ANESTHESIOLOGY

Addition of Liposomal Bupivacaine to Standard Bupivacaine *versus* Standard Bupivacaine Alone in the Supraclavicular Brachial Plexus Block: A Randomized Controlled Trial

Timmy Chi Wing Chan, M.B.B.S., Janus Siu Him Wong, M.B.B.S., Fengfeng Wang, Ph.D., Christian Xinshuo Fang, M.B.B.S., Colin Shing-yat Yung, M.Med.Sci., Manson Tak Hei Chan, M.B.B.S., Will Shing Him Chan, M.B.B.S., Stanley Sau Ching Wong, M.D.

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ABSTRACT

Background: The analgesic effect of adding liposomal bupivacaine to standard bupivacaine in supraclavicular brachial plexus block is not known. The authors hypothesized that addition of liposomal bupivacaine would reduce acute postoperative pain compared to standard bupivacaine alone.

Methods: A randomized controlled trial was conducted. Patients and outcome assessors were blinded. Eighty patients undergoing distal radial fracture fixation during regional anesthesia with supraclavicular brachial plexus block were randomized into two groups. The liposomal bupivacaine group received 10 ml 0.5% plain bupivacaine immediately followed by 10 ml 1.33% liposomal bupivacaine (n = 40). The standard bupivacaine group received 20 ml 0.5% plain bupivacaine (n = 40). The primary outcome was weighted area under curve (AUC) numerical rating scale pain score at rest during the first 48 h after surgery. Secondary outcomes included weighted AUC scores for pain with movement, overall benefit with analgesia score, and other functional scores.

Results: For the primary outcome, the liposomal bupivacaine group was associated with statistically significantly lower weighted AUC pain score at rest (0.6 *vs.* 1.4; $P < 0.001$) in the first 48 h. Of the secondary outcomes, no difference between treatment groups reached statistical significance with the exception of weighted AUC score for pain with movement (2.3 *vs.* 3.7; adjusted $P < 0.001$) and overall benefit with analgesia score (1.1 *vs.* 1.7; adjusted $P = 0.020$) in the first 48 h, as well as numerical rating scale pain score at rest (0.5 *vs.* 1.9; adjusted $P < 0.001$) and with movement (2.7 *vs.* 4.9; adjusted $P < 0.001$) on postoperative day 1. Differences in numerical rating scale pain scores on postoperative days 2, 3, and 4 did not reach the level of statistical significance. There were no statistically significant differences in sensory function.

Conclusions: Liposomal bupivacaine given *via* supraclavicular brachial plexus block reduced pain at rest in the early postoperative period.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Liposomal bupivacaine is Food and Drug Administration–approved for use in peripheral nerve blocks including interscalene, popliteal sciatic, and adductor canal blocks
- Reports of the efficacy and clinical utility of adding liposomal bupivacaine for surgical infiltration or in peripheral nerve blocks are mixed, indicating modest reduction of postsurgical pain

What This Article Tells Us That Is New

- This patient- and outcome assessor–blinded randomized controlled trial compared 20 ml plain 0.5% bupivacaine with 10 ml 0.5% bupivacaine plus 10 ml liposomal bupivacaine in supraclavicular blocks for radial fracture fixation
- Pain scores were statistically lower in the the liposomal group, but oxycodone consumption, recovery, and sleep quality scores were not different between groups during the first 48 h after surgery
- Individual daily assessment of group differences revealed group differences on postoperative day 1, but not postoperative days 2 to 7, indicating the greatest effect occurs in the first 24 h
- Future studies delineating differential clinical efficacy among higher-risk patient subgroups are needed

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This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 638.

Brachial plexus blocks are commonly used to provide regional anesthesia for patients undergoing distal radial fracture surgery, which is one of the most commonly performed orthopedic surgeries. Regional anesthetic nerve blocks have been associated with improved postoperative analgesia.[1] However, single-injection nerve blocks are limited by a short duration of action and the possibility of rebound pain.[2] The role and analgesic efficacy of single-injection brachial plexus blocks for distal radial fracture surgery are currently uncertain.[3–5] Results from two randomized controlled trials showed rebound pain at around 24 h after surgery in patients given brachial plexus block compared to those who received general anesthesia.[3,4] Various medications to extend analgesia have been studied with the goal of improving postoperative analgesia and minimizing rebound pain, but prolongation appears to be limited and overall benefit uncertain.[6] Hence, there is currently no Food and Drug Administration (Silver Spring, Maryland)–approved medication that is reliable in prolonging analgesic effect beyond 24 h.[7] Continuous peripheral nerve catheters can extend postoperative analgesia, but are technically demanding, time-consuming, and associated with increased risks and complications.[1]

Liposomal bupivacaine (Exparel, Pacira Pharmaceuticals Inc, USA) is a multivesicular formulation of bupivacaine that enables rapid absorption and prolonged release of bupivacaine. A number of clinical trials have studied liposomal bupivacaine when given as local surgical site infiltration.[8,9] For distal radial fracture surgery, local surgical site infiltration of liposomal bupivacaine was not better than standard plain bupivacaine for postoperative pain control.[10] The analgesic efficacy of injecting liposomal bupivacaine in regional nerve blocks may be more promising.[11,12] Addition of liposomal bupivacaine in the interscalene brachial plexus block was shown to reduce postoperative pain after shoulder surgery compared to placebo and standard bupivacaine.[11,12] Liposomal bupivacaine is Food and Drug Administration (Silver Spring, Maryland)–approved for local surgical site infiltration, interscalene brachial plexus block, sciatic nerve block in the popliteal fossa, and adductor canal block, but not for other nerve blocks. The effect of adding liposomal bupivacaine in the supraclavicuar brachial plexus block and its ability to provide surgical anesthesia without general anesthesia is unclear.

In this study, a randomized controlled trial with blinding of patients and outcome assessors was conducted to determine whether adding liposomal bupivacaine to standard bupivacaine in the supraclavicular brachial plexus block would improve acute postoperative pain control compared to standard bupivacaine alone in patients undergoing distal radial fracture surgery. Due to delayed release with liposomal bupivacaine,[13] liposomal bupivacaine was added to standard bupivacaine in order to provide a sufficiently rapid regional nerve block for surgery. Our primary hypothesis was that acute postoperative pain scores in the first 48 h after surgery will be lower in patients who receive liposomal bupivacaine in addition to standard bupivacaine compared to standard bupivacaine alone.

Materials and Methods

This study was conducted at Queen Mary Hospital in Hong Kong, China. It was approved by the local university's institutional review board (IRB) (UW21–046), and the local certificate for clinical trial or medicinal test was obtained from the Pharmacy and Poisons Ordinance (102058). The study was registered at https://clinicaltrials.gov on November 12, 2021, before patient recruitment (NCT05118399). There were some changes in https://clinicaltrials.gov that should be clarified. The title of the project was initially registered on https://clinicaltrials.gov as "The Analgesic Effect of Adding Liposomal Bupivacaine to Long-acting Local Anesthetic for Supraclavicular Brachial Plexus Block in Distal Radius Fracture Surgery: A Randomized Controlled Trial" and later changed to the current title. This change was made to specify the local anesthetic used (standard bupivacaine) and also to shorten the title (by removing "Distal Radial Fracture Surgery"). The primary outcome was changed from "pain scores at rest from 0 to 6 h after surgery" to "weighted area under curve [AUC] pain scores at rest in the first 48 h after surgery." The longer time frame was thought to be clinically more relevant and more appropriately matched to the expected duration of action of liposomal bupivacaine. In addition, rebound pain usually occurred at around 24 h after brachial plexus block.[3,4] These changes were made in June 2021 before patient enrollment but were updated later on https://clinicaltrials.gov in July 2023. There were some inaccuracies in the study status on https://clinicaltrials.gov: the status of the study was listed as "recruiting" in May 2023 and "active and not recruiting" in July 2023, but the study including patient recruitment and follow-up was completed by March 2023. Written informed consent was obtained from all patients involved in the trial. Patients were informed that the use of liposomal bupivacaine in the supraclavicular nerve block had not been studied before and that there was no information on its efficacy and safety for such application. The term "off–label" was not specifically used. There is no well-

Fengfeng Wang, Ph.D.: Department of Anaesthesiology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China.

Christian Xinshuo Fang, M.B.B.S.: Department of Orthopaedics and Traumatology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China.

Colin Shing-yat Yung, M.Med.Sci.: Department of Orthopaedics and Traumatology, Queen Mary Hospital, Hong Kong, China.

Manson Tak Hei Chan, M.B.B.S.: Department of Anaesthesia, Pain & Perioperative Medicine, Queen Mary Hospital, Hong Kong, China.

Will Shing Him Chan, M.B.B.S.: Department of Anaesthesia, Pain & Perioperative Medicine, Queen Mary Hospital, Hong Kong, China.

Stanley Sau Ching Wong, M.D.: Department of Anaesthesiology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China.

recognized term for "off-label" in Cantonese, which was the language used for communication with patients. A secure password-protected REDCap (USA) database was used to record and store study data.

A randomized controlled trial was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The dates of recruitment were from December 16, 2021, to November 30, 2022. The last day of follow-up was on March 8, 2023. Patients between 18 and 90 yr old with an American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status of I to III scheduled for distal radial fracture fixation (open reduction and internal fixation with volar approaching locking plate) and patients with informed consent to participate in the study were eligible for recruitment. Patients were informed that the use of liposomal bupivacaine in the supraclavicular nerve block had not been previously evaluated in clinical studies. Exclusion criteria included the following: ulnar shaft or neck physis fracture; revision surgery; previous fractures or surgery in the affected distal radius; surgery involving more than the affected arm; higher energy and high-grade fracture cases (*e.g.*, road traffic accident, open fractures); cases with painful conditions affecting the upper limb before surgery such as cervical spine, shoulder, elbow, other hand and wrist problems; cases with baseline (preinjury) Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) score worse than 10 of 100; respiratory compromise (requires long-term oxygen); history of seizures; pre-existing neurologic disorder or deficit; chronic opioid user (use for 3 months or more); presence of chronic pain condition (pain duration greater than 3 months); alcohol or substance abuse; psychiatric illness; impaired mental state; local infection; allergy to analgesic drug (local anesthetic drugs, paracetamol, nonsteroidal anti-inflammatory drugs, opioids; impaired renal function [defined as effective glomerular filtration rate less than 30 ml per min per 1.73 m^2]; impaired liver function defined as plasma bilirubin greater than 34 µmol/l; international normalized ratio 1.7 or greater, alanine aminotransferase greater than 100 U/l, aspartate aminotransferase greater than 100 U/l); coagulopathy (platelet count less than 100,000/ml and/or international normalized ratio 1.5 or greater) or the use of anticoagulants (not including aspirin) that precludes the use of supraclavicular brachial plexus block; pregnancy; patient refusal for regional nerve blocks; patient refusal to join the clinical trial; patient unable or unwilling to attend a postoperative rehabilitation program; and injury on duty.

Patients were randomly allocated to receive supraclavicular brachial plexus block using standard plain bupivacaine only (standard bupivacaine group) or supraclavicular brachial plexus block using liposomal bupivacaine in addition to standard bupivacaine (liposomal bupivacaine group). A computer-generated random sequence was used to select the allocation order. This was prepared by a statistician unaware of the nature of the clinical study. The sequence was concealed in opaque envelopes and opened by an investigator just before nerve block injection. The patients and outcome assessors who collected outcome data were blinded. The investigators who collected data outcome were not allowed in the rooms where drug preparation and nerve block administration were performed. The anesthetists who performed the supraclavicular brachial plexus block were not adequately blinded, but were not involved in collection of outcome data. Since liposomal bupivacaine is opaque white in appearance while standard bupivacaine appears colorless, all syringes and tubing for nerve block injection were covered using aluminum foil in order to avoid distinction between the two groups and maintain blinding. However, the distal end of the tubing just proximal to the needle had to be exposed to allow for visualization of negative aspiration. A separate anesthetist (not the one performing the nerve block) prepared the drugs for injection in a separate room (all blinded staff including the surgeon and the patient were not allowed to enter this room). This anesthetist was not involved in data collection or nerve block injection.

Regional Nerve Block

All supraclavicular brachial plexus blocks were performed under ultrasound guidance using a 22-gauge 50-mm insulated block needle (SonoPlex, PAJUNK, Germany). The anesthetist performing the nerve block decided whether a nerve stimulator was needed. A specialist anesthetist competent in performing ultrasound guided supraclavicular brachial plexus blocks performed the nerve blocks. Local skin infiltration with 2% lignocaine (2 to 3 ml) was given before needle insertion. The brachial plexus was identified posterolateral to the subclavian artery. The needle was advanced to the brachial plexus, and local anesthetic was deposited under ultrasound guidance above the first rib and next to the subclavian artery. Local anesthetic was injected after negative aspiration. Any immediate complications (*e.g.*, intravascular puncture, paresthesia, and pneumothorax) were recorded. For the standard bupivacaine group, 20 ml 0.5% plain bupivacaine was injected using two separate 10-ml syringes. A volume of 10 ml 0.5% plain bupivacaine was injected and immediately followed by another 10 ml 0.5% plain bupivacaine (total 20 ml 0.5% plain bupivacaine). For the liposomal bupivacaine group, 10 ml 0.5% plain bupivacaine was injected first, and then immediately followed by 10 ml 1.33% liposomal bupivacaine (133 mg). Two 10-ml syringes were used for injection in both groups in order to maintain blinding. Surgery was performed under regional anesthesia alone (without general anesthesia) for both groups of patients. Regional anesthesia was considered inadequate if there was still pain on pinching of the surgical site with use of an artery forceps just before surgical incision. Patients with an inadequate block were given general anesthesia according to the protocol.

Intraoperative Procedure

Sedative premedication was not given. Standard monitoring was given to all patients. Sedation was provided with

intravenous propofol *via* a target–controlled infusion system. The Marsh effect site model was used to achieve an effect site concentration of 0.5 to 1.5 mcg/ml. Propofol concentration was titrated to keep patients under light sleep where they could be easily aroused with verbal stimulation. Surgery was performed under regional anesthesia alone with the supraclavicular brachial plexus block. Intravenous ondansetron 4 mg was given 30 min before the end of surgery in both groups of patients for antiemetic prophylaxis.

The operation was performed with the patient's arm abducted on an arm board, and a tourniquet was applied to the upper arm and inflated to 250 mmHg. A volar modified Henry's incision was placed with the pronator quadratus muscle split to reveal the distal radius volar surface at the fracture site. The fracture fragments were temporarily reduced and stabilized by K–wires, percutaneously if necessary. A 2.4-mm (DePuy Synthes, USA) volar locking plate was used for fixation in all patients. Intraoperative fluoroscopy was used to ensure appropriate fracture reduction and implant placement. The pronator quadratus muscle was not repaired. The tourniquet was released for hemostasis, and a 10-gauge vacuum suction drain was placed in all patients. Final suturing was performed with 2-0 Vicryl (Ethicon, USA) and 3-0 Biosyn (Medtronic, USA). The patient was placed in a compression bandage postoperatively.

General anesthesia was required only for patients with failed regional nerve block. They were induced with intravenous propofol 1.5 to 3 mg/kg, fentanyl 0.25 to 2 mcg/kg, and atracurium 0.5 mg/kg. Endotracheal intubation or laryngeal mask airway insertion was used for airway management. General anesthesia was maintained with sevoflurane, oxygen, and air, titrated to give a fractional inspired oxygen tension of 35 to 50%. Nitrous oxide was not used. Sevoflurane was titrated to 0.7 to 1.5 minimum alveolar concentration. Intravenous morphine at a dose of 0.05 to 0.1 mg/kg was given before surgical incision. Ondansetron 4 mg was given 30 min before the end of surgery. Reversal was achieved with neostigmine 50 mcg/kg and atropine 20 mcg/kg.

Perioperative Analgesic Regimen and Assessment

The analgesic protocol and pain assessment were the same in the 2 groups. Perioperative multimodal analgesic regimen was used. All patients received oral paracetamol 1,000 mg and oral celecoxib (Macleods Pharmaceuticals, India) 200 mg 1 h before surgery. Intraoperative analgesic medication was not given. Local wound infiltration was not given. Pain at rest was assessed every 5 min in the postanesthesia care unit (PACU). Intravenous morphine sulphate at a dose of 2 mg was given if the numerical rating scale pain score at rest was higher or equal to 4 of 10, and repeated every 5 min until the numerical rating scale pain score became less than 4 of 10. Respiratory rate, oxygen saturation, blood pressure, and heart rate were monitored every 5 min in the PACU. Patients stayed in the PACU for at least 30 min before being discharged back to

the ward. Regular oral analgesic medication was given for 3 days: paracetamol 1,000 mg twice daily and celecoxib 200 mg twice daily. Oral oxycodone (OxyNorm, Mundipharma AG, United Kingdom) 5 mg four times a day as required was prescribed for breakthrough pain. Patients could request oral oxycodone if their numerical rating scale pain score was equal to or above 4 of 10. Patients were assessed every day while they were in hospital and were usually discharged on postoperative day 1. They were followed up after hospital discharge with daily phone follow-up to postoperative day 7, and assessed at the orthopedic clinic for follow-up at 2, 6, and 12 weeks after surgery.

Postoperative Care

Diet as tolerated was allowed on postoperative day 0. Standardized physiotherapy was provided for both groups of patients. All patients were encouraged to mobilize their fingers and wrist joint actively immediately after surgery each hour. A compressive stocking, Tubigrip (Mölnlycke AB, Sweden), was given after the drain was removed on postoperative day 1. The arm was elevated to the chest level. Patients were allowed to be discharged on postoperative day 1 with a standardized information leaflet instructing early mobilization and postoperative wound care. All patients were referred to a rehabilitation center with standardized physiotherapy and an occupational therapy protocol that encouraged early active mobilization up to 6 weeks after surgery. Strengthening and passive range of motion exercises were initiated from 6 weeks onwards.

Outcomes

Acute Postoperative Outcomes (Up to Postoperative Day 7). The primary outcome was the weighted area under the curve (AUC) numerical rating scale pain score in the first 48 h after surgery when patients were at rest (numerical rating scale 0 to 10, where 0 was no pain and 10 was the worst possible pain). Numerical rating scale pain scores with movement (maximal wrist flexion and extension) during the first 48 h were evaluated as a secondary outcome. Pain scores were collected by an investigator who was unaware of patient group allocation. These were collected at 4, 8, and 12 h after surgery on postoperative day 0 and then at three timepoints on postoperative day 1 (8:30 AM, 12:00 noon, and 4:00 PM). They were then collected once a day from postoperative days 2 to 7. The consumption of oxycodone (OxyNorm) in the ward and after discharge and dose of rescue intravenous morphine consumption in the PACU were also recorded. Overall benefit of analgesia score, which evaluated patient benefit from postoperative treatment based on the combination of opioid symptom distress, pain relief, and patient satisfaction, was assessed once a day until postoperative day 7.[14] Quality of Recovery (QoR) test was assessed once a day up to postoperative day 7 using the Chinese QoR questionnaire.[15] Sensory and

motor assessment of the affected upper limb were tested at 15 min and at 2 and 24 h after surgery. Sensation to pin prick and cold was tested over the following areas: C5 (lateral shoulder), C6 (thumb), C7 (third finger), and C8 (fourth finger) dermatomes.[16] Sensation was rated using a 0 to 10 scale. Motor assessment was done by recording grip strength and bicep contraction. Motor function was rated as 0 (paralysis), 1 (paresis), and 2 (normal power).[17] Sleep disturbance was evaluated daily using a 0 to 10 scale, where 0 represented no sleep disturbance and 10 represented the most disturbance possible.

Longer-term Postoperative Outcomes. Longer-term outcomes were assessed at 2, 6, and 12 weeks after surgery. The presence or absence of pain and the severity of pain (if pain was present) at rest and with movement (maximal wrist flexion and extension) using the numerical rating scale pain scale was assessed. Health-related quality of life was assessed using the Chinese version of the 12-Item Short Form Survey, version 2 (SF-12v2).[18] Two summary scores in the SF-12v2 were reported: a mental component score and a physical component score. Upper limb functional scores were assessed using the validated Chinese version of the QuickDASH.[19] Hand grip power was assessed at 2, 6, and 12 weeks after surgery. Psychologic status was evaluated using the Depression and Anxiety Symptom Stress Scale.

Adverse Effects. Patients were assessed for nerve block–related adverse effects on the same day after the nerve block and on postoperative day 1. Opioid-related adverse effects were assessed on postoperative day 1 and postoperative day 7. Nerve block–related adverse effects included phrenic nerve palsy, recurrent laryngeal nerve palsy, Horner's syndrome, failed block, neurologic injury, pneumothorax, intravascular injection, and local anesthetic toxicity. Opioid-related adverse effects included pruritus, dizziness, nausea, and vomiting.

Statistical Analysis. The intention-to-treat population was defined as all patients who received regional nerve block and for whom at least one post-dose observation was recorded for the primary outcome. The per-protocol population comprised patients who complied with the protocol in this study. The primary outcome was analyzed in both the intention-to-treat and per-protocol populations for sensitivity analysis. All other outcomes were analyzed in the intention-to-treat analysis population only.

The primary outcome was the weighted AUC numerical rating scale pain scores at rest in the first 48 h after surgery. The AUC was calculated by summing the areas beneath the curve between each pair of adjacent observations (20). The AUC's units were derived from the product of the units utilized for t_i and y_i. The weighted AUC was AUC divided by the total time, and expressed in the same scale and in the same unit as the numerical rating scale (scale 0–10).

$$AUC = \frac{1}{2} \sum_{i=0}^{n-1} (t_{i+1} - t_i)(y_i + y_{i+1})$$

$$Weighted\ AUC = \frac{AUC}{48h}$$

where y_i is the pain intensity score at time point t_i.

The weighted AUC numerical rating scale pain score at rest from 0 to 48 h after distal radial fracture surgery was 1.1 (SD, 1.8) for patients who received brachial plexus block in our previous clinical trial.[5] In order to detect a difference in mean numerical rating scale pain score of 1.3 of 10 with a power of 0.8 and at a 5% significance level, a sample size of 31 patients per group was required. Sample size was calculated based on the method for sample size estimation in clinical trials.[20] To consider for potential patient dropout and loss to follow-up, we recruited 40 patients into each group.

The baseline characteristics of the two groups were compared using standardized differences.[21,22] The standardized differences were calculated for each variable by dividing the mean difference between the groups by the pooled SD. An imbalance in a factor was identified if the absolute value of its standardized difference was greater than $1.96 \times \sqrt{(2/40)} = 0.438$.[23] Continuous data for primary and secondary outcomes were analyzed using either the independent samples t test or the Mann–Whitney U test, depending on the distribution of the data. Categorical data were analyzed using the Pearson chi-square test. The Hochberg procedure was used to correct for P values in multiple-hypotheses for all secondary outcomes.[24] Missing data before the first nonmissing score were replaced by the median score receiving the same treatment, while the missing data after the last nonmissing score were replaced using the method of last observation carried forward. IBM SPSS Statistics version 29.0 (IBM Corp., USA) and R version 4.3.2 (2024, URL https://www.r-project.org) were used to analyze the data.

Results

In this clinical trial, 86 patients were assessed for eligibility, and 6 were excluded (fig. 1). Two patients did not meet the inclusion criteria, and four patients declined to participate. A total of 80 patients were randomly assigned to standard bupivacaine (n = 40) or liposomal bupivacaine (n = 40) groups in the intention-to-treat population. One patient in the standard bupivacaine group (patient took another oral analgesic medication in the ward) and one patient in the liposomal bupivacaine group (patient required reoperation after the first surgery) were excluded based on the protocol in the per-protocol population (fig. 1). Details of patient characteristics, including age, body weight, sex, ASA status, procedure or surgery total time (min), and total anesthetic time (min), are shown in table 1. The results showed that the two groups were relatively well-balanced in terms of age,
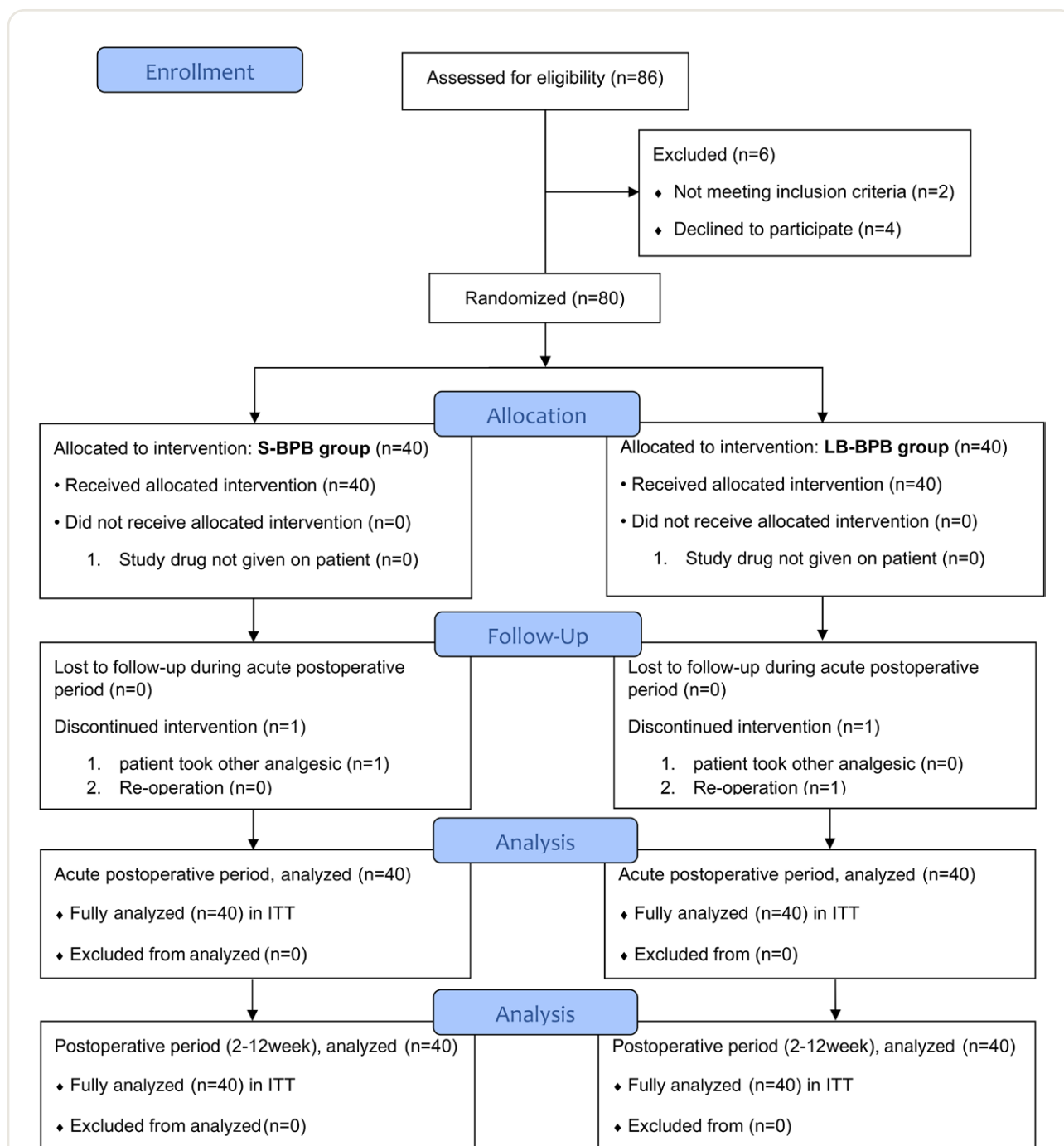
Fig. 1. Flow diagram of patients involved in this study. ITT, intention-to-treat; LB-BPB. liposomal bupivacaine group; S-BPB. standard bupivacaine group.

body weight, duration of surgery, and duration of anesthesia, but may have some imbalances in sex and ASA classification.
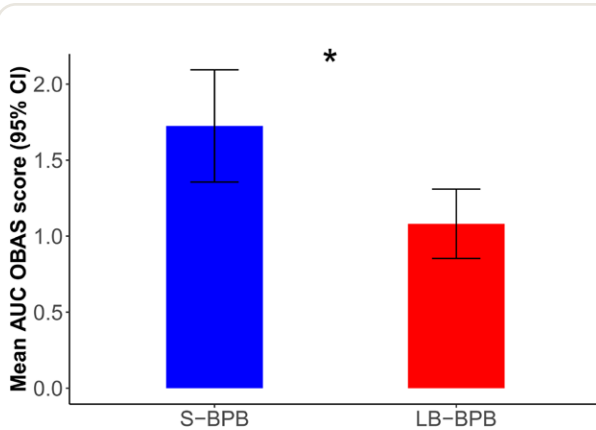
Weighted AUC Numerical Rating Scale Pain Score at Rest. The primary outcome of our study was the weighted AUC numerical rating scale pain score (scale 0–10) at rest in the first 48h after surgery. The weighted AUC numerical rating scale pain score at rest in the liposomal

bupivacaine group was lower than the standard bupivacaine group with statistical significance (mean [95% CI], 0.6 [0.4 to 0.9] *vs.* 1.4 [1.0 to 1.8]; *P* < 0.001). We conducted a sensitivity analysis using the per-protocol population, which took into account only the participants who completed the study as planned. The observed difference in weighted AUC numerical rating scale pain score at rest between the liposomal bupivacaine and standard

Table 1. Patient Characteristics

	Liposomal Bupivacaine (n = 40)	Standard Bupivacaine (n = 40)	Standardized Difference
Age, yr	63 [55–69]	64 [53–70]	0.083
Body weight, kg	60 [53–65]	65 [50–73]	0.280
Sex			0.690
Female	33 (82.5%)	23 (57.5%)	
Male	7 (17.5%)	17 (42.5%)	
ASA Physical Status			
I	10 (25%)	5 (12.5%)	
II	28 (70%)	32 (80%)	0.457
III	2 (5%)	3 (7.5%)	0.608
Duration of surgery, min	55 [43–63]	57 [44–71]	0.080
Duration of anesthesia, min	81 [68–99]	79 [66–107]	0.258

Ranges refer to interquartile range.

ASA, American Society of Anesthesiologists.

Fig. 2. Weighted area under the curve (AUC) values for overall benefit with analgesia score (OBAS) in the first 48 h after surgery. Values are expressed as mean (95% CI). The liposomal bupivacaine (LB-BPB) group was associated with lower weighted AUC OBAS with statistical significance. S-BPB, standard bupivacaine group*P < 0.05 after Hochberg correction.

bupivacaine groups remained statistically significant even after accounting for potential deviations from the study protocol, which was consistent with our primary analysis.

Weighted AUC Score for Secondary Outcomes. The weighted AUC numerical rating scale pain score with movement during the first 48 h after surgery was lower in the liposomal bupivacaine group compared to the standard bupivacaine group with statistical significance (mean [95% CI], 2.3 [1.7 to 2.8] *vs.* 3.7 [3.2 to 4.2]; adjusted $P < 0.001$). Additionally, the weighted AUC overall benefit with analgesia score was statistically significantly lower in the liposomal bupivacaine group during the first 48 h after surgery (mean [95% CI], 1.1 [0.9 to 1.3] *vs.* 1.7 [1.3 to 2.1]; adjusted

Table 2. Weighted AUC Values for Overall Benefit with Analgesia Score, Oxycodone Consumption, QoR, and Sleep Disturbance during the First 48 h after Surgery

|	Liposomal Bupivacaine Mean (95% CI)	Standard Bupivacaine Mean (95% CI)	Adjusted P Value
Overall benefit with analgesia score	1.1 (0.8–1.3)	1.7 (1.3–2.1)	0.020*
Oxycodone consumption (mg)	0.1 (0.0–0.2)	0.3 (0.1–0.4)	0.084
QoR	17.1 (16.8–17.4)	16.9 (16.4–17.3)	0.664
Sleep disturbance	3.1 (2.4–3.8)	3.7 (2.8–4.5)	0.387

Data were analyzed by Independent-samples *t* test or Mann-Whitney U test.

*P value by Hochberg procedure was < 0.05. AUC, area under the curve; QoR, Quality of Recovery.

$P = 0.020$; fig. 2). There were no statistically significant differences between the two groups in weighted AUC scores for postoperative oxycodone consumption, QoR, and sleep disturbance during the first 48 h after surgery (table 2).

Acute Postoperative Secondary Outcomes (up to Postoperative Day 7). Numerical rating scale pain score at rest was lower in the liposomal bupivacaine group compared to the standard bupivacaine group on postoperative day 1 with statistical significance (mean [95% CI], 0.5 [0.3 to 0.8] *vs.* 1.9 [1.3 to 2.5]; adjusted $P < 0.001$; fig. 3; table 3). Numerical rating scale pain score with movement was also lower in the liposomal bupivacaine group on postoperative day 1 with statistical significance (mean [95% CI], 2.7 [2.0 to 3.3] *vs.* 4.9 [4.2 to 5.6]; adjusted $P < 0.001$; fig. 3; table 3). Differences between treatment groups did not rise to the level of statistical significance for numerical rating scale pain scores at rest and with movement at other time points during this period (including from postoperative day 2 to postoperative day 7). Differences between the two treatment groups also did not reach statistical significance for oxycodone consumption, overall benefit with analgesia score, QoR, and sleep disturbance from postoperative day 1 to postoperative day 7 (fig. 4).

Sensory and Motor Function. There were no statistically significant differences in sensory assessment of the affected upper limb, including C5 (lateral shoulder), C6 (thumb), C7 (third finger), and C8 (fifth finger) from 15 min to 24 h after surgery between the standard bupivacaine and liposomal bupivacaine groups. Differences between treatment groups also did not rise to the level of statistical significance in motor assessment by recording grip strength and bicep contraction from 15 min to 24 h between these two groups.

Longer-term Outcomes. Differences between treatment groups did not rise to the level of statistical significance in numerical rating scale pain scores both at rest and with movement at postoperative 2 weeks, 6 weeks, and 12 weeks after applying the Hochberg correction (table 4).
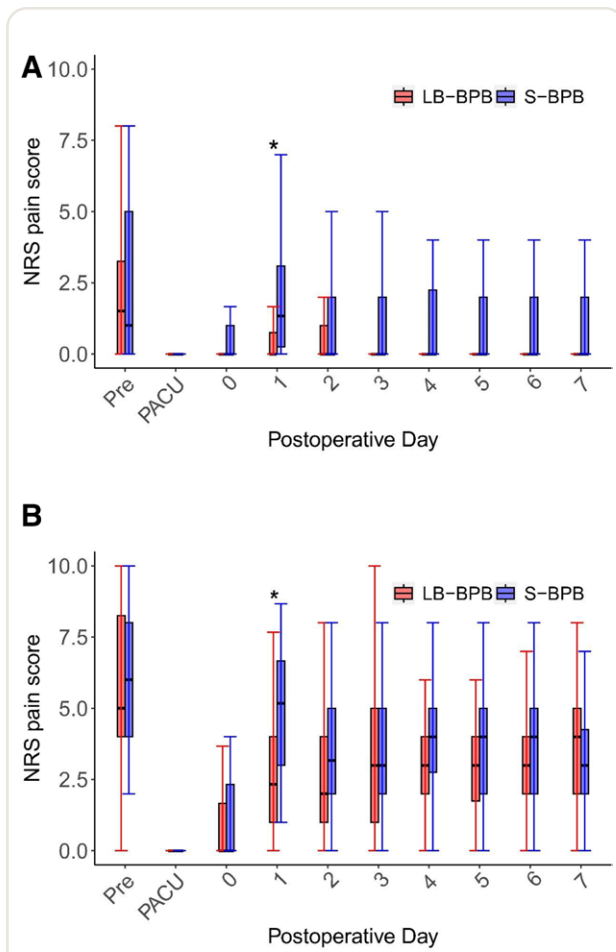
Fig. 3. Numerical rating scale (NRS) pain scores from before surgery to postoperative day 7. (*A*) Pain score at rest. (*B*) Pain score with movement. Values were expressed as median (interquartile range). Liposomal bupivacaine was associated with statistically significant lower numerical rating scale pain scores at rest and with movement on postoperative day 1 compared to the standard bupivacaine group. *$P < 0.05$ after Hochberg correction. Pre, the same day before surgery; PACU, postanesthesia care unit (30 min after surgery)

Table 3. Numerical Rating Scale pain scores from before surgery to Postoperative Day 7

|	Liposomal Bupivacaine Mean (95% CI)	Standard Bupivacaine Mean (95% CI)	*P* Value
Pain scores at rest			
Pre	2.2 (1.3 to 3.0)	2.2 (1.4 to 3.0)	0.894
PACU	0.4 (–0.2 to 0.9)	0.4 (–0.1 to 0.9)	0.992
Postoperative day 0	0.4 (0.1 to 0.8)	0.5 (0.2 to 0.8)	0.298
Postoperative day 1	0.5 (0.3 to 0.8)	1.9 (1.3 to 2.5)	< 0.001*
Postoperative day 2	0.9 (0.3 to 1.6)	1.3 (0.6 to 2.0)	0.212
Postoperative day 3	0.8 (0.2 to 1.4)	1.2 (0.6 to 1.8)	0.067
Postoperative day 4	0.8 (0.2 to 1.4)	1.3 (0.7 to 1.9)	0.038
Postoperative day 5	0.8 (0.2 to 1.4)	1.2 (0.6 to 1.7)	0.170
Postoperative day 6	0.9 (0.3 to 1.5)	1.2 (0.6 to 1.7)	0.265
Postoperative day 7	0.7 (0.2 to 1.3)	0.9 (0.4 to 1.3)	0.273
Pain scores with movement			
Pre	5.9 (5.0 to 6.8)	5.9 (5.2 to 6.5)	0.842
PACU	0.4 (–0.2 to 0.9)	0.4 (–0.1 to 0.9)	0.992
Postoperative day 0	1.0 (0.5 to 1.5)	1.1 (0.6 to 1.6)	0.844
Postoperative day 1	2.7 (2.0 to 3.3)	4.9 (4.2 to 5.6)	< 0.001*
Postoperative day 2	2.8 (2.0 to 3.6)	3.7 (3.0 to 4.4)	0.037
Postoperative day 3	3.5 (2.6 to 4.4)	3.7 (3.0 to 4.3)	0.506
Postoperative day 4	3.4 (2.6 to 4.2)	3.9 (3.2 to 4.5)	0.167
Postoperative day 5	3.2 (2.4 to 4.1)	3.8 (3.1 to 4.5)	0.143
Postoperative day 6	3.4 (2.5 to 4.2)	3.7 (2.9 to 4.4)	0.397
Postoperative day 7	3.5 (2.7 to 4.3)	3.2 (2.6 to 4.3)	0.774

*Adjusted *P* value by Hochberg procedure was < 0.05.
PACU, postanesthesia care unit; Pre, the same day before surgery

Additionally, there were no statistically significant differences in QuickDASH, Depression and Anxiety Symptom Stress Scale, hand grip power scores, and short form –12v2 scores (including both mental component score and physical component score) between the two groups at 2 weeks, 6 weeks, and 12 weeks after Hochberg correction (table 5).

Adverse Effects. There were no nerve block–related adverse effects on the same day after nerve block injection and on postoperative day 1. In the standard bupivacaine group, dizziness and nausea were reported by one patient on postoperative day 1. No adverse effect was reported in the liposomal bupivacaine group on postoperative day 1. One patient experienced dizziness on postoperative day 7 in the standard bupivacaine group, and one patient had pruritus on postoperative day 7 in the liposomal bupivacaine group.

At 2 weeks after surgery, four patients in the standard bupivacaine group and four patients in the liposomal bupivacaine group reported hypoesthesia over the operated upper limb. Six patients in the standard bupivacaine group and five patients in the liposomal bupivacaine group had hypoesthesia at 6 weeks after surgery. One patient in the standard bupivacaine group and three patients in the liposomal bupivacaine group reported having hypoesthesia at 12 weeks after surgery.

Discussion

In this study, a randomized controlled trial was performed to compare the postoperative analgesic effect of adding liposomal bupivacaine to standard bupivacaine *versus* standard bupivacaine alone in the supraclavicular brachial plexus block. The addition of liposomal bupivacaine resulted in statistically significantly lower weighted AUC pain scores at rest in the first 48 h after surgery compared to standard bupivacaine alone. With the exception of weighted AUC pain scores with movement and weighted AUC overall benefit with analgesia score in the first 48 h, as well as numerical rating scale pain scores at rest and with movement on postoperative day 1, the differences between treatment groups did not reach statistical significance for any of the other secondary outcome measures after Hochberg correction. It is worthy of note that differences
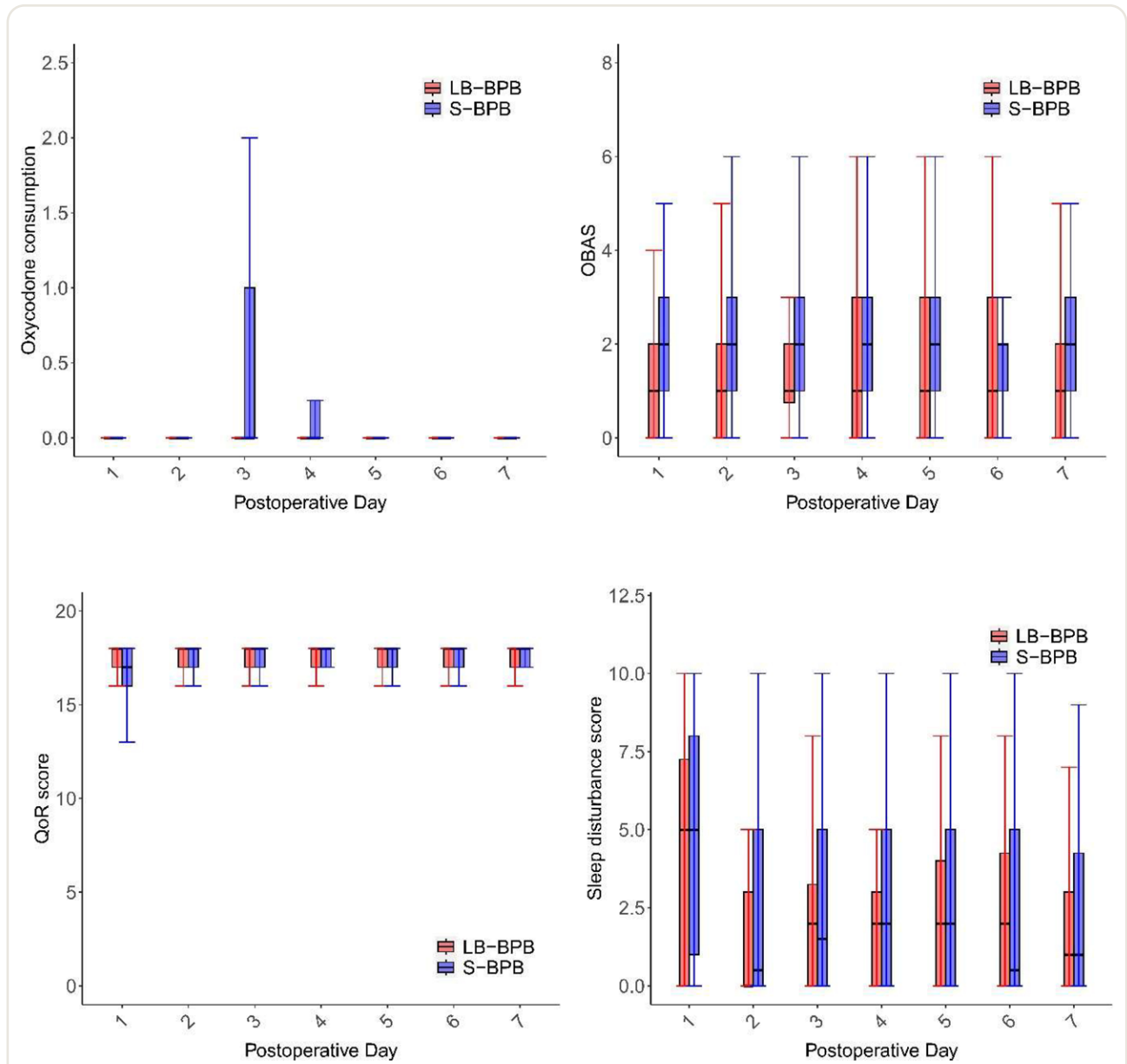
Fig. 4. Oxycodone consumption (in tablet, 5 mg per tablet), overall benefit with analgesia score (OBAS), Quality of Recovery (QoR), and sleep disturbance scores from postoperative days 1 to 7. Values are expressed as median (interquartile range). No comparison between the two treatment groups reached statistical significance. Oxycodone consumption: oral oxycodone consumption. LB-BPB. liposomal bupivacaine group; S-BPB. standard bupivacaine group.

in pain scores at rest and with movement on postoperative days 2, 3, and 4 did not rise to statistically significant levels. There were no statistically significant differences in sensory function between the two groups. The combination of liposomal bupivacaine and standard bupivacaine provided surgical anesthesia without the need for conversion to general anesthesia.

The difference in numerical rating scale pain scores between groups was most prominent on postoperative day 1, where there was statistically significant decrease in numerical rating scale pain scores at rest (effect size [adjusted 95% CI],

−1.4 [−2.5 to −0.2]) and with movement (effect size [adjusted 95% CI], −2.3 [−4.3 to −0.3]) in the liposomal bupivacaine group (fig. 3). There is no clearcut method to define clinically relevant difference in pain scores when comparing between treatment groups.[25,26] Nevertheless, a numerical rating scale pain score difference of 1.4 and 2.3 (0 to 10 pain scale) between groups at rest and with movement may be considered as small and moderate in effect size, respectively. Numerical rating scale pain scores of 4 or above have been shown to indicate moderate to severe acute postoperative pain associated with the need for additional analgesic and

Table 4. Numerical Rating Scale Pain Scores at 2, 6, and 12 Weeks after Surgery

	Liposomal Bupivacaine Mean (95% CI)	Standard Bupivacaine Mean (95% CI)	P Value
Pain scores at rest			
2 weeks	1.1 (0.5–1.7)	0.8 (0.3–1.3)	0.425
6 weeks	1.0 (0.4–1.6)	0.5 (0.1–0.8)	0.128
12 weeks	0.8 (0.3–1.2)	0.4 (0–0.7)	0.165
Pain scores with movement			
2 weeks	2.2 (1.5–2.9)	1.7 (1.1–2.3)	0.281
6 weeks	1.8 (1.2–2.4)	1.3 (0.8–1.9)	0.210
12 weeks	1.4 (0.8–1.9)	0.7 (0.2–1.2)	0.063

Table 5. Functional Scores for QuickDASH, Depression and Anxiety Symptom Stress Scale, Hand Grip Power, and SF-12v2 at 2, 6, and 12 Weeks after Surgery

	Liposomal Bupivacaine Mean (SE)	Standard Bupivacaine Mean (SE)	P Value
QuickDASH			
2 weeks	54.4 (47.5–61.2)	48.2 (41.6–54.9)	0.196
6 weeks	38.6 (32.1–45.0)	32.2 (25.0–39.3)	0.146
12 weeks	19.9 (14.9–25.0)	16.6 (11.6–21.6)	0.177
Depression score			
2 weeks	4.4 (2.4–6.3)	4.8 (2.5–7.1)	0.481
6 weeks	4.3 (2.2–6.3)	3.5 (1.6–5.3)	0.396
12 weeks	2.9 (1.1–4.7)	2.3 (1.2–3.4)	0.983
Anxiety score			
2 weeks	4.6 (3.0–6.1)	4.1 (2.5–5.7)	0.832
6 weeks	3.6 (2.2–4.9)	3.4 (1.8–4.9)	0.616
12 weeks	2.8 (1.7–3.8)	2.6 (1.5–3.7)	0.507
Stress score			
2 weeks	6.2 (3.9–8.5)	6.0 (3.8–8.2)	0.961
6 weeks	5.3 (3.1–7.4)	4.5 (2.4–6.6)	0.716
12 weeks	3.5 (1.9–5.1)	2.5 (1.2–3.7)	0.139
Hand grip power (operated side)			
2 weeks	5.3 (4.3–6.3)	7.8 (5.4–10.2)	0.298
6 weeks	6.8 (5.2–8.3)	10.6 (8.6–12.6)	0.016*
12 weeks	12.4 (10.3–14.4)	16.0 (13.8–18.2)	0.004*
Hand grip power (nonoperated side)			
2 weeks	21.2 (19.0–23.4)	23.1 (20.6–25.5)	0.128
6 weeks	20.9 (18.5–23.2)	23.7 (20.8–26.5)	0.132
12 weeks	22.1 (19.6–24.7)	25.8 (22.8–28.8)	0.095
Physical component score (SF-12v2)			
2 weeks	37.6 (34.6–40.6)	34.2 (31.0–37.4)	0.862
6 weeks	39.5 (36.1–42.8)	40.4 (37.2–43.7)	0.675
12 weeks	47.4 (44.6–50.1)	46.8 (43.6–50.0)	0.119
Mental component score (SF-12v2)			
2 weeks	52.0 (48.1–56.0)	52.5 (48.7–56.4)	0.845
6 weeks	54.4 (50.4–58.4)	53.3 (49.9–56.7)	0.308
12 weeks	57.9 (54.6–61.2)	57.9 (55.5–60.3)	0.371

*Adjusted P value by Hochberg procedure was > 0.05.
QuickDASH, Quick Disabilities of the Arm, Shoulder and Hand; SF-12v2, 12-Item Short Form Survey, version 2.

relevant pain-related interference.[27] Using this cutoff point (numerical rating scale 4 or greater), the percentage of patients with moderate to severe pain during movement on postoperative day 1 was 67.5% in those with standard bupivacaine *versus* 27.5% in patients from the liposomal bupivacaine group. These findings suggests that liposomal bupivacaine helped alleviate rebound pain and reduced the proportion of patients who experienced moderate to severe pain during the first 24 h after supraclavicular brachial plexus block. Liposomal bupivacaine was also associated with statistically significantly lower overall benefit with analgesia scores in the first 48 h (effect size [adjusted 95% CI], –0.6 [–1.1 to –0.1]), which is a multidimensional instrument to evaluate patient benefit from postoperative treatment based on the combination of opioid symptom distress, pain relief, and patient satisfaction.[14] The finding of lower overall benefit with analgesia scores also supports that there was clinically relevant analgesic benefit when using liposomal bupivacaine in the early acute postoperative period. However, the reduction in pain intensity was not sufficient to impact other outcomes including postoperative opioid consumption and quality of recovery, as well as longer-term outcomes such as chronic pain, upper limb functional scores, and health-related quality of life. The decision to use liposomal bupivacaine in the supraclavicular brachial plexus block depends on numerous factors such as patient factors, type of surgery, rehabilitation, and cost. It may be particularly worthwhile to consider using liposomal bupivacaine for patients at elevated risk of experiencing significant postoperative/rebound pain or chronic postsurgical pain. Risk factors associated with rebound pain include young age, female sex, and bone surgery.[28] Predictors of poor postoperative pain control such as psychologic factors, high body mass index, preoperative pain, use of preoperative analgesic, and high temporal summation of pain on quantitative sensory testing could also be used to identify patients who may benefit more from liposomal bupivacaine.[29–32]

In this clinical trial, we evaluated the use of liposomal bupivacaine in the supraclavicular brachial plexus block, which has not been Food and Drug Administration–approved.

Liposomal bupivacaine (in combination with low volume of standard plain bupivacaine) was used to provide surgical anesthesia without need for general anesthesia. When liposomal bupivacaine was given *via* the interscalene brachial plexus block, peak plasma bupivacaine levels reached an early peak at 6 h followed by a maximum peak at 48 h after injection.[12] Therefore, plain bupivacaine was added in the liposomal bupivacaine group because of concerns with delayed onset of regional anesthesia. Previous clinical trials on liposomal bupivacaine for regional nerve blocks were performed in combination with general anesthesia.[11,12,33] However, supraclavicular brachial plexus blocks are commonly used alone to provide regional anesthesia for surgeries involving the arm, forearm, and hand, including distal

radial fracture fixation.[34] In this trial, 10 ml 0.5% standard plain bupivacaine was used in combination with liposomal bupivacaine in order to provide a sufficiently rapid block for surgical anesthesia. There were no failed blocks, and the total anesthetic time was not prolonged, suggesting that this is a feasible approach to achieve surgical anesthesia.

Our results are similar to a randomized controlled trial by Vandepitte *et al.* that compared the addition of liposomal bupivacaine against standard bupivacaine alone in ultrasound–guided interscalene brachial plexus block.[11] They found lower worst pain scores and overall benefit with analgesia score in the first week after surgery, but there were no differences in other secondary outcomes such as opioid consumption and upper limb function. One difference from the current study was that Vandepitte *et al.* demonstrated pain reduction during 1 week, while our study found pain reduction only in the first 48 h. This may be due to difference between measurement of pain intensities in the two studies—pain at rest and with movement in our study *versus* worst pain scores with Vandepitte *et al.* Differences in surgical procedure and type of brachial plexus block may also have contributed to differences in the results. It should also be noted that the typical analgesic duration of liposomal bupivacaine (72 h) may not explain an analgesic difference lasting 1 week. Another randomized controlled trial that compared the addition of liposomal bupivacaine *versus* standard bupivacaine in combination with dexamethasone as an adjunct in the interscalene brachial plexus block found lower pain scores in favor of liposomal bupivacaine that reached statistical but not clinical significance.[33] The effect and role of liposomal bupivacaine given *via* regional nerve blocks is still unclear due to the paucity of published clinical trials. A systematic review by Ilfeld *et al.* concluded that there was insufficient data to support or refute its use *via* regional nerve blocks due to a lack of useful data.[7] A systematic review and meta-analysis by Hussain *et al.* demonstrated statistically significant reduction in pain scores with perineural liposomal bupivacaine 24 to 72 h after surgery, but they questioned the clinical significance of the difference.[35] Of the nine clinical trials included in this meta-analysis, only five were published articles that underwent peer review,[35] again demonstrating the lack of available clinical evidence on this topic. Furthermore, there were differences in the types of nerve blocks used, and ultrasound guidance to enhance accuracy of drug delivery was not used in a number of the clinical trials.[35] It has been postulated that contact between bupivacaine and tissue induces a local inflammatory response that produces an acidotic environment, thereby impeding tissue penetration by bupivacaine molecules and reducing its effect.[35–37] This issue may be reduced when medication is accurately deposited close to the target nerve structures under ultrasound guidance.

Ultrasound and lung function assessment were not used to assess for hemidiaphragmatic paresis. Patients were evaluated clinically by an anesthetist for the presence of shortness of breath and signs of respiratory impairment in the PACU, in the ward on the same day after surgery and on postoperative day 1. The incidence of hemidiaphragmatic paresis has been reported to be between 44 and 70% after supraclavicular brachial plexus block.[38–40] These studies assessed hemidiaphragmatic function up to 30 min after nerve block. The use of long-acting local anesthetics such as liposomal bupivacaine could potentially result in prolonged hemidiaphragmatic paresis. None of our study patients developed shortness of breath or respiratory impairment, suggesting that liposomal bupivacaine did not result in clinically significant respiratory compromise. In two clinical studies where hemidiaphragmatic paresis were 45% and 70% after supraclavicular brachial plexus block, none of the patients developed shortness of breath or respiratory compromise, which is in agreement with our findings.[38,39]

There were some limitations to this study. One limitation is that the clinical trial only studied the effect for distal radial fracture surgery, and results may not apply to other types of upper limb surgeries where supraclavicular brachial plexus block may be used. While we have demonstrated the feasibility of adding liposomal bupivacaine in the supraclavicular brachial plexus block, such use is currently not Food and Drug Administration–approved and would be off-label. Another limitation was that our primary outcome (pain score at rest) was not functional, and the use of a functional outcome such as overall benefit with analgesia score may have been more ideal. Although we covered the syringes and tubing, the anesthetists performing regional nerve block were not adequately blinded and should not be considered as masked to treatment group assignment. One reason is that the viscosity of liposomal bupivacaine is considerably higher than plain bupivacaine, and this may be differentiated upon injection. A second reason is that the distal end of the tubing just proximal to the needle was exposed to allow confirmation of negative aspiration. A third reason is that liposomal bupivacaine may appear different from plain bupivacaine on ultrasound image. However, the anesthetists who performed the regional nerve blocks were not involved in outcome assessment. Another limitation was that the dose of bupivacaine was different between the two groups (183 mg for the liposomal bupivacaine group and 100 mg for the standard bupivacaine group). The dose of bupivacaine between groups was also different in other clinical studies that investigated the use of liposomal bupivacaine in interscalene brachial plexus blocks.[11,33] Whether this would significantly affect postoperative analgesia is unclear. Patients in this study were managed as inpatients, which may limit the generalizability of the results in those that are managed in an ambulatory setting. Finally, the sample size was calculated based on the primary outcome. This is a common approach in clinical trials.[41] However, power analysis for secondary outcomes was not performed *a priori*, and the study may have been underpowered to detect clinically significant differences for these outcomes.

In conclusion, the addition of liposomal bupivacaine in the supraclavicular brachial plexus block reduced postoperative pain at rest in the first 48 h after distal radial fracture

surgery compared to standard bupivacaine alone. The combination of liposomal bupivacaine with low-volume standard bupivacaine in the supraclavicular brachial plexus block reliably provided surgical anesthesia. Liposomal bupivacaine administered in the supraclavicular brachial plexus block may provide clinically relevant analgesic benefit in the early postoperative period.

Correspondence

Address correspondence to Dr. S. Wong: Room 424, Block K, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China. wongstan@hku.hk

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