PROTOCOL

Title
Bilateral cervical plexus block for anterior cervical spine surgery: a randomised placebo-controlled trial

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1.0 Introduction

1.1 Background

Anterior cervical discectomy and fusion (ACDF) is a common surgical procedure for cervical spine disease. Recently, there had been increasing focus on reducing the length of hospital stay after this procedure. Whilst the mean length of stay has been report to be approximately two days, some centres are performing this procedure in an outpatient setting. (1-4) The approach for anterior cervical disc arthroplasty is the same for ACDF, and there is a trend towards performing this procedure in the outpatient setting too. (5) We will hereafter refer to these two operations under the heading anterior cervical spine surgery (ACSS).

Pain and nausea have been reported as the most common reasons for prolonged admission or re-admission after ACDF. (6, 7) Pre-emptive analgesia with regional anaesthesia is a method used to improve postoperative pain management. The superficial cervical plexus block (SCPB) has been used for neck surgeries for this reason. (8) The cervical plexus is formed by the anterior rami of the upper four cervical nerves, and lies deep to the prevertebral fascia on scalenus medius. In a SCPB, local anaesthesia is infiltrated at the punctum nervosum, anaesthetising four superficial branches of the cervical plexus: the lesser occipital, the great auricular, the transverse cervical, and the supraclavicular nerves. The distribution of these nerves includes the anterolateral neck, and the pre- and post-auricular areas. SCPB is preferred to deep cervical plexus block as the deep block is associated with a greater risk profile without conferring significant benefit. (9)

The SCPB has been shown to provide good relief of incisional pain after thyroid and carotid surgery, and relief of occipitonalchual pain after neurosurgical procedures. (8-11) It may also theoretically reduce opioid use and therefore reduce opioid related side effects, such as nausea and vomiting, and respiratory depression. In addition, an aim of the SCPB would be to improve the overall quality of recovery from surgery and anaesthesia from the patient perspective.

Whilst SCPB has been studied in thyroid and carotid surgery, there is a paucity of data for ACSS. Wang et al. conducted a randomised controlled trial (RCT) comparing general anaesthesia with bilateral combined deep and superficial cervical plexus block on patients undergoing a single level ACDF. (12) The surgeon, anaesthetist, and patient were, necessarily, not blinded. There was no predefined primary outcome. It was a single centre study conducted in Shijazhuang, China that enrolled 169 patients to receive general anaesthesia and 187 patients to receive cervical plexus anaesthesia. Relevant results from this RCT include a trend towards better post-operative pain
control in the first 24 hours for the patients receiving cervical plexus anaesthesia, with significantly less amounts of post-operative analgesia and anti-emetic requirements. Intra-operative haemodynamic stability, and patient satisfaction scores, were greater in the general anaesthesia group.

The only trial we are aware of studying SCPB in ACSS is an RCT conducted by Mariappan et al. comparing unilateral SCPB with no block in patients undergoing single or two level ACDF. (13) The primary outcome was the 40-item quality of recovery questionnaire score (QoR-40) measured at 24 hours post-surgery. The patients were blinded, but the surgeon and anaesthetist were not. It was a single centre study conducted in Toronto, Canada that enrolled 23 patients to each group. The QoR-40 scores were significantly better in the SCPB group (179 [116-195] vs. 157 [97-196]) (median [interquartile range]).

The disadvantages of this trial include the small number of patients, the lack of investigator blinding, and the lack of a placebo. Their chosen cutoff of 10 points as representative of a clinical improvement in the QoR-40 score is not reflective of the current literature (see section 3.1). In addition, we believe a bilateral SCBP yields superior outcomes to a unilateral block as the surgical incision can sometimes reach, or cross, the midline. Finally, the block was landmark based, rather than ultrasound guided. Ultrasound guided SCPB have greater efficacy and reduced local anaesthetic toxicity compared to the landmark technique. (14, 15) We will address these issues in our proposed study.

1.2 Rationale

Placebo-controlled trials are particularly important when outcomes are based on patients’ subjective rating. (16) To our knowledge, there are no placebo trials investigating SCPB for ACSS. There are no trials registered with the World Health Organisation International Clinical Trials Registry Platform relating to SCPB and ACSS.

This trial is justified because there is a need to: 1) demonstrate the true treatment effect of this intervention; 2) control for the bias that is associated with tangible intervention; 3) provide a quantification of the adverse events of this intervention.

The anticipated benefits of SCPB in ACSS include: a reduced length of hospital stay due to improved post-operative recovery; an improved patient experience; decreased opioid requirements.
Alternatively, a placebo-controlled trial may demonstrate no benefit form SCPB, and in that case an unnecessary percutaneous procedure and administration of a medication will be avoided.

1.3 Aim

To investigate the effect bilateral cervical plexus block with local anaesthesia has on post-operative recovery in patients undergoing anterior cervical spine surgery (ACSS).

1.4 Hypothesis

Bilateral SCPB is superior to placebo in patients undergoing ACSS in improving post-operative recovery as measured by the QoR-40 score at 24 hours.

2.0 Study population

2.1 Eligibility criteria

Inclusion criteria:
- age ≥ 16 years old
- undergoing anterior cervical discectomy and fusion
- undergoing anterior cervical disc arthroplasty
- isolated cervical spine trauma requiring anterior fusion only

Exclusion criteria:
- multitrauma
- undergoing anterior cervical vertebrectomy and reconstruction
- undergoing posterior fixation in addition to anterior surgery
- undergoing surgery for malignancy
- allergy to ropivacaine or bupivacaine
- pregnant patients
- neurologic or psychiatric condition that would prevent completion of the QoR-40 questionnaire

2.2 Participant recruitment

Patients will be identified by the consultant neurosurgeons involved in the trial in the outpatient setting. Patients will be screened for trial eligibility after they have been consented for surgery. Potential participants will have their inclusion and exclusion criteria checked against a printed eligibility criteria checklist to be completed by the surgeon for all patients screened. Patients will be screened and enrolled in a consecutive manner. Patients will have until the day prior to surgery to consider participation.

There is no cost to the patient, nor will there be financial renumeration, for participation in the trial.

2.3 Participant enrolment

Each potentially eligible patient will receive a study enrolment number. A screening log will be stored for all patients. The date of evaluation, and the inclusion and exclusion criteria met and not met will be recorded in an electronic database. This number will be stored in the patient’s medical record and on all study documents.

Eligible patients will be enrolled after the informed consent process has been completed.

2.4 Information and consent

Patients will undergo an informed consent process with their treating neurosurgeon in the clinic setting. A patient information form in plain English will be provided to each participant. Phone interpreters will be used as required.

Patients will be informed of any new information relevant to the treatment being studied that becomes available during the trial. Patients will be free to withdraw from the study at any time without giving a reason.

2.5 Centres

Macquarie University Hospital
3.0 Outcomes

3.1 Primary outcome

The primary outcome will be the QoR-40 score measured at 24 hours post-operation completion time.

The ‘quality of recovery’ score was developed to provide a patient-orientated assessment of the quality of recovery after surgery and anaesthesia. (17) The score was expanded to the QoR-40, and was validated, and shown to be reliable, when completed on the first post-operative day. (18) The score measures five dimensions of patient experience: pain; emotional state; physical independence, comfort; and psychological support. A systematic review showed that the QoR-40 was a widely used, valid, reliable, and responsive tool for assessing quality of recovery from a patient perspective. (19)

The minimum clinically important difference (MCID) can be thought of as the smallest change that is important to a patient, and is an especially important concept in studies involving patient-reported outcomes. (20) There are various methods of determining MCID. A 2016 study, using the anchor method, determined the MCID to be 6.3 for the QoR-40. (21) Based on cardiac studies, one author argued that a change of 5-7 signifies a clinically important difference in the QoR-40 score. (22) A randomised study of patients undergoing cervical spine surgery predefined their MCID a change of 10. (13) In a prospective study of patients undergoing neurosurgery procedures, the mean (SD) QoR-40 at post-operative day 1 in 92 patients undergoing spinal surgery was 160 (15). (23) Based on the distribution-based approach of determining MCID (that is, half standard deviation) the MCID would be 7.5. Taking this into account, we chose a change of 7.5 to signify a clinically important change in a spinal surgery setting.

3.2 Secondary outcomes

- 24 hour opioid usage (converted to equivalent units of oral morphine)
- Numeric pain rating scale for neck pain at 1 hour, 3 hours, 6 hours, and at 24 hours post-operative time
- Incidence of nausea, vomiting, dysphagia, or hoarseness in the first 24 hours after surgery
- The 36-Item Short Form Health Survey measured pre-operatively and at 6 weeks
- Hospital length of stay

4.0 Trial design

4.1 Design

This is a pragmatic, multi-centre, triple-blind, parallel-group, randomised controlled placebo trial. The anticipated recruitment period is for 24 months.

Patients will continue their regular analgesia medication, including on the morning of surgery. NSAIDs will be stopped at least 48 hours prior to surgery. The pre-operative opioid dose will be converted to an equivalent oral dosage of morphine in a 24 hour period to allow standard calculation. If the patient is on ‘as needed' opiate medication, the highest dose they took in a 24 hour period in the week before surgery will be used to calculate the daily dose.

All patients will undergo general anaesthesia. The patients randomised to the intervention group will have a cervical plexus block administered under ultrasound guidance with a local anaesthetic solution, whilst patients randomised to the placebo group will be injected with a saline solution.

All patients will be admitted to the high dependency unit (HDU) post-operatively.

The primary endpoint is the QoR-40 score at 24 hours after surgery. It will be measured by blinded assessors. The study flowchart is demonstrated in Figure 1.

The trial design is pragmatic to focus on real-world patient-orientated outcomes, rather than trying to measure efficacy in an ideal scenario. As such, the inclusion criteria are based on the type of surgery being performed rather than the indication for surgery. Also, the retractor system and interbody devices used were not pre-specified, but based on surgeon’s preference.

4.2 Interventions

All patients will receive standardised monitoring and an anaesthetic regimen consisting of induction with intravenous fentanyl, propofol and a non-depolarising muscle relaxant (NDMR) to facilitate endotracheal intubation. Anaesthesia will be maintained with oxygen, air, and sevoflurane.
After induction of anaesthesia, bilateral ultrasound guided SCPB is placed by an anaesthetist experienced in delivering the block. Patients randomised to the local anaesthetic group will receive 15mL of 0.2% ropivacaine on each side (totalling 30mLs); the placebo group will receive 15mLs of 0.9% saline on each side. The cervical plexus is composed of purely sensory nerves, so a low concentration local anaesthetic was chosen to reduce the risk of local anaesthetic toxicity and inadvertent motor block. (24)

All patients will receive skin infiltration at the incision site of 5mls of 0.25% bupivicaine with 1:400,000 adrenaline by the surgeon prior to incision, a local standard of care.

The technique for the SCPB described below is similar to the method described by the New York Society of Regional Anaesthesia (NYSORA) for ultrasound guided SCPB. (25)

After the patient is positioned and the skin prepared with a chlorhexidine-alcohol scrub, the transducer is placed on the neck, overlying the sternocleidomastoid muscle (SCM) at its midpoint (approximately the level of the cricoid cartilage). Once the SCM is identified, the transducer is moved posteriorly until the tapering posterior edge is positioned in the middle of the screen. At this point, the brachial plexus and/or the interscalene groove (between the anterior and middle scalene muscles) should be identified. Then, the needle is passed through the skin, platysma and prevertebral fascia, placing the tip adjacent to the superficial cervical plexus. 15mL of the solution is administered to envelop the plexus.

Intraoperatively, all patients will receive 4mg of intravenous (IV) dexamethasone after induction of anaesthesia and before surgical incision. During closure, patients will receive 1g of IV paracetamol followed by 4mg of IV ondansetron or 1mg of IV granisetron for postoperative nausea and vomiting (PONV) prophylaxis. Additional analgesia will be provided with incremental boluses of fentanyl as indicated.

At the end of the surgery, sevoflurane will be turned off and the neuromuscular blockade will be reversed with neostigmine (50 mg/kg IV) and glycopyrrolate (10 mcg/kg IV) or sugammadex. Patients were taken to the post-anaesthetic care unit (PACU) and then to the HDU, or directly to the HDU.

The general post-operative care of the patients will be directed by the local standard practice in terms of monitoring and assessment of neurological status, pain, PONV, and level of sedation.

Patients will be asked to rate their pain upon arrival and at regular intervals using an 11 point visual analogue scale by the recovery nurse (0 = no pain to 10 = the worst pain imaginable; D= Difficult to
assess, U= Unconscious). This score is recorded separately when at rest and with patient movement. The character of pain will be recorded as one of five choices (Dull, Pressure, Radiating, Sharp, Throbbing). Nausea and vomiting will be assessed using a scoring system (0= No nausea 1= occasional nausea, 3= Nausea and occasional vomiting, 4= Constant vomiting). The level of sedation will be recorded using an analogue score (0= wide awake, 1= Easy to rouse, 2= Drowsy, 3= Difficult to rouse, 4= Unrousable). To maintain a pain score of <4, or the patient being clinically comfortable, an opioid will be administered IV every two to five minutes as needed. The choice of opioid will be at the discretion of the anaesthetist.

Difficulty with postoperative nausea and vomiting will be treated with 0.5mg of IV droperidol and/or 4mg of IV Ondansetron.

In the first post-operative day, patients will receive regular paracetamol (1g four times a day) and oral opiates or a patient controlled analgesia (PCA), at the discretion of the anaesthetist.

4.3 Randomisation

A patient will be randomised to the study once they have met the eligibility criteria. The day prior to surgery, the pharmacy will receive the randomisation code, allocating the patient to one of the two groups. The randomisation of participants will occur via a central computer generated randomisation service - the Macquarie Clinical Trials Unit (who will not be involved in patient care, data collection or analysis).

Due to expected differences in dissection technique, stratified randomisation will be performed based on the number of levels operated on (dichotomised to ≤2 or >2).

4.4 Concealment

The pharmacy will produce the solution after receiving the randomisation notice, and will send the blinded solution to theatre on the day of surgery in a vial marked “Ropivacaine 0.2% OR Placebo 15mL” along with the patient’s name, study enrolment number, and expiry date.

4.5 Blinding
The surgeon and anaesthetist will be blinded to the solution being injected. The surgeon performing
the operation will follow up with the patient six weeks later and will remain blinded to their study
allocation.

The patient will not be aware which solution they will be receiving and will remain blinded to the
study arm they are allocated to after the operation.

The investigators conducting the questionnaires will not be aware of the treatment given to the
patient.

5.0 Statistics and analysis

5.1 Sample size calculation

The primary endpoint is the QoR-40 score at 24 hours post-operatively. We used an MCID of 7.5
for the QoR-40, as discussed above. We calculated that with a dichotomous analysis (one way
ANOVA) between the two groups, a 128 patient trial has 80% power at the 5% significance level,
with a medium effect size (Cohen’s f=0.25).

5.2 Confounders

Potential confounders include:

1. Number of levels operated on*
2. Revision surgery
3. Opioid tolerant v opioid naive patients**
4. Adjuvant analgesia
5. Smoking
6. Worker’s compensation status
7. Level operated on

* Dichotomised into ≤2, or >2

** The pre-operative opioid dose will be calculated over a 24 hour period and converted to
equivalent units of morphine.
5.3 Statistical analysis

Baseline characteristics will be summarised by treatment group to assess comparability. The primary outcome will be analysed with a one way ANOVA test. Data will be reported as mean (SD). All reported P values will be two sided.

Linear regression analyses are planned for the 24 hour opioid usage; for the pre-operative and 6 week SF-36 results; and for the log transformed data of the hospital length of stay. A general residual model will be applied. The residuals will be tested for normality. If the assumption of normality is violated, a Box-Cox transformation will be performed.

A logistic regression analysis is planned for the incidence of nausea, vomiting, dysphagia, or hoarseness in the first 24 hours after surgery. The results of the numeric pain rating scale will be compared between groups using a Mann-Whitney U test.

6.0 Data collection and storage

All forms will be completed in English. Data will be collected directly from patients after enrolment. All paper copies of collected data will be stored in a locked filing cabinet in the Chief Investigator’s office. All paper copies will be identified by the patient’s study enrolment number. The database of patient’s names and enrolment numbers will be stored on a password protected hard drive, thus preserving the de-identification of the paper copies.

All data will be entered into an electronic trial database stored on a password protected external hard drive that will remain in the office of the chief investigator. Baseline characteristics will be entered into the trial database. The QoR-40 questionnaire will be completed by the patient with an investigator 24 hours after surgery. Patients will follow up with their treating neurosurgeon 6 weeks after surgery and final data collection will occur at this time.

Information and data will be stored for 10 years and then be erased. The Chief Investigators only will have access to the filing cabinet and hard drive.

7.0 Ethics

A Human Research Ethics Application is being submitted through the National Health and Research Council.
8.0 Safety

8.1 Adverse events

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (26) A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect. (26)

All adverse events will be recorded. When a serious adverse event occurs, it will be reported immediately to the Macquarie University Human Research Ethics Committee (HREC). The chief investigator will review all documentation related to the event, and provide a written report to the HREC. Adverse events related to the SCPB to be recorded are:

- allergic reaction to local anaesthetic solution
- local anaesthetic toxicity
- accidental intravascular injection of local anaesthetic
- SCPB site haematoma
- upper limb paresis
- Horner’s syndrome
- phrenic nerve palsy

Each adverse event has a less than 1% chance of occurring with this procedure.

8.2 Early termination

An interim analysis is not planned for this trial.
The investigators have the right to terminate the study at any time for clinical or administrative reasons. The chief investigator will contact all participants and the HREC to inform them of the trial termination.

8.3 Unblinding

If life-threatening adverse event occurs in the intra-operative period, unblinding will occur when the anaesthetist for the case calls pharmacy to request emergency unblinding.

9.0 Confidentiality

All questionnaires and other records will be identified only by the patients study enrolment number to maintain participant confidentiality. All paper records will be stored in a locked cabinet accessible only to the chief investigators. Electronic information will be stored on a password protected hard drive accessible only to the investigators.

Clinical information will not be released without the written permission of the patient, except as necessary for the HREC.

Published results will not contain any personal data that could allow identification of individual patients.
10.0 References


