Trials

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Ultrasound-guided supraclavicular block versus Bier block for emergency reduction of upper limb injuries: statistical analysis plan

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Abstract

Background Ultrasound-guided supraclavicular block (UGSCB) is an emerging technique gaining interest amongst emergency physicians that provides regional anaesthesia to the upper limb to tolerate painful procedures. It offers an alternative to the more traditional technique of a Bier block (BB). However, the effectiveness or safety of UGSCB when performed in the emergency department (ED) is unclear.

Methods SUPERB (SUPraclavicular block for Emergency Reduction versus Bier block) is a prospective open-label non-inferiority randomised controlled trial comparing the effectiveness of UGSCB versus BB for closed reduction of upper limb fractures and/or dislocations. Adult patients presenting with upper limb fracture and/or dislocation requiring closed reduction in ED were randomised to either UGSCB or BB. Once regional anaesthesia is obtained, closed reduction of the injured part was performed and immobilised. The primary outcome is maximal pain experienced during closed reduction measured via a visual analogue scale (VAS). Secondary outcomes include post-reduction pain, patient satisfaction, total opioid requirement in ED, ED length of stay, adverse events and regional anaesthesia failure.

Results Primary outcome analysis will be performed using both the intention-to-treat and per-protocol populations. The between-group difference in maximum pain intensity will be assessed using linear regression modelling with trial group allocation (UGSCB vs BB) included as a main affect. A pre-specified non-inferiority margin of 20 mm on the VAS scale will be used to establish non-inferiority of UGSCB compared to BB.

Conclusion SUPERB is the first randomised controlled trial to investigate the effectiveness and safety of UGSCB in the ED. The trial has the potential to demonstrate that UGSCB is an alternative safe and effective option for the management of upper extremity emergencies in the ED.

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Introduction

Background and rationale

Closed reduction of upper limb fractures and/or dislocations are common in the emergency department (ED). Traditionally, Bier block (BB) is advocated which involves injection of local anaesthetic intravenously to anaesthetise the arm with a tourniquet proximally to prevent systemic spread [1]. An alternative is ultrasound-guided supraclavicular block (UGSCB) where the brachial plexus is identified on ultrasound at the supraclavicular fossa and local anaesthetic is injected around these nerves to anaesthetise the arm [2, 3]. It is unknown whether

UGSCB performed by emergency physicians is effective or safe.

The SUPraclavicular block for Emergency Reduction versus Bier Block (SUPERB) trial [4] will be the first randomised controlled trial (RCT) comparing UGSCB to BB for providing regional anaesthesia for the closed reduction of upper limb fractures and/or dislocations in the ED. The primary hypothesis is non-inferiority of UGSCB compared to BB for the primary outcome measure of maximal pain during closed reduction, as reported by the participant on a 10-cm visual analogue scale (VAS; [5]). Secondary outcome measures include pain at 1-h post-procedure, patient satisfaction, ED length of stay, analgesic requirements, adverse events and adjunct therapies or treatment failure.

This document constitutes the statistical analysis plan (SAP) for the SUPERB trial, finalised before completion of data collection and commencing analysis of participant data.

Objectives

(1) Assess effectiveness of UGSCB for closed reduction of upper limb fractures or dislocations performed by emergency physicians when compared with BB, with a non-inferiority hypothesis for patient-reported procedural pain.
(2) Determine feasibility, safety, ED length of stay, and patient satisfaction of UGSCB versus BB for the closed reduction of upper limb fractures or dislocations.

Methods

Trial design

The SUPERB trial is an open-label, single-site, non-inferiority RCT with a 1:1 allocation ratio, comparing regional anaesthetic modality (UGSCB vs BB) for adult patients with upper limb fracture and/or dislocation requiring closed reduction and immobilisation in the ED.

Patient population

Eligible patients will be adults presenting to the ED with an upper limb fracture and/or dislocation requiring closed reduction, who have no contraindication to either UGSCB or BB.

Inclusion criteria

- Aged 18 or older
- Capacity to provide written informed consent
- Upper limb fracture and/or dislocation requiring ED closed reduction and immobilisation

Exclusion criteria

- Refusal of consent
- Local anaesthetic allergy
- Open fractures, unstable fractures and/or dislocations that require urgent surgical fixation.
- Pregnancy
- Anticoagulation
- Chronic lung disease
- Skin infection of the supraclavicular site of injection
- Previous surgery or radiation therapy to the supraclavicular region
- Severe hypertension (> 160 mmHg)
- Compartment syndrome
- Congenital or idiopathic methaemoglobinaemia
- Sickle cell disease
- Peripheral vascular disease
- Peripheral neuropathy
- Cardiac conduction delay.

Intervention

Patients are randomised to receive either UGSCB or BB as regional anaesthesia for the closed reduction of their upper limb injury. Full details of these interventions are outlined in the study protocol [4].

Bier block (BB)

The participant will have cardiorespiratory monitoring attached, and an intravenous cannula (IVC) inserted distally on the affected limb. The limb will be elevated to enhance venous drainage, after which the BB cuff will be inflated proximally to 100 mmHg above the patient's systolic blood pressure. Prilocaine (0.5%, 5 mg/kg to maximum of 250 mg) or lignocaine (0.5%, 3 mg/kg to maximum of 200 mg) will be injected via the IVC on the affected limb. Closed reduction will be performed following assessment of adequate regional anaesthesia, followed by the slow release of the BB cuff after 30 min.

Ultrasound-guided supraclavicular block (UGSCB)

The participant will have cardiorespiratory monitoring attached. The supraclavicular region will be cleaned with chlorhexidine with full sterile precautions. Using ultrasound imaging of the supraclavicular fossa, local anaesthetic (20 ml of 0.75% ropivacaine) will be injected inferior and superior to the brachial plexus

bundle. Closed reduction will be performed following assessment of adequate regional anaesthesia.

Randomisation and blinding

Randomisation is conducted via a web-based central randomisation service (Griffith University Clinical Trials Randomisation Service) and occurred using block randomisation of size 4–6 (size randomly selected) with a 1:1 ratio to ensure equal numbers in each group. Due to the nature of the intervention prohibiting blinding, the trial is open label with participants and treating clinicians aware of trial group allocation. However, outcome assessors and data analysts will be masked to the group allocation.

Sample size

Sample size calculations were performed to detect non-inferiority, using a margin of 20 mm [6] on the 10-cm VAS scale, with an estimated standard deviation of the VAS pain score of 30 mm [7] and estimated true between group difference of 0. To achieve 80% power with one-sided α of 0.025, primary outcome data for 72 participants was required (36 for each group allocation). To allow for 5% attrition, recruitment of a total sample size of 76 participants was planned (i.e. at least 38 participants per intervention arm).

Outcomes

Primary outcome

The primary outcome is maximal level of pain experienced during closed reduction, as reported by the participant on a 10-cm VAS. The participant will mark their level of pain on a printed VAS scale anchored with "no pain" at 0 cm and "pain as bad as it could possibly be" at 10 cm. The non-inferiority margin was defined as a 20-mm difference on the 10-cm VAS scale [6].

Secondary outcome

Secondary outcome measures include:

- Pain at 1-h post-procedure (or immediately prior to discharge if under 1-h post-procedure) measured using the 10-cm VAS
- Patient satisfaction measured using the 10-cm VAS
- ED length of stay
- Analgesia measured as total opioid use (pre-hospital and in ED) measured using oral morphine equivalent in milligrams
- Pain VAS and patient satisfaction at 24–72 h post-discharge from the emergency department, measured using a separate 10-cm VAS
- Management including number of sedations required, number of inpatient transfers and number of operations
- Adverse events
- Adjunct therapies or treatment failure

Data management plan

The data management plan is outlined in our published protocol [4].

Framework

The primary analysis will evaluate whether non-inferiority can be established for UGSCB in comparison to BB for the primary outcome measure of maximal pain experienced during closed reduction. Non-inferiority will also be evaluated for secondary outcomes recorded as pain on the 10-cm VAS scale. Other secondary outcomes will be evaluated for superiority of UGSCB over BB.

Statistical analysis

Analysis principles

Data analysis will be conducted once data collection is completed and all outcomes will be analysed collectively. The analysis principles are as follows:

(1) All analysis will be conducted on the intention-to-treat population, with outcome data for all participants analysed according to their random group allocation, regardless of the actual intervention received (i.e. BB or UGSCB) or the occurrence of protocol deviations. Notably, only participants with complete primary outcome data will be included. As intention-to-treat analysis may bias towards a finding of no effect, per-protocol analysis will also be performed for comparisons with a non-inferiority hypothesis and reported alongside the intention-to-treat analysis [8, 9]. The per-protocol population will consist of all participants who received their allocated intervention and who had no protocol deviation expected to affect the efficacy of regional anaesthesia and analysis. No interim analysis were planned or conducted.
(2) Tests of non-inferiority will employ one-sided significance testing with type I error rate (α) of 0.025. Other statistical significance tests will be two-sided, with α of 0.05.
(3) 95% confidence intervals (CI) will be reported for all between-group comparisons.
(4) Primary and key secondary outcomes have been pre-specified.
(5) Formal adjustment for multiple hypothesis testing will not be applied. For this reason, only findings

from the primary outcome analysis will be regarded as definitive, whereas secondary outcome findings will be treated with due consideration for the multiple comparisons conducted.

(6) Continuous variables will be evaluated for the appropriateness of parametric methods, such as linear regression, by assessing their distribution for marked skew, influential outliers and heteroscedasticity. Formal hypothesis tests for normality will not be reported [10]. Continuous variables with substantial non-normality will be analysed with appropriate non-parametric methods, specifically median regression.

(7) Missing data will be reported but not imputed, with best–worst case sensitivity analysis used to test robustness of study findings as required [11]. If the proportion of multiple imputation is non-negligible, multiple imputation of missing data will be performed.

(8) Analysis will be performed using Stata (StataCorp), v14.2 or later.

Datasets analysed

Analysis will be conducted on the modified intention-to-treat population, in which all randomised participants are included in the statistical analysis as part of their random group allocation, regardless of the details of the actual intervention performed or the occurrence of protocol deviations. Protocol deviation is defined as incidences when the intended intervention (i.e. UGSCB or BB) was not performed or failed, requiring an alternative technique to be undertaken. The incidence of protocol deviation will be presented as percentage and a description of the alternative techniques implemented will reported.

As cross-over and other forms of protocol nonadherence may bias towards a null effect, for comparisons with a non-inferiority hypothesis (including the primary outcome), analysis of the per-protocol population will also be performed and reported. This population will consist of all participants who received their randomly allocated intervention, without any protocol deviation expected to influence the efficacy of regional anaesthesia and analgesia.

Trial profile

Consistent with the Consolidated Standards of Reporting Trials (CONSORT) statement [12], the progress of participants through the SUPERB trial will be demonstrated using a flow diagram. The flow diagram will report the number of participants assessed for eligibility, the number of participants who were enrolled and randomised and the number who were excluded as well as the reasons for exclusion. For enrolled participants, the flow diagram will report the number randomised to each intervention as well as the intervention received. Participants that are excluded from the analysis post intervention (if any) will be enumerated. The level and timing of withdrawal or lost to follow-up data, and reasons for this will also be presented. A draft CONSORT flowchart is displayed in Fig. 1.

Patient characteristics

Patient baseline characteristics will be presented by group allocation. Categorical variables will be summarised as frequency and percentage, using the number of participants with non-missing data as the denominator. Continuous variables will be summarised using the mean and standard deviation or the median and interquartile range, depending upon the normality of their distribution.

Reported baseline characteristics will include:

- Age (as a continuous variable as well as a categorical variable in keeping with subgroup analysis)
- Gender
- Sex
- Affected side
- Diagnosis
- Baseline pain score, as reported by the patient using the 10-cm VAS tool.

Primary outcome

Main analysis

The primary outcome is maximal pain intensity during the procedure as measured using the 10-cm VAS tool recorded by the participant post closed reduction. The between-group difference in pain intensity will be assessed using linear regression modelling with trial group allocation (UGSCB vs BB) included as a main affect. Using the pre-specified non-inferiority margin of 20 mm on the VAS scale, non-inferiority of UGSCB compared to BB will be established if the 95% CI for the effect of allocation to the UGSCB group lies below this margin. Between group mean difference and 95% CI will also be reported.

Primary outcome analysis will be performed using both the intention-to-treat and per-protocol populations. If non-inferiority of UGSCB is established, a further assessment for superiority will be conducted, consistent with the CONSORT extended statement for reporting of non-inferiority trials [13]. This analysis will be conducted using the intention-to-treat population.

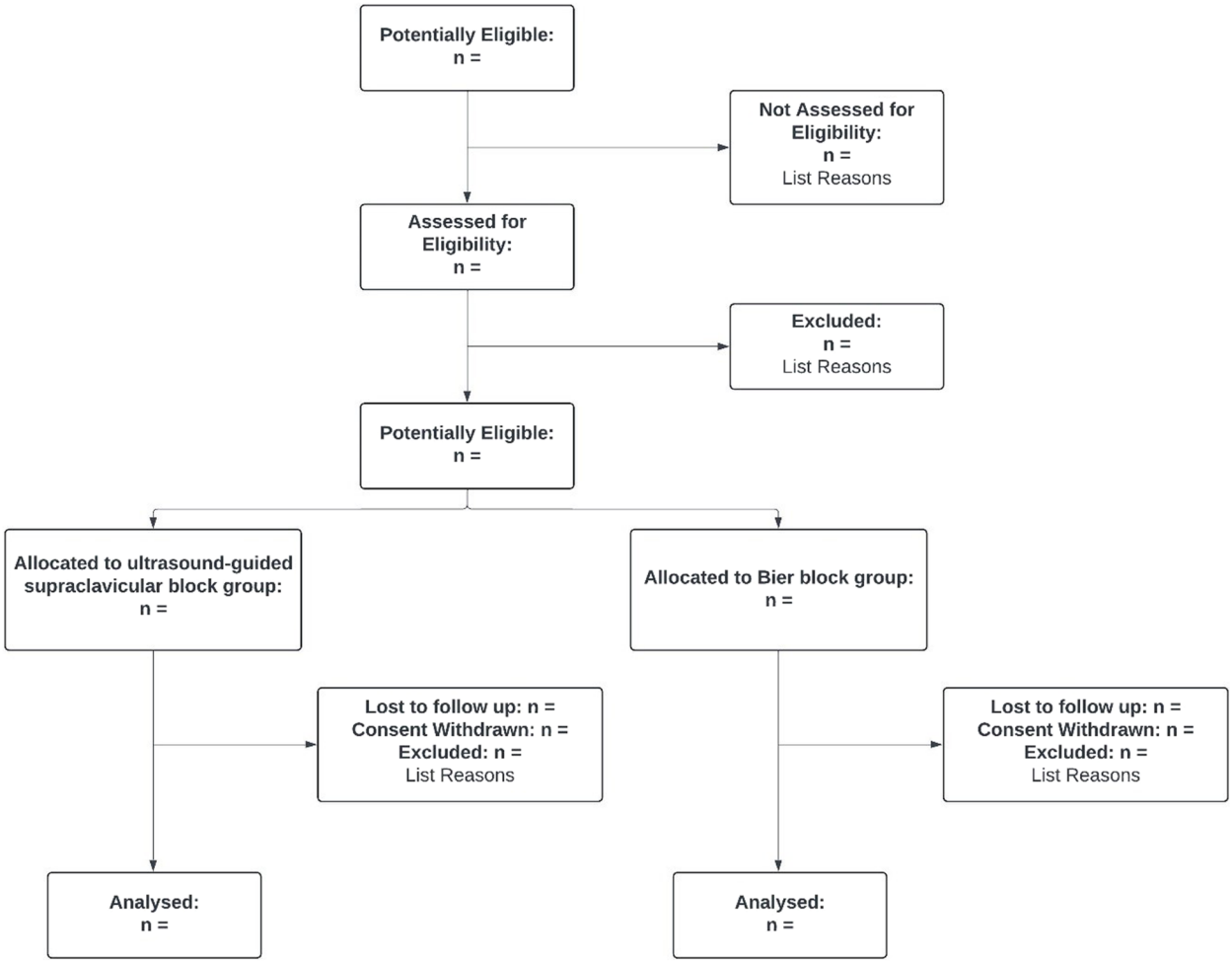

Fig. 1 CONSORT flowchart

Adjusted analysis

Additional adjusted analysis will be performed with the addition of the following covariates to the linear regression model: sex, age (as a continuous variable) and baseline pain score. The adjusted effect of group allocation in the multivariable model will be reported alongside the 95% CI. If the proportion of participants without complete data for the adjusted analysis is greater than 5%, multiple imputation of missing data will be conducted.

Subgroup analysis

Prespecified exploratory subgroup analysis will be conducted, defined by the following baseline criteria:

- Sex: male vs female
- Age: < 60 vs ≥ 60

Within each subgroup, the difference in pain intensity between the UGSCB and BB groups will be assessed using linear regression modelling, with reporting of mean difference and 95% CI. Interactions between subgroup and the effect of trial group allocation will be evaluated by linear regression modelling, with the inclusion of an interaction term between trial group and subgroup.

Analysis of secondary outcomes

Secondary outcomes analysed will include pain at 1-h post-procedure, participant satisfaction, ED length of stay, analgesia in total oral morphine equivalents, requirement for further management of the forearm injury (including number of participants requiring sedation, inpatient transfer and manipulation or operation), adverse events / complications and requirement for adjunct therapy or treatment failure. Proposed analyses are summarised in Table 1.

Table 1 Outcome measures and planned analyses

Variable	Analysis	Findings presented
Primary outcome		
Maximum pain intensity (measured using 10-cm VAS tool)	Linear regression To be analysed in ITT and PP populations; adjusted and subgroup analysis will also be performed	Between-group mean difference and 95% CI Statistical significance of hypothesis of non-inferiority of UGSCB
Secondary outcomes		
Pain at 1 h post-procedure (10-cm VAS)	Linear regression	Between-group mean difference and 95% CI
Pain at 24–72 h post-procedure (10-cm VAS)	Linear regression	Between-group mean difference and 95% CI
Patient satisfaction at 1 h post-procedure (10-cm VAS)	Linear regression	Between-group mean difference and 95% CI
Patient satisfaction at 24–72 h post-procedure (10-cm VAS)	Linear regression	Between-group mean difference and 95% CI
ED length of stay	Median regression	Between-group difference in medians and 95% CI
Treatment time	Median regression	Between-group difference in medians and 95% CI
Analgesia requirement (total oral morphine equivalents)	Linear regression	Between-group mean difference and 95% CI
Requirement for adjunct therapy or treatment failure	Logistic regression	Between-group odds ratio and 95% CI
Inpatient hospital transfer	Logistic regression	Between-group odds ratio and 95% CI
Adverse events	Logistic regression	Between-group odds ratio and 95% CI

VAS visual analogue scale, *ITT* intention-to-treat, *PP* per protocol, *CI* confidence interval, *UGSCB* ultrasound-guided supraclavicular block, *ED* emergency department

Pain at 1 h post-procedure

Pain at 1-h post-procedure, or just prior to discharge if this occurs in less than 1 h, was measured using the 10-cm VAS scale. The between-group difference in pain intensity at this interval will be compared between the USGSB and BB groups using linear regression modelling. Mean between-group difference and 95% CI will be reported.

Pain at 24–72 h post-procedure

Pain levels will be measured at 24–72 h post discharge from the ED, using the 10-cm VAS scale conducted via email. The between-group difference in pain intensity at this interval will be compared between the USGSB and BB groups using linear regression modelling. Mean between-group difference and 95% CI will be reported. An adjusted analysis will also be conducted with time elapsed in hours from the procedure until response time included as a covariate in the linear regression model.

Patient satisfaction

Patient satisfaction was measured using a 10-cm VAS scale anchored with "extremely dissatisfied" at 0 cm and "extremely satisfied" at 10 cm. This constitutes a validated method to measure patient satisfaction [14]. This outcome was measured at 1 h post procedure, or just prior to discharge if this occurs in less than 1 h, and again by follow up email 24–72 h post-discharge from the ED. At each time point, mean between-group difference and 95% CI will be reported.

ED length of stay and treatment time

The ED length of stay will be measured from the time of triage to time of readiness to be discharged. The distribution of this variable is expected to demonstrate significant positive skew, and so will be summarised using median and interquartile range, with median regression used to estimate between-group difference in medians and 95% CI. Time from initial clinical review to readiness for discharge (treatment time) and time from randomisation to readiness for discharge (length of stay post-randomisation) will also be reported, with summary statistics and effect estimates calculated similarly.

Analgesia requirement

Total opioid use will be recorded, including pre-hospital administration by the ambulance service as well as opioids administered in the ED. Opioids administered will be converted to total oral morphine in mg using an opioid equianalgesic calculator (Australian and New Zealand College of Anaesthetic Faculty of Pain Medicine opioid calculator: http://www.opioidcalculator.com.au). Opioid administration in total oral morphine equivalents will be compared between groups using linear regression, with mean between-group difference and 95% CI reported.

Median regression modelling will be used as an alternative to linear regression modelling if the distribution of total oral morphine equivalents administered departs markedly from normality. This assessment will be determined by the presence of marked positive skew or influential outliers, supplemented by the Shapiro–Wilk test, with details of this assessment provided in the text or supplementary materials as appropriate.

Additional management

The number of patients who required an additional technique to achieve successful reduction, in addition to the randomly allocated treated of UGSCB or BB, or experienced failure of the allocated treatment to provide adequate analgesia for closed reduction will be compared between groups. In addition to UGSCB and BB, techniques that may be performed to achieve reduction may include treatment with intravenous opioids, inhaled nitrous oxide, haematoma block and procedural sedation. The number of patients requiring each additional therapy will be reported by group allocation. The odds of requiring adjunct therapy or experiencing treatment failure will be compared using logistic regression with the resulting odds ratio and 95% CI reported. The number of patients requiring inpatient transfer, with or without manipulation or operation at another hospital will be compared between groups using logistic regression, with the resulting odds ratio and 95% CI reported.

Adverse events

The incidence of adverse events will be reported by group allocation, including intravenous extravasation, local bruising / haematoma, pneumothorax, arterial puncture, phrenic nerve palsy / paralysis, methaemoglobinaemia and local anaesthetic toxicity. The number of patients experiencing at least one adverse event will be compared between group allocations using logistic regression, with the resulting odds ratio and 95% CI reported.

Trial status

As of the 12 July 2024, recruitment and data collection for the SUPERB trial has been completed.

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Not applicable.

Authors' contributions
The statistical analysis plan was formulated by contribution from the following authors: Dr PJ, Co-investigator and Biostatistician (Primary author for SAP), Dr HT, Principal Investigator and contributor to SAP, Dr PS, Co-investigator and contributor to SAP.

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Availability of data and materials
The data generated from the study will be stored in REDCap and can be accessed by all listed authors. Data will be made readily available from the principal investigator upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was obtained from Metro South Human Research Ethics Committee (HREC/2022/QMS/89716) on 21 December 2022. Participants deemed eligible for the trial were provided with information sheet and consent form. Written informed consent was obtained from all participants prior to intervention or data collection. Signed consent forms can be provided on request.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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