Local and Regional Anesthesia

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Effectiveness of Combining Lidocaine and Ropivacaine on the Duration of Analgesia and Anesthesia of an Infraclavicular Brachial Plexus Block

Mathias T Steensbæk[1], Jens L Temberg[1], Sina Yousef[1], Sanja Pisljagic[1], Christian Steen-Hansen[1], Anders K Nørskov[1,2], Kai HW Lange[1,2], Christian Rothe[1], Lars H Lundstrøm[1,2]

[1]Department of Anesthesia and Intensive Care, Copenhagen University Hospital - North Zealand, Hillerød, Denmark; [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence: Mathias T Steensbæk, Department of Anesthesia and Intensive Care, Copenhagen University Hospital - North Zealand, Dyrehavevej 29, 3400, Hillerød, Denmark, Email mathias.therkel.steensbaek.01@regionh.dk

Background: Combining local anesthetics for peripheral nerve blocks may change block characteristics, resulting in altered onset and block duration. We aimed to investigate the block characteristics of an infraclavicular brachial plexus block regarding block duration, pain after block cessation, and patient satisfaction by using a combination of lidocaine-epinephrine and ropivacaine.

Methods: In this retrospective cohort study, 103 patients undergoing ambulatory hand or wrist surgery received an infraclavicular brachial plexus block with either a combination of ropivacaine 5 mg/mL combined with lidocaine 20 mg/mL and epinephrine 5 µg/mL (COMBI group) or only ropivacaine 5 mg/mL (ROPI group). The primary outcome was "Total block duration". Secondary outcomes were "Time until block begins to subside", "Pain after complete block cessation (Numerical Rating Scale 0–10)", and "Patient experience of nerve block". All outcomes were patient-reported. Multivariable regression analyses were used to adjust for predefined potential confounders.

Results: "Total block duration" (mean ± SD) was 655±215 minutes in the COMBI group and 961±195 in the ROPI group; mean difference of 309 minutes; $P<0.001$. "Time until block begins to subside" was 396±120 minutes in the COMBI group and 642 ±214 minutes in the ROPI group; $P<0.001$. The median "Pain after block cessation" on a Numeric rank scale (NRS) was 5.0 (IQR 3.0–8.0) in the COMBI group and 6.0 (IQR 4.0–7.0) in the ROPI group; $P=0.80$. In the COMBI group, 60% were satisfied with block quality versus 38% in the ROPI group; $P=0.042$. Multivariable adjusted analyses confirmed the results regarding block duration and pain after block cessation but not satisfaction.

Conclusion: Combining lidocaine-epinephrine and ropivacaine reduced the duration of analgesia by approximately 5 hours. Pain after block cessation was moderately high in both groups.

Keywords: infraclavicular, nerve, block, ropivacaine, lidocaine, duration

Introduction

Peripheral nerve blocks (PNBs) are used more frequently as the primary anesthetic or combined with intravenous anesthetics as multimodal anesthesia for various orthopedic surgical procedures.[1] Local anesthetics (LA) have varying onset time and duration of effect, leading to clinical classification as short-, intermediate-, and long-acting LA based on pharmacodynamic and pharmacokinetic properties.[2–6]

During lengthy surgical procedures, a long-lasting PNB is preferable, requiring the use of a long-acting LA. A shorter block duration may be adequate in short surgeries, especially when limited postoperative pain is expected. A quick onset time may be favored in a fast-paced work setting, and a short or intermediate block duration may also enable patients to begin early postoperative mobilization. The effects of combining LA for peripheral nerve blocks are poorly understood.

Received: 9 November 2024
Accepted: 9 November 2024
Published: 16 April 2025

Still, clinicians may combine different categories of LA to affect the onset time, duration, and quality of a peripheral nerve block.[6–10]

A common rationale for combining a short-acting with a long-acting local anesthetic may pertain to a faster block onset, while still maintaining prolonged anesthesia and analgesia on par with sole use of a long-acting local anesthetic. Thus, achieving a potentially ideal block with a fast onset and long duration.[11]

Prior studies have primarily found that combining short- or intermediate-acting LAs with long-acting LA significantly reduces block onset and duration compared to long-acting LAs.[12–19] However, other studies have found no significant difference in block characteristics when combining LAs.[9,20,21]

The infraclavicular brachial plexus block (IBPB) is a commonly used PNB.[22] Few studies have investigated the effects of combining different categories of LA in an IBPB.[17,23,24] None of these have investigated the combination of lidocaine with ropivacaine in an IBPB, solely focusing on bupivacaine as the long-acting LA.

We aim to expand the research on how combining local anesthetics affects block duration by exploring the impact of lidocaine-epinephrine and ropivacaine on analgesia length after hand or wrist surgery with an IBPB. Furthermore, we aimed to evaluate patients' satisfaction with the nerve block at postoperative follow-up.

Materials and Methods

Our hospital directorate approved this single-center retrospective cohort study as part of an observational quality assurance study (service evaluation) investigating peripheral nerve blocks for surgery. As such, approval from The Scientific Ethics Committees was waivered. Before scheduled surgery and data collection, informed consent and e-signatures were obtained from all included patients. Data was hereafter collected over the following 24 hours. An internal statistical analysis plan was composed before data extraction and statistical analyses. The present paper is written in accordance with "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies".[25]

Setting and Population

Data was collected from 13th September 2021 to 13th September 2022 at the Departments of Anaesthesia and Orthopaedic Surgery at the Copenhagen University Hospital – North Zealand, Hillerød, Denmark. We included patients over 18 years of age scheduled for elective hand or wrist surgery in an outpatient setting. Indications for surgery included distal radius fractures, distal antebrachium fractures, osteoarthritis, metacarpal fractures, Dupuytren's contracture, carpal tunnel syndrome, tendon ruptures, and ligament ruptures. All patients were scheduled for surgery with an IBPB as the sole type of anesthesia. No other adjuvants, anxiolytics, sedatives, or hypnotics were administered during the preoperative, intraoperative, or post-operative period, as this is not standard practice in our elective surgery unit. All patients were prescribed a standard regimen of 1000 mg acetaminophen (paracetamol) four times daily with or without 400 mg ibuprofen three times daily (depending on need, allergies, or intolerance). Prescribed opioids were either 10 mg morphine or 5 mg oxycodone up to 6 times daily depending on the patients' analgesic needs.

Data Sources and Validation

The patient and treating anesthesiologist registered baseline data at the bedside in the Research Electronic Data Capture (REDCap) application. Follow-up data regarding "Total block duration", "Time until block starts to subside", "Pain after block cessation", and "Patient satisfaction with nerve block" was registered by the patients using an SMS-based survey and registered in REDCap. Patients were instructed regarding the interpretation of survey questions and how to answer the survey via the SMS link. The survey was sent 24 hours after block administration. Unique civil registration numbers (CPR numbers) enabled data linkage and retrospective data collection from participants' electronic health records. Authors MTS, JLT, and LHL independently validated the extracted data using predefined screening filters. If data entries did not fulfill the quality criteria, the entries were cross-checked with the patient's electronic health records to ascertain valid entries. In the presence of inconsistencies, data entries from the electronic health record were used.

The following data were retrieved for the assessment: characteristics of the PNB (type, concentration, and volume of LA); characteristics of the patients (age, sex, body mass index (BMI), chronic opioid consumption prior to surgery); characteristics of the surgery (osseous surgery, postoperative opioid prescribed to the patient).

Intervention and Outcomes

The following LAs were used for the PNBs: lidocaine 20 mg/mL + Epinephrine 5 µg/mL (Lidokain-Adrenalin 20 mg/5 mikrog/mL, SAD, Amgros I/S, Copenhagen, Denmark) and ropivacaine 5 mg/mL (Ropivacaine 5 mg/mL, Fresenius Kabi AB, Uppsala, Sweden).[2–6] The type and volume of LA used for the IBPB and the applied method of combining LA were decided by the attending anesthesiologist performing the block. For outcome assessment, the combination of lidocaine-epinephrine and ropivacaine served as the comparator (COMBI group), while pure ropivacaine served as the control (ROPI group).

Primary Outcome

- "Total block duration" was defined as the time from a successful block, as assessed by the providing anesthesiologist, to return to baseline sensory function reported by the patient.

Secondary Outcomes

- "Time until block begins to subside" was defined as the time from a successful block to the first sensation of block remission reported by the patient.
- "Pain after complete block cessation" was patient reported on a numerical rating scale (NRS) from 0 to 10 (0 defined as no sensation of pain and 10 as the worst pain imaginable) after total block cessation.
- "Patient satisfaction with nerve block" was patient-reported on a 3-point Likert Scale: Unsatisfied, Neutral, Satisfied 24 hours postoperatively.

Peripheral Nerve Block Technique

All IBPBs were performed by highly experienced attending anesthesiologists, who combined lidocaine-epinephrine and ropivacaine according to preference.

Intravenous access was established in the contralateral arm of the patients and all patients were monitored according to hospital standards (non-invasive blood pressure, pulse oximetry, and 3-lead electrocardiography).

A lateral and sagittal in-plane technique described by Klaastad et al was utilized with a high-frequency linear ultrasound probe (Sonosite Nanomaxx Ultrasound System with a 10–5 Mhz probe - Sonosite Inc., Bothell, WA, USA).[26] Patients were placed in a supine position. Ultrasound was used to identify the axillary artery and vein and the lateral, medial, and posterior cords of the brachial plexus when possible. The needle was inserted medial to the coracoid process and inferior to the clavicle with subsequent ultrasound-guided slow advancement and repositioning as deemed necessary. The attending anesthesiologist determined whether to use a single- or multi-shot injection technique.

Statistical Methods

Continuous variables were reported using mean ± standard deviation. Non-normally distributed variables were reported with median and interquartile ranges (IQR). Categorical variables were reported using frequencies and percentages. Where applicable, unpaired two-sample *t*-test (continuous variables) and Fisher's exact test/Pearson's Chi-square test (categorical variables) were used as a significance test. The Wilcoxon rank sum test was used if the normality assumption was not fulfilled. The Welch two-sample test was used if the assumption of equal variances was not fulfilled. Distribution was explored and investigated regarding linearity, residuals, and variance homogeneity.

We performed multivariable linear regression analyses as sensitivity analyses to adjust for predefined potential confounding factors in continuous outcomes. Data on "Total block duration", "Time until block begins to subside", and "Pain after complete block cessation" in the two groups were analyzed to adjust for the following potential confounders: age; sex; BMI; type, dose and volume of LA; type of surgery; chronic opioid use; and postoperative opioid prescription. "Patient satisfaction with nerve block" was analyzed dichotomously as "Satisfied" versus

"Unsatisfied or Neutral", and multivariable logistic regression analysis adjusting for confounders was performed as a sensitivity analysis.

Two-sided P-values less than 0.05 are considered statistically significant. All statistical analyses were conducted using the statistics program R version 4.3.3.

Results

166 patients who received an IBPB were screened for the study. Of these, 28 patients did not respond to the survey. Further, 35 patients were excluded from our analyses during data validation (Figure 1). In total, 103 patients (37 in the ROPI group and 66 in the COMBI group) were included in our final analyses.

Table 1 presents the patients' baseline and perioperative characteristics. There were baseline differences regarding sex, total volume of local anesthetic, postoperative opioids prescribed to patients, and osseous surgery.

All comparisons of outcomes are presented in Tables 2 and 3. The primary outcome, "Total block duration", was 655 ±215 minutes in the COMBI group and 961±195 in the ROPI group; the mean difference was 306 minutes (95% CI 223–389),

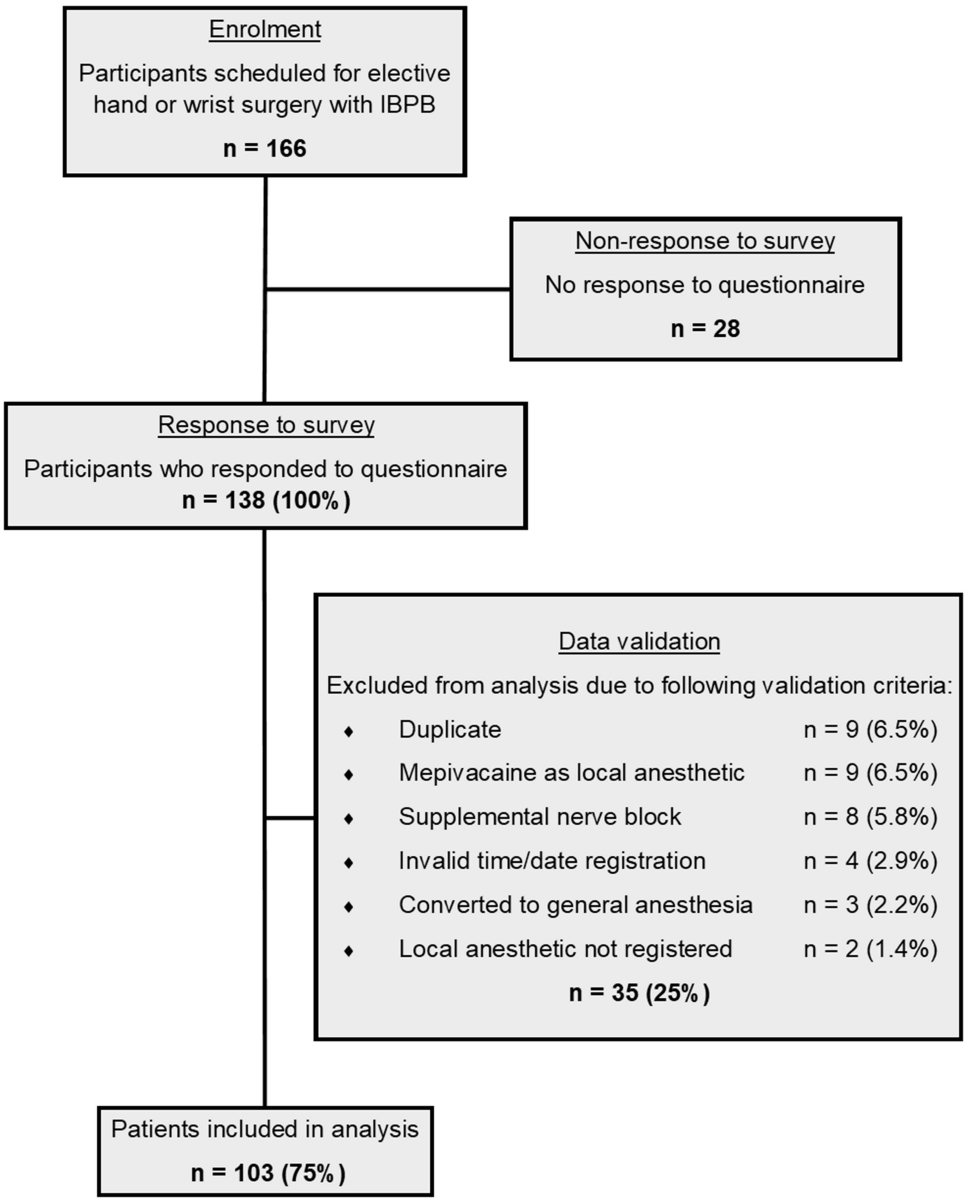

Figure 1 Flowchart of study selection and data validation.

Table 1 Baseline & Perioperative Characteristics

	ROPI Group	COMBI Group	*p*-value
Number of Included Patients	37	66	
Baseline Characteristics			
Age (years)	62 ± (15)	62 ± (12)	0.59[a]
Female (n)	28 (76%)	35 (53%)	**0.024**[b]
BMI	24.3 (3.6)	25.2 (4.2)	0.25[a]
BMI Group (n)			0.48[c]
Normal (18–25 kg/m^2)	22 (59%)	31 (47%)	
Overweight (25–30 kg/m^2)	11 (30%)	26 (39%)	
Obese (30–50 kg/m^2)	4 (11%)	5 (8%)	
Missing	0 (0%)	4 (6%)	
ASA Score (n)			0.39[c]
I	18 (49%)	24 (36%)	
II	16 (43%)	37 (56%)	
III	3 (8.1%)	3 (4.6%)	
Missing	0 (0%)	4 (6.1%)	
Perioperative Characteristics			
Volume of Local Anesthetic	24 ± (5)	26 ± (5)	**0.045**[a]
Volume Category of Local Anesthetic (n)			0.12[b]
<25 mL	20 (54%)	22 (33%)	
25–29 mL	6 (16%)	14 (21%)	
>29 mL	11 (30%)	30 (45%)	
Missing	0 (0%)	0 (0%)	
Chronic Opioid Consumption Prior to Surgery (n)	4 (11%)	4 (6.1%)	0.45[c]
Missing	0 (0%)	5 (7.6%)	
Postoperative Opioids Prescribed to Patient (n)	31 (84%)	36 (55%)	**0.005**[b]
Missing	3 (8.1%)	10 (15%)	
Osseous surgery (n)	31 (84%)	40 (60%)	**0.004**[b]

Notes: Values: mean (standard deviation); numbers (column percentages of total within group). Significant p-values <0.005 are emphasized with bold font. [a]Wilcoxon rank sum test. [b]Pearson's Chi-squared test. [c]Fisher's exact test.
Abbreviations: (n), number of patients; BMI, Body Mass Index; ASA, American Society of Anesthesiologists; kg, kilograms; m, meters; mL, milliliters.

Table 2 Primary Outcome

	ROPI Group	COMBI Group	Mean Difference	95% CI	*p*-value
Number of Included Patients	37	66			
Primary Outcome Measures					
Total Block Duration (minutes)	961 ± (195)	655 ± (215)	306	223 to 389	**<0.001**[a]

Notes: Values: mean ± (standard deviation); numbers (column percentages of total within group). [a]Welch Two Sample *t*-test.
Abbreviations: CI, Confidence Interval; (n), number of patients.

P<0.001. "Time until block begins to subside" was 396±120 minutes in the COMBI group and 642±214 minutes in the ROPI group; the mean difference was 246 minutes (95% CI 180–312), *P*<0.001.

Median "Pain after complete block cessation" was NRS 5.0 (IQR: 3.0–8.0) in the COMBI group and 6 (IQR: 4.0–7.0) in the ROPI group, *P*=0.80.

"Patient satisfaction with nerve block" was 60% (40 of 66 patients) in the COMBI group versus 38% (14 of 37 patients) in the ROPI group, *P*=0.042.

In alignment with unadjusted analyses, the multivariable linear regression analyses showed a significant decrease in "Total block duration" (Table 4) and "Time until block begins to subside" (Supplementary Material: Table S1) in the

Table 3 Secondary Outcomes

	ROPI Group	COMBI Group	Mean Difference	95% CI	*p*-value
Number of Included Patients	37	66			
Secondary Outcome Measures					
Time Until Block Begins to Subside (minutes)	642 ± (214)	396 ± (120)	246	180 to 312	**<0.001**[a]
Missing (n)	0 (0%)	2 (2.8%)			
Pain After Complete Block Cessation (NRS) (median)	6.0 (4.0, 7.0)	5.0 (3.0, 8.0)	—	—	0.80[b]
Patient satisfaction with nerve block (n)			—	—	**0.042**[c]
Unsatisfied or Neutral	16 (43%)	18 (27%)			
Satisfied	14 (38%)	40 (60%)			
Missing	7 (19%)	8 (12%)			

Notes: Values: median (interquartile range); numbers (column percentages of total within group). Significant p-values <0.005 are emphasized with bold font. [a]Two Sample *t*-test. [b]Wilcoxon rank sum test. [c]Pearson's Chi-squared test.
Abbreviations: CI, Confidence Interval, NRS, Numerical Rating Scale, (n), number of patients.

Table 4 Total Block Duration – Linear Regression Analyses

Covariates & Factors	n	Beta	95% CI	*p*-value
Univariable Analysis (Unadjusted)	103			
COMBI Group				
No		—	—	
Yes		−306	−391 to −221	**<0.001**
Multivariable Analysis (Adjusted)	83			
COMBI Group				
No		—	—	
Yes		−322	−423 to −220	**<0.001**
Age		1.8	−1.6 to 5.2	0.30
Sex				
Female		—	—	
Male		73	−35 to 182	0.18
BMI Group				
Normal (18–25 kg/m^2)		—	—	
Overweight (25–30 kg/m^2)		129	25 to 232	**0.015**
Obese (30–50 kg/m^2)		−40	−245 to 165	0.70
Total Volume of Local Anesthetic				
<25 mL		—	—	
25–29 mL		80	−55 to 215	0.24
>29 mL		51	−62 to 165	0.37
Chronic Opioid Consumption Prior to Surgery				
No		—	—	
Yes		71	−120 to 262	0.46
Osseous Surgery				
No		—	—	
Yes		54	−61 to 168	0.35
Postoperative Opioids Prescribed to Patient				
No		—	—	
Yes		−82	−202 to 38	0.18

Notes: Significant p-values <0.005 are emphasized with bold font.
Abbreviations: CI, Confidence Interval; n, number of patients; BMI, Body Mass Index; kg, kilograms; m, meters; mL, milliliters.

COMBI group when adjusting for potential confounders. Similarly, "Pain After Complete Block Cessation" was no different in the adjusted analysis (Supplementary Material: Table S2).

When adjusting for confounders, "Patient satisfaction with nerve block" was no longer significantly different (P=0.090) (Supplementary Material: Table S3).

Discussion

Our results demonstrated that a combination of lidocaine-epinephrine and ropivacaine in an IBPB for hand and wrist surgery reduced the total block duration by approximately 5 hours compared to a block with ropivacaine alone. However, the combination did not have an apparent effect on pain after complete block cessation.

The decrease in block duration aligns with earlier findings. However, these studies were not examining lidocaine-epinephrine and ropivacaine or an IBPB.[12–19]

Studies on combining local anesthetics for IBPB reveal conflicting findings. Özmen et al observed faster onset and longer analgesia with lidocaine and bupivacaine, while Pongraweewan found no differences in onset or duration.[23,24] Laur reported quicker onset but unchanged duration with mepivacaine-epinephrine added to bupivacaine.[17] Aguilera et al found 0.5% bupivacaine, with epinephrine and dexamethasone, prolonged analgesia and sensorimotor block compared to 0.25% bupivacaine with 1% lidocaine but had a slower onset.[27] Valery found no impact on analgesia with a lidocaine-ropivacaine combination in a sciatic nerve block.[21] These differences may have arisen from variations in techniques, anesthetics, adjuvants, and study methods.

The observed significant reduction in block duration in this study has important clinical implications. Shortened block duration may benefit surgical cases where rapid postoperative mobilization or limited postoperative pain is desirable. However, achieving optimal block duration requires careful consideration of surgical context, postoperative pain management, and patient needs.

In both groups, the median pain scores were moderately high. When performing a PNB for surgery, an aim may be to achieve a long block duration. Assuming it is beneficial to be pain-free for as long as possible while the post-surgical pain intensity subsides as time passes. Despite a difference of more than five hours in block duration between the ROPI and the COMBI group, there was no apparent effect on median pain scores immediately after block cessation.

Postoperative pain after block cessation may be mitigated by adjuvants, patient counseling, peripheral nerve catheters, and multimodal oral/IV analgesics.[28] However, only data on postoperative opioids prescribed to the patient was available in our database. Despite a standardized regimen of prescribed postoperative analgesics, no data on patient compliance were accessible.

Patient satisfaction was higher with lidocaine and ropivacaine; however, it was statistically non-significant after adjusting for confounders. A longer-lasting nerve block may not necessarily result in higher patient satisfaction. Loss of motor function in the post-surgical period or other unaccounted factors, such as block technique and block quality during surgery, may weigh heavily on satisfaction.

The use of epinephrine as an adjuvant to lidocaine may have affected the block durations in our sample. However, it seems unlikely to have affected the observed difference in duration compared to ropivacaine alone; if anything, the difference would likely have been greater if epinephrine was not used as an adjuvant.

This study's limitations include its retrospective, observational design and reliance on patient-reported outcomes. While efforts were made to minimize observer bias and adjust for confounding, the non-randomized nature of the data introduces potential selection bias. Additionally, recall and response bias may arise due to the difficulty of precise reporting of block cessation times, which may have been challenging for patients, potentially affecting the accuracy of duration assessments. A larger sample size and randomized controlled trials with low risk of bias are needed to validate these findings.

Since onset times were not registered, we cannot conclude whether combining lidocaine-epinephrine and ropivacaine resulted in a faster onset.

However, if the rationale for combining short- and long-acting local anesthetics is to achieve a faster onset and prolonged block duration, clinicians should carefully evaluate the potential for a significant reduction in block duration when using a lidocaine-epinephrine and ropivacaine combination.[12,18]

This may be advantageous in cases of short-duration surgery and limited postoperative pain, as quick block cessation can facilitate early mobilization and reduce the risk of joint stiffness and swelling in wrist surgery.[29] Nonetheless, the

decision to use this approach should depend, among other factors, on the type of surgery, surgical duration and the need for rapid postoperative rehabilitation and physical therapy.

Conclusion

Combining lidocaine-epinephrine and ropivacaine reduced the duration of analgesia after an infraclavicular brachial plexus block by approximately five hours. Pain after block cessation was moderately high in both groups. Patient satisfaction may be higher when performing a nerve block with combined lidocaine-epinephrine and ropivacaine versus pure ropivacaine. Confirmative results from randomized controlled trials with a low risk of bias are warranted.

Abbreviations

PNB, Peripheral nerve block; LA, Local anesthetic; IBPB, Infraclavicular brachial plexus block; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology Statement; BMI, Body Mass Index; REDCap, Research Electronic Data Capture.

Data Sharing Statement

All anonymized data will be available upon request to the authors.

Ethics Approval and Consent to Participate

This retrospective cohort study was part of an observational quality assurance study (service evaluation) prospectively investigating peripheral nerve blocks for surgery. Our hospital directorate approved the study and waived the need for further approval from The Scientific Ethics Committees due to the study's quality assurance design. As such, no approval from The Scientific Ethics Committees was needed. Informed consent and e-signatures were obtained from all included patients before scheduled surgery and data collection. The study complies with the Declaration of Helsinki.

Acknowledgments

We gratefully acknowledge Aurelien Xuan Bahuet in assisting with finalizing tables for the reported results.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Departmental resources provided funding for the study.

Disclosure

The authors do not have any competing interests to declare.

References

1. Cozowicz C, Poeran J, Memtsoudis SG. Epidemiology, trends, and disparities in regional anaesthesia for orthopaedic surgery. *Br J Anaesth*. 2015;115:ii57–ii67. doi:10.1093/bja/aev381
2. Covino BG. Pharmacology of local anaesthetic agents. *Br J Anaesth*. 1986;58(7):701–716. doi:10.1093/bja/58.7.701
3. Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth*. 1986;58(7):717–731. doi:10.1093/bja/58.7.717
4. Sanchez V, Arthur GR, Strichartz GR. Fundamental properties of local anesthetics. I. The dependence of lidocaine's ionization and octanol: buffer partitioning on solvent and temperature. *Anesth Analg*. 1987;66(2):159–165. doi:10.1213/00000539-198666020-00011
5. Strichartz GR, Sanchez V, Arthur GR, Chafetz R, Martin D. Fundamental properties of local anesthetics. II. Measured octanol: buffer partition coefficients and pKa values of clinically used drugs. *Anesth Analg*. 1990;71(2):158–170. doi:10.1213/00000539-199008000-00008
6. Taylor A, McLeod G. Basic pharmacology of local anaesthetics. *BJA Educ*. 2020;20(2):34–41. doi:10.1016/j.bjae.2019.10.002

7. Cunningham NL, Kaplan JA. A rapid-onset, long-acting regional anesthetic technique. *Anesthesiology*. 1974;41(5):509–511. doi:10.1097/00000542-197411000-00020
8. Moore DC, Bridenbaugh LD, Bridenbaugh PO, Thompson GE, Tucker GT. Does compounding of local anesthetic agents increase their toxicity in humans? *Anesthesia Analg*. 1972;51(4):579–585. doi:10.1213/00000539-197207000-00025
9. Gunjiyal MS, Mohammed S, Bhatia P, Chhabra S, Kumar M, Sharma A. Effect of combined versus sequential injection of 2% lidocaine and 0.5% bupivacaine on the onset and duration of supraclavicular brachial plexus block: a double blinded randomised controlled trial. *J Clin Anesth*. 2021;72:110313. doi:10.1016/j.jclinane.2021.110313
10. Nestor CC, Ng C, Sepulveda P, Irwin MG. Pharmacological and clinical implications of local anaesthetic mixtures: a narrative review. *Anaesthesia*. 2022;77(3):339–350. doi:10.1111/anae.15641
11. Choi J, Gadsden J. Local anesthetic mixtures for peripheral nerve blocks. In: Hadzic A, editor. *Hadzic's Textbook of Regional Anesthesia and Acute Pain Management, 2e*. McGraw-Hill Education; 2017.
12. Cuvillon P, Nouvellon E, Ripart J, et al. A comparison of the pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with Epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double-blind randomized study. *Anesthesia Analg*. 2009;108(2):641–649. doi:10.1213/ane.0b013e31819237f8
13. Gadsden J, Hadzic A, Gandhi K, et al. The effect of mixing 1.5% mepivacaine and 0.5% bupivacaine on duration of analgesia and latency of block onset in ultrasound-guided interscalene block. *Anesth Analg*. 2011;112(2):471–476. doi:10.1213/ANE.0b013e3182042f7f
14. Sripriya R, Sivashanmugam T, Rajadurai D, Parthasarathy S. Equal mixture of 2% lidocaine with Adrenaline and 0.5% bupivacaine 20 mL provided faster onset of complete conduction blockade during ultrasound-guided supraclavicular brachial plexus block than 20 mL of 0.5% bupivacaine alone: a randomized double-blinded clinical trial. *Reg Anesth Pain Med*. 2023;rapm–2023–104542. doi:10.1136/rapm-2023-104542
15. Almasi R, Rezman B, Kriszta Z, Patczai B, Wiegand N, Bogar L. Onset times and duration of analgesic effect of various concentrations of local anesthetic solutions in standardized volume used for brachial plexus blocks. *Heliyon*. 2020;6(9):e04718. doi:10.1016/j.heliyon.2020.e04718
16. Tryba M, Börner P. [Clinical effectiveness and systemic toxicity of various mixtures of prilocaine and bupivacaine in axillary plexus block] Klinische Wirksamkeit und Systemtoxizität verschiedener Mischungen von Prilocain und Bupivacain zur axillären Plexusblockade. *Reg Anaesth*. 1988;11(2):40–49.
17. Laur JJ, Bayman EO, Foldes PJ, Rosenquist RW. Triple-blind randomized clinical trial of time until sensory change using 1.5% mepivacaine with epinephrine, 0.5% bupivacaine, or an equal mixture of both for infraclavicular block. *Reg Anesth Pain Med*. 2012;37(1):28–33. doi:10.1097/AAP.0b013e318236bc30
18. Chen L, Wang Q, Shi K, et al. The effects of lidocaine used in sciatic nerve on the pharmacodynamics and pharmacokinetics of ropivacaine in sciatic nerve combined with lumbar plexus blockade: a double-blind, randomized study. *Basic Clin Physiol Pharmacol*. 2013;112(3):203–208. doi:10.1111/bcpt.12008
19. Abdelhady I, Ghallab M, Zaki M, Abdelrahman K, Soliman A. Comparative study between bupivacaine 0.5% vs. bupivacaine 0.5% plus lidocaine 2% vs. lidocaine 1.5% in ultrasound guided axillary brachial plexus block for brachiocephalic fistula formation in chronic renal failure patients. *Anaesth Pain Intensive Care*. 2022;26(6):743–748. doi:10.35975/apic.v26i6.2055
20. Ribotsky BM, Berkowitz KD, Montague JR. Local anesthetics. Is there an advantage to mixing solutions? *J Am Podiatr Med Assoc*. 1996;86(10):487–491. doi:10.7547/87507315-86-10-487
21. Valery P, Aliaksei M. A comparison of the onset time of complete blockade of the sciatic nerve in the application of ropivacaine and its equal volumes mixture with lidocaine: a double-blind randomized study. *Korean J Anesthesiol*. 2013;65(1):42–47. doi:10.4097/kjae.2013.65.1.42
22. Chin KJ, Singh M, Velayutham V, Chee V. Infraclavicular brachial plexus block for regional anaesthesia of the lower arm. *Cochrane Database Syst Rev*. 2010;(2):Cd005487. doi:10.1002/14651858.CD005487.pub2
23. Özmen Ö, Alici H, Dostbil A, Cesur M. The effect of addition of lidocaine to bupivacaine on anesthesia beginning time, block time, and block quality in lateral sagittal infraclavicular block. *Turk J Med Sci*. 2013;43:542–547. doi:10.3906/sag-1207-22
24. Pongraweewan O, Inchua N, Kitsiripant C, Kongmuang B, Tiwirach W. Onset time of 2% lidocaine and 0.5% bupivacaine mixture versus 0.5% bupivacaine alone using ultrasound and double nerve stimulation for infraclavicular brachial plexus anesthesia in ESRD patients undergoing arteriovenous fistula creation. *J Med Assoc Thai*. 2016;99(5):589–595.
25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806–808. doi:10.1136/bmj.39335.541782.AD
26. Klaastad Ø, Smith HJ, Smedby Ö, et al. A novel infraclavicular brachial plexus block: the lateral and sagittal technique, developed by magnetic resonance imaging studies. *Anesth Analg*. 2004;98(1):252–256. doi:10.1213/01.Ane.0000094337.75996.Ae
27. Aguilera G, Tabilo C, Jara A, Aliste J. 0.25% bupivacaine-1% lidocaine vs 0.5% bupivacaine for ultrasound-guided infraclavicular brachial plexus block: a randomized controlled trial. *Reg Anesth Pain Med*. 2024;rapm–2024–105511. doi:10.1136/rapm-2024-105511
28. Barry GS, Bailey JG, Sardinha J, Brousseau P, Uppal V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. *Br J Anaesth*. 2021;126(4):862–871. doi:10.1016/j.bja.2020.10.035
29. Zhou Z, Li X, Wu X, Wang X. Impact of early rehabilitation therapy on functional outcomes in patients post distal radius fracture surgery: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2024;25(1):198. doi:10.1186/s12891-024-07317-0