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ARTICLE

# Comparison of the pharmacological properties of 0.375% bupivacaine with epinephrine, 0.5% ropivacaine and a mixture of bupivacaine with epinephrine and lignocaine – a randomized prospective study

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**ABSTRACT**

One of the methods of anesthesia for orthopedic and plastic procedures for the upper limb is the brachial plexus block. The aim of the study was to compare the pharmacodynamic and pharmacokinetic properties of three commonly used local anesthetic solutions used for axillary brachial plexus blockade. Sixty patients scheduled for surgery of the upper limb were enrolled for the study. 3 different local anesthetic solutions: 0.375% bupivacaine with epinephrine (group B), 0.5% ropivacaine (group R) and a mixture of 0.5% bupivacaine with epinephrine and 2% lignocaine in a 1:1 ratio (group BL) were used to anesthesia. The study assessed the delay time of sensory and motor blockade and the duration of sensory and motor anesthesia of the operated limb. There were no significant differences in the onset of sensory block between the study groups. In the BL group, the onset of the motor block was significantly shorter than in group B and group R. The duration of the sensory and motor blockade was significantly longer in group B and group R than in the group BL. The solution of 0.375% bupivacaine with epinephrine and 0.5% ropivacaine used for axillary brachial plexus anesthesia provide the same level of the block. Addition of short acting local anesthetic – lignocaine to long acting bupivacaine decreases the time to onset of motor blockade, but also shortens the duration of the sensory and motor blockade in the postoperative period, compared to long acting local anesthetics of higher potency: bupivacaine with epinephrine or ropivacaine.

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Regional anesthesia; brachial plexus block; local anesthetic

## Introduction

One of the commonly used methods of anesthesia for upper limb surgery is brachial plexus block. This regional anesthesia technique is a relatively simple procedure with suspected high effectiveness. The common use of ultrasound visualization significantly increased its effectiveness and safety and allows to reduce the volume of local anesthetics (LA) [1,2]. Application of long-acting local anesthetics allow to obtain not only the surgical anesthesia necessary for the procedure, but also provides good postoperative analgesia lasting up to several hours [3]. The anesthesiologist may choose among various local anesthetics, with different pharmacodynamics, pharmacokinetics and spectrum of possible side effects [4]. Most commonly used in Europe are: bupivacaine with or without the addition of epinephrine, ropivacaine or a mixture of two anesthetics like bupivacaine with epinephrine in combination with lignocaine. Bupivacaine is the most potent local anesthetic with the longest duration. At the same time the onset of surgical anesthesia is long, and its overdose or unintentional intravascular administration is associated with the highest risk of systemic toxicity of local anesthetics (LAST) with, in a critical situation, cardiac arrest resistant to resuscitation [4,5]. Safer alternative drug to bupivacaine is levobupivacaine – the pure S-isomer of bupivacaine with the same analgesic potency, but lower neuro- and cardiotoxicity [4]. The addition of epinephrine to bupivacaine solution reduces absorption of local anesthetic into the blood, which prolongs duration of the block and reduces the risk of side effects. Some clinicians mix long acting local anesthetic – bupivacaine with short-acting LA – lignocaine [6,7]. It usually leads to faster onset of the block and shortens its duration. The second alternative drug to bupivacaine is ropivacaine, which has a somewhat lower potency and a shorter duration, with a weaker systemic toxicity. In addition, ropivacaine is a vasoconstricting agent, so there is no reason to add epinephrine. At low concentrations, ropivacaine induces sensory anesthesia without a deep motor blockade. However, this effect is not seen in higher concentrations of ropivacaine [4]. There are no reports in the literature comparing the basic pharmacological properties of local anesthetics commonly used in peripheral nerve blocks and the effects of adding short-acting local anesthetic (lignocaine) to long acting LA (bupivacaine). So now the choice of local anesthetic often depends on the doctor's personal preferences.

The aim of the study was the comparison of the pharmacology of three different local anesthetic solutions used for brachial plexus block from axillary approach: 0.375% bupivacaine solution with epinephrine, 0.5% ropivacaine and a mixture of 0.5% bupivacaine with epinephrine and 2% lignocaine in a 1:1 ratio, by assessing the clinical features of the procedure performed, i.e. time to the onset of sensory and motor block, and the duration of the surgical anesthesia of the operated limb.

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Table 1. Hollmen scale for sensory block assessment.

| Hollmen scale |
|---|
| 1 Normal sensation of pinprick. |
| 2 Pinprick felt as sharp pointed but weaker compared with same area in other limb. |
| 3 Pinprick recognized as touch with blunt. |
| 4 No perception of pinprick. |

Table 2. Hollmen scale for motor block assessment.

| Hollmen scale |
|---|
| 1 Normal muscle function. |
| 2 Slight weakness in function. |
| 3 Very weak muscular action. |
| 4 Complete loss of muscle action. |

## Materials and methods

### Calculation of the sample size

Planning of the experiment we calculated the size of the study groups. The strength of the test was set at 80% with the significance level of the test $\alpha = 5\%$. Based on the literature and clinical observations, we assumed that the time from the brachial plexus block to the occurrence of the sensory blockade is approximately $10 \pm 2$ min, and differences between studied groups should be minimum 2 min. Mathematical analysis of the data showed that each group should consist of minimum 16 patients.

### Patients qualification and randomization

The study was prospective, randomized and carried out in the Department of Orthopedics and Traumatology and in the Department of Anaesthesiology and Intensive Therapy. The study obtained the consent of the Local Bioethics Committee. 63 patients who underwent scheduled surgery of the upper limb (hand, forearm and elbow) were enrolled to the study. Patients with systemic diseases that could affect the function of the peripheral nervous system and sensory perception such as diabetes, rheumatoid arthritis, systemic lupus erythomatosus were excluded.

The randomization of the patients for study groups was performed with dedicated software available free at the website http://www.randomization.com. The result of the randomization was then forwarded to an anesthesiologist nurse who was a member of the research team who, according to the study protocol, prepared the appropriate anesthetic solution simultaneously concealing the result of the allocation. The anesthesiologist who performed the brachial plexus block (the physician experienced in the procedure) and assessed the result of the block was not aware of the local anesthetic solution (blinding the sample). At the end of the study, randomization was deciphered, and the analysis of collected data was performed.

### The course of anesthesia and surgery

After intravenous premedication of the patient with 1 mg midazolam (Midanium, Polfa Warsaw) and 100 μg fentanyl (WZF Fentanyl, Polfa Warsaw) axillary brachial plexus block with ultrasound (SonoSite M-Turbo, SonoSite, US) and neurostimulation (Stimuplex HNS12, BBraun, Germany) was performed. Four main nerves (radial, ulnar, median and musculocutaneus) were identified and confirmed. At a current intensity of 0.5 mA and after negative aspiration test through a stimulator needle (Stimuplex A, 21Gx2′, $0.80 \times 50$mm, BBraun, Germany) one of three local anesthetic solutions was injected: 0.375% bupivacaine with epinephrine 1:200,000 – group B, 0.5% ropivacaine – group R or a mixture of 0.5% bupivacaine with epinephrine 1:200,000 with 2% lidocaine in a 1:1 proportion – group BL. The volume of the LA solution for anesthesia varied from 20 ml to 30 ml. Doses and concentrations of LA solutions were chosen to maximize the effectiveness of the block without the risk of overdosing [8–10]. All surgeries required the use of pneumatic tourniquet with cuff pressure 100 mmHg above the current systolic blood pressure. During the brachial plexus block and subsequent surgery, standard haemodynamic monitoring and fluid therapy were performed. After the procedure, the patient was admitted to postoperative unit at the Department of Orthopedics and Traumatology.

### Evaluation of effectiveness of the blockade

The characteristics of the axillary brachial plexus block performed with different local anesthetics were determined by measurement:

- time from the completion of anesthesia to the occurrence of a sensory blockade
- time from the completion of anesthesia to the occurrence of a motor blockade
- time from the onset to the resolution of motor block
- time from the onset to the resolution of the sensory block

The measurement of the latency time of the sensory and motor blockade started at the time of completion of the local anesthetic injection (point 0) and were assessed in 1 min intervals. The measurement of the degree of sensory block was based on physical examination of pain sensation (pricking with a pin) on the surface of the hand innervated by individual terminal nerves. The occurrence of the sensory block was considered to be the 3rd degree in the Hollmen's scale (Table 1) [11].

The degree of the motor blockade by assessment of flexion of the elbow (musculocutaneous nerve) and adduction, abduction and opposition of the thumb (radial, ulnar and median nerve). The motor block was considered to be complete when achieved 3 in Hollmen's scale (Table 2) [11].

Lack of satisfactory sensory and/or motor block (grade 1 or 2 in Hollmen's scale) was defined as an incomplete sensory and/or motor block. The necessity of additional general anesthesia for performing the surgery was also registered.

The duration of sensory block was measured from the moment of sensory anesthesia to the emergence of post-operative pain, which required administration of rescue analgesic (ketoprofen 100 mg iv with NRS $> 4$). These data were obtained from nursing reports. The duration of the motor block was based on the period from the moment of motor block to the return of the fingers function (2 points in the Hollmen's scale), which was recorded by patients with an accuracy of 10 min.

### Statistical analysis

The raw data were subjected to a statistical analysis in Statistica 10.0. (Statsoft Inc, Tulsa, IL, USA). Each analysis involved testing for normality of distribution with the Shapiro–Wilk *W*-test. For normally distributed variables, means and standard deviations were calculated and comparisons employed Student's *t*-test. When a variable was not normally distributed, parameters calculated comprised the median, maximum and minimum, and the Mann–Whitney *U*-test was used for comparisons. To describe the features on the nominal and ordinal scale, the number (n) and relative number (%) were used. Statistical analysis of this type of

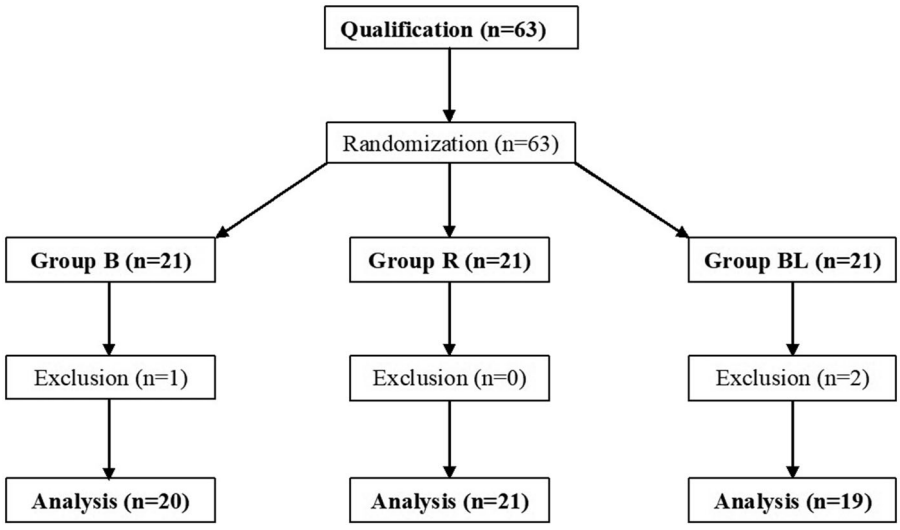


Figure 1. Flow diagram of patients included in the trial according to randomization protocol.

Table 3. Demographic characteristic of studied patients.

| | Group B $n=20$ | Group R $n=21$ | Group BL $n=19$ | $p$ |
|---|---|---|---|---|
| Sex (M:F) | 12:8 | 14:7 | 13:6 | n.s. |
| ASA classification (I:II) | 7:13 | 10:11 | 9:10 | n.s. |
| Age (years) | 46 ± 18.1 | 48.5 ± 18.4 | 51.8 ± 18.8 | n.s. |
| BMI | 26 ± 4.2 | 26.7 ± 4.5 | 26.8 ± 3.8 | n.s. |

Data presented as mean value ± standard deviation. n.s.: not significant.

Table 4. The volume of local anesthetics and unsatisfactory brachial plexus block.

| | Group B $n=20$ | Group R $n=21$ | Group BL $n=19$ | $p$ |
|---|---|---|---|---|
| Local anesthetic volume (ml) | 30 (26–30) | 30 (27–30) | 30 (28–30) | n.s. |
| Unsatisfactory motor block, *n* (%) | 6 (30%) | 3 (14.3%) | 3 (15.8%) | n.s. |
| Unsatisfactory sensory block, *n* (%) | 1 (5%) | 2 (9.5%) | 1 (5.3%) | n.s. |
| General anesthesia, *n* (%) | 1 (5%) | 2 (9.5%) | 1 (5.3%) | n.s. |

Data presented as median value and range, n.s.: not significant.

Table 5. Time from performing the block to the onset of sensory and motor blockade.

| | Group B $n=20$ | Group R $n=21$ | Group BL $n=19$ | $p$ |
|---|---|---|---|---|
| Sensory block (minutes) | 13.2 ± 5.2 | 13.7 ± 9.6 | 10.8 ± 4.7 | n.s. |
| Motor block (minutes) | 26.2 ± 8.2 | 25.5 ± 10.9 | 19 ± 9.3 | 0.0146[a] 0.0492[b] |

Data presented as mean ± standard deviation. n.s.: not significant.
[a]Statistical significance between groups B and BL.
[b]Statistical significance between groups R and BL.

data was carried out with the $\chi^2$ test. In all calculations, $p < 0.05$ was established as the level of statistical significance [12].

## Results

Patients enrolled to the study ($n = 63$) were randomly assigned to one of three groups. Three patients were excluded from the study due to inability of all the necessary data for analysis. The final results of 60 patients were assessed (Figure 1).

No intraoperative and postoperative complications were observed during the study. Also, there were no postoperative side effects of peripheral nerves blocks at a distant time (up to 6 months after surgery).

The study did not show statistically significant differences in demographic data such as sex, age, BMI (body mass index), physical state ASA (American Society of Anesthesiology) between studied groups (Table 3).

In all three groups comparative volumes of local anesthetic were used. The unsatisfactory motor block was more frequent in group B, but the difference was not statistically significant. There were no statistically significant differences in the occurrence of unsatisfactory sensory block. In the course of the entire study, it was necessary to add general anesthesia in 4 cases to enable performing the surgery (Table 4).

Table 5 shows the average time from performing brachial plexus block to onset of sensory and motor blockade. There were no significant differences in the onset time of sensory block between the study groups. In the BL group, however, the onset of the motor block was significantly faster than in groups B and R.

Table 6. The duration of sensory and motor block after axillary brachial plexus anesthesia.

| | Gruop B $n = 20$ | Gruop R $n = 21$ | Group BL $n = 19$ | $p$ |
|---|---|---|---|---|
| The duration of sensory block (minutes) | 768.5 ± 167.9 | 707.2 ± 154.9 | 530.5 ± 108.7 | <0.0001[a]<br>0.0002[b] |
| The duration of motor block (minutes) | 690.4 ± 151.5 | 625.1 ± 180 | 436 ± 104.7 | <0.0001[a]<br>0.0003[b] |

Data presented as mean ± standard deviation. n.s.: not significant.
[a]Statistical significance between groups B and BL.
[b]Statistical significance between groups R and BL.

The duration of the sensory and motor block was significantly longer in both groups with the anesthesia of the brachial plexus performed with a single local anesthetic than in the group where a mixture of two local anesthetics (bupivacaine/lignocaine) was used. The differences in the duration of the sensory and motor block between the B group and the R group was not statistically significant (Table 6).

## Discussion

The choice of the local anesthetic, its volume and concentration in the solution, and thus the dose of the injected drug, affect a number of parameters of the peripheral nerve block. It determines the onset of block, the duration of analgesia and motor block. The total dose of local anesthetic also directly correlates with the risk of side effects (total overdosing).

In our study the measured parameters of brachial plexus block (delay of sensory and motor blockade, duration of motor and sensory blockade) using 0.375% bupivacaine with epinephrine and 0.5% ropivacaine did not differ between the two groups. Similar results were achieved by Watanabe et al. who in their study did not notice differences in time from the end of the procedure until the administration of rescue painkillers and during the duration of the motor blockade of the operated limb. Researchers found that ropivacaine and levobupivacaine (used in equal concentrations of 0.375%) provided the same level of postoperative analgesia [13]. In the study of Mageswaran et al. brachial plexus blockade with 0.5% levobupivacaine resulted in a significantly faster sensory and motor block compared to 0.5% ropivacaine, with comparable postoperative analgesia 6 h after performing the block [14]. Piangatelli et al. however claimed that ropivacaine induces faster onset of motor block than levobupivacaine with shorter analgesic effect. In this study, however, the difference between the concentrations of local anesthetics was 0.25% (0.75% ropivacaine vs. 0.5% levobupivacaine) [15]. With similar pharmacologic properties and the lack of inevitable advantages of any of the drugs in clinical trials, the safety profile may support the choice of ropivacaine for volume blocks in regional anesthesia.

In our study, the addition of lignocaine to the solution of bupivacaine with epinephrine significantly accelerated the onset of brachial plexus block, but only motor, the onset of sensory block was similar in all study groups. In addition, the duration of block and post-operative analgesia was significantly shorter in patients who had performed the block with bupivacaine/epinephrine and lignocaine than in patients who were anesthetized with ropivacaine alone or with bupivacaine with epinephrine alone. In the study of Rohan et al. lignocaine with epinephrine was added to ropivacaine, which resulted in faster sensory and motor block with unaffected time of post-operative analgesia [16]. Adding lignocaine to hyperbaric levobupivacaine shortens the duration of spinal anesthesia comparing to the levobupivacaine alone and allows to reduce the time spent in the post-operative ward, which may be particularly useful for short-term surgery [17]. In the study of Župčic et al. lignocaine in combination with levobupivacaine accelerated the onset of paravertebral block and, simultaneously, shortened its duration [18]. In addition, adding of lignocaine to a long acting local anesthetic was more likely to cause intraoperative haemodynamic changes (variables of stroke volume, hypotension), but these results cannot be directly interpolated to brachial plexus block or peripheral nerves blocks, where the systemic effect of the blockade is minimal.

The mixture of lignocaine and long-acting local anesthetic shortens the time required to achieve full block of the brachial plexus, but at the expense of length of postoperative analgesia. Hadzic emphasizes, that when different local anesthetics are mixed, their anesthetic potential, time to achieve surgical anesthesia, duration of the block are more unpredictable, and the clinical benefits of the combination use are low. If there is required long-term anesthesia, also in the postoperative period, using single, long-acting local anesthetic is the optimum choice. For short procedures with expected mild post-operative pain local anesthetics of shorter duration of action (mepivacaine, lignocaine) should be preferred [19]. However, long-term sensory blockade is usually equal to long term motor deficit that can affect the patient's satisfaction with the surgery and hospitalization. Clinical trial performed by Fredrickson et al. showed no differences in patients' satisfaction after brachial plexus anesthesia with a short-acting local anesthetic (lignocaine) and a mixture of lignocaine and ropivacaine [20]. The authors concluded that long-term motor blockade after brachial plexus blockade does not decrease the level of patients' satisfaction with the procedure.

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## Disclosure statement

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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