



## Research article

# Onset times and duration of analgesic effect of various concentrations of local anesthetic solutions in standardized volume used for brachial plexus blocks

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## ABSTRACT

Visualization of the nerve structures of brachial plexus allows anesthesiologists to use a lower dose of local anesthetics. The content of this low dose is not unequivocal, consequently, the pharmacokinetics of local anesthetics used by various authors are difficult to compare. In this study, the onset times and duration of the analgesic effect of local anesthetic mixture solutions used for brachial plexus blocks are investigated and the quality of anesthesia is compared. 85 unpremedicated American Society of Anesthesiologist physical status I-III, 19-83-year-old patients scheduled for upper limb trauma surgery are assigned to four groups for the axillary-supraclavicular block with lidocaine 1% and bupivacaine 0,5% 1:1 mixture (Group LB) or bupivacaine 0.33% (Group BS) or lidocaine 0,66% (Group LS) or bupivacaine 0.5% and lidocaine 1% 2:1 mixture (Group BL). 0.4 ml/kg was administered to the four groups. The onset time was significantly shorter in the lidocaine group (LS  $13.0 \pm 1.02$ ) than in the other study groups (LB  $16.64 \pm 0.89$ ; BS  $17.21 \pm 0.74$ ; BL  $16.92 \pm 0.51$  min  $\pm$ SEM,  $p = 0.002$ ). No differences were observed in the onset times between LB, BS, and BL groups ( $p > 0.05$ ). Statistical differences were found in the duration of local anesthetics between LB ( $392.9 \pm 20.4$ ), BS ( $546.4 \pm 14.9$ ), LS ( $172.85 \pm 7.8$ ), and BL ( $458.7 \pm 11.9$  min  $\pm$ SEM,  $p = 0.001$ ). Lidocaine does not shorten the onset times, but significantly decreases the duration of action of bupivacaine when used in mixture solutions. Lidocaine exhibits a good quality of block in the applied dose, while other solutions have excellent quality. Bupivacaine without lidocaine has the longest duration of action to achieve the longest postoperative analgesia.

## 1. Introduction

The ultrasound-guided peripheral nerve blockade techniques (Kapral et al., 1994) have several advantages for patients undergoing trauma surgery with infrequent complications (Kettner et al., 2011; Neal, 2016). The variations of nerve structures can be visualized by sonography reducing the volume needed to achieve complete nerve blockade (Harper et al., 2010; Riazi et al., 2008) with a high success rate (Chan et al., 2007; Jochum et al., 2013; Kumar et al., 2014). Smaller doses of local anesthetics are associated with incomplete nerve blockades (Barrington and Kluger, 2013), while higher doses are not recommended because of the potential risk of local anesthetic systemic toxicity (Neal et al., 2010). The site of a peripheral nerve catheter is often in the same region of the surgery, so the placement of peripheral nerve catheters prior to surgery

can be controversial (Ilfeld, 2017). Therefore the single-shot injection technique is extensively used for intraoperative anesthesia and post-operative pain management, even though the duration of the effect of local anesthetics is limited.

There are some studies in the literature in which the authors intended to determine the minimal effective volumes of different local anesthetic solutions. Local anesthetic agents were frequently used in form of a mixture in these studies in the hope that the beneficial properties of each component can be exploited, the quality of block can be increased, while the risk of side effects or the local anesthetic systemic toxicity can be decreased.

In trauma patients with hand and forearm surgery tourniquet is often used. Since the axillary approach to the brachial plexus cannot result in sufficient anesthesia of the upper arm supplemental supraclavicular

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injections were administered to eliminate the tourniquet discomfort or pain.

In accordance with our former experience we chose to employ low concentration of LAs without adjuvants, therefore in this study 1:1 mixture of lidocaine 1% and bupivacaine 0.5%, or 2:1 mixture of bupivacaine 0.5% and normal saline, or 2:1 mixture of lidocaine 1% and normal saline or 2:1 mixture of bupivacaine 0.5% and lidocaine 1% without epinephrine were used at 0.4 ml/kg, with the maximum volume of 30 ml (Felfernig et al., 2010; Hull et al., 2016; Kaur, 2015; Leurcharumsee et al., 2017; Nakayama et al., 2017). On the one hand, this study aimed to compare the onset times and duration of action of four different local anesthetic solutions with a consistent dosage regimen to find a distinguishable difference. On the other hand, the quality of anesthesia achieved by the same volume (0.4 ml/kg) of four local anesthetic solutions was evaluated with a novel composite outcome scale. It was hypothesized that the lidocaine content of the local anesthetic solution shortens the onset time and the duration of the effect of bupivacaine in a dose-dependent manner. The quality of blocks achieved by the same volumes of different local anesthetic solutions was supposed to be similar.

## 2. Material and methods

### 2.1. Patients

Total of 93 American Society of Anesthesiologist physical status I-III consecutive adult patients aged between 19 and 83 years old scheduled for elective or emergency trauma surgery of hand and forearm under ultrasound-guided BPB were assigned to this randomized-prospective observational study after approval by the University Research Ethics Board (2017/6940), Pécs University Medical School, Hungary. All of the patients received detailed information about the planned peripheral nerve blockade techniques and surgeries, then written informed consents were obtained.

Patients were excluded if continuous peripheral nerve catheter technique or bilateral block was planned, or the patient refused to participate. Exclusion criteria included psycho-mental conditions interfering with consent or assessment; pre-existing chronic pain condition or daily analgesic or sedative consumption; sedative or analgesic

premedication; pre-existing neurological disorders affecting the brachial plexus; obstructive sleep apnea; contraindications to peripheral nerve blockade including local skin infections or allergy to local anesthetic agents. After exclusion, eligible patients for the study were randomized to four local anesthetic mixture solution groups and analyzed as presented in a Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Figure 1).

### 2.2. Methods

20-23 G short peripheral intravenous lines were inserted in the nondependent arm, with routine monitoring readily available in the block-room of the operating suite (Ilfeld and Liguori, 2017; Russon et al., 2010). Standardized ultrasound-guided axillary-supraclavicular approach to the brachial plexus was performed under sterile conditions by the same anesthesiologist. The supraclavicular block was performed with the traditional in-plane, single injection cluster approach (Choi et al., 2017), then the axillary approach was performed in the supine position, with the upper arm in 90° abduction and the elbow in flexion on the operating table. The most appropriate in-plane or out-of-plane technique was employed, according to the actual anatomical position of the vessels and nerve structures (Brattwall et al., 2016; Coventry and Satapathy, 2011; Ranganath et al., 2014). A 25G 40 mm non-insulated normal bevel needle (Sterican, B.Braun, Melsungen, Germany) was used with a high-frequency UST 5524 5–10 MHz linear probe (Ultrasound Aloka Prosound SSD-4000, Japan). Nerve stimulation was not used. No sedative or analgesic agent was administered for pre-medication. Consented study participants were assigned randomly into 4 groups (LB, BS, LS, and BL) according to the concentration of lidocaine and bupivacaine in the mixture solution (Table 1).

The targeted maximum single shot volume was 30 ml, therefore the calculated volumes were administered from the pre-prepared 30 ml solutions in each group. The standardized dose was 0.4 ml/kg BW divided into five approximately equal doses for the SC divisions of the BP, the musculocutaneous (MC), radial (R), ulnar (U), and median (M) nerves (Table 2). The performance time (time between insertion and removal of the needle) was assessed, the mean procedural time was around 5 min after preparation and sonography mapping for the two regions.

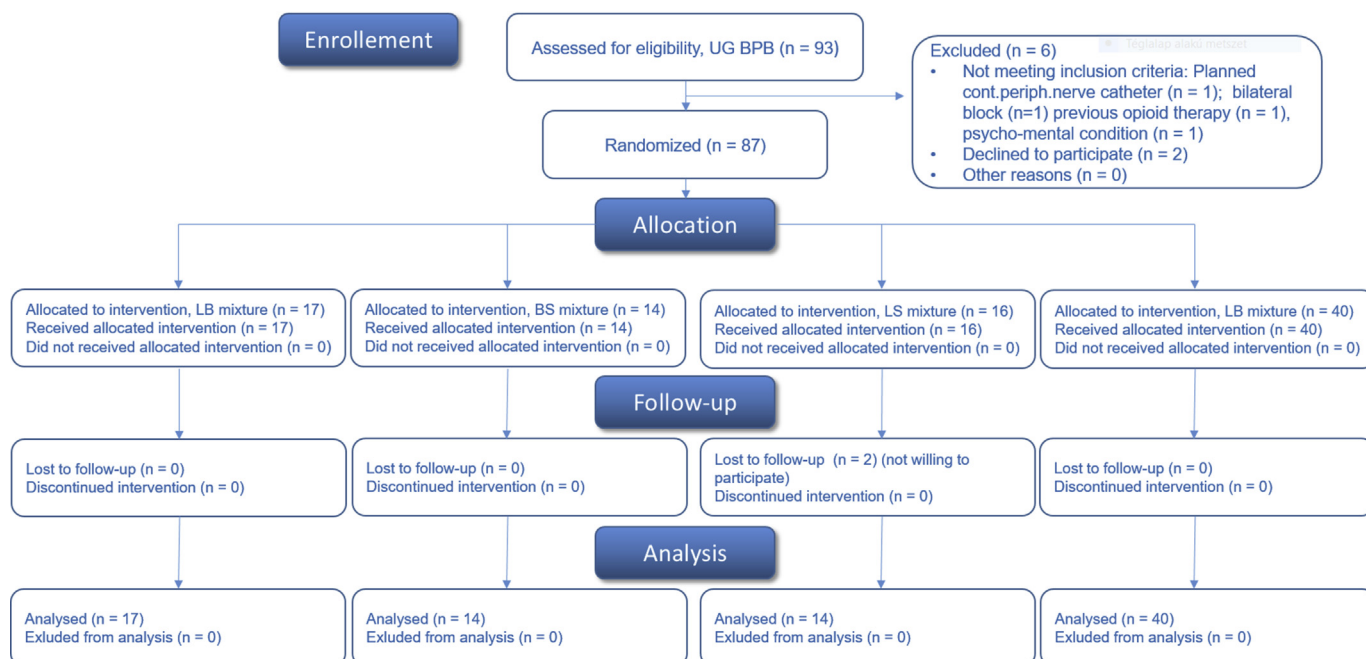


Figure 1. CONSORT diagram of the study.

**Table 1.** The volume and mass of the local anesthetic in the 30 mL solutions and the percent composition (percent by mass, %) of solutions in the four groups (LB, BS, LS and BL; L = lidocaine, B = bupivacaine, S = saline).

	LB - 1:1	BS 2:1	LS 2:1	BL 2:1
Lidocaine 1%	15 ml/150 mg	-	20 ml/200 mg	10 ml/100 mg
Bupivacaine 0,5%	15 ml/75 mg	20 ml/100 mg		20 ml/100 mg
normal saline (ml)	-	10	10	-
volume (ml)	30	30	30	30
conc. (%)	L 0,5/B 0,25	B 0,33	L 0,66	B 0,33/L 0,33

After the administration of local anesthetics, standard anesthesia monitoring was started in the operating room. Data were collected as preoperative values (T0); intraoperative mean values (Top); post-operative values straight after surgery (Tpop); 6 and 24 after surgery (T6; T24) including measurement of heart rate (HR), non-invasive arterial blood pressure (NIBP), and verbal numeric rate (VNR, 11 point scale) of pain intensity.

### 2.3. Assessment of the quality of anesthesia

The extent of sensory and motor blockade was assessed every 2–3 min in the corresponding region after the total dose of local anesthetic was injected until the blockade was defined as complete, or 20 min. The sensory blockade of the brachial plexus dermatomes was estimated using a touch, and pinprick test. A von Frey filament with a standard target force of 10 gr (Touch Test® Sensory Evaluator, Red 5,07; USA) was used for the assessment of the loss of protective sensation. A complete sensory block was defined by loss of sensation of filament prick and touch on all four nerve distribution. Sensory distribution was assessed on the area of the skin overlying the thenar eminence for the median nerve, dorsum of hand for the radial nerve, 5th digit and its fingertip for ulnar nerve, and lateral region of the forearm for the musculocutaneous nerve. Sensory block was assessed on a 3 point scale from 0 to 2, as complete (2) - loss of sensation to touch; partial (1) - loss of sensations to pinprick; or normal sensation (0). The motor blockade was evaluated by rating the muscle contraction functions corresponding to the four nerves (elbow and wrist extension for radial nerve; biceps flexion for musculocutaneous nerve, wrist flexion for the median nerve, and the thumb adduction and flexor carpi ulnaris flexion for ulnar nerve). Motor block was assessed as a complete motor block (2), reduced motor strength (1), or normal motor function (0).

Onset time for sensory or motor block was defined as the time interval between the end of total local anesthetic administration and complete sensory or motor block. A complete sensory block was defined by the anesthetic block (score 2) on all nerve distributions. A complete motor block was defined as the absence of voluntary movement on hand and forearm (score 2).

When the block was assessed as complete the tourniquet was placed (if needed), and the procedure was started. The outcome quality and success rate of brachial plexus block were assessed by a composite tool designed for evaluating the loss of sensory (S, 0–4: failed to excellent), motor function (M, 0–4: failed to excellent), the coping of the patient (C,

0–4: failed to excellent) and the postoperative pain at the end of surgery and 24 h after (P, 0–4: pain before the end of surgery to long-lasting - 24 h - analgesia). The overall quality of peripheral nerve blockade was evaluated by independent examiners, based on the aggregate 0–16 point scale. Under 7 Point the block was defined as failed, 8–11 = Tolerable; 12–13 = Good; 14–16 = Excellent (Almasi et al., 2020). The brachial plexus block was considered as failed if the tourniquet discomfort or pain required conversion to general anesthesia, despite the excellent block quality at the site of operation.

The duration of anesthesia was defined as the time between the end of the local anesthetic injection for brachial plexus block and the return of the sensory function reported by the patient or the necessity for first analgesic medication.

The study was conducted comparing the onset times and the duration of sensory effects of the same volumes of LB, B, L, and BL for brachial plexus block. Midazolam and fentanyl consumption were analyzed in the four groups, the outcome quality of blocks, vital parameters, verbal numeric rates for the assessment of intensity of pain (VNR) values, and non-steroid analgesic consumptions were compared between the four groups. We assessed the reported pain intensity of the patients before the peripheral nerve blockade (VNR0). 6 and 24 h after the plexus blockade the VNR values were evaluated and compared to the VNR0.  $(VNR0 - VNR6)/(VNR0) * 100 = PAR6$  (PAin Relief %).

### 2.4. Statistics

The IBM SPSS Statistics (Windows, version 24, 2016) was used in our analyses. Paired samples t-test, Kruskal-Wallis test combined with the Mann-Whitney U test for post hoc testing were used in analyzing the ordinal data. The Chi-square test was used for comparison of the categorical variables between the groups. One way ANOVA combined with Bonferroni post hoc test was used in analyzing the variance of linear data between groups.  $P < 0.05$  was considered significant. Priori power calculation was performed by GPower 3.1.9.2 version (Erdfelder et al., 1996): Effect size  $f = 0.4$ ,  $\alpha$  err = 0.05; power = 0.85; number of groups = 4; total sample size = 84.

### 2.5. Randomization and blinding

Randomization was based on a single sequence of random assignments. Two independent researchers were responsible for randomization. Avoiding the alternation method (e.g. presenting, or enrolment

**Table 2.** Local anesthetic dosage regimens (mL) applied for hand and forearm surgery according to bodyweight (SC = Supraclavicular approach, AX = axillary approach, MC = musculocutaneous, R = radial, U = ulnar and M = median nerve).

Brachial Plexus		Bodyweight (kg)			
		50 – (55)	60 – (65)	70 – (75)	75 <
SC		4	4	5	5
AX	MC	4	5	5	5
	R	4 – (5)	5 – (6)	6 – (7)	7
	U	4 – (5)	5 – (6)	6 – (7)	7
	M	4	5	6	6
Volume (mL)		20 – (22)	24 – (26)	28 – (30)	30

order), the shuffled 4-card deck method with allocation concealment and masking was used. The patient's ID, date, time, and other information were recorded. The duration of the operation was an influencing factor during the randomization because an expectedly longer surgery excluded the choice of lidocaine solution alone. A nurse prepared the syringe with local anesthetic mixture according to the number of choices. This nurse was the only person who was aware of the treatment options, but neither the researcher and the coordinator nor the patient and the surgeon knew what LAs the respective patient received.

The research coordinator performed all of the brachial plexus blockades and collected procedural data and kept a record of cases. Every case was recorded in a logbook with adequate protection. Patients, the operating team, nurses, and observers involved in the quality assessment of blocks and the follow-up data collection were unaware of group allocation. The research coordinator after the brachial plexus blockade was not present in the operating theatre at the time of tourniquet inflation and the beginning of the surgery. The researchers measured the outcome of the patients, the intra- and postoperative parameters, drug consumptions, and verbal numeric rates were collected and matched after a while, the list of cases was provided in the form of a spreadsheet program by an observer-blinded assistant and was statistically evaluated by an independent analyst.

### 3. Results

The study was completed with 85 patients allocated into four comparable study groups, the demographic data, and clinical characteristics of which were statistically similar. ( $p < 0.05$ ) (Table 3). Ultrasound-guided supraclavicular and axillary approach to brachial plexus was successfully performed to all participants according to standardized dosage regimens. There were no statistical difference in the injected volumes and in the volumes per bodyweight between groups ( $p > 0.05$ ). The onset time was significantly shorter ( $13.0 \pm 1.02$  min) in the lidocaine group (LS) when compared with that in the LB, BS, and BL groups however, there were no significant difference detected in the onset times between LB, BS and BL groups ( $p > 0.05$ ) (Figure 2a). The motor onset time was shorter ( $17.5 \pm 2.7$  min) in the bupivacaine group (BS) when compared with that in the LB ( $19.9 \pm 3.2$ ), LS ( $20.8 \pm 2.3$ ), and BL ( $18.0 \pm 2.7$ ) groups. Statistical differences were observed between the groups (BS vs. LS  $p = 0.013$ ; BL vs. LS  $p = 0.007$ ). Statistical difference was found between the sensory and motor onset times in the LB, BS, LS, and BL groups ( $p < 0.019$ ) (Figure 2b,c).

Statistical differences were observed in the duration between the four groups (LB  $392.9 \pm 20.4$  min vs BS  $546.4 \pm 14.9$  min vs LS  $172.8$  mins  $\pm 7.8$  and BL  $458.7 \pm 11.9$  min;  $p = 0.001$ ) (Figure 2d) (Table 4). There were no tourniquet discomfort or pain in the four study groups, and no evidence of complications of brachial plexus blockade was observed in the follow-up period. The differences in the patient numbers in the four

study groups do not affect the statistical analysis. None of the patients was admitted to the postoperative care unit.

Small doses of anxiolytic or analgesic medication were used to achieve the patient's comfort during surgery, if necessary. There were no statistical differences in the intraoperative consumption of midazolam and fentanyl ( $p > 0.05$ ) and in the postoperative consumption of diclofenac ( $p > 0.05$ ) between the four groups. The motor quality of block in the LS group ( $3.5 \pm 0.13$ ) was significantly lower when compared with it in the other study groups (LB  $3.88 \pm 0.08$ , BS  $4.0 \pm 0$ , BL  $3.97 \pm 0.02$  SEM;  $p = 0.00$ ) groups. The postoperative pain quality score was statistically lower in the LS group ( $2.85 \pm 0.09$  vs LB  $3.0 \pm 0$  vs BS  $3.0 \pm 0$  and BL  $3.0 \pm 0$  SEM;  $p = 0.016$ ). The outcome quality of blocks based on sensory, motor function, coping and postoperative pain (SMCP scale, aggregate points) was lower but not statistically significant in the LS group ( $13.42 \pm 0.41$ ) vs LB ( $14.11 \pm 0.19$ ), vs BS ( $14.14 \pm 0.23$ ) vs BL ( $14.2 \pm 0.16$  SEM;  $p = 0.28$ ). The outcome quality of anesthesia evaluated by the SMCP scale was Excellent (14–16) in Group LB, BS, and BL, the quality of anesthesia in the LS group was assessed as Good (12–13) (Table 5).

The means of the mean arterial pressures (MAP) and heart rates (HR) during surgery were regarded as the baseline. There was no significant difference in the change of blood pressure and heart rate (before, 6, and 24 h after the brachial plexus blockade, MAP0,6,24/MAPBaseline;  $p > 0.05$ , HR0,6,24/HRBaseline;  $p > 0.05$ ).

The pain intensity VNR6 scores tended to zero in the LB ( $0.58 \pm 0.21$ ), BS (0.0), and BL ( $0.07 \pm 0.05$  SEM) groups 6 h after the blocks ( $p = 0.00$ ), while VNR6 was statistically higher in the LS group ( $2.21 \pm 0.33$  SEM;  $p = 0.00$ ). The lowest mean VNR24 score was observed in the BS group ( $1.14 \pm 0.2$ ) vs LB ( $1.94 \pm 0.23$ ) vs LS ( $1.57 \pm 0.22$ ) vs BL ( $1.47 \pm 0.15$  SEM;  $p = 0.049$ ). The ratio of a point drop in VNR6 or VNR24 to VNR0 in percent was regarded as pain relief (PAR6 and PAR24, respectively). There was no evidence of pain relief in the LS group 6 h after brachial plexus blockade ( $-2.5\% \pm 26.6$  SEM) vs LB ( $83.85\% \pm 5.81$ ) vs BS ( $100\% \pm 0$ ) vs BL ( $98.54\% \pm 1.1$  SEM;  $p = 0.00$ ). Significant reduction in pain was observed in all four study groups 24 after BPB, the greatest PAR24 was observed in the BS group ( $62.73\% \pm 6.75$ , vs LB  $45.1\% \pm 4.62$  vs LS  $35\% \pm 13.24$  vs BL  $50.47\% \pm 6.29$ ;  $p < 0.05$ ) but there was no significant difference between the four groups ( $p > 0.05$ ) (Table 6).

### 4. Discussion

In this study, the onset time and duration of different local anesthetics solution without adjuvants in standardized volume were compared for brachial plexus blockade under ultrasound guidance.

To the best of our knowledge, this is the first work that demonstrates distinguishable differences in the duration of the analgesic effect of various local anesthetic mixed solutions. Lidocaine alone is only recommended for short operations and expectedly less painful upper limb

**Table 3.** Demographic Data and Clinical Characteristics of the Study Groups.

	LB (n = 17)	BS (n = 14)	LS (n = 14)	BL (n = 40)	p
Age (yr)	55.76 $\pm$ 4.19	51.85 $\pm$ 5.31	51.85 $\pm$ 6.07	51.5 $\pm$ 2.78	0.883 <sup>a</sup>
Gender (M/F)	9/8	3/11	4/10	17/23	0.255 <sup>b</sup>
Weight (kg)	81.88 $\pm$ 5.44	70.0 $\pm$ 2.89	68.92 $\pm$ 3.58	75.67 $\pm$ 2.27	0.086 <sup>a</sup>
BMI (kg/m <sup>2</sup> .5)	27.06 $\pm$ 1.47	26.51 $\pm$ 1.34	25.97 $\pm$ 1.45	26.04 $\pm$ 0.73	0.908 <sup>a</sup>
ASA status (I/II/III)	5/12/0	5/7/2	6/7/1	19/18/3	0.563 <sup>b</sup>
Duration of surgery (min)	69.52 $\pm$ 6.19	70.71 $\pm$ 10.64	43.21 $\pm$ 6.45	72.82 $\pm$ 6.45	0.076 <sup>a</sup>
Tourniquet (min)	46.27 n = 11	44.83 n = 12	*27.4 n = 10	57.32 n = 31	*0.047 <sup>a</sup>

Values are presented as mean  $\pm$  standard error of mean, except for sex and ASA status which are presented as frequencies.

Asterisk indicates statistical significance,  $p < 0.05$ .

ASA: American Society of Anesthesiologist.

BMI: new formula body mass index =  $1.3 \times$  bodyweight (kg)/height (m)<sup>2.5</sup>.

<sup>a</sup> One-way ANOVA.

<sup>b</sup> Chi-square test.

**Table 4.** Pharmacokinetic characteristics of study groups.

	LB (n = 17)	BS (n = 14)	LS (n = 14)	BL (n = 40)	p
Volume (ml)	30.1 ± 1.4	26.57 ± 1.05	27.57 ± 1.0	28.5 ± 0.59	0.127 <sup>a</sup>
Volume/BW (ml/kg)	0.37 ± 0.01	0.38 ± 0.01	0.40 ± 0.01	0.38 ± 0.006	0.268 <sup>a</sup>
Onset time (sensory)	16.64 ± 0.89	17.21 ± 0.74	*13.0 ± 1.02	16.92 ± 0.51	*0.002 <sup>a</sup>
Onset time (motor)	19.94 ± 0.78	17.57 ± 0.72	*20.85 ± 0.60	18.00 ± 0.42	*0.001 <sup>a</sup>
Duration	*392.9 ± 20.4	*546.4 ± 14.9	*172.8 ± 7.8	*458.7 ± 11.9	*0.001 <sup>a</sup>

Values are presented mean ± standard error of mean.

<sup>a</sup> One-way ANOVA.

\* Statistically significant, Bonferroni post hoc test.

conditions. Since the quality of anesthesia achieved by mixture solutions or single local anesthetic agents is the same, the combination of local anesthetics is not recommended to increase the quality of nerve blockade. Long-lasting bupivacaine without lidocaine has the longest duration of action to achieve the longest possible postoperative analgesia. The use of mixture solutions can be used if excellent anesthesia with submaximal duration is pivotal, however, bupivacaine alone should be considered if the long-lasting postoperative analgesia is the main goal of the brachial plexus blockade.

Before the advent of the ultrasound guidance for peripheral nerve blocks, high volumes of local anesthetic solutions were used. Under ultrasound guidance, the doses of local anesthetics can be decreased. Recently the employment of low volumes is advocated, however, there is no content or volume uniformity concerning “low dose” local anesthetic applied for peripheral nerve blocks. The pharmacokinetics of different local anesthetic solutions mentioned in various articles are difficult to compare. Ribotsky studied 1% plain lidocaine, 0.25% plain bupivacaine and a 50/50 mixture of 1% lidocaine and 0.25% bupivacaine and did not find a significant difference in the onset times for the three solutions, but bupivacaine had the most prolonged duration of action (Ribotsky et al., 1996). O'Donnell performed effective surgical anesthesia (n:5) with 1 ml 2% lidocaine/epinephrine per nerve (O'Donnell and Iohom, 2009). Formerly the same authors used axillary approach with 20 ml 1:1 lidocaine 2% and bupivacaine 0.5% mixture with epinephrine and clonidine for upper limb surgery (O'Donnell et al., 2009), while in the same year Duggan et al. found, that the minimum effective anesthetic volume in 50% and 95% of patients (n:21) was 23 mL and 42 mL of 50:50 mixture of lidocaine 2% and bupivacaine 0.5% with epinephrine (Duggan et al., 2009). Recently, Ferraro et al. determined the minimum effective volume in 90% of patients (n:19) of 0.5% bupivacaine with epinephrine as 1.56 mL per nerve for axillary brachial plexus block (Ferraro et al., 2014). Gadsden et al. used a sequential administration of LAs with 15 mL of mepivacaine 1.5% followed by 15 mL of bupivacaine 0.5% for

interscalene brachial plexus blockade (Gadsden et al., 2012). Siva-shanmugam also used the 1:1 mixture of 2% lidocaine with epinephrine and 0.5% bupivacaine at 0.5 ml/kg for brachial plexus blockade (Siva-shanmugam et al., 2015).

Although the volumes, concentrations, and the content of adjuvants of these LA solutions were remarkably different, the authors consonantly achieved complete nerve blockades with a so-called “low volumes” of LA under US guidance. The way of approach to assessing the quality of the achieved peripheral nerve blockades was also different. The pharmacokinetics of various local anesthetic solutions are hardly comparable.

One of the aims of our study was to avoid local anesthetic systemic toxicity with the implementation of lower concentrations in sufficient volume to achieve satisfactory nerve blockade. Formerly we had tried to use volumes of 1-1.5–2 ml per nerves, however, the ratio of the patient with partial or insufficient nerve blockades or lower duration of action or higher intensity of postoperative pain was observed.

The meticulous pinprick, touch, and flexion tests in the distribution of the four terminal nerves were performed before the operation to predict the occurrence of the complete blockade of the brachial plexus. This only determines the technical quality of the block and the timing of the surgery. However, after it has already been defined as the complete onset of sensory and motor blockade, few patients can feel disturbing sensation or pain during the incision period. After the time point, when the anesthesiologist lets the team start the operation, testing the sensory and motor functions of the four nerves is not informative anymore. Regarding the quality of the nerve blockade from the viewpoint of the surgeon, the focus is on the following questions. Does the incision is painful for the patient? Can the patient move the extremity being operated? Is the movement or pain disturbing? Can the situation be better with sedation?

As muscle relaxation is essential for shoulder surgery, the wrist and hand surgery requires little muscle relaxation but excellent quality of sensory blockade. Sometimes the moderate movement of the hand doesn't disturb the operation, sometimes a tiny movement of the patient

**Table 5.** The quality characteristics of study groups.

	LB (n = 17)	BS (n = 14)	LS (n = 14)	BL (n = 40)	p
Midazolam (n; mg)	11; 2.13 ± 0.30	9; 2.16 ± 3.32	8; 2.50 ± 0.21	21; 2.16 ± 0.13	0.127 <sup>a</sup>
Fentanyl (n; mcg)	1; 50 ± 0.0	2; 50 ± 0.0	4; 56 ± 6.2	5; 50 ± 0.0	0.268 <sup>a</sup>
NSAIDpop (n; mg)	10; 82 ± 7.5	7; 75 ± 0.0	4; 94 ± 0.4	25; 78 ± 3.0	0.05< <sup>b</sup>
SMCP scale	14.11 ± 0.19	14.14 ± 0.23	13.42 ± 0.41	14.20 ± 0.16	0.28 <sup>b</sup>
Sensory	3.82 ± 0.13	3.78 ± 0.15	3.64 ± 0.19	3.72 ± 0.11	0.896 <sup>b</sup>
Motor	3.88 ± 0.08	4.00 ± 0.00	*3.50 ± 0.13	3.97 ± 0.02	0.00 <sup>b</sup>
Coping	3.41 ± 0.12	3.35 ± 0.13	3.42 ± 0.13	3.50 ± 0.08	0.8 <sup>b</sup>
Postop pain	3.0 ± 0.0	3.0 ± 0.0	2.8 ± 0.1	3.0 ± 0.0	0.016 <sup>b</sup>
E/G/T (n; %)	16/1/0; 94/6/0	12/2/0; 86/14/0	8/4/2; 58/28/14	33/7/0; 82/18/0	<0.001 <sup>c</sup>

Values are presented as number, or mean ± standard error of mean. SMCP indicates the aggregate points (0–16) of Sensory (0–4), Motor quality (0–4) of blocks, coping and postoperative pain of the patients in the study groups. E/G/T indicate the Excellent, Good and Tolerable category of outcome.

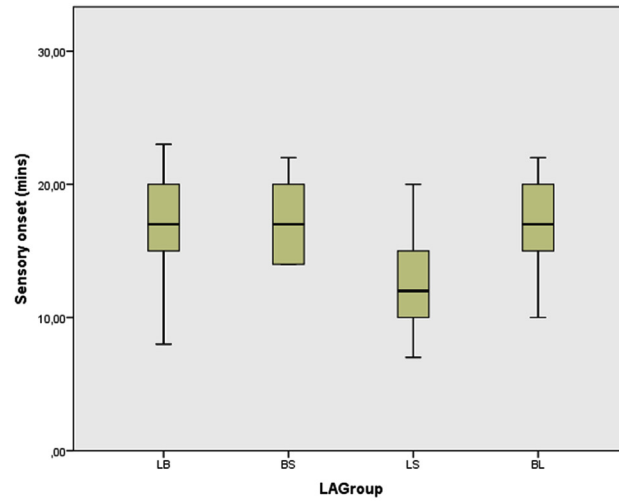
<sup>a</sup> One-way ANOVA.

<sup>b</sup> Kruskal-Wallis test.

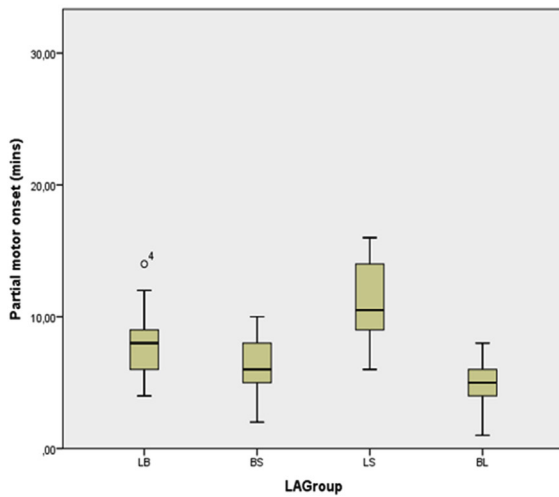
<sup>c</sup> Chi square test.



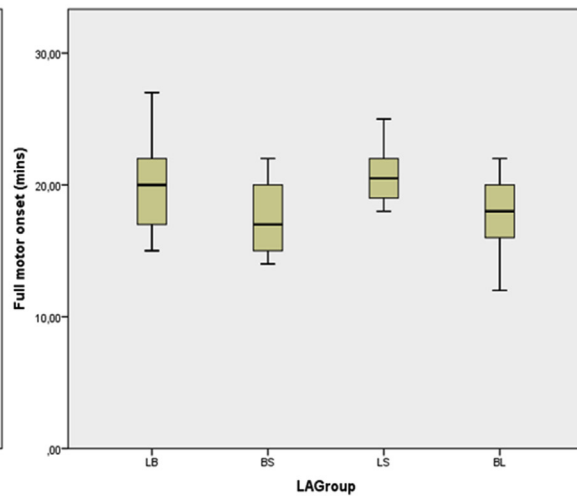
**a** The sensory onset times of study groups



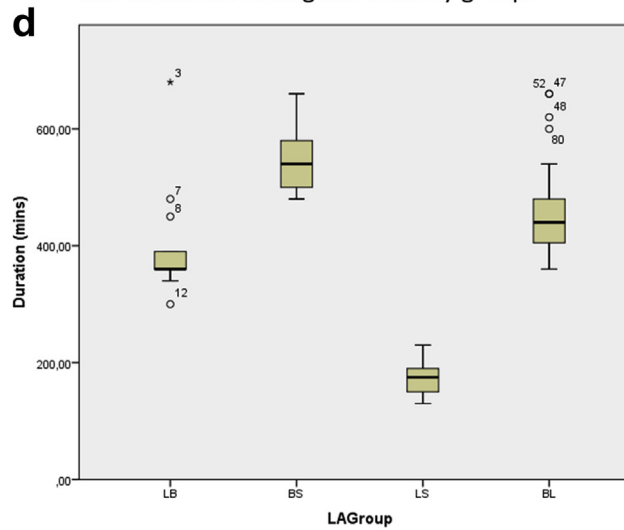
**b** The motor onset times of study groups



**c**



**d** The duration of analgesia of study groups



(caption on next page)

**Table 6.** The postoperative characteristics of study groups.

	LB (n = 17)	BS (n = 14)	LS (n = 14)	BL (n = 40)	p
NIBPO (s/d, mmHg)	159/91	149/82	136/75	142/83	
MAP op (mmHg)	104.76 ± 2.42	98.85 ± 3.1	93.26 ± 2.74	95.52 ± 1.86	0.018
MAP0/MAPop (%)	109.12 1.66	106.54 1.47	102.82 2.29	108.22 1.46	0.131
MAP6/MAPop (%)	96.41 1.29	96.46 1.2	97.75 1.35	96.53 1.1	0.914
MAP24/MAPop (%)	95.23 1.24	95.5 1.83	97.31 1.42	94.68 1.31	0.701
HR0 (/min)	78.0	72.35	79.28	77.2	0.548
HR op (b/min)	75.1	68.71	77.35	72.5	0.183
HR0/HRop (%)	103.6 2.87	105.84 2.96	102.63 2.87	107.04 2.49	0.691
HR6/HRop (%)	96.82 1.54	98.08 1.99	93.27 2.02	97.49 1.0	0.199
HR24/HRop (%)	95.51 1.89	98.22 2.58	93.29 2.66	97.12 1.18	0.385
VNR0	3.52 ± 0.32	3.28 ± 0.42	2.71 ± 0.41	3.42 ± 0.27	0.002 <sup>a</sup>
VNR6	0.58 ± 0.21	0.0	2.21 ± 0.33	0.07 ± 0.05	0.000 <sup>a</sup>
VNR24	1.94 ± 0.23	*1.14 ± 0.20	1.57 ± 0.22	1.47 ± 0.15	0.049 <sup>a</sup>
PAR6 (%)	78.92 ± 7.36	100.0 ± 0.0	-2.5 ± 26.6*	96.08 ± 2.68	*0.000 <sup>a</sup>
PAR24 (%)	42.45 ± 5.08	62.73 ± 6.75	35.0 ± 13.24	49.20 ± 6.26	0.095 <sup>a</sup>

Values are presented as number, or mean ± standard error of mean.

One-way ANOVA, Bonferroni post hoc test.

NIBP indicates Noninvasive blood pressure, MAP indicates mean arterial pressure, 0: preoperative values, 6, 24: six and twenty four hours after injection; HR: Heart rate; Op indicates the values of means during surgery; VNR: Pain intensity, Verbal Numeric Rating Scale; PAR indicates Pain intensity relief.

<sup>a</sup> Kruskal-Wallis test.

\* Statistical significance.

can be perplexing. The environment is challenging the perseverance, the surgeon can assess this as a disturbing movement, irrespective of the quality of the implemented nerve blockade. In this way, the motor block evaluation with the SMCP scale is a global assessment of the patient's movement during surgery. This type of assessment is not appropriate for the fine determination of the motor function, it is only a rough estimation from the viewpoint of the surgeon.

Regional anesthesia of the upper extremity can be achieved by blocking the brachial plexus at varying levels along the course of the trunks, divisions, cords, and terminal nerves. The four most frequently used approaches are the interscalene block, the supraclavicular block, the infraclavicular block, and the axillary block. Each technique has its own unique set of advantages, limitations, and indications for use. The interscalene approach is suitable for the surgery of the shoulder. Sub-arachnoid or epidural injection, local anesthetic systemic toxicity due to intravascular injection, injury of the vertebral artery, pneumothorax, and phrenic nerve block can be the problematic issues during interscalene blockade. The supraclavicular block provides anesthesia and analgesia to the upper extremity below the shoulder. It is the most effective block for all regions of the upper extremity often with little or no sparing of peripheral nerves if an adequate technique is used. The most important risks of this method are pneumothorax, injury of subclavian artery, local anesthetic systemic toxicity due to intravascular injection, transient Horner's syndrome, and phrenic nerve palsy. Ultrasound guidance decreases the incidence and intensity of the phrenic nerve palsy and reduces the risk of pneumothorax, however, the higher volumes and concentrations of the injected local anesthetic solutions are associated with a higher incidence of Horner's syndrome and local anesthetic systemic toxicity.

The infraclavicular block is an alternative approach to the axillary block and can be useful for procedures and conditions requiring perineural catheter technique and for surgery of the elbow and below. Like the axillary approach, this technique minimizes the occurrence of pneumothorax and eliminates the risk of Horner's syndrome, phrenic nerve palsy, and neuraxial complications. Traditionally the axillary approach is used for surgery of the forearm, wrist, and hand with or without the use of pneumatic tourniquets (Boezaart, 2008; Brattwall et al., 2016; Brown et al., 2010; Mian et al., 2014).

Without premedication and intraoperative sedation, some patients struggle with various levels of tourniquet discomfort during forearm, wrist, and hand surgery under regional anesthesia provided by the axillary approach of the brachial plexus.

There are some techniques for the elimination of tourniquet discomfort in clinical practice (e.g. intercostobrachial nerve block). The intercostobrachial nerve block is indicated for medial/posterior upper arm surgery. Another indication is to alleviate the discomfort due to the tourniquet applied to the upper arm. The use of this block is controversial and questioned because the intercostobrachial nerve block does not block the ischemic, compressive components that cause the tourniquet pain; this is accomplished by brachial plexus block with supplemental intraoperative sedation (Neal et al., 2009; Sebastian, 2017), additional cutaneous anesthesia is not necessary. Regarding the supraclavicular approach, for analgesia, lower concentrations and low volumes of local anesthetic solutions can be used with which the risk of the local anesthetic toxicity, Horner's syndrome, and phrenic nerve palsy can almost entirely be abolished. In respect of the anatomy, the position of the nerves to the hand at the level of the divisions is central within the nerve trunks, thus they require higher volumes or concentrations of

**Figure 2.** a. The sensory onset times of study groups. The sensory onset time was significantly shorter ( $13.0 \pm 1.02$  min) in the lidocaine group (LS) when compared with that in the LB, BS, and BL groups. Figures are presented as mean ± standard deviation. b,c. The motor onset times of study groups. Panel b (left) represents the partial motor onset times, Panel c (right) represents the full motor onset times. The full motor onset time was shorter ( $17.5 \pm 2.7$  min) in the bupivacaine group (BS) when compared with that in the lidocaine-bupivacaine group (LB  $19.9 \pm 3.2$ ), lidocaine-saline group (LS  $20.8 \pm 2.3$ ), and bupivacaine-lidocaine group (BL  $18.0 \pm 2.7$ ) groups. Statistical differences were observed between groups with one-way ANOVA (BS vs. LS  $p = 0,013$ ; BL vs. LS  $p = 0,007$ ). Statistical difference was found between the sensory and motor onset times in the LB, LS, and BL groups. Figures are presented as mean ± standard deviation. d. The duration of analgesia of study groups. Statistical differences were observed in the duration of analgesic effect of local anesthetic between the four groups LB, BS, BL and with the shortest duration in the LS group. Figures are presented as mean ± standard deviation.

local anesthetic solution (Cousins et al., 2012). Admittedly, the full anesthetic blockade of the upper arm is not necessary for forearm, wrist, and hand surgery. The axillary-supraclavicular approach of brachial plexus with the applied dosage regimen of 0.4 ml/kg (30 ml, maximal volume) of diluted local anesthetics has been proved to be an effective and reliable technique to eliminate the tourniquet discomfort and to provide satisfactory analgesia during surgery and postoperative period in unmedicated trauma patients. Lidocaine is often used with bupivacaine in daily practice to accelerate the onset time of bupivacaine. In this study, the lidocaine content of the local anesthetic mixture didn't shorten the onset times of bupivacaine but significantly decreased the duration of analgesic action of bupivacaine in a dose-dependent manner. The onset time of the lidocaine solution alone was significantly shorter. Admittedly the onset time of the full motor blockade was prolonged with the use of low concentration lidocaine despite the shorter sensory onset time. Lidocaine alone exhibited a good quality of block at the applied dose in this study, due to the inferior quality of motor blockade while the other solutions achieved excellent quality evaluated by a novel SMCP scale based on the sensory-motor function, coping and postoperative pain.

All patients stayed in the hospital at least 24 h after the surgery during this study. The use of the 11 points (0–10) verbal (or visual) rating scale for the measurement of the pain intensity is a simple and informative tool. 6 and 24 h after the plexus blockade the VNR values were evaluated and compared to the VNRO. The VNRpop values were 0 due to the sufficient nerve blockades. However, the patients reported some degrees of pain intensity at 6 h after the nerve block. In the lidocaine group, the pain intensity statistically returned to the preoperative level, there was no statistical difference between the VNRO and VNR6 values, consequently, there was no pain relief. This observation implies that lidocaine has the shortest duration of analgesic effect and it cannot alleviate the postoperative pain intensity properly. After the time point, when the pain intensity returned to the preoperative level no further anodyne effect is expected from the peripheral nerve blockade postoperatively. Since the lidocaine content decreases the duration of the analgesic effect of bupivacaine in mixed solution, the pain relief in the LB and BL groups was smaller than in the BS group.

The randomization is one of the best ways to reduce bias. However, randomization is one of the most problematic issues in clinical studies at the same time. In large clinical research, simple randomization can generate similar numbers of patients among groups. However, randomization can be problematic in a relatively small sample size study. The block randomization method engenders equal group sizes over time (Suresh, 2011; Lim and In, 2019). The permuted block design is controversial because the last allocation of a block is always deterministic. In this way, the permuted block design does not prevent selection bias if the block sizes are known. Neither the alternation technique nor the permuted block randomization method was used. Because of the allocation concealment, the block sizes were not known. Since the study reached more than 60 patients (15–15 patients for the four planned groups), it was anticipated that each group would have at least 15 patients. Although modern computer technology eliminates the simplicity of analysis as a determinative factor in the choice of the study design (Berger, 2008; Berger and Antsygina, 2015), a limitation of the study is the simple randomization resulted in a different number of the patient in the study groups and the randomization influenced by the duration of the surgery. In the future, we should focus on newer techniques, (e.g. maximum tolerated imbalance procedures), which can eliminate this randomization weakness.

We conclude that lidocaine does not shorten the onset times, but significantly decreases the duration of action of bupivacaine when used in mixture solutions. Lidocaine exhibits a good quality of block in the applied dose, while other solutions achieve excellent quality. Bupivacaine without lidocaine has the longest duration of action to achieve the longest postoperative analgesia.

## Declarations

### Author contribution statement

R. Almasi: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

B Rezman: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Z Kriszta: Performed the experiments; Analyzed and interpreted the data.

B Patczai: Performed the experiments.

N Wiegand and L Bogar: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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### Competing interest statement

The authors declare no conflict of interest.

### Additional information

No additional information is available for this paper.

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