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Effect of Lidocaine 2% versus Bupivacaine 0.5% and 1 versus 2 dual separate injections on onset and duration of ultrasound-guided wrist blocks: A blinded 2x2 factorial randomized clinical trial

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ABSTRACT

Background: Local anesthetics are often selected or mixed to accomplish faster onset of anesthesia. However, with ultrasound guidance, local anesthetics are delivered with greater precision, which may shorten the onset time with all classes of local anesthetics. In this study, we compared onset time and duration of ultrasound-guided wrist blocks with a fast onset versus a longer lasting local anesthetic administered via single or dual (spatially separate) injections at the level of the mid-forearm.

Materials and methods: In this randomized clinical trial, 36 subjects scheduled for carpal tunnel release were randomly assigned to receive ultrasound-guided median and ulnar nerve blocks with Lidocaine 2%, or Bupivacaine 0.5% via single or dual injections (n=9 in each group). Subjects fulfilled the study requirements. The main outcome variables were onset and duration of sensory blockade, which were tested separately in 2 (drug) x 2 (injection) ANOVAs with interaction terms.

Results:

Sensory block onset time did not differ significantly between subjects given Lidocaine 2% (9.2 ± 3.4 min) or Bupivacaine 0.5% (9.5 ± 3.1 min) **[p = 0.76; mean difference -0.3 ± 1.1 min (95% CI -2.5, 1.9)]** or between the single (9.6 ± 2.8 min) and dual (9.1 ± 3.6 min) injection groups **[p = 0.69; mean difference -0.4 ± 1.1 min (95% CI -1.8, 2.6)]**. Sensory duration was longer for subjects in the Bupivacaine 0.5% group (27.3 ± 11.6 h) than for subjects in the Lidocaine 2% group (8.4 ± 4.1 h) **[p < 0.001; 95% CI of difference 12.7 – 25.1].** However, sensory duration in the single (15.7 ± 12.5 h) and dual (19.4 ± 13.1 h) injection groups did not differ significantly **[p = 0.28; mean difference -3.7 ± 4.3 h (95% CI -12.6, 5.1)]**.

Conclusions: No significant effect was found for onset time between Lidocaine 2% and Bupivacaine 0.5% used in ultrasound-guided wrist blocks. Dual injections did not shorten onset time. Since mean nerve block duration was longer with Bupivacaine 0.5%, our results suggest that the selection of local anesthetic for the median and ulnar nerve at the level of the mid-forearm should be based on the desired duration of the block, and not on its speed of onset.

KEY POINTS SUMMARY

Question: Is there a difference in onset time and duration of sensory block between Lidocaine 2% and Bupivacaine 0.5% and between single and dual spatially separate injections, in median and ulnar nerve blocks?

Findings: There was no clinically significant difference in onset or duration of sensory block between Lidocaine 2% and Bupivacaine 0.5% or between single and dual injections.

Meaning: Selection of local anesthetic for the median and ulnar nerves at the level of the mid-forearm can be based on the desired duration of the ultrasound-guided wrist block and not on its speed of onset.

GLOSSARY OF TERMS

ZOL: Ziekenhuis Oost-Limburg (Genk, Belgium)

ASA: American Society of Anesthesiologists

PACU: post-anesthesia care unit

NRS: Numeric Rating Scale

ANOVA: Analysis of variance

INTRODUCTION

Ultrasound-guided median and ulnar nerve blocks at the mid-forearm (e.g., wrist blocks) are often used to provide anesthesia and analgesia for patients having hand and wrist surgery.[1-3] Incomplete or slow onset of a block may delay the patient's readiness for surgery, whereas short duration of a block may result in inadequate postoperative analgesia. When selecting local anesthetics, many clinicians choose faster-acting Lidocaine over longer-acting Bupivacaine, or may mix local anesthetics, to achieve faster onset of blockade. However, mixing Lidocaine and Bupivacaine in brachial plexus blocks does not speed up onset and may even shorten duration of the blockade.[4]

Success and speed of block onset depend on exposure of a sufficient area of the nerve to the local anesthetic, and on the concentration and type of the local anaesthetic.[5] Advances in ultrasound-guided nerve blocks have allowed reliable monitoring of needle placement and distribution of local anesthetics that was not possible before the use of ultrasound.[6] Hence, differences in onset times may be smaller between "fast" and "long" onset anesthetics because they can be delivered with greater precision by ultrasound-guidance.

In this study, we compared the onset time and duration of distal median and ulnar nerve (wrist) blocks with Lidocaine 2% versus Bupivacaine 0.5%. We also assessed the effect of single versus dual (spatially separate) injections on the onset and duration of the neural blockade.

We hypothesized that in the distal peripheral nerves, onset time and duration of sensory block differ between Lidocaine 2% and Bupivacaine 0.5% administered via single and dual (spatially separate) injections.

MATERIALS AND METHODS

This randomized clinical trial included subjects scheduled for carpal tunnel release surgery at the ambulatory care center at Ziekenhuis Oost-Limburg (ZOL), a large tertiary care hospital in Genk, Belgium. The Ethics Committee at ZOL, Genk, Belgium approved the study protocol in October 2017 (17/060U). The study was approved and registered prior to first patient enrollment by the European regulatory authorities (EudraCT 2017-003694-34, October 2nd, 2017, Principal Investigator Catherine Vandepitte). Written informed consent was obtained from all subjects. This manuscript adheres to the applicable CONSORT guidelines.

Inclusion criteria were men and women 18-80 years of age; American Society of Anesthesiologists (ASA) physical status I, II or III; able to understand the purpose and risks of the study; and able to discern cold, pinprick, and light touch. Subjects were excluded if they were pregnant; had a history of allergic or adverse reaction to local anesthetics; had infection at the planned block sites, bodyweight <40 kg or body mass index >44 $kg \cdot (m^2)^{-1}$, had any chronic neuromuscular deficit affecting the peripheral nerves or muscles of the surgical extremity or any chronic condition or psychiatric disorder that would interfere with the neurological or study assessments.

After Informed Consent, subjects were randomized to receive either Lidocaine 2% or Bupivacaine 0.5% in single or dual (spatially separate) injections of the median and ulnar nerves in the anterior mid-forearm (first patient enrolled March 7th, 2018, Figure 1). An online randomization program http://www.graphpad.com/quickcalcs/randomize1.cfm was used to assign subjects to the treatment arms. The randomized allocations were placed in individually sealed envelopes by a research associate not involved in the protocol tests or assessments, and the randomized sequence was stored in a password-protected computer accessible only to the

biostatistician. Each sealed envelope was opened immediately prior to treatment by an unblinded anesthesiologist who performed the nerve blocks. The unblinded anesthesiologist was not further involved in the subjects' assessments. Subjects, surgeons, and research personnel collecting postoperative data were blinded to group allocation as injection block sites were concealed by a broad forearm bandage over both injection sites on all subjects.

Mid-forearm blocks of the median and ulnar nerves

All subjects had an intravenous line placed prior to performing the blocks, and standard ASA monitoring was applied. Anesthesiologists experienced in administering regional anesthesia under ultrasound guidance performed all blocks. Injection pressure was monitored throughout the procedure to standardize injection force at <15 psi. Block injections were performed outside of the operating room at least 30 min prior to surgery to allow sufficient time for block assessments. All subjects received sedation with midazolam 1mg and ketamine 5 mg IV prior to the block procedure.

Ultrasound-guided perineural injections of local anesthetic were administered with a 25-gauge needle. In the single injection group, the median and ulnar nerves were blocked distally (i.e., 5-7 cm above the palmar crease) with either Lidocaine 2% or Bupivacaine 0.5%. In the dual injection group, the median and ulnar nerves were blocked distally with either Lidocaine 2% or Bupivacaine 0.5%, and with additional injections 5 cm proximally. The single and dual injection groups received the same volume of local anesthetic (6mL/nerve). The injection sites were concealed with a bandage to blind research personnel conducting the post-block assessments.

As per institutional protocol, all subjects received acetaminophen 1 g, dexamethasone 5 mg,

and ondansetron 4 mg intravenously prior to the start of surgery. Block failure was defined as the absence of complete sensory blockade in the median and ulnar nerve territories as assessed by cold, pinprick, and light touch 30 min after block injections.

Per study protocol, subjects with incomplete blocks at 30 min received a rescue nerve block or general anesthesia, and were excluded from further analysis.

Sensory and follow-up assessments

Sensory block of the median nerve was assessed at the tip of the third digit; sensory block of the ulnar nerve was assessed at the tip of the fifth digit. Subjects rated their sensory effects as 0 (normal sensation), 1 (paresthesia), or 2 (no sensation). Sensory scores were reported from the end of the block injections in 5-min intervals up to 30 min, then every 15 min until operation room entry. A forearm tourniquet was used in all subjects. Thereafter, sensory block was assessed after surgery every 15 min until post-anesthesia care unit (PACU) discharge, and hourly from PACU discharge until full recovery of sensory function or discharge from the hospital. All subjects were discharged with a standardized postoperative pain treatment consisting of acetaminophen/paracetamol (1g Q6h).

Before discharge home, subjects were trained to self-perform the sensory assessments at the tips of the third and fifth digits. Follow-up phone calls were made twice a day starting the evening of day 0 (discharge from the ambulatory care center) through day 7 (end of the first postoperative week), and on postoperative day 30, to obtain subject reports of sensory effects, postoperative pain, numbness and weakness in the surgical hand, adverse events, and use of pain medications.

Postoperative assessments included pain intensity scores using the Numeric Rating Scale (NRS) (pain at rest, pain during movement, and worst pain the last 24 h), sensory ratings to cold, pinprick, and light touch (0: normal sensation, 1: paresthesia, 2: no sensation), rating of numbness and weakness of the surgical hand, postsurgical medication use, and adverse events. NRS scores were obtained before the other assessments were obtained.

Statistical analysis

Continuous variables are presented as mean ± standard deviation; discrete categorical variables as n (%).

For sensory onset, subject reports to score "1" were evaluated for cold, pinprick, and light touch. Sensory onset time was calculated by subtracting the time the last block was completed from the time at which the subject reported a score of "1" (paresthesia) for at least two of the three modalities. For subjects who reported "2" (anesthesia) for the three modalities at the first protocol assessment (5 min), onset time was recorded as 5 min. Sensory onset was calculated separately for the median and ulnar nerves, and their difference tested by paired *t* test. If not statistically different, onset times for the median and ulnar nerves were combined using the longer onset time.

For sensory duration, subject reports to score "0" (complete sensation) were evaluated for cold, pinprick, and light touch. Sensory duration was calculated by subtracting the sensory onset time (described above) from the time at which the subject reported "0" for all three modalities. Sensory duration was calculated separately for the median and ulnar nerves, and their difference tested by paired *t* test. If not statistically different, duration times for the median and ulnar nerves were combined using the longer duration time.

Two separate 2x2 ANOVAs were conducted to evaluate the research hypotheses that onset time (min) and duration (h) of sensory block differ between Lidocaine 2% and Bupivacaine 0.5%

administered via single or dual injections. The interaction of the drug and injection groups was included in each ANOVA. Assumptions were checked that the population of each group for each predictor is normally distributed (Box plot) and that the population variances of each group are equal (Levene's test).

NRS pain scores, any occurrence of reported numbness-weakness in the postoperative interval, supplementary use of opioids, and the occurrence of adverse events were described. Tests of differences among groups for reported adverse events were not planned as their numbers were anticipated to be small, and subjects could report more than one event.

P-values <0.05 were deemed statistically significant. Analyses were performed with the Statistical Package for the Social Sciences (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, version 26.0. Armonk, NY:IBM Corp).

Onset time of a nerve block is difficult to assess accurately. For this reason, sample size for this study was estimated on duration of the sensory block from one of our previous studies of the wrist block using Bupivacaine 0.5%.[7] We assumed a minimum difference important to detect of 24 h (standard deviation 12 h), type I error (alpha) of 0.01, and power 0.90 (two-sided test of two independent drug groups with unequal variances). To accommodate potential block failures and losses to follow-up, the calculated sample size (n=14 subjects) was increased to 18 subjects (allowing n=9 subjects in each drug-injection group).

RESULTS

Thirty-six patients scheduled for carpal tunnel release were enrolled at the hand surgery service at ZOL and randomly assigned (n = 9) to each of four groups (Figure 1). The groups differed **in some demographic characteristics and clinical features such as age and BMI** but **none of these factors** were found to confound the analyses **of sensory onset and duration** (Table 1). All blocks resulted in successful surgical anesthesia. Sensory onset did not differ significantly between the median and ulnar nerves (9.0 ± 3.0 min and 8.7 ± 3.2 min, respectively **[$p_{paired\ t}$ = 0.44; mean difference 0.3 ± 0.4 min (95% CI -0.5, 1.2)]** (Table 2); thus, the onset data were combined using the higher value (min) for the median or ulnar nerve in the analysis. There was no significant interaction between the drug (Lidocaine 2% versus Bupivacaine 0.5%) and injection (single versus dual) groups [**p = 0.92; mean difference for Lidocaine 2% 9.2 ± 1.1 min (95% CI 6.9, 11.4); mean difference for Bupivacaine 0.5% 9.5 ± 1.1 min (95% CI 7.2, 11.8)]** (Table 2). For Lidocaine 2%, sensory onset was 9.4 ± 2.5 and 8.9 ± 4.3 min in the single and dual injection groups, respectively. For Bupivacaine 0.5%, sensory onset was 9.7 ± 3.3 and 9.3 ± 3.1 min in the single and dual injection groups, respectively. Sensory onset did not differ significantly between subjects given Lidocaine 2% or Bupivacaine 0.5% **[p = 0.76; mean difference -0.3 ± 1.1 min (95% CI -2.5, 1.9)]** or between the single or dual injection groups **[p = 0.69; mean difference -0.4 ± 1.1 min (95% CI -1.8, 2.6)]** (Figure 2).

An extreme outlier in the Bupivacaine 0.5% single injection group was not included in the duration analyses because the subject's sensation to the three modalities could not be accurately determined, returning sometime between the last study phone call and the 30-day follow-up visit. Sensory duration did not differ significantly between the median and ulnar nerves (16.3 ± 11.0 h and 23.9 ± 28.1 h, respectively **[$p_{paired\ t}$ = 0.10; mean difference -7.6 ± 4.5 h (95% CI -16.8, 1.5)]** (Table 2); thus, the data were combined using the higher value (h) for the median or ulnar nerve in the analysis. There was no significant interaction between the drug (Lidocaine

2% vs Bupivacaine 0.5%) and injection (single vs double) groups [**p = 0.73); mean difference for Lidocaine 2% 8.4 ± 2.9 h (95% CI 2.5, 14.3; mean difference for Bupivacaine 0.5% 27.2 ± 3.0 h (95% CI 21.1, 33.2)]** (Table 2). Sensory duration was longer for subjects in the Bupivacaine 0.5% group (27.3 ± 11.6 h) than for subjects in the Lidocaine 2% group (8.4 ± 4.1 h) **[p < 0.001; mean difference 18.9 ± 3.0 h (95% CI 12.7 – 25.1)]** (Figure 3). However, sensory duration did not differ significantly between subjects in the single (15.7 ± 12.5 h) and dual (19.4 ± 13.1 h) injection groups **[p = 0.28; mean difference -3.7 ± 4.3 h (95% CI -12.6, 5.1)].**

Mean pain (NRS) scores from discharge through day 30 were low and did not differ between the single and dual injection groups (1.05 ± 0.52 vs 1.17 ± 0.80, respectively).

Numbness and weakness were evenly distributed between the injection groups throughout the follow-up period. During the first follow-up phone call on the evening of discharge, 64% (6 subjects in the Lidocaine 2% group and 17 subjects in the Bupivacaine 0.5% group) reported numbness; 72% (9 subjects in the Lidocaine 2% group and 17 subjects in the Bupivacaine 0.5% group) reported weakness. By the evening of the third follow-up day, both numbness and weakness largely dissipated (Table 3).

No subject used opioid medications during the period of this study. No adverse events occurred during this study.

DISCUSSION

Clinicians often select or mix local anesthetics to accomplish faster onset of anesthesia, albeit at the expense of block duration, and additional injections are often used to enhance the onset and success of nerve blocks. However, Gadsden and colleagues have shown that mixing short acting local anesthetics in brachial plexus blocks may not result in faster onset of the block; instead, duration of blockade is shorter than that provided by a long acting local anesthetic alone.[4]

In our study, injection of a "fast" onset (Lidocaine 2%) or a "long" duration (Bupivacaine 0.5%) local anesthetic for ultrasound-guided distal median and ulnar blocks (e.g., wrist) yielded similar onset times with the expected longer block duration of Bupivacaine.

The similar block onset time was an unexpected finding, given that Lidocaine has faster onset time in large nerves and plexus blocks[8]. Moreover, Lidocaine 2% has four times the mass of local anesthetic (20 mg/mL) compared to Bupivacaine 0.5% (5 mg/mL). Our observation may be the result of more precise ultrasound-guided injections and monitoring of local anesthetic spread which may result in more effective exposure of the nerves to local anesthetic. This may decrease the difference in speed onset among different local anesthetics. Additionally, the smaller amount of connective tissue around the median and ulnar nerves may result in faster diffusion of local anesthetic in contrast to the larger amounts of connective tissue around larger nerves. Regardless of mechanism, these findings have clinical relevance as they challenge the traditional practice of using Lidocaine instead of Bupivacaine for faster onset or the common practice of mixing local anesthetics to enhance onset while preserving the duration of the block.

In our study, median and ulnar blocks with Bupivacaine 0.5% did not result in clinically relevant slower onset. Importantly, the block duration with Bupivacaine alone was not

decreased, as in the case with mixtures of Bupivacaine with Lidocaine[4]. Our findings suggest that Bupivacaine alone can be used for the same onset speed and desired duration of the block, without the need to mix local anesthetics.

Another implication of our study is that a single injection of local anesthetic with adequate spread is sufficient for success. Indeed, under the conditions of our study, additional injection at another location along the nerve does not appear to have clinical benefit in terms of speed of onset or duration of the block. This finding was also unexpected, as additional injections *alongside the length of the nerve* increase nerve exposure to local anesthetic that may affect block onset, duration, quality and success rate.

Our results may differ from that found for the large nerves and plexi because of variation in the quantity, thickness, interconnections and other anatomical features of the connective tissues around the distal peripheral nerves. Moreover, *in vitro* studies suggest that the length of exposure of a nerve to local anesthetic may affect blocking characteristics.[9] It is possible that smaller peripheral nerves, such as the median and ulnar nerves, may have a "ceiling effect" for block onset and duration that is obtained with a single injection. Ponrouch et al. also found that sensory onset was not affected by a local anesthetic volume of 1.5% mepivacaine in ultrasound-guided median and ulnar nerves blocks[10], sensory duration was increased with the larger volume of local anesthetic. Therefore, it is possible that injections along the axis of larger peripheral nerves may have clinical benefits, but less so in the smaller, distal nerves.

Fredrickson et al. reported that a combination of a distal peripheral nerve block with a more proximal block in the same upper extremity increased sensory and motor block intensity when assessed at 15 min[11]. Likewise, combining peripheral nerve blocks at the forearm (distal) with proximal (supraclavicular) blocks shortened onset time by 5.6 min, compared to either block

alone [from 20 (15-30) to 15 (10-25) min].[12] However, the latter observations could have resulted from faster onset of the forearm nerve block, since they did not report the onset time for individual blocks (plexus versus peripheral injection).

Finally, as expected, duration of sensory block was about three times longer with Bupivacaine 0.5% than with Lidocaine 2% for both single and dual median and ulnar injections.

Limitations

Peripheral nerve blocks differ widely in their sensory block characteristics. Although we tested the expected area of sensory blockade for the median and ulnar nerves, anatomical variability may have influenced the accuracy of our data. The large variability in block duration may have made it difficult to detect smaller differences in block offset. It is possible that some of the patient-related numbness we observed was related to the surgical intervention and was not block-related. Likewise, some patients may have had subclinical pre-existing paresthesia that did not improve immediately after their surgery. Of note, large inter-patient variability in block duration is commonly observed in neural blockade and results from multiple factors, such as variability in amount and quality of connective tissues of nerves, and variability in sensitivity to local anesthetics[13].

In conclusion, under the conditions of our study using ultrasound-guided injections for median and ulnar nerve blocks, Lidocaine 2% and Bupivacaine 0.5% anesthetics have similar onset time. This suggests that for these blocks, local anesthetic may be chosen for desired duration, rather than for speed of onset of the block. Likewise, when the spread of local anesthetic in wrist blocks appears adequate on ultrasound, additional injections along the nerve may not confer a clinical benefit.

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REFERENCES

1 Macaire P, Singelyn F, Narchi P, Paqueron X. Ultrasound- or nerve stimulation-guided wrist blocks for carpal tunnel release: a randomized prospective comparative study. Reg Anesth Pain Med. 2008; 33:363–8

2 Gebhard RE, Al-Samsam T, Greger J, Khan A, Chelly JE. Distal nerve blocks at the wrist for outpatient carpal tunnel surgery offer intraoperative cardiovascular stability and reduce discharge time. Anesth Analg. 2002; 95(2):351–5

3 Soberón JR, Crookshank JW, Nossaman BD, Elliott CE, Sisco-Wise LE, Duncan SF. Distal peripheral nerve blocks in the forearm as an alternative to proximal brachial plexus blockade in patients undergoing hand surgery: a prospective and randomized pilot study. **J Hand Surg Am.** 2016; 41(10):969–77

4 Gandhi K, Lindenmuth DM, Hadzic A, Xu D, Patel VS, Maliakal TJ, Gadsden JC. 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.

5 Franz DN, Perry RS. Mechanisms for differential block among single myelinated and non-myelinated axons by procaine. J Physiol. 1974;236(1):193-210.

6 Marhofer P, Eichenberger U, Stöckli S, Huber G, Kapral S, Curatolo M, Kettner S. Ultrasonographic guided axillary plexus blocks with low volumes of local anaesthetics: a crossover volunteer study. Anaesthesia. 2010; 65(3):266–71.

7 Vandepitte CF, Van Boxstael S, Duerinckx JF et al.: Effect of Bupivacaine Liposome Injectable Suspension on Sensory Blockade and Analgesia for Dupuytren Contracture Release. **J Hand Surg Glob Online.** 2019; 1:191-197

8 Strichartz, G. R., Sanchez, V., Arthur, G. R., Chafetz, R., & Martin, D. (1990). 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.

9 Raymond SA, Steffensen SC, Gugino LD, Strichartz GR. The role of length of nerve exposed to local anesthetics in impulse blocking action. Anesth Analg. 1989; 68(5):563-70

10 Ponrouch M, Bouic N, Bringuier S et al. Estimation and pharmacodynamic consequences of the minimum effective anesthetic volumes for median and ulnar nerve blocks: a randomized, double-blind, controlled comparison between ultrasound and nerve stimulation guidance. Anesth Analg. 2010; 111(4):1059–64.

11 Fredrickson MJ, Ting FSH, Chinchanwala S, Boland MR. Concomitant infraclavicular plus distal median, radial, and ulnar nerve blockade accelerates upper extremity anaesthesia and improves block consistency compared with infraclavicular block alone. Br J Anaesth. 2011; 107(2):236–42.

12 Meco BC, Ozcelik M, Oztuna DG et al. Can we gain an advantage by combining distal median, radial and ulnar nerve blocks with supraclavicular block? A randomized controlled study. J Anesth. 2015; 29(2):217–22.

13 Gadsden J: Local Anesthetics: Clinical Pharmacology and Rational Selection. Hadzic's Peripheral Nerve Blocks and Anatomy for Ultrasound Guided Regional Anesthesia, 2nd edition. Edited by Hadzic A, Carrera A, Clark T, Gadsden J, Karmakar M, Sala-Blanch X, Vandepitte C, Xu D, New York, McGrawHill, 2012, pp29-40