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## SCIENTIFIC ARTICLE

# Minimum effective concentration of bupivacaine for axillary brachial plexus block guided by ultrasound<sup>☆</sup>



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### KEYWORDS

Regional anesthesia;  
Brachial plexus block;  
Bupivacaine;  
Ultrasound;  
Axillary block;  
Minimum effective concentration

### Abstract

**Introduction:** The use of ultrasound in regional anesthesia allows reducing the dose of local anesthetic used for peripheral nerve block. The present study was performed to determine the minimum effective concentration (MEC90) of bupivacaine for axillary brachial plexus block.

**Methods:** Patients undergoing hand surgery were recruited. To estimate the MEC90, a sequential up-down biased coin method of allocation was used. The bupivacaine dose was 5 mL for each nerve (radial, ulnar, median, and musculocutaneous). The initial concentration was 0.35%. This concentration was changed by 0.05% depending on the previous block; a blockade failure resulted in increased concentration for the next patient; in case of success, the next patient could receive or reduction (0.1 probability) or the same concentration (0.9 probability). Surgical anesthesia was defined as driving force  $\leq 2$  according to the modified Bromage scale, lack of thermal sensitivity and response to pinprick. Postoperative analgesia was assessed in the recovery room with numeric pain scale and the amount of drugs used within 4 h after the blockade.

**Results:** MEC90 was 0.241% [ $R^2$ : 0.978, confidence interval: 0.20–0.34%]. No patient, with successful block, reported pain after 4 h.

**Conclusion:** This study demonstrated that ultrasound guided axillary brachial plexus block can be performed with the use of low concentration of local anesthetics, increasing the safety of the procedure. Further studies should be conducted to assess blockade duration at low concentrations.

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**PALAVRAS-CHAVE**

Anestesia regional;  
Bloqueio do plexo  
braquial;  
Bupivacaína;  
Ultrassom;  
Bloqueio axilar;  
Concentração mínima  
efetiva

**Concentração mínima efetiva de bupivacaína para o bloqueio do plexo braquial via axilar guiado por ultrassom****Resumo**

**Introdução:** O uso do ultrassom na anestesia regional permite a redução da dose de anestésico local utilizada para o bloqueio de nervos periféricos. O presente estudo foi conduzido com o objetivo de determinar a concentração mínima efetiva (CME90) de bupivacaína para o bloqueio do plexo braquial via axilar (BPVA).

**Métodos:** Pacientes submetidos a cirurgias da mão foram recrutados. Foi usado um método de alocação "biased coin" seqüencial "up-down" para estimar a CME90. A dose de bupivacaína foi de 5 mL para cada nervo (radial, ulnar, mediano e musculocutâneo). A concentração inicial de era 0,35%. Essa concentração era alterada em 0,05% dependendo do bloqueio anterior: a falha do bloqueio resultava em aumento da concentração para o próximo paciente; no caso de sucesso, o próximo paciente poderia receber ou redução (probabilidade de 0,1) ou mesma concentração (probabilidade 0,9). A anestesia cirúrgica foi definida como força motora  $\leq 2$  segundo a escala de Bromage modificada, ausência de sensibilidade térmica e de resposta ao pinprick. A analgesia pós-operatória foi verificada na sala de recuperação anestésica com escala numérica de dor e a quantidade de analgésicos utilizados até 4 horas após o bloqueio.

**Resultados:** A CME90 foi de 0,241% [R2: 0,978, Intervalo de Confiança: 0,20%–0,34%]. Além disso, nenhum paciente com sucesso do bloqueio apresentou dor após 4 horas.

**Conclusão:** Este estudo demonstrou que pode-se realizar o BPVA guiado por ultrassom utilizando-se baixas concentrações de anestésico local, aumentando a segurança do procedimento. Novos estudos devem ser realizados para avaliar a duração de bloqueios com baixas concentrações.

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**Introduction**

A successful peripheral nerve block depends on the correct identification of nervous structures and the injection of a suitable dose of local anesthetic around it in order to obtain a complete impregnation of all the nerves involved in the surgery. For axillary brachial plexus blockade (ABPB), in which the failures are typically attributed to improper needle placement or septation of the brachial plexus sheath in axillary region,<sup>1,2</sup> volumes up to 80 mL have been used to increase the success rate.<sup>3</sup> However, the use of large amounts of local anesthetic increases the chance of systemic toxicity, which is the major complication of regional anesthesia. Although the incidence of systemic toxicity is less than 0.2%, this complication is difficult to treat and potentially fatal.<sup>4,5</sup>

The introduction of ultrasound into clinical practice of regional anesthesia made it possible to visualize the nerve structures, allowing greater accuracy in the administration of local anesthetics. The minimum effective volume of local anesthetic for blocking some peripheral nerves had been investigated, and studies have shown that effective blockades may be achieved with small volumes of anesthetic, which reduces the likelihood of systemic toxicity.<sup>6–11</sup> However, the clinical applicability of low volumes and the limitation of identifying intraneural injections by ultrasound have been questioned.<sup>12</sup>

Reducing the local anesthetic concentration may limit the total dose administered without changing the volume

injected. However, the minimum concentration of local anesthetic to obtain a safe ABPB without compromising the blockade quality and effectiveness has not been established yet.

The aim of this study was to calculate the minimum effective concentration of 20 mL bupivacaine without epinephrine, which reached surgical anesthesia dose for axillary brachial plexus block guided by ultrasound for hand surgery in 90% of patients (MEC90).

**Material and methods**

The present study used a step-up/step-down model to determine the MEC90 of bupivacaine in ultrasound guided ABPB.

This protocol was approved by the Ethics Research Committee of our institution (Ref 0482/11) and registered in the Clinical-Trials.gov (protocol NCT01838928). Patients aged between 18 and 65 years, with indication for anesthesia and analgesia brachial plexus block, undergoing elective surgery of the hand with less than 2 h duration, physical status ASA I, II or III according to the American Society of Anesthesiologists, and body mass index (BMI)  $<35 \text{ kg m}^{-2}$  were included in the study between the years 2011 and 2012, after signing the informed consent form. Patients with disorders that prevented the assessment of motor sensitive function, cognitive impairment or active psychiatric condition, infection at the blockade puncture site, bleeding disorders or history of allergy to bupivacaine were excluded from the study.

**Table 1** Modified Bromage scale.

Grade	Definition
4	Full muscle strength in relevant muscle groups
3	Reduced strength, but able to move against resistance
2	Ability to move against gravity, but not against resistance
1	Discrete movements (trembling) of muscle groups
0	Lack of movement

After inclusion in the study, demographic data of all patients were recorded. Then, routine monitoring for surgical procedure was performed with ECG, noninvasive blood pressure, and pulse oximetry. Peripheral venous access was obtained in the upper limb contralateral to the surgery for infusion of crystalloid solution and sedation with midazolam ( $0.03 \text{ mg kg}^{-1}$ ).

Axillary brachial plexus block was performed with the ultrasound M-Turbo<sup>®</sup> guidance and 13–6 MHz linear transducer (SonoSite, Bothell, WA, USA) and a peripheral nerve stimulator Stimuplex<sup>®</sup> DIG RC (B. Braun, Melsung, Germany) with the patient in supine position. Skin antisepsis was performed with chlorhexidine; transducer was protected with sterile plastic; and puncture site was infiltrated with 1% lidocaine (2 mL). After the brachial plexus nerves' visualization by ultrasound the puncture was performed with a 22 G needle for electrostimulation 50 mm AEQ 2250 (BMD Group, Venice, Italy). Neurostimulator was used to confirm the identification of the four nerves (median, ulnar, radial, musculocutaneous) separately. A dose of 5 mL bupivacaine without epinephrine was slowly injected around each nerve visualized with ultrasound, completing a total of 20 mL. The 5 mL dose was defined based on current regional anesthesia protocols of our institution. If there was any resistance to the solution injection, the patient complained of severe pain, or an increase in nerve diameter was visualized, and the needle was repositioned. The local anesthetic dispersion was carefully monitored by the image so it went around the nerve perimeter.

The end of the local anesthetic solution injection was considered the time zero to assess the blockade effectiveness. An anesthesiologist who was not present during the injection and was unaware of the anesthetic concentration assessed the motor, thermal, and sensory blocks. This assessment occurred every 5 min, from time zero until the block was considered effective, but limited to 30 min. After that time, if the block was not appropriate, a complementation was performed.

Modified Bromage scale<sup>6,11</sup> (Table 1) was used to assess motor function. The following muscles were evaluated: finger flexors (median nerve), finger extensors (radial nerve), finger adductors (ulnar nerve) and elbow flexion (musculocutaneous). The score was obtained for each of the four nerves.

Thermal sensation was assessed with gauze and alcohol and pain sensitivity with the pinprick test with a 23 G needle. Both assessments were performed separately for each nerve and sensation, and the following locations were

used: hypothenar eminence (ulnar nerve), thenar eminence (median nerve), dorsum of hand (radial nerve), and lateral aspect of the forearm (musculocutaneous nerve).

Latency was defined as the period between time zero and the time that surgical anesthesia was obtained.

Surgical anesthesia was considered effective if motor scale was less than or equal to 2, if there was no feeling of pain and cold for all nerves, and if there was no need for supplementation (local or general anesthesia) during surgery. Patients who exhibited any degree of blockade failure received supplementation with nerve local anesthesia, distal to the axilla and guided by ultrasound, or conversion to general anesthesia.

All patients received subcutaneous injection of 2% lidocaine with epinephrine (3 mL) to complement the intercostal nerve block, due to the use of pneumatic tourniquet in the middle third of the arm. During surgery, propofol infusion ( $25\text{--}40 \text{ mcg kg}^{-1} \text{ min}^{-1}$ ) was used for sedation until Ramsay score = 3.

After surgery, patients were admitted to the post-anesthesia care unit and remained monitored until they reached the conditions of discharge as outpatients. While remaining in the PACU, postoperative analgesia was assessed through a numerical pain scale (0 = no pain and 10 = worst pain ever experienced by the patient) and the total analgesic requested by the patient up to 4 h after the ABPB was quantified.

## Statistical analysis

In this study, the primary objective was to estimate the minimum effective concentration of a 5 mL bupivacaine solution per nerve (total of 20 mL) for axillary brachial plexus blockade guided by ultrasound. For this, an allocation method of biased coin up-down sequence was used to estimate the MEC90.<sup>13</sup> The local anesthetic initial concentration was 0.35%. This dose was chosen based on the clinical experience of our service and also on statistical simulations in various doses. Each subsequent dose was based on previous dose. The success or failure of the ABPB determined the decrease or increase of local anesthetic concentration for the next patient, respectively. After an effective block, the next patient was randomized with a probability of 0.1 to receive the next lower dose and randomized with a probability of 0.9 to receive the same dose. These probabilities were calculated as follows:

Probability for dose reduction (P1):  $P1 = (\text{desired MEC} - 1) \times (\text{desired MEC})^{-1}$

Probability for dose maintenance (P2):  $P1 = 1 - P1$

In this study, we chose to perform the calculation to estimate the minimum effective concentration in 90% of cases, thus:

$$- P1 = (1 - 0.9)/0.9 \approx 0.1$$

$$- P2 = 1 - P1 \approx 0.9$$

The sequence was examined using logistic regression to calculate the minimum effective concentration for 90% of cases.

For sample size calculation, simulations were performed assuming a fixed biased coin model and a minimum number of positive responses. A significance level of 5% ( $\alpha=0.05$ ) was considered. A sample size of at least 46 patients was selected after testing with a variety of settings, each with simulations of both responses and corresponding doses selected by the sequential allocation method described above, and starting with various initial doses.

Nonparametric data are presented as medians and quartiles (P25–P75). Categorical data are presented as absolute and relative frequencies. Calculations were performed using Microsoft Excel for Windows™ (Microsoft Corp., Redmond, WA, USA), GraphPad Prism™ for Windows (GraphPad Software Inc., San Diego, CA, USA), and IBM SPSS Statistics™ 20.0 for Mac (SPSS Inc., Chicago, IL, USA).

## Results

Forty-six patients were enrolled and their demographic and surgical characteristics are shown in Tables 2 and 3, respectively. No patient who met the inclusion criteria was excluded from the study.

The present study showed that the MEC90 for a total of 20 mL solution of bupivacaine without epinephrine for axillary brachial plexus block guided by ultrasound was 0.241% [correlation coefficient –  $R^2$ : 0.978; confidence interval (CI): 0.20–0.34%].

According to the results shown in Fig. 1, there is a strong positive correlation between the success probability and observed concentrations. Fig. 2 illustrates the

**Table 2** Demographic characteristics of patients.

Age (years) <sup>a</sup>	35.5 (28–44.5)
Sex (M/F)	32/14
ASA	
I	31 (67.4%)
II	15 (22.6%)
BMI ( $\text{kg m}^{-2}$ )	24.9 (22.5–26.8)

BMI, body mass index.

<sup>a</sup> Data presented as median (quartiles).

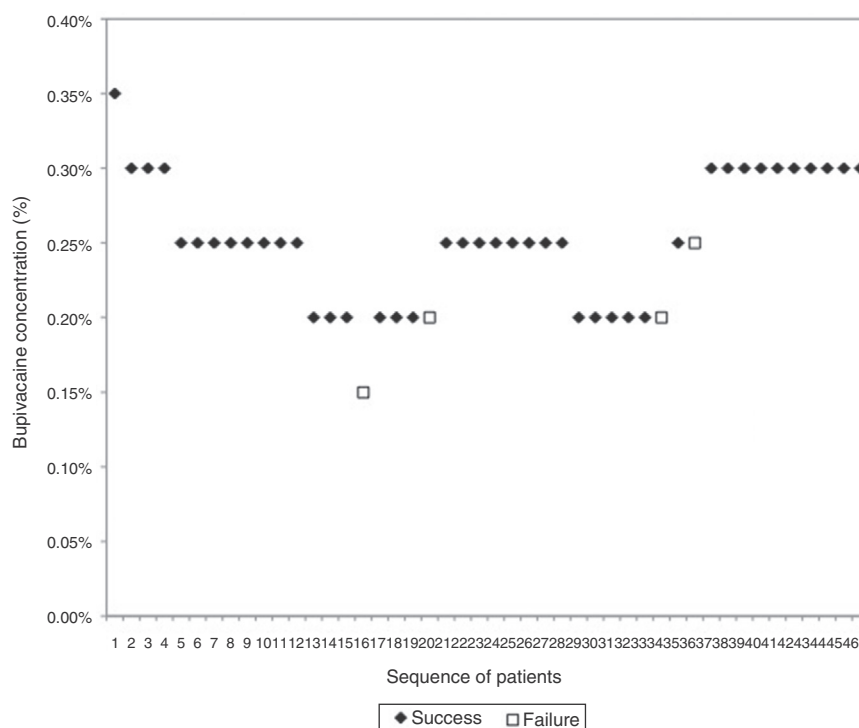
**Table 3** Distribution of surgical procedures ( $n=46$ ).

Metacarpal fracture	17
Extensor tendon injury	6
Excision of bone tumor	5
Flexor tendon injury	5
Phalanx pseudoarthrosis	3
Synovectomy	3
Dupuytren	3
Scaphoid fracture	3
Synthesis material removal	1
Duration, min (P25–P75) <sup>a</sup>	55(40–78, 75)

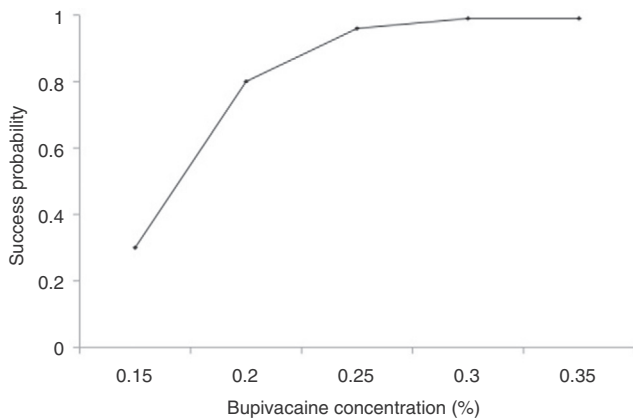
<sup>a</sup> Data presented as median (quartiles).

correlation between success probability and observed concentrations.

Considering all study patients, the mean latency time was 15 (10–20) min. Considering only patients who



**Figure 1** Graphical representation of the up-down sequence of subsequent patients.



**Figure 2** Correlation between concentration and success probabilities.

**Table 4** Latency for different concentrations.

Dose	Number of blocks/successful	Latency (min) <sup>a</sup> (P25–P75)
0.15%	0/1	–
0.20%	11/13	25 (25–30)
0.25%	17/18	20 (15–22.15)
0.30%	13/13	15 (10–16.15)
0.35%	1/1	5

<sup>a</sup> Data presented as median (quartiles).

received blockades with 0.25% concentration (the nearest MEC90 concentration), the mean latency time was 20 (15–22.15) min. Mean latency times for each assessed concentration are summarized in Table 4. Blockade duration was not determined in this study.

There was 100% blockade failure with the use of 0.15% bupivacaine. However, all blockades performed with a concentration equal to or greater than 0.30 were successful (Fig. 1).

No patient included in the protocol showed absence of specific response to neurostimulator or intraoperative pain. All patients considered as failure maintained median nerve motor function, and two patients also maintained radial nerve motor function. The lack of thermal sensitivity was also observed in these patients, although maintaining the motor function.

Two surgical procedures exceeded the expected duration of surgery and lasted more than 120 min, without complications for the patient or need for supplemental anesthesia.

All surgical procedures for which patients received successful blocks were performed uneventfully, and there was no need for local and systemic anesthetic supplementation. Moreover, all patients reported no pain 4 h after the ABPB (EAV=0). There were no complications, such as vascular puncture or local anesthetic intoxication, during the study. All patients were discharged on the same day of the surgery, without the need for hospital readmission.

## Discussion

Peripheral nerve block success is based on the accuracy with which the nerves are located and impregnated by the anesthetic. However, other important factors affecting its success rate and quality are the concentration and volume of anesthetic injected near the nerves.<sup>14</sup> The use of ultrasound has introduced a new perspective on regional anesthesia. This technology enables a real-time visualization of the entire procedure, allowing the anesthesiologist to precisely position the needle around the structure to be blocked. Thus, ultrasound enables a decrease in the volume or concentration used during the blockade. This study has proved it possible to achieve a successful axillary brachial plexus block guided by ultrasound with low concentrations of local anesthetic.

Adverse events, such as systemic toxicity, may be dose-dependent. Therefore, prevention of adverse events is crucial to promote patient safety during regional anesthesia.<sup>5</sup> Some guidelines for regional anesthesia include local anesthetic dose limitation through the use of smaller volumes and concentrations during blockade. The use of low doses of local anesthetic provides a safer blockade with less risk of complications, particularly associated with the systemic toxicity of these anesthetics. Despite the development of effective techniques for treating such complications, such as the use of lipid solutions,<sup>15,16</sup> the use of low doses of local anesthetics promotes a blockade with an anesthetic mass of a wide range of safety relative to the toxic dose.

One way to reduce the dose of local anesthetic is by decreasing the volume used for the blockade. In a previous study conducted by our group, the axillary brachial plexus blockade was successful with approximately 1.6 mL of 0.5% bupivacaine with epinephrine 1:200,000 per nerve.<sup>11</sup> O'Donnell and Iohom also showed similar results using 2% lidocaine.<sup>6</sup> However, the use of low volume technique is probably difficult to reproduce in clinical practice. On the other hand, the present study used a volume more close to that used in clinical practice, probably making the technique easier to be applied.

It is known that the local anesthetic concentration is an important factor influencing the latency time of peripheral nerve block. The local anesthetic penetration into the nerve root is affected by the concentration of the solution used.<sup>17</sup> It is suggested that increasing the local anesthetic concentration around the nerve increases the concentration gradient and may facilitate the diffusion of anesthetic molecules into the nerve, and thereby reducing the nerve block latency time. However, in the present study, we found a median latency close to the median latency obtained in our previous study, with low volumes.<sup>11</sup> One possible explanation is that, despite the low concentration, the total mass of bupivacaine used in this study was greater than that used in the study with low volumes. Furthermore, a study comparing different concentrations but maintaining the anesthetic mass fixed in ABPB revealed that the motor latency, but not the sensory latency, was smaller when using larger volume of local anesthetic.<sup>18</sup> Thus, this is not a defined issue, requiring further studies to elucidate the matter.

The use of lower concentrations of local anesthetic may bring some benefits. Pippa et al. reported that the use of high concentrations of local anesthetic for interscalene brachial plexus block is associated with a greater number of complications, such as phrenic nerve paralysis and hypotension.<sup>19</sup> Furthermore, *in vitro* studies have shown that the use of local anesthetics is associated with cytotoxic effects, including induction of apoptosis in Schwann cells, mitochondrial injury, caspase activation, and increased cytoplasmic calcium. However, all these effects were related to the time of exposure and higher concentration of the drug used, which theoretically suggests greater safety when using lower concentrations of local anesthetic.<sup>20</sup> Moreover, the use of lower concentrations may decrease the postoperative motor block time, which may be more comfortable for some patients.<sup>21</sup> Finally, the dose required to produce a successful block may be clinically relevant in pediatric patients or when the combination of different blocks is required for the surgery due to the potential risk of systemic toxicity.

This study has some limitations. Initially, we do not measure the duration of ABPB using low doses of bupivacaine. The use of low doses of local anesthetic decreases block duration, defined as the time between the end of the blockade onset and recovery of motor and sensory functions.<sup>22</sup> As it was not known how the use of low concentrations would influence the block duration, it was decided to include procedures planned to last up to 2 h.

Furthermore, this study was not designed to assess the minimum effective concentration of local anesthetic for postoperative analgesia, and further studies should be performed to evaluate this topic. However, no patient with successful block reported pain 4 h after the blockade.

We also know that the results were limited to obtain the MEC90 to a 5 mL solution of bupivacaine for each ABPB nerve, and it may not represent the same concentration for smaller volumes. More studies should be conducted to evaluate the efficacy of different volumes for this concentration. Finally, one should not extrapolate this result to other peripheral nerve blocks.

In summary, this study suggests that with the use of ultrasound it is possible to obtain surgical anesthesia with concentrations close to 0.25% bupivacaine when using 5 mL volume of anesthetic for each brachial plexus nerve (radial, median, ulnar, and musculocutaneous) by axillary route, decreasing the local anesthetic dose used and increasing the procedure safety. More studies should be conducted to determine the effects that low concentrations of bupivacaine may have on blockade duration.

## Conflicts of interest

The authors declare no conflicts of interest.

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