Comparison of the effects of perineural versus systemic dexamethasone on low dose Interscalene Brachial Plexus Block: A randomized trial

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A. Title:

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B. Hypothesis

Perineural dexamethasone added to the local anesthetic ropivacaine for low dose, ultrasound guided interscalene brachial plexus block (US-ISB) provides similar duration analgesia to that of US-ISB with local anesthetic alone and intravenous dexamethasone.

C. Background and Rationale

Interscalene brachial plexus block (ISB) is regarded as the standard of care for analgesia after shoulder surgery providing superior analgesia and reducing opioid consumption.[1,2] ISB can have complications including ipsilateral phrenic nerve block resulting in diaphragmatic paralysis for the duration of the block which can result in temporary ventilatory compromise for patients with reduced respiratory reserve. Nonetheless, the benefits more often outweigh the risks in the appropriate patient population by reducing ventilatory depression associated with significant opioid use after painful upper extremity surgery. Shoulder surgery, previously requiring inpatient admission for pain control, is now commonly performed on an ambulatory basis facilitated by ISB analgesia. The effects of single injection ISB dissipate after several hours unmasking the moderate to severe pain of the surgical insult and require strong opioid analgesia. Efforts to prolong ISB duration by increasing local anesthetic (LA) dose are limited by their pharmacodynamics and narrow therapeutic window.

A broad cross section of surgical patients consistently ranks postoperative pain as their highest concern highlighting the necessity for prolonged and effective postoperative analgesia.[3,4] Strategies to prolong ISB analgesia include the placement of indwelling perineural catheters to allow for prolonged infusion.

Indwelling catheter techniques can be very effective and provide analgesia for several days but their utility is limited by technical challenges with placement, inherent secondary failure rate, and material cost.

Furthermore, not all anesthetists have the subspecialty training required to perform advanced indwelling catheter techniques nor is there universal capability to administer and manage an outpatient perineural catheter program. Centres that do offer outpatient perineural catheter programs are limited by geography in terms of patient eligibility. To address some of these issues, the addition of perineural adjuvants to local anesthetic (eg. clonidine, dexmedetomidine), have been investigated in an attempt to prolong peripheral nerve block duration with limited success.[5,6] The corticosteroid dexamethasone, has been added to local anesthetic solutions for ISB and has demonstrated promise in preliminary studies.[7] Several studies have demonstrated that perineural dexamethasone in conjunction with local anesthetic prolongs the duration of ISB with effect sizes that range from 40% to 75% (absolute effect ~ 6 to 10 hours) with perineural dexamethasone doses of 8 to 10mg.[8-11] Postulated mechanisms of action for perineural dexamethasone include attenuating the release of inflammatory mediators, reducing ectopic neuronal discharge, and inhibiting potassium channel mediated discharge of nociceptive C-fibres.[12-14]

Dexamethasone, however, is only approved for intramuscular or intravenous administration by Health Canada and therefore perineural use is currently off-label. Numerous studies have documented perineural use of dexamethasone without increased incidence of persistent neuropathy. Some concern was expressed with the preservative (sodium bisulfite) in multidose vials causing neurotoxicity. Specific toxicity studies in rat models have documented no histologic changes in nerves when sodium bisulfite (preservative) is directly applied to the nerve at pH7 and a concentration of 0.2% (concentration in commercial preparations of dexamethasone 0.1%).[15] In addition perineural corticosteroid administration

for chronic pain applications (e.g. epidural steroid injection) has a long history of safe administration without evidence of neurotoxicity.[16]

There are several reasons that warrant a new randomized trial. Chiefly, all of the previous trials do not reflect modern regional anesthetic practice. These trials utilized peripheral nerve stimulation (PNS) and local anesthetic volumes of 30 to 40 ml.[8-11] Modern ultrasound guided ISB (US-ISB) allows for more accurate, targeted deposition of local anesthetic with volumes ranging from 5 to 10 ml with no difference in block efficacy or duration compared to larger volumes (≥20ml).[17-20] Despite this, critics of low volume US-ISB persist with the belief that low-volume techniques, with their reduced local anesthetic dose, inherently produce a shorter duration block of lesser quality compared to higher volume. However by advocating for higher volume ISB, practitioners guarantee diaphragmatic dysfunction from ipsilateral phrenic nerve block (near 100% with volume ≥10ml). An ideal solution would be a local anesthetic with adjuvant mixture that allowed administration of lower volumes but with prolonged analgesic duration. The use of low dose local anesthetic with dexamethasone could be one such solution. A trial that demonstrates enhanced block quality and duration associated with perineural dexamethasone added to low dose local anesthetic may allow us to achieve both prolonged duration of effect and reduced side effects due to unwanted local anesthetic spread. This would create further significant benefits for patients and further promote the use of low dose local anesthetic techniques to anesthesiologists who do not currently use this technique.

Secondly, there is some data to suggest that systemic dexamethasone may also prolong block duration.[9] The most recent trial failed to show a difference in block duration between systemic and perineural dexamethasone. The conclusions of this trial were that the two modes of administration were equivalent

at prolonging block duration. This was methodologically incorrect, as the trial was not specifically designed as an equivalency trial with defined equivalency margins.

Our trial will add to the literature by determining if systemic dexamethasone is equivalent to perineural dexamethasone in terms of block duration with a properly designed equivalence trial. Should systemic dexamethasone be equivalent to perineural dexamethasone, anesthesiologists will not have to utilize dexamethasone off-label. Should the two administration modalities not be equivalent, anesthesiologists will be able to make informed decisions about its use.

D. Specific Objective

To investigate the effect of the addition of perineural dexamethasone (4mg) to ropivacaine on analgesic duration of low dose interscalene block compared to ropivacaine alone for interscalene block with systemic dexamethasone.

E. Methods

i. Inclusion Criteria/Sample population

1. Patients undergoing arthroscopic shoulder surgery
2. ASA functional status class I to III
3. Age 18 to 80 years
4. BMI ≤ 35 kg/m^2

ii. Exclusion Criteria

1. Lack of patient consent (including: inability to read or understand the ICF)
2. Allergy to dexamethasone or ropivacaine
3. BMI > 35 kg/m^2

4. Contraindications to low dose dexamethasone including peptic ulcer disease, systemic infection, glaucoma, active varicella/herpetic infections, diabetes mellitus

5. Contraindications to ISB including severe Chronic Obstructive Pulmonary Disease (Forced expiratory volume < 40% predicted), coagulopathy, pre-existing neurologic deficit in ipsilateral upper extremity, localized infection

6. Pregnant or nursing females

7. Chronic opioid use defined as > 30mg oral morphine or equivalent per day

8. Unable to take acetaminophen or celecoxib

iii. Protocol

Patients scheduled for arthroscopic shoulder surgery will be approached for participation by research assistants in the pre-operative anesthetic clinic. Patients providing informed consent will be allocated 1:1 in blocks of 10 using a computer generated random number table (randomization will be stratified by site) and blinding of group allocation will be maintained with sequentially numbered, sealed, opaque envelopes.

The following paragraph outlines standard of care practice (unless otherwise stated) for patients undergoing arthroscopic shoulder surgery at HoAC:

On the day of surgery, patients will be pre-medicated with oral acetaminophen 1000mg, and oral celecoxib 400mg, unless otherwise stated by the attending physician. Once intravenous access is secure and standard monitors applied (electrocardiogram, non-invasive blood pressure cuff, continuous oxygen saturation), patients will receive sedation with intravenous midazolam (1-2mg). The lateral aspect of the neck including the supraclavicular fossa ipsilateral to the surgical site will be cleansed with standard isopropyl alcohol/chlorhexidine gluconate solution. The US-guided ISB will be performed under sterile conditions by a staff regional anesthesiologist, regional anesthesia fellow, or residents under supervision.

The ISB will be performed using a 13-6 MHz 38-mm linear US probe with appropriate sterile barrier (M-Turbo®; SonoSite Inc., Bothell, WA) at the C6 nerve root level via posterior approach with a 22-gauge insulated 50-mm regional block needle (Stimuplex®; B.Braun Medical, Bethlehem, PA). After satisfactory position of the needle tip is achieved and visualized, the injectate will be administered slowly. The total volume injected is 6 ml to allow for the 1 ml of dead space in the block needle line and needle itself.

Control	Experimental
Ropivacaine 1% 3.5 ml + 0.9% saline 3.5 ml, total volume 7.0ml, final concentration 0.5% ropivacaine Intravenous infusion D5W with dexamethasone 4mg, 50 ml to be infused over 15 minutes	Ropivacaine 1% 3.5 ml + 0.9% saline 2.5 ml, 0.4% dexamethasone 1.0 ml, total volume 7.0 ml, final concentration 0.5% ropivacaine, dexamethasone 4mg Intravenous infusion D5W, 50ml

Dexamethasone has been sourced from Sandoz which contains sodium bisulfite, but not the preservative benzyl alcohol which is present in other preparations. The local anesthetic injectate will be prepared in a blinded syringe by trained block room nurses that are aware of group allocation but will take no further part in study procedures or assessments. This individual will prepare the injectate in a 10ml syringe labelled as followed 'ropivacaine 0.5% +/- dexamethasone 4mg' as well as the intravenous infusion labelled ’saline placebo or dexamethasone 4mg’. All other personnel - patients, anesthesiologists performing the ISB or caring for the patient in the operating theatre, anesthesia assistants, surgeons, research assistants performing outcome measures, and statisticians - will remain blinded.

The following two paragraphs outline standard of care practice (unless otherwise stated) for patients undergoing arthroscopic shoulder surgery at HoAC:

Patients will undergo general anesthesia with a standardized induction technique using fentanyl 1 - 4mcg/kg, and propofol 1-3mg /kg both at the discretion of the attending anesthesiologist and titrate to effect. Endotracheal intubation will be facilitated with rocuronium 0.6-1.0mg/kg if necessary or a

laryngeal mask airway can be placed for spontaneously breathing patients. Anesthesia will be maintained using the inhalational anesthetic sevoflurane (AbbVie) with an end-tidal concentration of 1.4 - 2%. The surgeon will infiltrate the arthroscopic port insertion sites with 10-40ml total volume of bupivacaine 0.25% (1:200,000 epinephrine) or lidocaine (as determined by the attending physician). Muscle relaxation will be reversed using a combination of neostigmine (0.04mg/kg) and glycopyrrolate (0.007mg/kg) if necessary. Standard anti-emetic prophylaxis with the serotonin antagonist ondansetron (4mg) will be given. For the purpose of this study, patients will not receive additional dexamethasone regardless of group allocation.

Upon arrival to the recovery room, pain (Verbal Response Score ≥4 or patient request for analgesia) will be treated with intravenous hydromorphone (solely for this study) in 0.2-0.4mg increments every 5 minutes as needed. Postoperative nausea will be treated (as needed) with an additional dose of ondansetron (1mg), droperidol (0.625mg), dimenhydrinate (50mg) or prochlorperazine at the discretion of the attending physician. Capillary blood glucose will also be assessed and recorded for this study. Once oral intake is initiated, patients will receive one of several analgesic preparations as needed: Tylenol #3® (acetaminophen 325 mg/codeine 30 mg/caffeine 15 mg per tablet), or oxycocet (acetaminophen 325 mg/oxycodone HCl 5 mg per tablet), oxycodone 5-10 mg, or hydromorphone 2-4 mg if intolerant to codeine at the discretion of the attending physician. Upon discharge from hospital, patients will receive a prescription for Tylenol #3® as needed, or hydromorphone or oxycocet if intolerant to codeine at the discretion of the attending physician.

After discharge, patients will complete a home pain diary with information that will be collected by research personnel during postoperative telephone calls. Patients will be asked to record the time at which they first experience pain at the surgical site, the time when they first consumed prescribed opioid

analgesics for surgical site pain and when they regained preoperative baseline hand strength. Postoperatively patients will be requested to document interval oral analgesic consumption, presence of nausea or vomiting, presence of weakness in the operative arm, and presence of paresthesia (numbness or tingling) in the operative arm. The doses of oral codeine, hydromorphone, or oxycodone consumed by each patient will be converted into equianalgesic doses (oral morphine equivalents). Conversion ratios will be employed according to the general monograph for opioids in the Canadian Pharmacists' Association Compendium of Pharmaceuticals and Specialties (36th ed., 2001) as follows: oral oxycodone: oral morphine sulphate = 1:1.5, oral hydromorphone:oral morphine sulphate = 1:5, and oral codeine: oral morphine sulphate = 6.6:1. The Opioid conversion table has been appended to this protocol.

All patients will be followed-up by telephone on post operative days 1 and 7 (+/- up to 5 days depending on patient availability) to collect the following study data: NRS pain scores, onset of pain and return of the affected hand to normal strength; side effects or complications experienced [(e.g. paresthesia - numbness or tingling, infection at ISB site) in the operative arm, and whether the numbness or tingling was located distal or proximal to the operative site]; and, the quantity, frequency and onset of opioid consumption. Additional information will not be asked, however if an adverse event (AE) was mentioned during telephone follow-up visits, this will be documented in the AE log and assessed accordingly by the QI. Additional follow-up telephone visits may be conducted as required in the event of a Serious Adverse Event (SAE) or Adverse Reaction (AR) and will be reported in accordance with the Site Guidance on Safety Reporting document

iv. <u>Primary Outcome</u>

- Duration of sensory block – defined as time from end of injection to first sensation of pain at surgical site

v. <u>Secondary Outcomes</u>

- Time to first opioid consumption – from end of injection to time to first oral opioid consumption
- Duration of motor block - from end of injection to time of baseline preoperative biceps and hand strength
- Oxygen saturation on room air 1 hour after arrival to recovery room
- Opioid consumption on POD 1 at 12 hours/bed time if patient retires to bed before the 12hr time point), 24 hours and 7 days
- NRS for pain at 12hrs/Bed time (if patient retires to bed before the 12hr time point), 24hours, 7 days
- Blood glucose in recovery room
- Persistent paresthesia in the operative arm at 7 days
- Localized infection at block site at 7 days
- Postoperative nausea

vi. Sample size calculation

Based on our clinical experience with low dose US-ISB (ropivacaine 0.5% 5ml) as well as previously published work, we expect mean sensory block duration of 12 hours with a standard deviation of 4 hours. Based on the literature, we expect a mean prolongation of block time associated with perineural dexamethasone to be approximately 50% thereby increasing block duration to 18 hours. Defining an equivalency margin of 2 hours, we estimate that 87 patients per group (174 total) will be required to reliably test our hypothesis given $\alpha=0.05$ and $\beta=0.9$. To account for incomplete data or loss to follow-up, the plan is to recruit 90 patients per group (180 total).

vii. Statistical analysis

Demographic data will be summarized and expressed using appropriate measures of central tendency and dispersion for continuous data, means and standard deviations will be provided (medians and interquartile ranges for non-normally distributed data) and for categorical data counts and percentages will be displayed. The primary outcome, time to first sensation of pain at the surgical site, will be compared between the two groups using a two sample equivalence test of means. Secondary outcomes that are time based will also be assessed in the above manner (time to first analgesic request, duration of motor block). Continuous secondary outcomes (opioid consumption, NRS) will be assessed with repeated measures ANOVA while blood glucose will be assessed with the t-test. Categorical outcomes (paresthesia,

infection, nausea) will be compared with the Chi square or Fisher's exact test for the case of low expected cell counts.

viii. Trial conduct and Data collection/management

The coordinating centre for this trial will be Sunnybrook Health Sciences Centre where the study coordinator and central data clerk will be based. A physician lead will be available at SHSC to answer patients' questions about the study as well as acting as a resource for the site specific study coordinator regarding patient eligibility and education of required hospital staff. The master randomization list will be kept at SHSC.

Data will be collected on a customized case report form (CRF) that includes all relevant demographic and intra-operative data as well as each outcome sought. Patients will be provided with a home diary to complete that will capture all outcomes sought that are not obtained in hospital. CRFs and home diaries will be completely de-identified with only patient study number, age (in years), and gender as identifiers. Data from the CRFs will be entered into a database at each site on secure, password protected computers with hospital network backup. The master file linking identifying data (name, MRN, date of birth) and study number will be kept in a separate file on a secure, password protected computer with hospital network backup.

CRFs will be divided into 2 categories: "CRFs" and "Source-CRFs". "Source-CRFs" are the documents used by the RA or patient to directly capture study data. They include: the pain diary, side effect questionnaires and the sensory and motor block assessments. "CRFs" will be completed with data transcribed from a source document. They include: Preoperative details, intra-operative data collection and medication administered in the Post Anesthesia Care Unit (PACU) and Day Surgical Unit (DSU) all obtained from medical records.

Data collection plan

Data will be collected according to the Source-CRFs/CRFs. All data collection will be conducted by a research staff member, either a research assistant or a co-investigator, who is blinded to the patient's treatment allocation.

1. Identifying information, exclusion criteria, surgical procedure description and anesthesia data will be collected preoperatively.
2. Procedure details, including: sedative used, procedure duration (end of injection), pain on injection and the presence of blood will be collected during the block procedure.
3. Pinprick sensation in the C4-T1 dermatomes at 10 and 20 minutes post block (to characterize presence/absence of block). Pain Sensation is characterized as a: (2) = sharp sensation, (1) = dull sensation only, or (0) = no sensation.
4. Motor function (elbow flexion for biceps) at 10 and 20 minutes post block. Power is graded using (2) = normal movement, (1) = reduced movement and (0) = no movement.
5. Intra-operative anesthesia data collection. Time of first Incision, administered anesthesia and time procedure ended.
6. Room air pulse oximetry 1 hour after admission to PACU/recovery room (to characterize respiratory function near discharge)
7. Blood Glucose level in PACU.
8. An account of analgesia administered in PACU.
9. Numerical rating scale (NRS) pain scores 1 hour after admission to PACU to PACU/recovery room
10. Information regarding post block complications (including pain and bruising around the block site) will be collected in a 1 week postoperative telephone call with the patient.
11. Time to first pain sensation in the shoulder, analgesic use and return of the affected hand to normal strength will be captured in the take home patient diary and reported at follow-up telephone calls.
12. NRS pain scores, analgesia consumption and side effects experienced will be captured at: 12hours/bed time, 24 hours and 7 days post-operatively in the patient's diary reported at follow-up telephone calls.

Upon achieving enrolment of the specified 180 patients and data is collected, the database will be verified, and analyzed by the biostatistician.

ix. Data safety monitoring plan

This study involves the off-label use of dexamethasone. Consequently, an application to Health Canada will be made to obtain regulatory approval for the use of perineural dexamethasone. All adverse events will be documented (serious or not, related or not, expected or not) and reported following the Site

Guidance on Safety Reporting document. Serious adverse events are not expected. The severity of the adverse event will be coded as mild, moderate, or severe. The association with the intervention will be coded as unrelated, unlikely related, possibly related, probably related, or definitely related. The principal investigator will review all adverse events and act as safety monitor. These will be communicated to Health Canada and the Research Ethics Board of each respective institution. The independent reviewers will determine if the off-label use of dexamethasone contributed in any way to the adverse event and will make recommendations to either terminate, or modify study protocols.

The following are potential side effects often associated with surgical procedures that are not considered adverse events related to this study (obtained confirmation from five other physicians who declare no conflict of interest) and will therefore not need to be assessed and recorded by the QI in cases where these side effects are reported by study patients while they are in hospital and at home during post-operative follow-up telephone interviews:

- Headache/dizziness/nausea/vomiting/wheezing
- Bruising in the arm
- Gritty feeling in the eye/blurred vision/mild visual disturbance
- Bradycadia/tachycardia
- Complications associated with general anesthesia such as major cardiac events
- Local anesthetic toxicity
- Hemidiaphragmatic paresis (temporary)
- Hoarse voice (temporary)
- Horner's syndrome (temporary)
- Pruritus
- Changes in blood pressure
- Oxygen saturation below 90%
- Pain, cellulitis, or muscle spasm in areas other than the nerve block injection

A single interim analysis will be performed at 50% enrolment. If the data analysis indicates equipoise no longer exists, the study will be stopped early. The Haybittle-Peto threshold will be utilized (p=0.001).

F. <u>Significance/implications</u>

This trial will have a positive impact by determining whether perineural dexamethasone is truly equivalent to systemic dexamethasone in terms of prolonging ISB duration. If the two modalities of administration are equivalent, then anesthesiologists will not have to administer an off-label medication and achieve similar results with the standard indication for dexamethasone, prophylaxis for post-operative nausea and vomiting. Secondly, this will allow anesthesiologists to gain confidence in low-volume techniques that may decrease the incidence of respiratory complications in patients receiving ISB without compromising analgesic benefits.

G. Investigators

The investigators have extensive experience performing regional block procedures as well as numerous peer reviewed publications and successful grant application. Investigators at each site have dedicated academic time to ensure completion of the project. The principal investigator (SC) has completed a post-graduate degree with training in epidemiology and the conduct of multi-centre randomized trials.

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