome of this trial was the pain severity score at rest at six hours postoperatively (i.e. from end of surgery), as measured on a Numerical Rating Scale (NRS; 0=no pain, 10=worst pain imaginable). Shoulder surgery patients generally spend a total of three hours in PACU I and II. Thus the six hour time point usually occurs after hospital discharge. This time point was selected because it allows evaluation of the analgesic effectiveness of the block itself by giving enough wash out time for the opioids that were administered intraoperatively or in the PACU. Conversely, delaying the measurement to a later time point may be problematic as it coincides with the wear off of the nerve blocks administered, as the duration of analgesic efficacy of these blocks is estimated to be 8 hours.[79]

The choice of NRS pain scores reflects its validity, reliability, and wide use to quantify acute postoperative pain,[97] as well as the flexibility of permitting an assessment of postoperative pain over the phone. Pain scores less than or equal to 3, 4 to 6, and 7 or greater are considered to represent mild, moderate, and severe pain respectively.[98]

The NRS pain severity scores were evaluated before discharge by the study coordinators who were not involved in patient care and who were blinded to patient allocation, while post-discharge pains scores were documented by patients themselves in the patient diary provided. (**Appendix II**)

3.7.2 Pain at other time points

a. Rest pain was also evaluated at seven additional postoperative time points: 0, 30, 60 and 90 minutes, as well as 12, 18, and 24 hours, corresponding to PACU stay (0, 30, 60, 90 minutes), evening after surgery (12 hours), morning after surgery (18 hours), and the maximum reported duration of local anesthetic action for ISB[72,99] and SSNB[75] (24 hours). These specific time points are frequently selected for evaluation of the effect of nerve blocks on pain following shoulder surgery,[72,74,99-114] as they are considered milestones reflecting the interplay between two phenomena: i) the worst possible postoperative pain usually occurring during the first day following surgery, only to improve thereafter, as well as ii) the transition from maximum block effectiveness (minimal pain) to block wear off and complete reliance on oral medications for pain management.[115-117] Thus, the measurements of pain severity scores at these time points would be expected to capture the fluctuations in pain severity produced by the aforementioned phenomena.[118,119] Rest

pain *per se* was chosen as a secondary outcome (as opposed to dynamic pain) because patients routinely have their upper extremity immobilized in a sling following shoulder surgery.

b. Mean pain scores over five time points during the first 24 hours (0, 6, 12, 18, 24 hours) were assessed, as an outcome reflective of patients' overall efficacy of pain control.

c. The proportion of patients experiencing moderate-to-severe pain, defined as NRS≥4 during the first 24 hours following surgery was assessed.

3.7.3 Quality of recovery

The impact of surgical and anesthetic interventions on perioperative quality of life and ability to resume routine life activities was assessed using the QoR-15 assessment tool.[120,121] (**Appendix II**) The validated QoR-15 scale is a patient-related outcome measure with 15 questions.[89] Satisfactory QoR reflects scores in two major domains of the scale relating to physical well-being (pain, physical comfort, physical independence) and mental well-being (mental state, psychological support). The minimum possible score is 0, indicating very poor QoR; and the maximum score is 150, indicating excellent QoR. The minimum clinically important difference on the QoR-15 scale is 8 units.[122] Though not clinically meaningful, a baseline assessment of this outcome was performed preoperatively (before surgery) to evaluate baseline differences between the two groups. QoR-15 assessment was repeated at hospital discharge as well as at 24 hours postoperatively by the study coordinators. The QoR-15 scores were expressed as mean (95% confidence interval).

3.7.4 Block characteristics:

a. Block procedural pain, defined as the worst pain experienced during administration of nerve blocks preoperatively, was expressed as an NRS score and reported as mean (standard deviation).

b. Block success, defined as occurrence of complete sensory block in the innervated area, was assessed and reported.

3.7.5 Safety and block complications assessed:

a. Hemodynamic complications: occurrence of bradycardia or hypotension (reported separately) during surgery, defined as a 30% drop in blood pressure or heart rate compared to baseline.

b. Block procedural complications: occurrence of intravascular injection, local anesthetic systemic toxicity, hematoma, pneumothorax, epidural spread, and Horner's syndrome detected during or immediately after block, or at discharge.

c. Respiratory complications: Occurrence of hypoxemia caused by phrenic nerve block produced by the spread of local anesthetics in the neck area, defined as oxygen saturation <95% during PACU stay.

d. Undesirable blocks: Occurrence of undesirable sensory and/or motor block in the hand during PACU stay, defined as sensory or motor block in the distribution of the median, radial, or ulnar nerves.

e. Neurological complications: occurrence of transient neurologic symptoms such as persistent pain, paresthesia, dysesthesia, sensory loss, and motor power weakness at two weeks following surgery, reported as proportions during follow-up at two weeks.

3.7.6 Other analgesic outcomes assessed:

a. Time to first reported pain and first postoperative analgesic request during PACU stay.

b. Time to first reported pain after discharge.

c. Recovery time, including duration of PACU I and PACU II stay was reported as mean (standard deviation).

d. Analgesic consumption during surgery, in PACU, and at 24 hours was documented, converted to intravenous morphine equivalent,[123] and reported as mean (standard deviation).

e. Opioid-related side effects during PACU stay, described as the patient proportion experiencing nausea and / or vomiting.

f. Patient satisfaction with analgesia provided for the two groups, measured before discharge using a NRS was reported as mean (95% confidence interval).

3.7.7 Success of blinding:

Success of blinding was assessed at discharge by comparing what proportion of patients give the correct answer in reply to the question: "which block do you think you received?"

3.8 Sample size

We based our sample size estimation for testing the one-sided SSNB non-inferiority hypothesis on the mean rest pain severity scores (NRS) at 6 hours following shoulder surgery. Our meta-analysis of RCTs examining the analgesic benefits of ISB in shoulder surgery estimated the mean and standard deviation of the NRS score for rest pain at six hours in patients undergoing similar shoulder surgeries and receiving ISB to be 3.28 units +/- 2.91.[79] The minimum clinically important

difference (MCID) in acute pain severity scores in the setting of orthopedic surgery and nerve blocks as reported in the anesthesia literature is equivalent to 1.6 units on the NRS.[118,124] Additional studies specific to shoulder and elbow surgery have reported the acute pain MCID to be 1.4 NRS units.[86,87] For the purpose of this study, we selected an MCID equivalent to 1.6 NRS units. The non-inferiority margin (Δ) of pain commonly used in studies examining analgesic interventions is 1 to 1.3 units on the NRS (or 10 to 13%).[125-127] For the purpose of this study, we select a Δ smaller than the MCID equivalent to 1.3 units. As we will calculate the mean difference of pain scores at six hours between the two groups (ISB-SSNB), and because our rationale entails an assumption that SSNB is not worse than ISB (i.e. ISB may have lower pain scores), we designated -1.3 (rather than + 1.3) as a non-inferiority margin. Assuming that the true difference in 6-hour pain severity score between the ISB and SAP treatment groups is 0%, a sample size calculation using a one-sided Type I error estimate of 5% (alpha = 0.05) a power (1-Beta) of 80% indicated that a sample of 63 patients per group would be needed. Based on prior prospective research experience in WCH, TWH, and NYGH, we expected approximately 10% incomplete follow up or drop out of recruited patients at worst. Consequently, we aimed to enroll a total of 70 patients per group, or a total of 140 patients for this study.

3.9 Recruitment

3.9.1 Detailed description of recruitment

Posters advertising the study to potential study candidates were displayed within the holding areas in the clinics of the shoulder surgeons involved in the study. The study was advertised as "***A clinical trial investigating the efficacy of novel shoulder blocks in controlling pain after shoulder surgery.***" The shoulder surgeons pre-screened and identified potential study candidates from the patient

population seeking treatment through their clinics. An information leaflet was provided to potential candidates, but surgeons did not actively recruit participants, and they referred interested patients to the study coordinator for additional information. The study coordinators could be reached at the phone numbers provided in the leaflet. The coordinators met patients in person immediately after the anesthesia assessment in the PAC, a few days prior to surgery. The pre-recruitment step served to briefly expose potential candidates to the study and provide them with information and the chance to obtain additional details if interested. This approach helped avoid the inconvenience of introducing the study to patients for the first time during their PAC appointment.

Actual recruitment occurred through the participating hospitals. Patients scheduled for shoulder surgeries were routinely referred to the PAC for an anesthesia consultation scheduled a few days prior to surgery. The study coordinator in each centre screened individual surgeons' booking schedules prepared weeks ahead of the actual surgery date, and identified all patients who meet the recruitment criteria, along with the timing of their PAC appointment. The coordinator arranged to meet with patients immediately after their anesthesia consult in the PAC to elaborate on the study, respond to questions, obtain informed consent, and perform a baseline assessment of some study outcomes. The phone numbers of the study coordinators were also provided for the answering of any questions.

3.9.2 Feasibility of recruitment

We confirmed the feasibility of recruitment prior to the study by reviewing the operating room schedules over a 12-month period at the three hospitals. Our review suggested a strong likelihood of recruitment of the targeted sample size from the participating centres.

As the nature of surgical procedures performed in the three centres is identical; and several of the shoulder surgeons operate in more than one of the study centres, we did not anticipate any difficulty in accruing study patients through all three centres. Nonetheless, we invested effort in promoting and maintaining recruitment throughout the study. This included reminders by research coordinators to the surgeons participating in the study and their clinic staff. Recruitment rates were reviewed periodically to ensure meeting the study timeline.

3.10 Study timeline

We required six months for pre-launch preparatory work, including obtaining ethics approval at the three study centres; identifying and training study personnel; preparing the study information leaflet, consent and data collection forms; constructing a study database; conducting standardized training on SSNB for study investigators performing blocks; and ensuring adequate coordination between surgeon clinics, study coordinator, and investigators.

The duration of study involvement for a patient from recruitment to complete follow-up was less than 3 weeks. **Appendix III** details the duration of study procedures. We recruited patients over a 24-month period, and we required six months to complete data entry, statistical analyses and manuscript writing. The entire project was completed in three years.

3.11 Assignment of interventions

3.11.1 Study coordination

The Applied Health Research Centre (AHRC) of St. Michael's Hospital is a research methods centre that was the trial data coordination centre; it provided support for data collection (via a web-based database), data management, and statistics.

3.11.2 Sequence generation

The randomization list was generated at the AHRC, and was stratified by centre using randomly varying block sizes of 2 and 4 with a 1:1 ratio. The randomization list was generated using appropriate statistical software and the randomization allocation was provided to investigators using a website dedicated to the study.

3.11.3 Sequence concealment

The randomization information for a particular patient was accessible online to investigators performing the study blocks. On the day of the scheduled procedure, after informed consent was obtained, investigators logged into the study website using their unique ID and provided the patient study ID to retrieve the result of randomization for one specific patient at a time. The result of randomization was not disclosed to the patient or coordinator. The anesthesiologist providing intraoperative care, as per routine practice, was different from the investigator performing blocks, and was therefore also blinded.

3.11.4 Implementation and blinding

The AHRC analyst generating the allocation sequence was not involved in any other study procedures. The research coordinator enrolling patients and collecting the outcome data, as well as the anesthesiologist providing intraoperative care during the surgery were not present in the block room during block performance or assessment of block success, and both were kept blind to the result of randomization. The anesthesiologist performing the interventions and assessing block success was aware of the nature of the intervention performed. However, this anesthesiologist did not have any further contact with the patient or role in the study. Patients

received either study intervention with the intent of keeping them blind to randomization assignment until the conclusion of the study and the collection of all outcome data. The principal investigator performing data analysis was not blind to group allocation, as testing for non-inferiority occurs in one direction and requires identifying the interventions performed.

3.11.5 Evaluating success of blinding

The success of maintaining patient blinding was evaluated at discharge after completion of the QoR questionnaire by asking patients which nerve block they think they had received.

3.11.6 Disclosure of allocation

The nature of allocation was not disclosed to patients under normal conditions. However, in the event of a health-threatening complication that could potentially be block-related, the blinding could be broken for a particular patient by the anesthesiologist who performed the block. If necessary, this anesthesiologist could refer to the study website. If this was not feasible, the AHRC analyst who initially generated the study sequence could be contacted and provided with the study ID; the corresponding intervention performed could then be identified.

3.12 Data management

3.12.1 Data collection

The nature of outcomes assessed and the timing of collection of these outcomes are outlined in **Appendix III**. A paper-based case report form (CRF) was prepared by the principal investigator for documentation of primary and secondary outcome. The QoR-15 questionnaire and the patient

diary were of this CRF. The CRF also contained a checklist to ensure collection of the following data:

- Demographic data, collected during the PAC visit (age, sex, weight, height, surgical side, ASA class)
- Baseline assessment of the QoR, collected during the PAC visit
- Baseline pre-existing pain symptoms prior to study interventions
- Data relating to procedural block complications and intraoperative hemodynamic adverse events, collected during the procedures
- Postoperative analgesic outcomes and first measurement of postoperative QoR, collected at patient discharge
- Evaluation of success of blinding, collected at patient discharge
- Follow up assessment of pain, analgesic consumption, and QoR at 24 hours following discharge, collected from the patient-completed diary.
- Follow up assessment for transient neurologic symptoms at 2 weeks, collected by a phone call.

These data were collected by the three study coordinators at their respective study centres, after receiving training on performing the study assessments and completion of CRF by the principal investigator. Subject confidentiality was maintained by using a study ID (not related to name, or date of birth) on all CRFs. The list linking patients' names to their corresponding study IDs was kept in a separate locked cabinet with access only to study personnel authorized by the site principal investigator.

3.12.2 Data entry

Electronic data capture (REDCap™) was used for this trial, meaning that all study data were transferred by the study coordinators at each study site from the paper-based CRF into electronic case report forms (eCRF). Appropriate training and security measures of study staff, (study coordinators, and all authorized study site personnel) was completed by AHRC staff prior to the study being initiated and any data being entered into the system for any study subjects.

The study data was kept on a secure in-house server at the AHRC throughout the duration of study, and will be kept up to 10 years after study completion. An encrypted CD of the tabulated study data will be stored by the principal investigator for up to 25 years after completion of the study.

3.12.3 Data completion – patient retention

Participants were free to withdraw from the study at any time, and the maximum anticipated attrition rate of recruited patients was estimated at 10%.

3.13 Data analysis

A P-value <0.05 was considered as the threshold of statistical significance for all statistical tests performed, unless otherwise indicated. We analyzed data using R statistical package version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). We used the Kolmogorov–Smirnov test to confirm the normality of data distribution.

3.13.1 Primary outcome analysis

Postoperative pain severity (NRS) scores (continuous data) at six hours following shoulder surgery were compared to test for non-inferiority. Specifically, we calculated the mean difference (90% CI) for the (ISB-SSNB) treatments and compared it to a non-inferiority margin equivalent to -1.3 units on the NRS using a one-sided t-test at a significance criterion of 0.05. The treatment effect was expressed as the difference in the means with 95% confidence interval.

3.13.2 Secondary analysis of the primary outcome

Since non-inferiority of SSNB was concluded, superiority was subsequently tested for using a t-test.

3.13.3 Pain at other time points

a. Rest pain severity scores at other time points: Postoperative pain severity (NRS) scores (continuous data) 0, 30, 60, and 90 minutes, as well as at 6, 12, 18, and 24 hours following shoulder surgery were compared using linear mixed effect modeling, and the mean difference (95% confidence interval) was calculated. Furthermore, as sex (female) and age are considered as predictors of (associated with) acute postoperative pain, additional analysis using linear mixed-effect modelling with sex and age as covariates was performed.

b. Mean pain scores for five time points during the first 24 hours (0, 6, 12, 18 , and 24 hours), expressed as mean (SD), was used to calculate the mean difference (90% CI) and to compare this difference to the non-inferiority margin of acute pain (-1.3 units).

c. Proportion of patients who developed moderate-to-severe pain at each time point during the first 24 hours following surgery was assessed for statistical significance using the Chi-square or Fisher's exact test as appropriate; the relative risk (95% CI) was reported.

3.13.4 Quality of recovery

The QoR score (continuous data) measured by the QoR-15 questionnaire and reported as means at discharge and 24 hours following shoulder surgery were calculated. The values for the two groups were compared by a t-test, and the mean difference (95% confidence interval) was also calculated. If statistically significant, the difference was compared to the MCID of the QoR-15 (8 units). The QoR scores at 24 hours were treated similarly.

3.13.5 Block characteristics

a. Block success (categorical data), expressed as proportions, was assessed for statistical significance using the Chi-square or Fisher's exact test as appropriate; the relative risk (95% CI) was calculated. For potential cases of block failure, we planned an intention-to-treat analysis.

b. Procedural pain (continuous data), expressed as mean (SD), were assessed for statistical significance using the student's t-test.

3.13.6 Block safety and complications

Serious block-related complications are relatively rare, and our study lacked sufficient power to make definitive conclusions regarding safety. Consequently, we did not expect to see differences in safety. However, the relative risk (95% CI) was calculated for the following safety outcomes:

a. Proportion of hemodynamic side effects (bradycardia, hypotension).

b. Proportion of procedural complications (immediately post-block and at discharge).

c. Proportion of block-related respiratory complications in the PACU (hypoxemia).

d. Proportion of undesirable sensory and / or motor block affecting the patient's hand during the PACU stay. Sensory or motor block of the hand is not a pleasant sensation nor is it required for shoulder surgery.

e. Proportion of block-related transient neurological complications at the two-week follow-up (paresthesia, motor weakness, new pain).

3.13.7 Other analgesic outcomes analysis

An exploratory analysis of the following analgesic outcomes was performed:

a. Time to first pain in PACU, time to first postoperative analgesic request after surgery, and time to first pain after discharge (continuous data), expressed as mean (SD), were analyzed using the Kaplan-Meier time-to-event method, and compared by the log rank test.

b. Total recovery time in PACU I and II (continuous data), expressed as mean (SD), was analyzed using the Kaplan-Meier time-to-event method, and compared by the log rank test.

c. Analgesic consumption during surgery, PACU stay (continuous data), and in the first 24 hours, expressed as mean (SD), were assessed for statistical significance using the student's t-test.

d. Proportions of opioid-related side effects, i.e. nausea and / or vomiting (categorical data), expressed as proportions, were assessed for statistical significance using the

Chi-square or Fisher's exact test as appropriate; the relative risk (95% CI) was calculated.

e. Patient satisfaction on an NRS (continuous data), expressed as mean (95 % CI), was compared using the Mann-Whitney U test.

3.13.8 Qualitative evaluation

The overarching goal of this study was to determine the differences between the two blocks; and, if they exist, determine whether they are clinically important. We therefore included an additional qualitative evaluation when differences were detected in the outcomes examined. This valuation commented on the magnitude of the difference and whether it was clinical meaningful.

3.13.9 Analysis of success of blinding

Success of blinding, reported as the proportion of patients who accurately guessed the nature of block they received was assessed for statistical significance using the Chi-square or Fisher's exact test as appropriate; the relative risk (95% CI) was calculated.

3.13.10 Reporting demographic data

Demographic characteristics of individuals at the time of baseline assessment were described using both means (standard deviations) and medians (interquartile ranges) for continuous data and percentages for categorical data. No further statistical testing was performed on demographic data.

3.13.11 Analysis of missing data and compliance

An intention-to-treat analysis is not appropriate for a non-inferiority comparison because it is biased towards the alternative, unlike superiority comparisons in which the bias is towards the null. Therefore the primary non-inferiority analysis used a per-protocol analysis. For all analyses that were not in the non-inferiority framework, an intention-to-treat analysis was used, especially for the analysis of data for failed blocks. An additional per-protocol sensitivity analysis was performed, and the effect on robustness of results was examined.

For missing data, my *a priori* plan was to ignore such data if their frequency was less than 5%; and to use a best/worst case scenario sensitivity analysis in the event that missing data exceeded 5%, and to examine the effect on robustness of results.

3.13.12 Stratification of analysis

The analysis of data was not stratified by study centre because patient acuity, surgeons, and the nature of surgical interventions was similar among the three study centres (NYGH, WCH, and TWH), and was tightly controlled by the study protocol.

3.14 Monitoring

A Data and Safety Monitoring Board (DSMB) was deemed not needed. This decision was made based on the facts that the study i) was relatively small, ii) examined relatively safe interventions, and iii) the risk of serious complications was low, even for ISB. An interim analysis was not planned as the study sample size was too small to warrant such an analysis.

Nonetheless, I planned to report any serious adverse events to the REB committees in the respective hospitals.

3.14.1 Auditing

A centralized data manager at the AHRC was responsible for conducting ongoing data review at all three study centres to ensure quality of data and recommend quality improvement measures as needed, such as re-training and source document verification procedures.

3.15 Ethical Considerations

3.15.1 Minimally-invasive placebo

A minimally-invasive placebo is selected to reduce the potential risk of injury associated with real nerve blocks, yet maintain patient blinding. While a real placebo carries the same risks of needle injury to nerves, a minimally-invasive low-volume subcutaneous saline injection placebo simulates nerve blocks while reducing pain associated with injection as well as minimizing potential risks (e.g. vascular puncture, nerve injury). Selection of minimally invasive placebo in studies of nerve blocks has recently been advocated[128] on ethical basis to reduce the risks associated with real placebo.

3.15.2 Research Ethics Board (REB) Approval

REB approval was received from the NYGH, WCH, and TWH REBs. There were no amendments to the original protocol approved.

3.15.3 Consent forms

Informed consent was obtained by study coordinators using consent forms approved by the local REB. Patients received a copy of the signed consent form. The study coordinators emphasized that the patient's decision to decline, enrol, or withdraw from the study at any stage would not have any influence on the subsequent care that they would receive.

3.15.4 Confidentiality

All information gathered during the course of the study has been stored in a secure, locked file cabinet at each site. Only research coordinators had access to the cabinet key. All data were de-identified by using patient study IDs instead of names to ensure confidentiality upon data entry and analysis. The forms linking patient identifiers to study ID were kept separate on secure electronic files. Only de-identified data were transferred between centres. The study databases are stored on password-protected files and computers in locked secure areas. Data will be destroyed 10 years after study publication.

Chapter 4: Results

4.1 Obtaining REB approval

The study was conducted at the three planned centers in Toronto: WCH, TWH, and NYGH. The PASS trial obtained REB approval at TWH on March 3rd, 2015 (application UHN 14-8577-A), at NYGH on March 13th, 2015 (application 15-0005), and at WCH on June 23, 2015 (application 2014-0107-B). The University of Toronto Human Research Ethics Program also approved the study. The study was registered on www.ClinicalTrials.gov (NCT02517437) on August 7, 2015.

4.2 Securing funding

In collaborating with my co-investigators, I sought funding for this study through several grant applications. This included six grant applications, three of which were successful, as detailed below.

1. The Canadian Anesthesiologist Society New Investigator Award (Operating grant, not received)
2. The Physician Services Inc. Foundation Mentored Research Award (Operating grant, not received)
3. The NYGH research and innovation grant (Operating grant, not received)
4. The University of Toronto department of Anesthesia Merit Award (Salary support, received, $70,000 for 2015-2016)
5. The Ontario Ministry of Health and Long-Term Care (Alternative Funding Plan) Innovation Award based at the University Health Network (Operating grant, received, $122,800)

6. The Ontario Ministry of Health and Long-Term Care (Alternative Funding Plan) Innovation Award based at Women's College Hospital (Operating grant, received, $7,680)

4.3 Preparatory phase

Once funding was received, the preparatory phase (didactic training and volunteer scanning) for co-investigators was implemented. A total of 15 anesthesiologists attended the standardized training session held at the Marriott Hotel in Toronto on June 13th, 2015 and all successfully completed the training. The session was facilitated by invited national and international authorities on the SSNB, including Drs. Vincent Chan (University of Toronto), Sugantha Ganpathy (University of Western Ontario), and Sanjib Adhikary (University of Pennsylvania). Subsequently, I obtained research and / or observer privileges at the three participating centers to observe co-investigators perform the SSNB on actual patients and confirm consistency of their technique and success of their blocks.

In collaboration between myself and the AHRC research staff, an eCRF was completed on June 5th, 2015, based on the paper-based CRF, and further tailored to the specific settings of each participating center. Furthermore, the research coordinators at the three participating centers completed training on data collection and entry using RedCap© on June 24th, 2015. After incorporating feedback received from co-investigators and research coordinators, the final version of the RedCap © database for the PASS Trial was launched on July 25th, 2015. Additional administrative preparatory steps included negotiating and signing a contract with the AHRC, the methodology center coordinating the study (signed June 5th, 2015), as well as data

transfer agreements between the coordinating centre and the other participating centers (signed by August 23rd, 2015).

4.4 Conducting the trial

Patient recruitment commenced in September 2015, and spanned a total of 29 months. The data for the last patient were collected on January 28th, 2018. The initially estimated recruitment time period was 24 months, but an additional five months were needed due to several factors including i) a slow start at WCH, ii) dropout of some of the co-investigators at TWH and NYGH, iii) illness and prolonged leave of one of the shoulder surgeons at NYGH, iv) an unexpected unpaid leave of one of the research coordinators at WCH, and v) a competing study that extended beyond its timeline at WCH. The completed study data was released to me for analysis on February 26th, 2018, after the AHRC analyst confirmed the quality of collected data and received satisfactory answers to all queries.

4.5 Demographic and baseline characteristics

Three hundred and twenty three patients were assessed for study eligibility. Of these, 68 patients were not eligible because of high BMI (37 patients), planned open surgical procedures (19 patients), high baseline opioid consumption (five patients), severe chronic obstructive pulmonary disease (three patients), pre-existing brachial plexus neuropathy (two patients), and pregnancy (two patients). The remaining 255 patients were approached for study participation; of these, 115 declined and 140 patients accepted and provided informed consent. As such, 54.9% (140/255) of eligible patients were actually recruited. **Figure-2** depicts the CONSORT diagram for the patient flow throughout the study. All 140 enrolled patients were randomized (ISB: 70 patients; SSNB:

70 patients); and all but four (ISB: 1; SSNB: 3) completed the study by completing and returning the patient diary. The baseline and demographic characteristics of study participants are shown in **Table-1**. Apart from age, where the mean age in the ISB group was 6.1 years younger than the SSNB group, patients in both study groups had similar baseline and demographic characteristics, including sex, BMI, ASA status, surgical side, duration of surgery, type of surgery, and baseline QoR-15 score. All study participants had arthroscopic shoulder surgeries, and a few had an additional open procedure (biceps tenodesis, distal clavicular excision).

4.6 Completeness of data

Data for the primary outcome were complete for 136 patients who returned the diaries, and missing data for all of the secondary outcomes was minimal (<5%). Because the primary outcome (pain severity scores at six hours) was measured after discharge and documented in the diary, the primary outcome and most of the secondary outcome results for the four patients who did not return the diary were missing. Thus, they were excluded from the analysis. Block success was confirmed in all patients who received the study interventions; thus all outcomes underwent a per-protocol analysis.

4.7 Primary outcome, pain at six hours

The acute pain severity at six hours was not different between the SSNB and ISB groups; expressed as mean (SD), the mean NRS scores was 1.35 (2.41) and 1.75 (2.49) for the ISB and SSNB groups, respectively (P=0.34). (**Table-2**) The mean difference (90% CI) for ISB-SSNB was -0.40 (-1.10, 0.30). When this was compared to -1.3 NRS units (Δ), the pre-selected non-inferiority margin for acute pain, the difference was found to be significantly less than Δ

(*P*=0.016). Additionally, the 90% CI of the mean difference (ISB-SSNB) crossed zero, but its lower boundary did not cross the non-inferiority margin, indicating non-inferiority of SSNB for the primary outcome. (**Figure-3**) As for the secondary analysis of the primary outcome, i.e. testing for superiority, the inclusion of zero in the 90% CI mitigated the need for this test, and indicated that SSNB was not superior to ISB.

4.8 Pain at other time points

The SSNB was similar to the ISB for pain control at almost all time points examined during the first 24 hours following surgery. Evaluating acute pain using linear mixed-effect modelling including time by treatment interaction revealed that the two study groups had similar rest pain NRS scores at almost all time points, with the exception of the 30-minute time point, where the mean difference (95% CI) for the ISB-SSNB favored ISB. The mean difference (95% CI) at 30 minutes was -0.84 (-1.59, -0.09). There were no other differences in pain scores during PACU stay and after hospital discharge. (**Table-3, Figure-4**) Qualitatively, reducing acute postoperative pain by 0.84 NRS units is not considered clinically important.

We also conducted a preplanned additional analysis of the pain scores using the pre-identified covariates (age and sex) that are known to influence the primary outcome. Analysis using linear effects modelling with these two covariates revealed statistically significant but not clinically important differences between the two groups in age- and sex-adjusted pain scores at 0 and 30 minutes, with differences favoring ISB by -0.81 (-1.56, -0.06), -0.84 (-1.59, -0.09), respectively. (**Table-4**) Qualitatively, the magnitude of these differences was not clinically important. Thus

these findings reaffirm the unadjusted analysis indicating absence of clinically meaningful differences in pain scores between the two groups.

Furthermore, the mean pain scores during the first 24 hours for the two groups were also similar; and the mean difference (95% CI) was 0.09 (-0.97, 1.15), i.e. neither statistically significant (*P*=0.85) nor clinically important. (**Table-2**) Additionally, the 90% CI of the mean difference was 0.09 (-0.80, 1.00) which is significantly less (*P*=0.005) than the non-inferiority margin (-1.3), and the lower confidence interval did not cross this margin, also indicating non-inferiority for mean pain scores.

Examining the proportion of patients experiencing moderate-to-severe acute pain during the first 24 hours suggested that fewer patients having the ISB experienced moderate-to-severe pain at 0 (by 12.1%), 30 (by 14.0%), and 90 (by 9.1%) minutes (during the PACU stay), with *P*-values of 0.048, 0.043, and 0.046, respectively. (**Table-5**) However, correcting for multiple measurements using the Bonferroni correction renders these differences non-significant, corroborating our results above. Qualitatively, such differences in proportions are minor.

4.9 Quality of recovery

The SSNB was similar to the ISB with respect to QoR. The mean difference (95% CI) in the overall QoR-15 scores for the two groups was not significant when measured at hospital discharge 3.95 (-3.52, 11.42) and at 24 hours postoperatively 2.93 (-4.76, 10.62). (**Table-2**) Additionally, no differences were detected when the scores for the five individual domains of the QoR-15 scale were compared for the two groups, both at discharge and at 24 hours. (**Figure-5)**

4.10 Block characteristics

The SSNB was similar to ISB for block procedural discomfort; patient-reported pain during administration of the block was not different between the two groups (P=0.82). (**Table-2**) All patients in both groups had successful blocks, as confirmed by sensory testing.

4.11 Safety outcomes

The SSNB was similar to ISB with respect to all the safety outcomes examined. Specifically, the two groups were not different for the risk of intraoperative hemodynamic complications (bradycardia, *P*=0.35; hypotension, *P*=0.21); block procedural complications (immediately post-block, *P*=0.51; at discharge, *P*=1.0); postoperative respiratory complications (hypoxemia, *P*=0.27); undesirable blocks of the hand in the PACU (numbness, *P*=0.07; weakness, *P*=0.1); and postoperative block-related neurologic complications at two weeks (paresthesia, *P*=0.51; motor weakness, *P*=0.55; new onset pain, *P*=0.1). (**Table-2**) None of the patients in either of the two study groups experienced any serious or catastrophic complications.

4.12 Other analgesic outcomes

The SSNB was similar to ISB with respect to the majority of the analgesic outcomes assessed. The two groups had similar time to first pain in PACU, duration of PACU I and II stay, time to first pain after hospital discharge, intraoperative analgesic consumption, cumulative 24-hour postoperative analgesic consumption, incidence of postoperative nausea and vomiting, and patient satisfaction with pain relief. (**Table-2**)

In contrast, patents in the SSNB group had slightly shorter time to first analgesic request (*P*=0.04) in PACU, with a mean difference (95% CI) equivalent to 11.5 minutes (0.3, 22.8). (**Table-2**) Qualitatively, the absolute magnitude as well as the relative magnitude of the difference (11.5 min is equivalent to 8.3% of the time to first analgesic request for the ISB group) were not clinically meaningful.

Additionally, patients in the SSNB group had a slightly higher IV morphine consumption (*P*=0.04) during their PACU stay, with a mean difference (95% CI) equivalent to -2.46 mg (-4.75, -0.17). Qualitatively, this difference is equivalent to half a tablet of Percocet (or 5 mg or oxycodone) and is thus not clinically meaningful. The lower end of the confidence interval of the difference (-4.75 mg morphine) is also not clinically meaningful.

4.13 Success of blinding

Less than half of the patients in each of the two study groups were able to correctly identify the nature of the intervention they received. This included 32 patients (46.4%) in the ISB groups and 19 patients (28.4%) in the SSNB group. Assuming that half of the participants are expected to guess the result of their assignment by chance alone, it seems that participants in the SSNB group were less likely than chance alone to guess their assignment. (**Table-2**)

Chapter 5: Discussion

5.1 Main study findings and interpretation

The results of this clinical trial demonstrate that using SSNB as an alternative to ISB provides non-inferior analgesic efficacy following ambulatory arthroscopic shoulder surgery. The pain control provided by SSNB at six hours following surgery (the primary outcome) was as good as (non-inferior) that of the ISB, and was also not different from that of ISB at all other time points during the first 24 hours, except at 30 minutes. The 30-minute time point corresponded to the PACU stay, where ISB was slightly more effective in treating pain; but the difference was not clinically important. Effectively, pain during PACU stay is promptly detected and easily managed by PACU staff using oral or systemic analgesics. These findings are also corroborated by the consistent lack of differences between the two blocks for other important analgesic outcomes, such as the overall mean pain scores for the first 24 hours, proportion of patients experiencing moderate-to-sever pain, cumulative 24-hour postoperative analgesic consumption, incidence of opioid-related side effects, and overall patient satisfaction with pain relief. Similarly, the two blocks were also not different for safety outcomes and QoR. When differences did exist between the two techniques, as in time to first analgesic request in PACU and cumulative PACU opioid consumption, these differences occurred during hospital stay, were small in magnitude, not clinically important, and easily manageable. Patients in whom the risk of respiratory and other complications preclude administering ISB for shoulder surgery may derive immediate benefit from our findings. For such patients, the SSNB can now appreciate the effective pain control and opioid sparing effects of nerve blocks, without the risks associated with ISB. From a technical standpoint, the SSNB continues to evolve into a simpler and potentially safer technique compared to the ISB. Newer approaches to SSNB involve injecting

local anesthetics along the sub-omohyoid muscle fascial plane, and do not require identification of the suprascapular nerve or injecting around it.[129]

5.2 Novelty

This is the first methodologically sound randomized controlled trial to demonstrate non-inferiority of the anterior single-injection SSNB to ISB in patients having ambulatory arthroscopic shoulder surgery. Several studies comparing SSNB to ISB have been published since the start of our trial, as illustrated in our recent meta-analysis;[130] but the vast majority of these trials examined the posterior rather than the anterior SSNB technique. However, it has been shown that ISB provides superior analgesia in the immediate postoperative period compared to posterior SSNB.[131] As for the anterior SSNB that we evaluated in the PASS trial, the number of published trials examining this technique is limited to three recent studies.[132-134] Both the first[132] and the second[133] of these trials compared continuous (catheter-based) ISB to continuous anterior SSNB, an intervention that is distinct from ours in that it provides a local anesthetic infusion through an indwelling catheter for several days, and thus does not allow measurement of the effect of our national / institutional standard, single-injection SSNB. Furthermore, the first study examined patients having shoulder replacement, a different population altogether, with clear implications on acute pain severity and analgesic requirements. Finally, this trial was a small study (25 patients per group) that examined changes in the respiratory vital capacity associated with these blocks, and was not powered to evaluate the analgesic effects.[132] Moreover, the second trial included 63 patients per group, examined the shoulder arthroscopy population, but primarily evaluated pain at 60 min, i.e. during PACU stay, and again, because of using continuous infusion, could not inform the analgesic efficacy of single-injection anterior SSNB

after discharge.[133] The third study examined single-injection anterior SSNB in patients having shoulder arthroscopy and concluded non-inferiority of SSNB to ISB for pain control;[134] but it had serious methodological limitations that I have outlined in a letter to the editor.[135] Most notably, this trial employed an area under the curve (AUC) statistic for evaluating postoperative pain (primary outcome); but the authors used sparse measurements to construct this curve and incorporated pre-surgical pain scores (two out of six points) into the calculation of the AUC, detracting from the validity of this outcome measure. Furthermore, the MCID and non-inferiority margin for postoperative pain AUC that were used in the power calculation and testing non-inferiority have yet to be defined. The authors' assumption that the same non-inferiority margin for one measurement (1.1 units) is applicable to the entire AUC is not based on evidence. For these reasons, my research question of interest has continued to be unanswered, despite the three aforementioned papers that were published during the conduct of the PASS trial.

5.3 Anatomical explanation

It is noteworthy that the posterior SSNB *per se* is the technique that was being promoted as an alternative to ISB at the outset of our study.[66,96,136] From an anatomical standpoint, the peripheral nerves that should be blocked to achieve sensory block for the entire shoulder joint and provide adequate pain control for shoulder surgery include the suprascapular, axillary, and lateral pectoral nerves.[137] Thus the posterior suprascapular block, alone, blocks only a portion (70%)[77] of the innervation to the shoulder joint, providing partial acute pain relief. In contrast, the recently described anterior SSNB technique that was used in this study is purported to be more effective than the posterior one because it is closer to the superior trunk of the brachial plexus.[138,139] The superior trunk is the brachial plexus branch that gives rise to all three

suprascapular, axillary, and lateral pectoral nerves that innervate the shoulder, and thus can provide sensory block and acute pain control to the shoulder joint and overlying tissues.[77,82] Indeed, cadaveric studies have shown that local anesthetics injected while performing the anterior SSNB spread to the superior trunk.[68] This recent realization of the anatomical differences between the anterior and posterior SSNBs explains why researchers have recently started investigating supplementary nerve blocks, such as the supraclavicular[140] block and infraclavicular[141] block, that, when combined with the posterior SSNB, may provide a sufficient cumulative analgesic effect to be compared with and potentially replace the ISB. It is also noteworthy that this change in the perceived role of the posterior SSNB in shoulder surgery has occurred in the past two years only,[131,134] i.e. while the PASS trial was in progress, underscoring the innovative aspect of our work and the correctness of our choice of the anterior SSNB as a potential ISB alternative.

5.4 Study strengths

The PASS trial has several strengths. The methodological rigour of this study draws from its design as a randomized controlled trial. The centrally-controlled randomization, concealment of allocation, use of sham blocks, and blinding of participants, anesthesiologists, as well as assessors reduced selection, performance, and detection biases, respectively. While I used a non-invasive placebo by subcutaneous injection in the neck, our assessment of the success of patient blinding indicated that it was successfully maintained. The standardized preparatory course the anesthesiologists completed and the role of the AHRC research methods center in training coordinators, issuing data queries, and checking data quality safeguarded the internal validity of our findings. My *a priori* identification of demographic characteristics that are associated with

pain, the outcome of interest, and subsequent adjusted analysis further protects our results against confounding. Additionally, the multi-centered and multi-investigator nature of the study suggests that the results are generalizable across hospitals that are university-affiliated (TWH, WCH) as well as community hospitals (NYGH). Generalizability is also served by the use of multimodal analgesia for management of acute pain, reflecting mainstream contemporary practices. As such, the PASS trial generates Level-IA evidence addressing a topical clinical need.[142]

5.5 Study limitations

The PASS trial also has some limitations. The findings of this trial are generalizable to the population, interventions, and clinical settings examined. For example, my results may not be generalizable to shoulder replacement surgery, the continuous SSNB intervention, or settings where blocks are used to provide surgical anesthesia without a general anesthetic. Next, my effort to convincingly demonstrate non-inferiority of SSNB required collecting data for a vast number of analgesic indicators. Thus the analysis of secondary outcomes was primarily exploratory, and we only corrected for repeated measurements of the same outcome. Notwithstanding, the risk of inflating type-I error is acknowledged. Furthermore, while the sample size was relatively big for such studies of analgesic interventions, I did not perform separate power analysis to ensure sufficient power for secondary outcomes. It should also be noted that my choice of pain at six hours (post-discharge) as the primary outcome does not necessarily reflect the patients' experience in the entire first 24 hours; an AUC outcome could have better served this purpose. But this was precluded by a lack of knowledge about the MCID for AUC of acute pain; consequently, I presented the mean of pain scores over 24 hours as an

alternative. I also could not detect a difference in respiratory and neurologic complications following blocks, which represented the underpinning of the study rationale; but this present study clearly did not have sufficient power to examine these outcomes. In fact, a clinical trial powered to detect a difference in these complications is unlikely to be feasible; as it requires 6,750 patients per study group to provide 80 % power with a 5% type-I error margin to detect a 20% reduction in an ISB complication risk of 5%. Finally, I did not assess respiratory function in study patients; being able to demonstrate benefit in this area to complement our findings of non-inferiority of analgesia would have been useful to practitioners and knowledge users. In retrospect, assessing time to become independent from oxygen supplementation following shoulder surgery would have been a clinically meaningful measure of respiratory function.

5.6 Conclusion and future direction

In conclusion, I have demonstrated that the anterior SSNB is an effective analgesic alternative to ISB for postoperative analgesia in patients having arthroscopic shoulder surgery. This investigation comparing the two blocks for pain control showed that SSNB was non-inferior to ISB at six hours, not different from the ISB for the vast majority of the analgesic outcomes examined, and worse by a small non-clinically important difference for a very few analgesic outcomes. These findings are generalizable to ambulatory arthroscopic procedures of the shoulder where surgery is performed under general anesthesia, and where patients receive multimodal analgesia. I expect that my results will encourage practitioners to incorporate this block into their practice, and inspire investigators to plan future research to study this novel block.

As far as incorporation of the SSNB into practice, the impediments should be minimal, as this block is performed in a superficial spot, which facilitates needle and targeted nerve visualization when done under ultrasound imaging.[143] The anatomical zone in which the SSNB is performed is also relatively far from major vascular and neurologic structures. Both of these factors speak to the technical simplicity and agreeability to practitioners. Based on these factors, the block would be classified as a basic-to-intermediate skill level intervention.[144] This should also facilitate integration into the regional anesthesia curriculum for anesthesia residency training, once the number of blocks needed to achieve competency has been identified.[14,145]

As far as safety is concerned, this study provides certain patient populations who are at a higher risk for complications the option to benefit from the superior pain control offered by nerve blocks, without entailing the risks associated with the ISB. Although we could not identify a difference in safety and block-related complications, we believe that patient safety is enhanced with the SSNB because the block is not performed in the neck. However, demonstrating the safety benefit in the setting of a clinical trial is challenging because of the aforementioned sample size requirement. Similarly, using administrative data is unlikely to provide useful information about safety because these databases will only capture catastrophic complications. Examining hospital databases which include individual patients' anesthesia and PACU records may be a feasible, yet cumbersome, way to evaluate this benefit. Such a study would allow examination of differences in important, yet not catastrophic, complications, such as the need to re-intubate patients after extubation, incidence and severity of postoperative hypoxemia, and delays in PACU discharge caused by the inability to wean patients from oxygen supplementation via facemask or nasal prongs.

The PASS trial substantiated the anterior SSNB with definitive evidence of analgesic efficacy; but as in the case of any new regional anesthesia technique, this evidence needs to be followed by future research to achieve a series of important goals. First, refining the block technique by identifying the ideal dose, local anesthetic spread pattern and block technique; these require future dose-ranging and radiologic studies. This knowledge is of paramount importance, as excessive or misplaced volumes may track back to the phrenic nerve causing hemidiaphragmatic paresis, defeating the purpose of using the SSNB. These studies, together with exploring the feasibility of using SSNB for surgical anesthesia, may help adoption of this technique by practitioners. Second, expanding the use of the SSNB to other populations should be investigated. Specifically, evaluating catheter-based continuous SSNB for extended analgesia will make it an option for procedures requiring provision of pain relief for an extended period of time, such as shoulder replacement. Finally, it may be worthwhile to investigate the block in patients with borderline respiratory function, as in morbidly obese or obstructive sleep apnea patients, to quantify respiratory benefits in these populations. Upcoming studies can also combine evaluation of analgesic effects with the use of ultrasound scanning for diaphragmatic assessment, a novel sensitive tool gaining popularity in assessing diaphragmatic function following blocks for shoulder surgery.[45] The above suggestions are consistent with the overarching theme of this trial, namely offering improved regional anesthesia techniques that enhance acute pain control and improve patient safety.

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Tables

Table-1: Patient Demographic Characteristics

Parameter	Interscalene Nerve Block (N=69)	Suprascapular Nerve block (N=67)
Age (years)	39.8 (14.5) 35.0 [25.0]*	45.9 (15.0) 48.0 [26.0]*
Sex (female)	16 (23.2)	21 (31.3)
Body Mass Index (kg m^{-2})	26.2 (3.2) 26.1 [4.8]*	26.1 (3.6) 26.5 [5.0]*
American Society of Anesthesiologists (ASA) physical status (I/II/III)	35 (50.7) / 31 (44.9) / 3 (4.3)	31 (46.3) / 31 (46.3) / 5 (7.4)
Surgical side (left)	29 (42.0)	28 (41.8)
Duration of surgery (minute)	104.7 (46.7) 98.0 [55.5]*	102.6 (38.3) 99.0 [57.0]*
Baseline Quality of Recovery-15 Score (units)	133.2 (11.9) 135.0 [17.00]*	133.5 (13.2) 138.0 [14.0]*

Arthroscopic Procedure**		
Shoulder Arthroscopy	28 (40.6)	28 (41.8)
Bankart Repair	4 (5.8)	3 (4.5)
Acromioplasty	19 (27.5)	20 (29.9)
Rotator Cuff Repair	16 (23.2)	14 (20.9)
SLAP	9 (13.0)	5 (7.5)
Biceps Tenodesis	5 (7.2)	10 (14.9)
Distal Clavicle Excision	1 (1.5)	3 (4.5)
Other	20 (29.0)	21 (31.3)

Results reported as mean (standard deviation), or * median [interquartile range] for continuous outcomes; and as number (percentage) for categorical outcomes.
**Patients can have more than one procedure during the same surgery

Age and sex (female) are established predictors of increased postoperative pain severity. The two groups were not balanced with respect to age. We present age- and gender-adjusted calculations in Table-4).

Table-2: Analysis of analgesic and other outcome results

Outcome	Interscalene Nerve Block (N=69)	Suprascapular Nerve block (N=67)	Mean difference (95% confidence interval) or relative risk	P-value
Mean pain score at 6 hours, mean (SD) **(Primary outcome)**	1.35 (2.41)	1.75 (2.49)	-0.40 (-1.22, 0.42) -0.40 (-1.10, 0.30)*	0.34 0.016*
Mean pain scores over five time points during the first 24 hours (0, 6, 12, 18, 24 hours), mean (SD)	3.29 (3.2)	3.20 (3.08)	0.09 (-0.97, 1.15) 0.09 (-0.80, 1.00)*	0.87 0.005*
Proportion of patients with moderate-to-severe pain (NRS≥4) at any time during the 24 hours (including PACU), count (%)	63 (91.3)	53 (79.1)	0.87 (0.75, 0.99)	0.05
Quality of recovery				
Quality of Recovery (QoR)-15 score at discharge	105.79 (20.61)	101.84 (23.70)	3.95 (-3.52, 11.42)	0.30
QoR-15 score at 24 hours	106.31 (24.52)	103.38 (21.16)	2.93 (-4.76, 10.62)	0.46
…..***Block characteristics***				
Block procedural pain (NRS), mean (SD)	0.64 (1.55)	0.70 (1.49)	-0.06 (-0.57, 0.45)	0.82

Incidence of successful block confirmed by sensory onset, count (%)	69 (100)	67 (100)	N/A	1.0
Safety and complications				
Incidence of intraoperative bradycardia, count (%)	11 (15.9)	7 (10.4)	0.66 (0.27, 1.59)	0.35
Incidence of intraoperative hypotension, count (%)	31 (44.9)	23 (34.3)	0.76 (0.50, 1.17)	0.21
Incidence of immediate post-operative block complications, count (%)	1 (1.4)	0 (0)	0.34 (0.01, 8.28)	0.51
Incidence of block complications at discharge, count (%)	0 (0)	0 (0)	N/A	1.00
Incidence of respiratory complications in PACU (hypoxemia), count (%)	6 (8.70)	10 (14.90)	1.72 (0.66, 4.46)	0.27
Incidence of undesirable blocks in the PACU, count (%)				
Hand numbness	60 (87.0)	50 (74.6)	0.86 (0.73, 1.01)	0.07
Hand weakness	61 (88.4)	52 (77.6)	0.88 (0.75, 1.02)	0.10
Incidence of post-operative block complication at two weeks, count (%)				
Paresthesia	1 (1.4)	0 (0)	0.34 (0.014, 8.28)	0.51
Motor weakness	2 (2.8)	1 (1.5)	0.51 (0.05, 5.55)	0.55

New onset pain	0 (0)	5 (7.5)	11.32 (0.64, 200.88)	0.1
…..***Other analgesic outcomes***				
Time to first pain sensation in PACU (minute)	129.2 (56.6)	112.7 (68.4)	16.5 (-4.6, 37.7)	0.13
Time to first analgesic request in PACU (minute)	139.3 (48.0)	127.8 (46.8)	11.5(0.3, 22.8)	0.04
Duration of post-anesthesia care unit phase one (PACU-I) stay (minute)	58.71 (23.06)	66.90 (44.65)	-8.19 (-20.19, 3.81)	0.18
Duration of PACU phase two (PACU-II) stay (minute)	124.16 (45.50)	125.18 (73.18)	-1.02 (-21.57, 19.53)	0.92
Time to first pain sensation after discharge (minute)	672.85 (441.63)	782.87 (477.17)	-110.02 (-264.66, 44.62)	0.17
Intraoperative IV morphine equivalent consumption (mg)	16.05 (6.84)	16.96 (6.74)	-0.91 (-3.19, 1.37)	0.44
Postoperative cumulative PACU IV morphine equivalent consumption (mg)	3.19 (6.31)	5.65 (7.29)	-2.46 (-4.75, -0.17)	0.04
Postoperative cumulative 24-hour IV morphine equivalent consumption (mg)	13.42 (12.58)	13.53 (15.32)	-0.11 (-4.82, 4.61)	0.96
Incidence of nausea and vomiting in the PACU, count (%)	18 (26.1)	26 (38.8)	1.49 (0.90, 2.45)	0.12

Patient satisfaction with pain relief at 24-hour (NRS)	7.13 (2.50)	7.26 (2.50)	-0.13 (-0.97, 0.71)	0.76
…..***Success of blinding***				
Correct answer to the question "which block do you think you received?", count (%)	32 (46.4)	19 (28.4)	2.18 (1.07, 4.45)	0.03

Data presented as mean (standard deviation), count (percentage), or mean difference (95% confidence interval), or relative risk (95% confidence interval)

(*) Mean difference (90% confidence interval) and one-tailed P-value for comparison to -1.3 units on an NRS, the non-inferiority margin for acute postoperative pain.

Abbreviations: IV, intravenous; mg, milligram; N, number of patients; N/A, not applicable; PACU-1, post-anesthesia care unit; PACU-2, same day surgery unit; SD, standard deviation;

Table-3: Analysis of the difference in pain scores for the two blocks using linear mixed-effect modelling including time by treatment interaction. (Before correction for baseline differences in age and sex)

Outcome	Interscalene Nerve Block (N=69)	Suprascapular Nerve block (N=67)	Mean difference (95% confidence interval)
Rest pain severity NRS score			
0 minutes	0.61 (2.15)	1.34 (2.16)	-0.73 (-1.48, 0.02)
30 minutes	0.97 (2.17)	1.81 (2.16)	-0.84 (-1.59, -0.09)*
60 minutes	0.76 (1.77)	1.36 (1.77)	-0.60 (-1.21, 0.01)
90 minutes	0.48 (1.38)	0.92 (1.38)	-0.44 (-0.92, 0.04)
6 hours	1.23 (2.40)	1.69 (2.39)	-0.46 (-1.29, 0.37)
12 hours	3.68 (3.04)	3.40 (3.04)	0.28 (-0.78, 1.34)
18 hours	5.39 (2.90)	4.84 (2.89)	0.55 (-0.45, 1.55)
24 hours	5.14 (2.49)	4.47 (2.50)	0.67 (-0.19, 1.53)

Data presented as mean (SD), and mean (95% confidence interval)

(*) Statistically significant

Differences in pains scores less than 1.6 on an NRS are not clinically important.

Table-4: Analysis of the difference in pain scores for the two blocks using linear mixed-effect modelling after adjusting for age and sex. Pain scores are adjusted for age (continuous covariate) and sex (male or female)

Outcome	Interscalene Nerve Block (N=69)	Suprascapular Nerve block (N=67)	Mean difference (95% confidence interval)	P-value
Rest pain severity NRS score				
0 minutes	0.57 (0.04, 1.10)	1.38 (0.83, 1.93)	-0.81 (-1.56, -0.06)*	0.03
30 minutes	0.97 (0.44, 1.50)	1.81 (1.26, 2.36)	-0.84 (-1.59, -0.09)*	0.03
60 minutes	0.75 (0.31, 1.19)	1.26 (0.81, 1.72)	-0.51 (-1.13, 0.11)	0.11
90 minutes	0.49 (0.15, 0.84)	0.91 (0.56, 1.27)	-0.42 (-0.91, 0.07)	0.09
6 hours	1.19 (0.59, 1.78)	1.74 (1.12, 2.35)	-0.55 (-1.33, 0.35)	0.20
12 hours	3.68 (2.93, 4.44)	3.40 (2.62, 4.18)	0.28 (-0.80, 1.36)	0.61
18 hours	5.51 (4.80, 6.22)	4.72 (3.99, 5.45)	0.79 (-0.22, 1.80)	0.12
24 hours	5.22 (4.60, 5.83)	4.38 (3.75, 5.01)	0.84 (-0.03, 1.71)	0.06

Data presented as mean (95% confidence interval)

(*) Statistically significant

Differences in pain scores less than 1.6 on an NRS are not clinically important.

Table-5: Proportion of patients having moderate to severe pain at each time point.

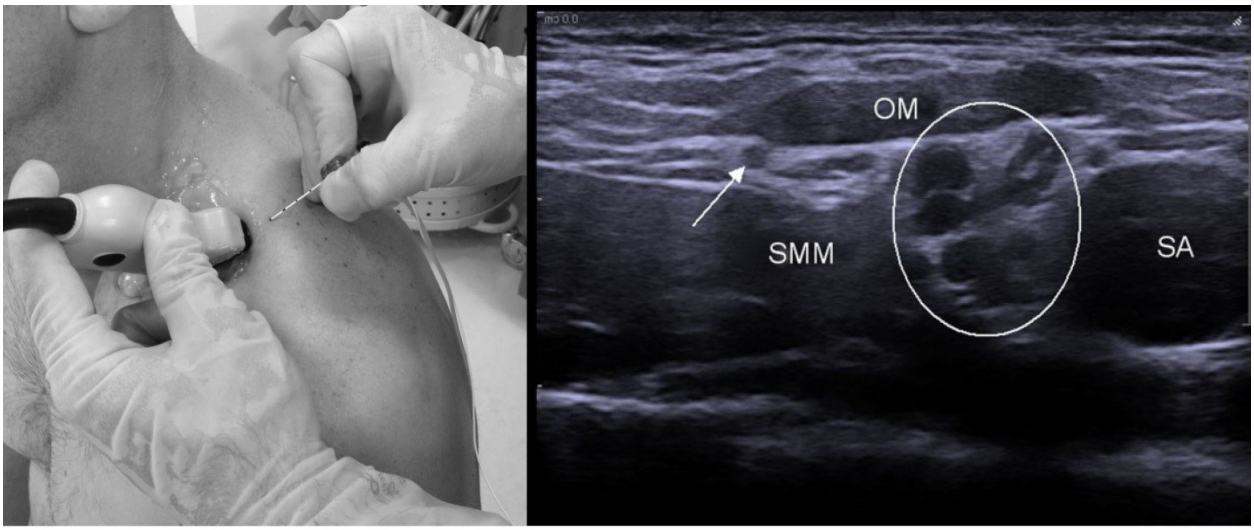
(moderate-to-severe pain: NRS≥4)

NRS Score Time Point	Interscalene Nerve Block (N=69)	Suprascapular Nerve block (N=67)	P Value
0 minutes (n/N)	6/68	14/67	0.048
30 minutes (n/N)	9/68	18/66	0.043
60 minutes (n/N)	6/69	12/66	0.105
90 minutes (n/N)	2/67	8/66	0.046
6 hours (n/N)	11/68	13/65	0.567
12 hours (n/N)	34/68	25/65	0.181
18 hours (n/N)	51/68	47/64	0.837
24 hours (n/N)	50/68	43/64	0.425

Time points 0-90 minutes correspond to recovery room stay
None of the P-value results reaches the threshold of statistical significance if a Bonferroni-Holm correction is used.

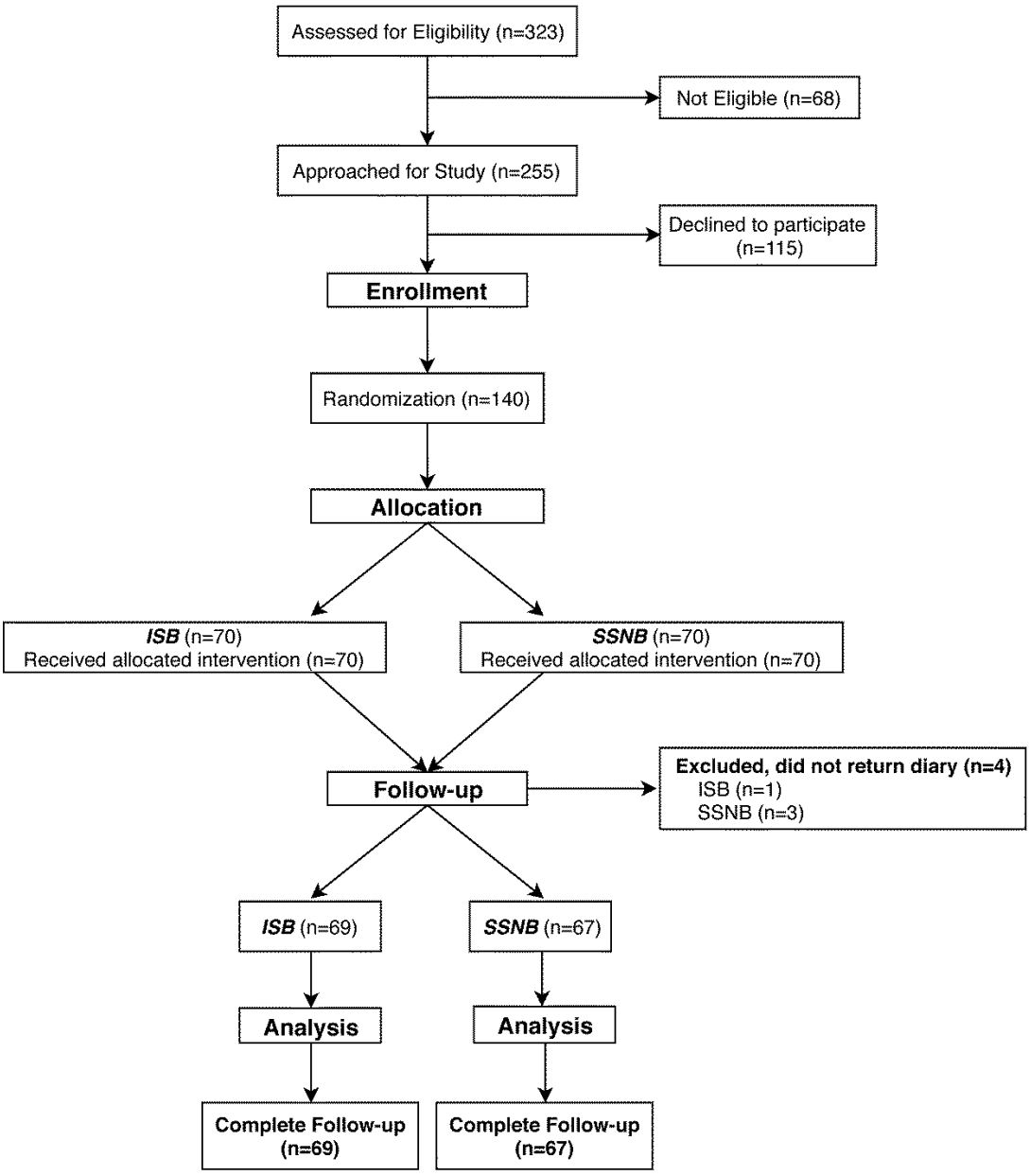
Figures

Figure-1: Suprascapular block technique



Anterior suprascapular nerve block in the supraclvicular fossa with in-plane needle insertion. OM: omohyoid muscle; SA: subclavian artery; SMM: scalenus medius muscle; white circle: supraclavicular part of the brachial plexus; Arrow: suprascapular nerve.
(Credit: Acta Anaesthesiol Scand 2014; 58: 1228–32)

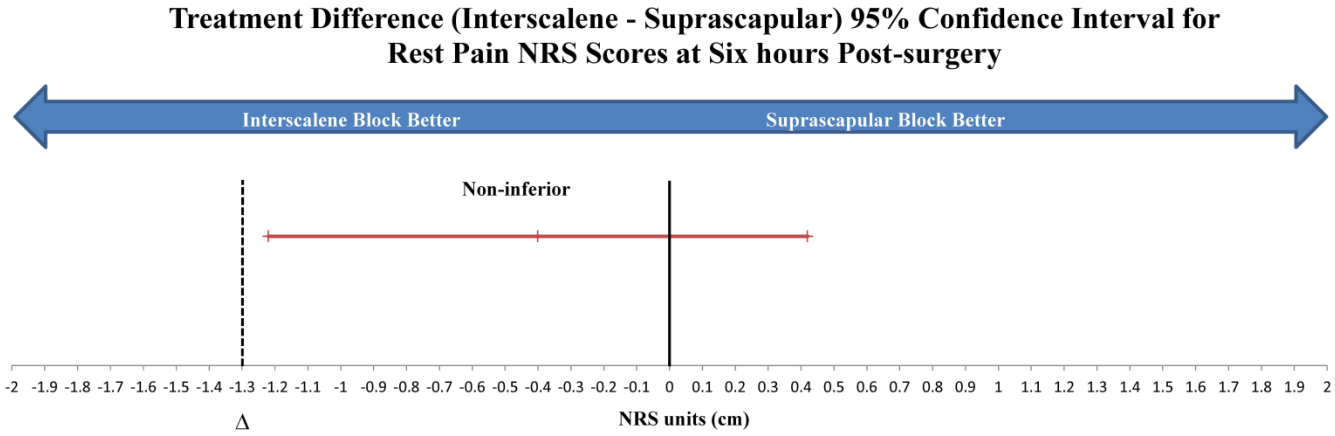
Figure-2: CONSORT flowchart



One patient in the interscalene group and three in the suprascapular group were excluded because patient diary was not returned (all outcome data are missing).

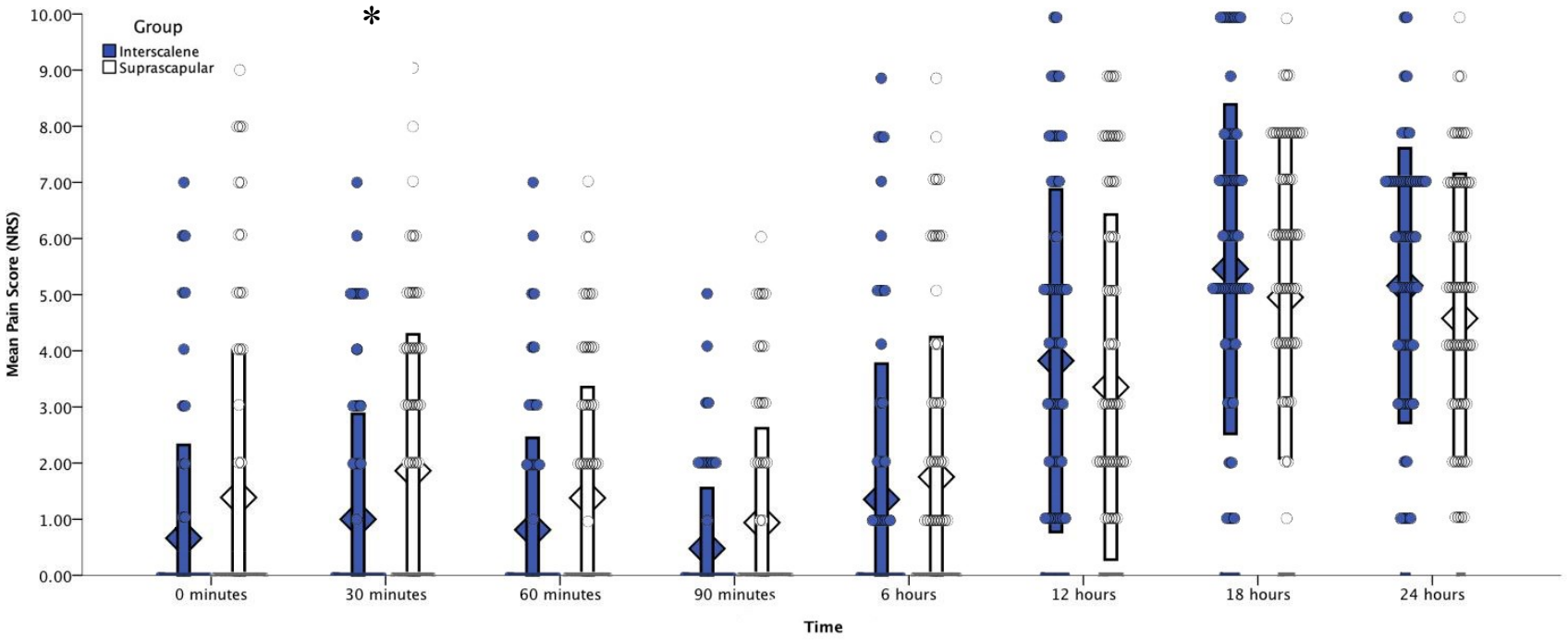
Abbreviations: ISB, interscalene block; SSNB, suprascapular block

Figure-3: Non-inferiority comparison



Δ: Non-inferiority margin, -1.3 NRS units.

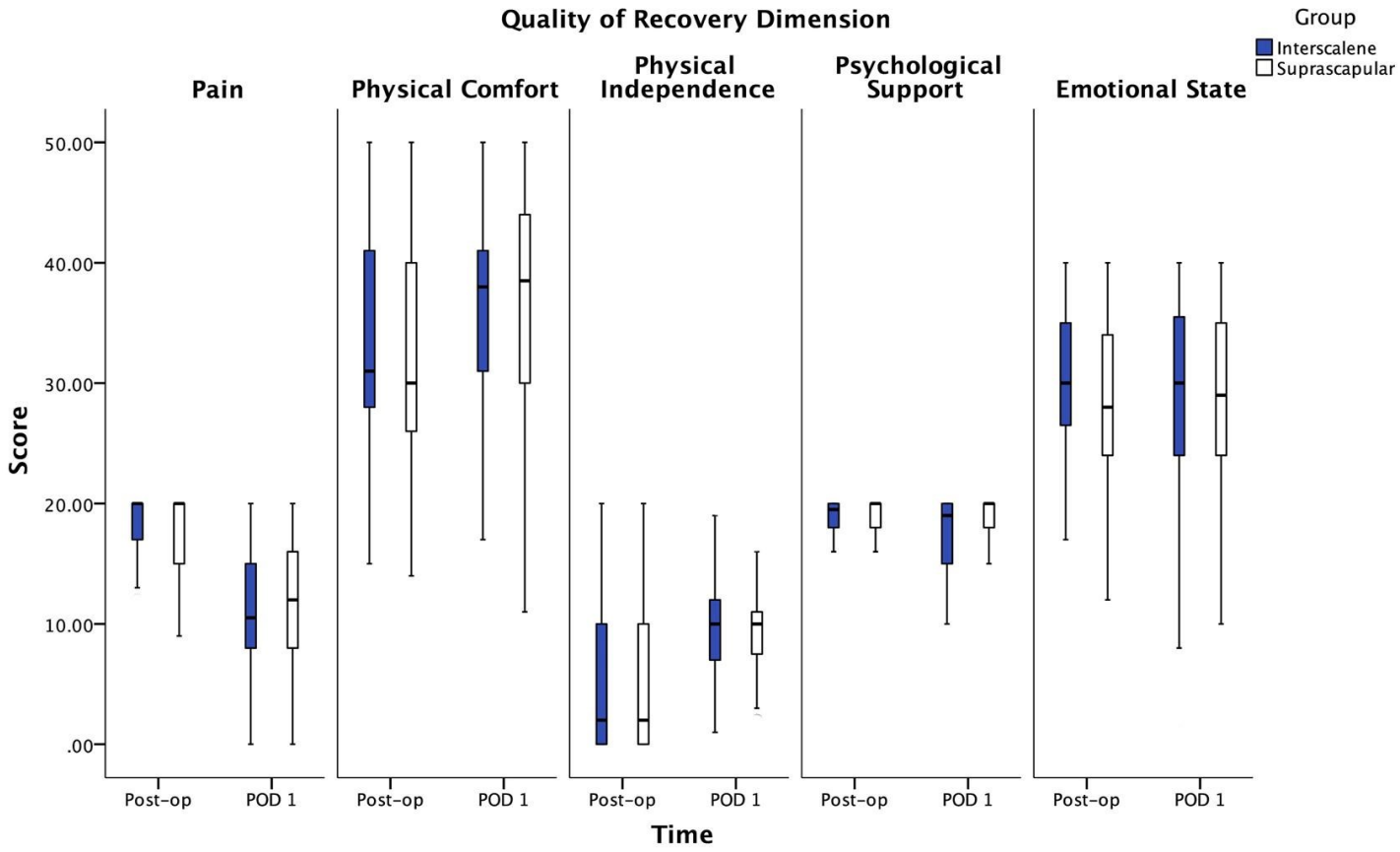
Figure-4: Box and whiskers plot of postoperative rest pain scores during the first 24 hours for the two study groups



(*) Statistically significant

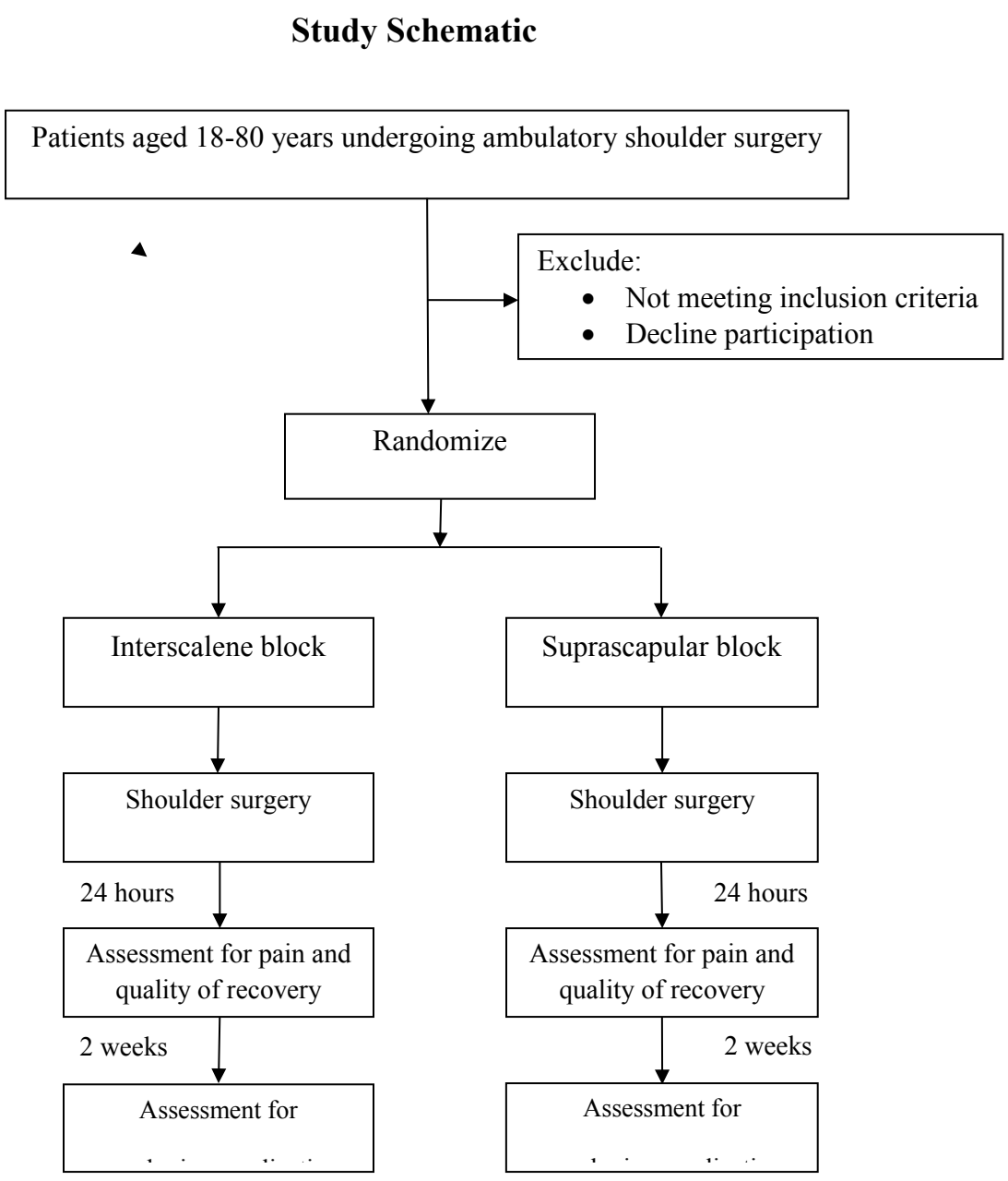
Abbreviations: ISB, interscalene block; SSNB, suprascapular block

Figure-5: Box and whiskers plot of the quality of recovery (QoR-15) domains for the two study groups at discharge and 24 hours postoperatively



Appendices

Appendix I: Study schematic



Appendix-II: Patient home diary

Patient Diary

SUBJECT ID #: _____

When did you first feel pain in the shoulder joint?

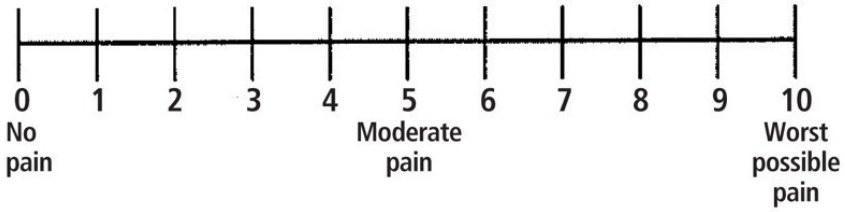
Date: _____ Time: _____
dd/mm/yyyy hh:min

Fill out this page after you get home from the hospital
(6 hours after surgery)

Please complete the following:

Pain:

- Please circle on the line where your pain is now.



Medications:

- When did you first take your pain medication(s)? _____

  hh:mm
- List the type of pain medication(s) you are taking. (please select one)

  □ **Tylenol #3** *or* □ **Percocet** **Other:** _____
- How many tablets of pain medication have you taken since you were discharged from hospital?

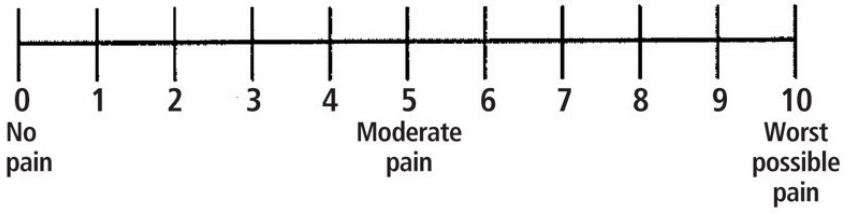
  Number of tablets taken:_____

Fill out this page in the night after you get home from the hospital
(12 hours after surgery)

Please complete the following:

Pain:

- Please circle on the line where your pain is now.



Medications:

- List the type of pain medication(s) you are taking. (please select one)

□ **Tylenol #3** *or* □ **Percocet** **Other:** _____

- How many tablets of pain medication have you taken since you last documented them in the diary?

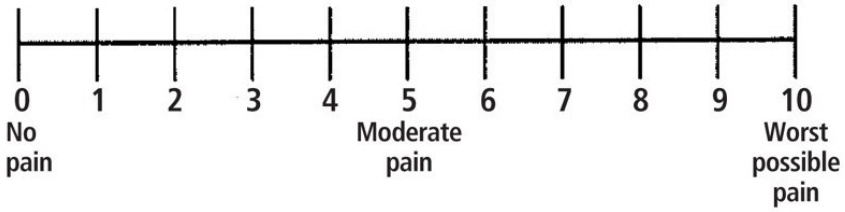
Number of tablets taken:_____

Fill out this page when you wake up on the morning after the surgery
(18 hours after surgery)

Please complete the following:

Pain:

- Please circle on the line where your pain is now.



Medications:

- List the type of pain medication(s) you are taking. (please select one)

☐ **Tylenol #3** *or* ☐ **Percocet** **Other:** _____

- How many tablets of pain medication have you taken since you last documented them in the diary?

Number of tablets taken:_____

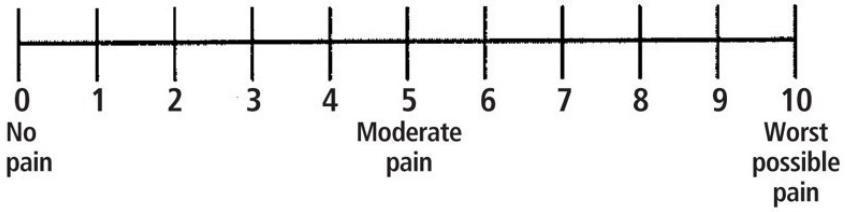
Fill out this page ONE DAY after you get home from the hospital

(24 hours after surgery)

Please complete the following:

Pain:

- Please circle on the line where your pain is now.



Medications:

- List the type of pain medication(s) you are taking. (please select one)

□ **Tylenol #3** *or* □ **Percocet** **Other:** _____

- How many tablets of pain medication have you taken since you last documented them in the diary?

Number of tablets taken:_____

Side effects:

- Answer yes or no if you have had any of the following in the last 24 hours:

Numbness/Tingling in shoulder, arm, forearm, hand	□ Yes	□ No	**Weakness in shoulder, arm, forearm, hand**	□ Yes	□ No
Pain or bruising in the neck where the anesthetic was injected	□ Yes	□ No	**Pain or bruising in the shoulder where the anesthetic was injected**	□ Yes	□ No
Nausea	□ Yes	□ No	**Vomiting**	□ Yes	□ No

Have you had any other side effects? If yes, please list them:

_____

Satisfaction:

- How satisfied you are with the pain relief you received for your shoulder surgery. Please mark an 'x' on the line where your satisfaction is now.

Not Satisfied 0_____10 Very Satisfied

Quality of recovery survey: At 24 hours

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time

PLEASE SEND TO US USING THE SELF-ADDRESSED ENVELOPE

Appendix III: Study timeline

Procedure	**Surgical assessment**	**Anesthesia assessment**	**Ambulatory surgery**					**Patient diary follow-up**	**Phone call follow-up**
Visit Number	1	2	3						4
Visit Day	>2 weeks before surgery	>2 days before surgery	Day of surgery					24 hours after surgery	2 weeks after surgery
Location	Surgeon clinic	PAC	Holding area	Block room	Operating room - surgery	PACU I	PACU II	Home	Home
Pre-Screening of potential candidates (by surgeon)	X								
Information leaflet	X								
Screening for inclusion criteria (by study coordinator)		X							
Informed consent		X							
Answering study-related questions		X	X						
QoR-15		X					X	X	
Premedication			X						
Randomization				X					
Performing ISB or SSNB				X					
Assessment of block success				X					
Analgesic outcomes									
Rest pain NRS score						X	X	X	X
Time to first analgesic request						X	X		
Opioid consumption					X	X	X	X	
Opioid-related side effects						X	X	X	
Discharge time						X	X		
Patient satisfaction							X		
Adverse event reporting				X	X	X	X	X	X