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ORIGINAL RESEARCH ARTICLE

The ED_{95} of lidocaine and prilocaine for ultrasound-guided brachial plexus blocks for surgical anaesthesia: a randomised controlled clinical trial

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Abstract

Background: Our trial addresses the gaps in the current literature by directly estimating the ED_{95} of short-acting local anaesthetics for ultrasound-guided axillary and supraclavicular brachial plexus blocks for surgical anaesthesia.
Methods: Four double-blind prospective studies were organized in two separate arms. Patients were randomised between studies A (lidocaine 1% with adrenaline) and B (lidocaine 2% with adrenaline) for axillary blocks and between studies C (prilocaine 1%) and D (lidocaine 1% with adrenaline) for supraclavicular blocks. All statistical modelling and analysis were performed using the modified continual reassessment method. The primary endpoint of the studies was the loss of cold and pin-prick sensations in the sensory distributions of the median, musculocutaneous, radial, and ulnar nerves.
Results: For axillary blocks, the estimated ED_{95} of lidocaine 1% with adrenaline was 40 ml (95% credibility interval: 89.5–99.2%), and lidocaine 2% with adrenaline was 15 ml (95% credibility interval: 87.4–97.5%) (studies A and B: 41 and 40 patients, respectively). The ED_{95} could not be determined for supraclavicular blocks as it fell outside the dose range considered in the studies (studies C and D: 31 and 42 patients, respectively).
Conclusions: We achieved a 95% success rate for axillary blocks using lidocaine (1% and 2%) with adrenaline within our dosing limits. For supraclavicular blocks, >40 ml of prilocaine 1% or lidocaine 1% with adrenaline may be required to consistently achieve a 95% success rate. Our studies highlight the continual reassessment method as a credible methodology for dose-finding studies in regional anaesthesia.
Clinical trial registration: EudraCT ref: 2010-018466-22.

Keywords: analysis; Bayesian; anaesthetics; local; brachial plexus block; dose-response relationship; drugs; lidocaine; prilocaine; surgical anaesthesia; ultrasound guidance

The brachial plexus provides sensory and motor innervation to the upper limb. The supraclavicular and axillary approaches to anaesthetise the brachial plexus are commonly used for upper limb surgeries. As a sole anaesthetic technique, a brachial plexus block improves patient experience, provides superior postoperative analgesia, and reduces opioid consumption.[1] Patients experience less postoperative nausea/vomiting, have a much shorter post-anaesthesia care unit stay, or bypass it altogether, achieving an earlier hospital discharge.[1–3] This technique benefits service providers economically by improving hospital efficiency.[4] These benefits are particularly valuable for American Society of Anesthesiologists (ASA) physical status classification level 3 or 4 patients who are at increased risk of cardiovascular and respiratory morbidity after general anaesthesia. Awake brachial plexus blocks, therefore, are considered an ideal anaesthetic technique for

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day-case surgery of the upper limb. However, the blocks must work reliably to maximise the benefits of regional anaesthesia. Central to this reliability is the optimal dose of a local anaesthetic, a key factor influencing both the success rate and the risk of local anaesthetic systemic toxicity.

Dixon's up-and-down method, commonly used for dose-finding studies in regional anaesthesia, is designed to perform testing at the 50th percentile of the dose-response curve.[5,6] The ED_{95} dose extrapolated from the estimated ED_{50} could be erroneous.[7] The modified continual reassessment method (CRM) is a sequential dose allocation and adaptive design based on the Bayesian analysis. It allows precise and direct estimates of the dose and associated credibility intervals at the chosen centile and has well-defined stopping rules.[8–10] The modified CRM utilises the data gathered from previous studies and the ongoing trial to estimate the dose of interest. It has built-in statistical efficiency (i.e. the ability to estimate a dose using a small sample size), minimising the number of patients exposed to suboptimal doses. In the context of day-case setting, short-acting local anaesthetics (e.g. lidocaine with adrenaline and prilocaine), are the primary choices for brachial plexus blocks.

There is a significant gap in the literature considering the ED_{95} of prilocaine and lignocaine with adrenaline for ultrasound-guided (USG) axillary and supraclavicular blocks. Recognising this gap and a marked variation in the doses of local anaesthetics reported in clinical practice and used in our institution, we conducted a dose-finding master protocol. Our trial directly explored the dose-response relationships at the 95th percentile using the modified CRM.[11–14] We aimed to improve our understanding of the relationship between the volume and the concentration of chosen local anaesthetics and address the marked variability in the doses used clinically.

The primary objective of this trial was to estimate the ED_{95} of lidocaine (1% and 2%) with adrenaline for USG axillary blocks, and prilocaine 1% and lidocaine 1% with adrenaline for USG supraclavicular blocks.

Methods

Patient recruitment

The trial was approved by the Leeds (West) ethics committee (ref: 10/H1307/104) (22 September 2010) and registered with EudraCT (ref: 2010-018466-22). Patients with ASA physical classification level 1–3 undergoing awake lower arm, forearm, and/or hand surgery under a brachial plexus block were included in the studies between November 2011 and December 2017. Patients younger than 18 years old, body mass index (BMI) >40 kg m^{-2}, pregnant women, patients unable to give informed consent, and those allergic to local anaesthetics were excluded. Written informed consent was obtained from all enrolled patients. An axillary or a supraclavicular brachial plexus block was offered to the patient, depending on the nature of the surgery and the established practice of the expert operator (anaesthetist) managing the theatre list. The trial included another arm to estimate the ED_{95} of levobupivacaine 0.25% for interscalene brachial plexus blocks. Unfortunately, discrepancies were found between case record forms and clinical notes for some patients during data verification, precluding the publication of data from this particular study arm.

Randomisation in the dose-finding master protocol

Patients enrolled in the axillary plexus block arm were randomised to either: study-A Axil-1 (lidocaine 1% with adrenaline 1:200 000), or study-B Axil-2 (lidocaine 2% with adrenaline 1:200 000). Patients enrolled in the supraclavicular block arm were randomised to either: study-C Supra-Prilo (prilocaine 1%), or study-D Supra-Lido- (lidocaine 1% with adrenaline 1:200 000). The patients were randomly allocated to a study using sequentially numbered sealed envelopes prepared by an independent pharmacist.

Choice of local anaesthetics and prior guesstimates

The choice of local anaesthetics for each arm was based on clinical practice at our institution. There is a lack of data in the literature on local anaesthetic optimal dose, and a wide variation in the volume used was reported both in the literature and our institution (27–40 ml for supraclavicular blocks and 15–40 ml for axillary blocks).[5,15,16] We combined this information with the experience of senior investigators, data from studies estimating ED_{50} and extrapolating ED_{95}, and safety information from the Summary of Medical Product Characteristics (SmPC) for local anaesthetics (e.g. maximum safe dose of lidocaine with adrenaline is 500 mg and for prilocaine 400 mg) to set dose levels and initial guesstimates to start the study.

Blinding

The anaesthetist conducting the block (the operator), the patient, and the independent assessor were blinded to the study drug and its volume. Another anaesthetist enrolled patients and prepared the study drug in the absence of the patient, the operator, or the assessor. The drug was equally divided into six syringes and completely covered with opaque tape. The assessor tested the block in the absence of the operator and the injector.

Performance of the block

Authors AB or PKG performed axillary plexus blocks, while PMH or PKG administered supraclavicular plexus blocks. PMH, PKG, and AB have extensive experience in regional anaesthesia (>1000 USG peripheral nerve blocks each). Once in the anaesthetic room, all patients were monitored as per the standard Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidance and had an i. v. access sited. None of the patients had a general anaesthetic but were offered i. v. propofol (20–30 mg) or midazolam (1–3 mg) as sedation, depending on the operator's routine practice. A SonoSite S-Nerve ultrasound machine (FUJIFILM SonoSite Europe, Amsterdam, Netherlands) with a linear array transducer (6–13 MHz) and a 22-G 2″ Stimuplex A needle (B. Braun Medical Ltd, Sheffield, UK) were used for each patient. Lidocaine 1%, 1–2 ml was infiltrated under the skin at the nerve block needle's entry point for all patients. A small volume (<0.25 ml) of saline was occasionally injected at the operator's request to confirm the needle tip's position before the study dose injection.

Supraclavicular plexus block: patients were placed in a reclining position (15–30 degrees), and the head turned to the contralateral side and rested on a pillow. The brachial plexus was identified in the supraclavicular fossa in a short-axis view of the subclavian artery. The needle was advanced from lateral to medial and caudal direction using an 'in-plane' approach under continuous ultrasound guidance. The local anaesthetic was injected in three zones around the plexus (i.e. superficial, middle, and between the subclavian artery and first rib, i.e. the

'corner pocket'), to ensure a good spread of local anaesthetic around the upper, middle, and lower trunk divisions.[17] The distribution of the total dose of local anaesthetic between three zones was at the discretion of the operator performing the block, based on the spread of the study drug seen on the screen and their clinical judgement.

Axillary plexus block: patients were placed in a reclining position with their shoulder abducted to 90 degrees and externally rotated while the elbow was flexed, and the arm was supported on a pillow. Four terminal branches of the brachial plexus (musculocutaneous, median, ulnar, and radial) were identified in the axilla in a short-axis view of the axillary artery. A proportion of the study drug was injected around each identified nerve using an 'in-plane' approach, advancing the needle anteroposterior under continuous ultrasound guidance. These proportions were determined by the operator conducting the block based on their clinical judgment and the spread of local anaesthetic seen on the screen.

Assessments and outcomes (supraclavicular and axillary blocks)

The efficacy of a block was assessed by testing the cold and the pinprick sensation in the sensory distribution of the median, ulnar, musculocutaneous, and radial nerves when a patient was in the anaesthetic room. An alcohol-soaked swab and a BD Blunt Fill 18-G short-bevelled needle were used to test these sensations.[11,12,17,18] The tip of a BD Blunt Fill 18-G needle is sharp enough to elicit a sensation of pinprick without puncturing the skin when the skin is indented with consistent pressure. The completion of an injection was recorded as the 'zero' minute, and sensory assessments were carried out every 10 min for the next 30 min. Compared with the same area on the contralateral arm, patients were requested to score the pinprick as sharp, touch or absent and the cold sensation on a scale of 0–10 (0=not cold at all and 10=as cold as the contralateral unanaesthetised arm). Both sides were checked to rule out any pre-existing neurological abnormality before the block was sited. A complete loss of sensation to cold (score=0) and sharpness in the sensory distribution of nerves mentioned above indicated a successful block. Failure to achieve this criterion after 30 min was recorded as an ineffective block. If there was no reduction in cold, pinprick, or both sensations in any one or more than one of the four nerves' distribution after 30 min, the block was deemed a technical failure. Patients who experienced an ineffective block had more local anaesthetic injected around the deficient nerve or at the site of surgery to provide complete anaesthesia, as preferred by the anaesthetist. In case of a technical failure, the next patient in the study had the same dose as per protocol.

Sample size calculations and statistical analysis

Each study was evaluated, and a sensitivity analysis was performed to calculate the sample size. The model suggested a maximal sample size of 40 evaluable patients to get reliable estimates of the ED_{95} for each study.[19]

The modified CRM is a sequential dose allocation method based on the Bayesian analysis.[19,20] It uses all the information available from previous studies and the current trial to estimate the study dose for a new cohort of patients. A cohort of two patients was recommended by the statistician for each study. Hence, the patients were randomised in a block of four in the axillary (studies A and B) and the supraclavicular arms (studies C and D). A one-parameter power model was used to estimate the 95th percentile of dose response among available dose levels for each study separately. Each dose level was associated with a prior guessed success rate by the trial investigators (according to the expert operator's experience and available data in the literature at the time of initiation of the trial). The posterior response probability of the dose level was then re-estimated after the inclusion of a cohort. The dose allocated to a new cohort of patients was the dose level with the updated posterior response probability closest to the efficacy target (i.e. 95%).

The decision to end the study was based on stopping criteria, i.e., all doses were likely inefficient (too high or too low), or an estimation of the ED_{95} had been reached with good precision, or 40 evaluable patients had been recruited.[21]

The dose-finding allocation was performed using R Studio version 1.2.5001.

Other recorded data such as age, sex, height, weight, BMI, ASA score, operation name, and surgery side were analysed using Microsoft Excel.

Results

Patients' personal characteristics are presented in Table 1, and CONSORT diagrams for recruitment are in Fig 1.

Axillary plexus blocks

Study-A Axil-1 (lidocaine 1% with adrenaline)

Forty-one patients were recruited for this study; 31 blocks were successful, and nine were ineffective. One patient suffered a technical failure in the territory of the median nerve. The next patient received the same dose of the study drug as per the protocol. The starting dose was 30 ml, and the dose for each subsequent cohort was calculated in real time by the modified CRM after considering the result of the previous recruitment. The study was stopped after 40 evaluable patients were completed. The estimated ED_{95} of lidocaine 1%

Table 1 Patient characteristics for subjects recruited in the studies. ASA, American Society of Anesthesiologists; BMI, Body mass index; SD, standard deviation.

Variable	Axillary plexus block (n=81)	Supraclavicular plexus block (n=73)
Sex, *n* (%)		
Male	55 (68)	29 (38)
Female	26 (32)	44 (62)
Age (yr), mean (range)	43 (17–89)	58 (19–89)
Weight (kg), mean (SD)	79.6 (17.2)	76.8 (16.4)
Height (m), mean (SD)	1.72 (0.97)	1.68 (10.1)
BMI (kg m^{-2}), mean (SD)	26.4 (4.4)	26.9 (4.3)
ASA grading, *n* (%)		
1	45 (56)	19 (26)
2	34 (42)	44 (60)
3	2 (2)	10 (14)
Operative side, *n* (%)		
Right	46 (57)	35 (48)
Left	35 (43)	38 (52)

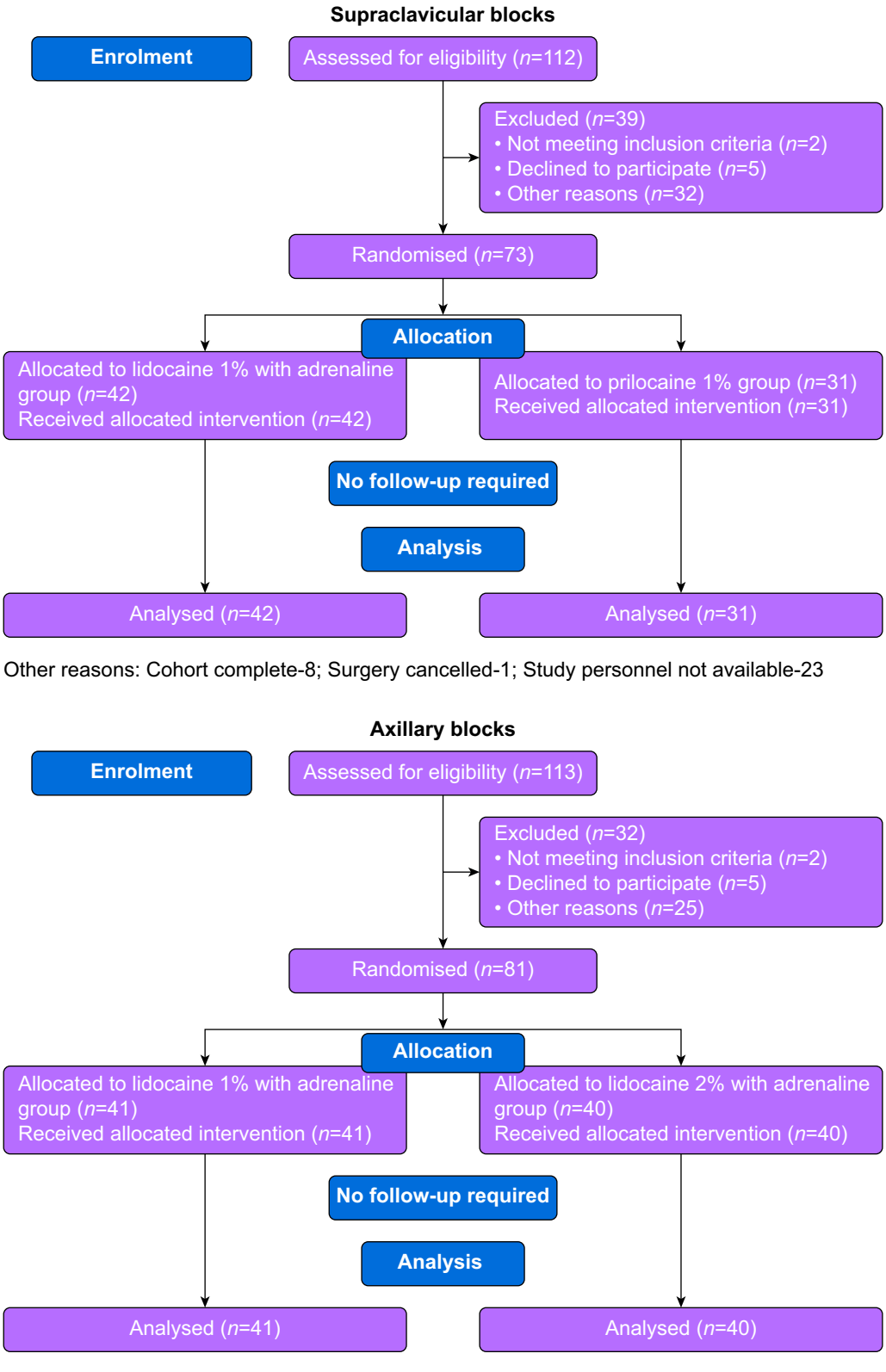

Figure 1. CONSORT diagrams for patient recruitment in the studies.

with adrenaline was 40 ml with an estimated posterior mean success of 96.3% (95% credibility interval: 89.5–99.2%).

Study-B Axil-2 (lidocaine 2% with adrenaline)

Forty patients were recruited to this group, with 35 successful and five ineffective blocks. The first cohort was administered 15 ml of the study dose, and subsequent doses were as advised by the modified CRM as explained earlier. The study was stopped after 40 evaluable patients were completed. The estimated ED_{95} of lidocaine 2% with adrenaline was 15 ml with an estimated posterior mean success of 93.7% (95% credibility interval: 87.4–97.5%).

Supraclavicular plexus block

Study-C Supra-Prilo (prilocaine 1%)

Of 31 patients recruited in this study, 30 were evaluable for the primary outcome. There were 20 successful blocks; 10 patients experienced an ineffective block, and one suffered a technical failure (ulnar nerve territory). The ED_{95} was not achieved, and the modified CRM suggested that a dose higher than 40 ml is indicated. The maximum safe dose advised by the manufacturer and in our study protocol for prilocaine is 40 ml. After the inclusion of 30 evaluable patients, the stopping rule associated with lack of efficacy according to the trial target (95% success) was met (i.e. the ED_{95} lies outside the studied dose range) (and the maximum safe dose). The estimated posterior mean probability of success for prilocaine 1%, 40 ml is 93.1% (95% credibility interval: 87–97%).

Study-D Supra-Lido (lidocaine 1% with adrenaline)

Forty-two patients were allocated to this group, and 40 were evaluable for the primary outcome. A total of 31 patients had a successful block, and nine had an ineffective one. Two patients suffered a technical failure with no appreciable block in the ulnar nerve distribution in both cases. After evaluating 40 patients, the ED_{95} was not achieved within the study dose range in the protocol at the end of the trial. The estimated posterior mean probability of success associated with lidocaine 1% with adrenaline (1:200 000) at the maximal dose (40 ml) was 92.2% (95% credibility interval: 82.4–97.6%).

Overall, our studies had four failures (technical), delivering success rates of >98% for axillary block and >95% for supraclavicular block, which are comfortably above the minimum success rates of 87% and 86%, respectively, defined in a European guideline for compatibility with expert practice.[22] Because of the lack of efficacy associated with the doses studied, 33 blocks were ineffective. Given the dose variation, these results are within the tolerance range expected in a pharmacodynamic study.

Figure 2 shows the dose allocation sequence, and Fig 3 displays a prior and posterior dose-response curve for each study.

Table 2 shows the number of patients with inadequate anaesthesia in the respective nerves for each study in the trial. One patient suffered postoperative nausea and vomiting in the supraclavicular group attributable to anxiety, but no other adverse effects were reported. Supplementary Table S1 has detailed data, including the dose, dose levels, initial guesstimates, posterior response probabilities and 95% credibility intervals for each dose-finding study, and Supplementary Table S2 shows the operations performed on patients participating in the trial.

Discussion

Lidocaine 1%, 40 ml or lidocaine 2%, 15 ml (both with adrenaline 1:200 000) is likely to provide surgical anaesthesia in 95% of patients for USG axillary plexus block. However, >40 ml of prilocaine 1% or lidocaine 1% with adrenaline 1:200 000 may be required to consistently achieve a 95% success rate for USG supraclavicular block.

The trial we report is the first to directly estimate the ED_{95} of the chosen short-acting local anaesthetics for axillary and supraclavicular blocks. Previous studies in the literature have used extrapolations to derive their ED_{95}, which could be erroneous.[7]

We used the modified CRM, a model-based adaptive Bayesian design for each study. In studies based on Bayesian design, the choice of priors influences the results and conclusions drawn from them.[23] We set well-informed, evidence-based priors before the trial onset, which were then constantly updated (i.e. posterior estimates of the previous cohort were used as priors for the next one). This approach addressed the concerns around the subjectivity of the choice of priors and their sensitivity analysis.[23] We used 95% credible intervals, analogous to confidence intervals, to express uncertainty around the ED_{95}. A confidence interval is a derived parameter with no distributional information. In contrast, a credible interval has the posterior distribution values within the chosen percentage range (e.g. 95% or 89% credible interval).[24] The credibilities of posterior probabilities determined are distributed over the range of a credible interval (e.g. values in the middle of the interval may have higher credibility than at its limits).[25]

Our studies explore and characterise the dose-response relationship of three commonly used local anaesthetic agents for two popular upper limb nerve blocks, and the conditions of the studies closely mimic everyday clinical practice. We used local anaesthetics in their clinically available off-the-shelf concentrations and varied the volume at each dose level, avoiding the need to dilute standard preparations, thereby aiding translation of our research and addressing a shortcoming of some pharmacodynamic studies. The CRM has been reported as a better-suited methodology for estimating ED_{95} than other dose-finding methods because of its efficiency.[26] Hence, we are pleased to report credible and clinically valuable data that could be translated into clinical practice.

Our results may differ from those of other studies in the literature because of the differences in the characteristics of local anaesthetics,[5] dose fractionation techniques,[14] research methods,[24] and the definition of a successful block used in this trial.[5,13,14,27,28]

For supraclavicular blocks, we limited the maximum injectate volume to 40 ml based on the operators' experience, thereby limiting the dose of a drug. The connective tissue in the supraclavicular fossa interlaces around the brachial plexus, encasing and unpredictably separating trunks and cords, which risks localisation and inadequate spread of a local anaesthetic.[5,29] The literature suggests that prilocaine and lidocaine could be approximately four times less potent than bupivacaine in clinical conditions.[30] These factors may account for the fact that we could not estimate the ED_{95} for the mentioned local anaesthetics for supraclavicular blocks. Prilocaine 1% and lidocaine 1% with adrenaline are potentially

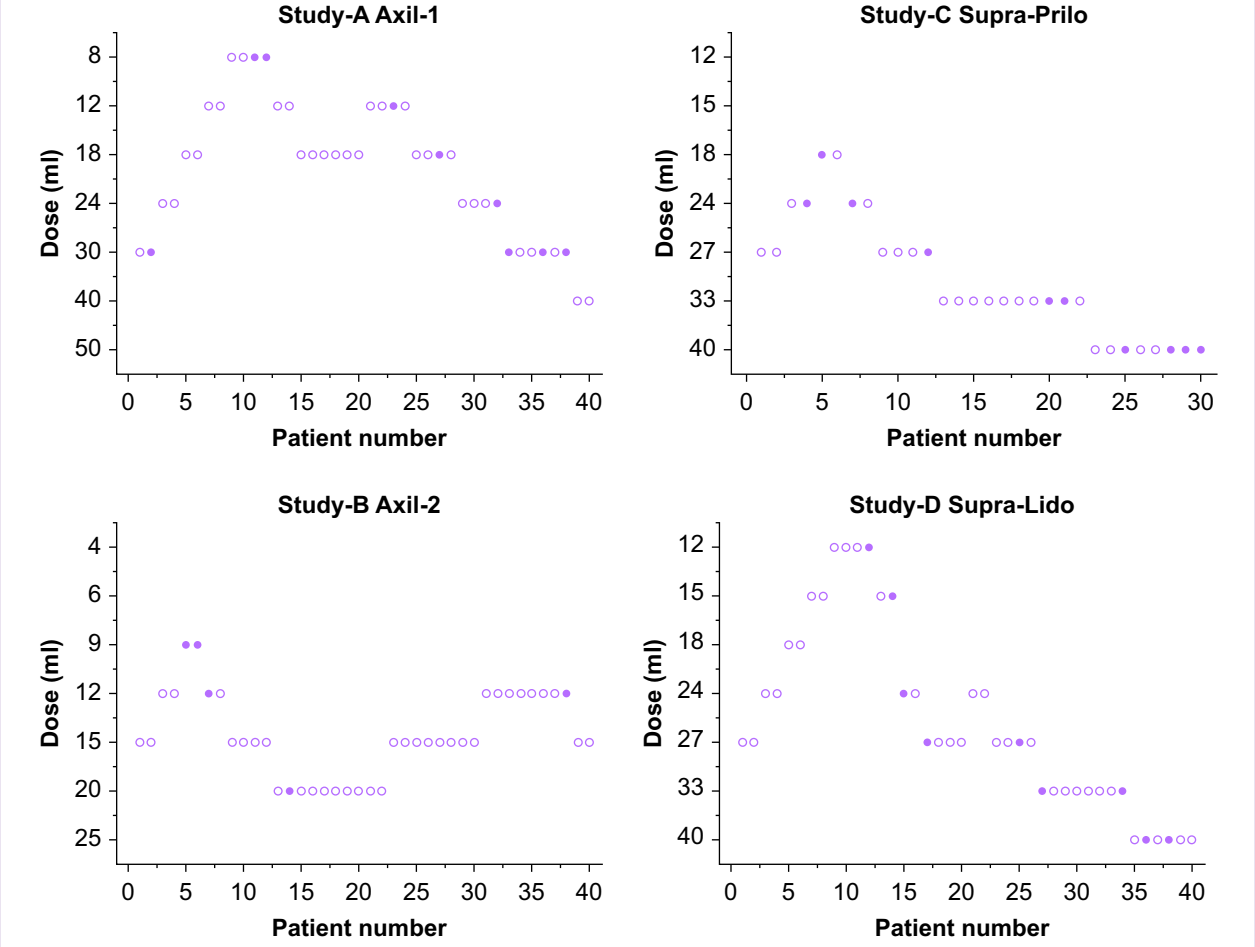

Figure 2. Dose allocation scheme: the figure shows the dose allocation sequence and patients' responses to the allocations for each study in the trial (hollow circle =successful block; filled circle =ineffective block). Study-A Axil-1, axillary blocks using lidocaine 1% with adrenaline; study-B Axil-2, axillary blocks using lidocaine 2% with adrenaline; study-C Supra-Prilo, supraclavicular blocks using prilocaine 1%; study-D Supra-Lido, supraclavicular blocks using lidocaine 1% with adrenaline.

low-efficacy agents for USG supraclavicular blocks, and doses beyond the maximum recommended safe dose may be required to consistently achieve a 95% success rate for awake surgeries for these agents. In case of a deficient supraclavicular block, performing a distal nerve top-up or local anaesthetic infiltration in the surgical field may require less additional local anaesthetic than would be required to ensure complete supraclavicular block success and so reduce the risk of local anaesthetic systemic toxicity posed by a higher dose. Distal nerve blocks with long-acting agents are commonly performed for day-case surgery to provide longer postoperative analgesia. It is, however, important to remember that the total doses of local anaesthetics are relevant to systemic toxicity.

Under our study's conditions, lidocaine 2% with adrenaline is more efficacious than lidocaine 1% with adrenaline for USG axillary plexus blocks, achieving the ED_{95} with a lower mass of the drug. Our findings demonstrate that the dose of a local anaesthetic required to achieve a successful block may change with its concentration, which explains the difference in the volumes estimated as ED_{95} of two concentrations of lidocaine with adrenaline (see Figure S1 Supplementary material). This is in contrast to ED_{50} studies, which show that the ED_{50} of a local anaesthetic agent depends upon the mass rather than the concentration of the drug.[31] Further studies are required to establish a definite relationship between the two agents. Our studies emphasise the need to directly estimate the dose at a higher percentile point on the dose-response curve (e.g. ED_{95}), to get clinically useful information.

The difference between the prior guessed probability of success and its posterior estimate is wider at every dose level for supraclavicular studies than axillary ones (Fig 3). Hence, our results reinforce the need to conduct formal dose-finding studies for peripheral nerve blocks, as an expert- or peer-reviewed dose may not always correctly predict the success rate in clinical practice.

Our studies have some limitations. We caution against generalising results reported to other dose fractionation techniques and local anaesthetic agents. All blocks were performed by three anaesthetists with extensive experience and expertise in USG upper limb blocks. We did not record the

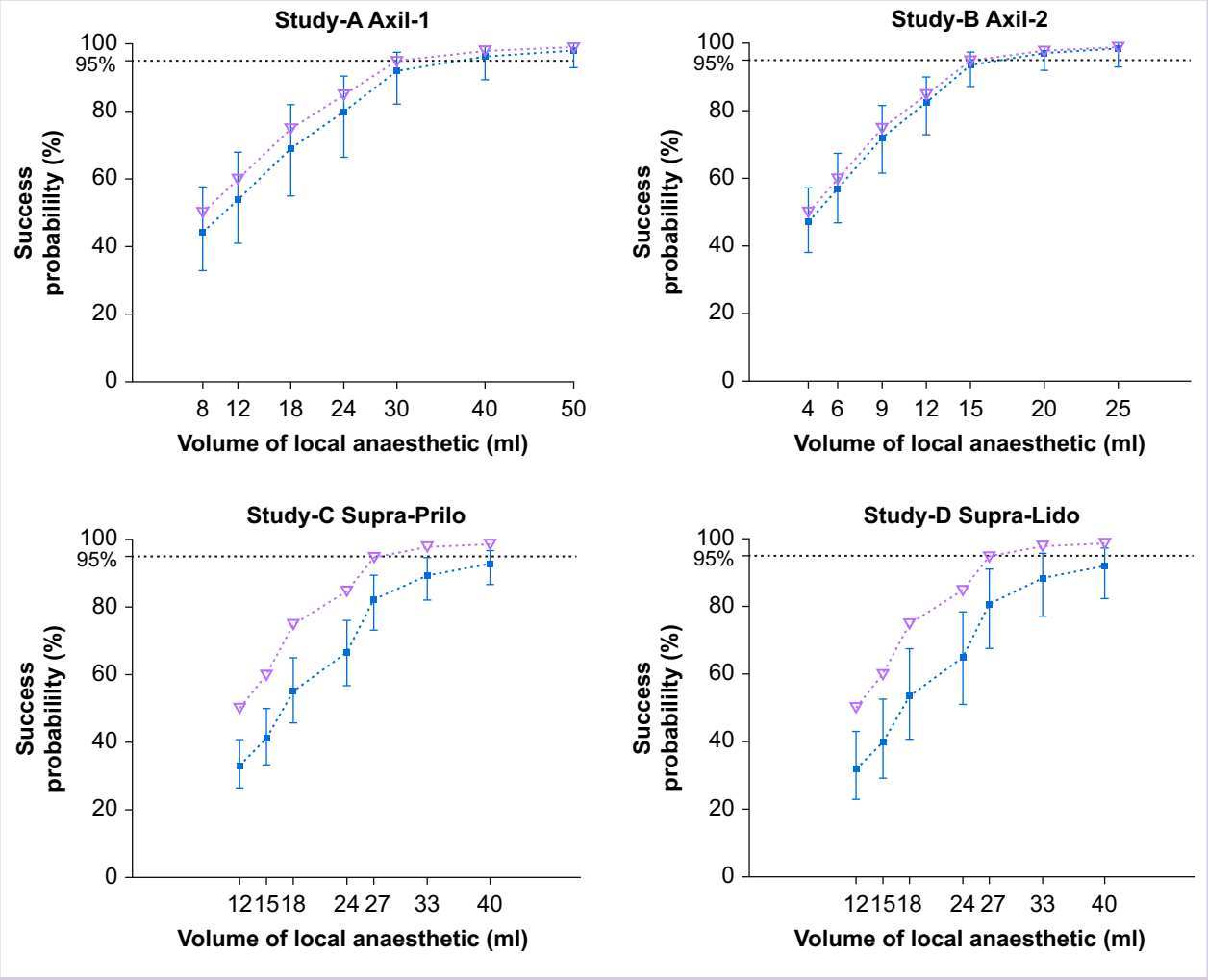

Figure 3. Initial guessed dose-success probabilities (purple inverted hollow triangles ∇), posterior mean probabilities of success (blue filled squares), and associated 95% credibility intervals (blue extended lines) for each study in the trial. Study-A Axil-1, axillary blocks using lidocaine 1% with adrenaline; study-B Axil-2, axillary blocks using lidocaine 2% with adrenaline; study-C Supra-Prilo, supraclavicular blocks using prilocaine 1%; study-D Supra-Lido, supraclavicular blocks using lidocaine 1% with adrenaline.

Table 2 The number of patients with inadequate anaesthesia in the respective nerves for each study in the trial. Study-A Axil-1, axillary blocks using lidocaine 1% with adrenaline; study-B Axil-2, axillary blocks using lidocaine 2% with adrenaline; study-C Supra-Prilo, supraclavicular blocks using prilocaine 1%; study-D Supra-Lido, supraclavicular blocks using lidocaine 1% with adrenaline.

	Radial	Median	Ulnar	Musculocutaneous
Study-A Axil-1 (Lidocaine 1% with adrenaline)	5	4	2	1
Study-B Axil-2 (Lidocaine 2% with adrenaline)	3	0	2	0
Study-C Supra-Prilo (Prilocaine 1%)	1	3	7	1
Study-D Supra-Lido (Lidocaine 1% with adrenaline)	1	3	8	1

duration of analgesia for patients participating in this study as they were usually discharged 30–60 min after surgery at our ambulatory unit. However, even a low volume of short-acting local anaesthetic could provide sufficient analgesia for ambulatory hand surgery.[13] We did not follow the study participants for any long-term complications. However, local anaesthetics were used within their safe dose limits, and all blocks were conducted by experts with years of experience in using the block techniques applied in this study. Also, the surgeons' clinic did not report any after operation.

Conclusions

Our studies provide high-quality and relevant information on the clinical efficacy of short-acting local anaesthetics used for axillary and supraclavicular brachial plexus blocks. This information will help set guidance that could improve training standards and the safety of these agents in clinical practice. Based on the precedence set by our unit and other studies in the literature, a model-based dose-finding approach such as the modified CRM, which could efficiently and directly determine point estimates at higher centiles of the dose-response curve, should be considered a preferred methodology for dose-finding studies in regional anaesthesia.[17,18,32,33]

Authors' contributions

Study design and planning: PMH, PKG, AV
Statistical support and data analysis: SZ, AV
Regulatory approvals and study conduct: AV, PMH
Patient recruitment and data collection: AV
Data acquisition: AB, PKG, PMH
Manuscript writing: AV, SZ
Critical review of drafts and final manuscript: all authors
Agree to be accountable for all aspects of the work: all authors

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Declaration of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2025.100385.

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