

Reducing the Concentration to 0.4% Enantiomeric Excess Hyperbaric Levobupivacaine (S75: R25) Provides Unilateral Spinal Anesthesia. Study with Different Volumes

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Summary: Imbelloni LE, Gouveia MA, Carneiro AF, Grigorio R – Reducing the Concentration to 4% Enantiomeric Excess Hyperbaric Levobupivacaine (S75: R25) Provides Unilateral Spinal Anesthesia. Study with Different Volumes.

Background and objectives: Unilateral spinal anesthesia may be obtained with hypobaric or hyperbaric solution. The objective of this study was to compare different doses of enantiomeric excess hyperbaric levobupivacaine to achieve unilateral spinal anesthesia.

Method: One hundred and twenty patients were randomized to receive 4 mg, 6 mg or 8 mg of 0.4% enantiomeric excess levobupivacaine. The solutions were administered at the L3-L4, with the patient in a lateral position and kept at this position according to dose administration for 5, 10 or 15 minutes. Sensory block (pinprick) and motor block (scale 0-3) were compared between the operated and contralateral sides.

Results: The onset of analgesia was rapid and comparable between groups. Sensory block was significantly higher in the operated than in non-operated limb at all times of evaluation. Increasing the dose by 1 mL (2 mg) corresponded to an increase of two segments in the mode for the operated side. In the operated side, motor block (MB = 3) of patients occurred in 31 (77.5%) with 4mg, 38 (95%) with 6 mg, and 40 (100%) with 8 mg. There was a positive correlation between increased dose, blockade duration, and hypotension. All patients were satisfied with the technique used.

Conclusions: Spinal anesthesia with different volumes of enantiomeric excess hyperbaric bupivacaine (S75: R25) provided a 78% incidence of unilateral spinal block, with the smallest dose used (4 mg) the most efficient.

Keywords: Anesthesia, Spinal; Orthopedics; Anesthetics; Bupivacaine/analogs & derivatives.

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INTRODUCTION

The difference in density between the cerebrospinal fluid (CSF) and local anesthetics is a factor that should be considered to restrict the distribution of solutions within the subarachnoid space. Theoretically, unilateral spinal block could be obtained with hypobaric¹ or hyperbaric² solution injected into

the subarachnoid space, with the patient in lateral position, so that the anesthetic forms a layer above (hypobaric) or below (hyperbaric) the midline.

In orthopedic outpatients undergoing lower limb surgeries involving only one member, unilateral spinal anesthesia has advantages over conventional anesthesia, such as fewer hypotension³, faster recovery from block¹, and increased patient satisfaction⁴. There are several reasons to control the maximum level of sensory block. Lower limb surgeries require low levels of sensory block, resulting in higher cardiocirculatory stability⁴. With small doses of local anesthetics, side effects such as prolonged motor blockade, hemodynamic instability, and urinary retention may be avoided^{5,6}. Lateral decubitus position, low doses of local anesthetic, needle orientation, and slow injection of anesthetic have been suggested as facilitators for unilateral spinal anesthesia^{7,8}.

Levobupivacaine in proportions of 75% levorotatory and dextrorotatory 25% was obtained in 1997⁹. It was marketed in isobaric solution and used in adults¹⁰ and children¹¹. In 2009, 50% enantiomeric excess bupivacaine was used in 0.4% hyperbaric solution in different volumes with excellent results in infraumbilical procedures¹². The aim of this prospective randomized study was to evaluate the incidence of unilateral block using different doses of 0.4% hyperbaric enantiomeric excess bupivacaine (S75: R25) with 5% glucose, administered to patients undergoing orthopedic surgery in only one limb in the lateral decubitus position.

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METHOD

The Ethics Research Committee approved the study protocol and all patients were informed and agreed to participate in the study. Exclusion criteria were hypovolemia, pre-existing neurological disease, coagulation disorders, thromboprophylaxis for less than eight hours, infection at the puncture site, agitation and delirium, and the presence of indwelling catheters.

The incidence of unilateral blockade in several studies ranges from 65% to 90%. Assuming a significance level of 5% and a power of 80%, we obtained the required number of 81 patients. We selected 120 patients to ensure against data loss.

A solution of 50% enantiomeric excess levobupivacaine at 0.4% with 5% glucose was prepared from 0.5% isobaric enantiomeric excess levobupivacaine (S75: R25) (specific gravity at 37°C of 1.0058 g.mL⁻¹) plus 1 mL of glucose 25%¹². Selected patients were ASA physical status I-II, without pre-anesthetic medication, aged between 20 and 60 years, scheduled for unilateral orthopedic surgery under spinal anesthesia. In all patients, pneumatic tourniquet was applied to the thigh and inflated to the maximum pressure of 350 mm Hg. Patients were randomly selected using coded envelopes prepared for the study and divided into three groups of 40 patients. Patients in Group 1 received 4 mg (1 mL), Group 2 received 6 mg (1.5 mL), and Group 3 received 8 mg (2 mL) of enantiomeric excess levobupivacaine (S75, R25) at 0.4% with gravity of 1.0107 g.mL⁻¹. Surgeries were knee videoarthroscopies, correction of ankle fractures with or without ligament injury, and implant removal below the knee.

After sedation with intravenous fentanyl (1 µg.kg⁻¹) and midazolam (1 mg), skin cleansing with chlorhexidine, and excess removal, spinal puncture was performed with the patient in lateral decubitus position with the involved limb down, through the median interspace L3-L4 after skin infiltration with lidocaine 1%, using a 27G Quincke needle (B. Braun Melsungen) without introducer. After observing CSF confirming the correct position of the needle, 4, 6 or 8 mg of 0.4% enantiomeric excess hyperbaric levobupivacaine (S75: R25) were administered at a rate of 1 mL.30s⁻¹. Patients remained in the lateral position according to dose used: 4 mg (5 minutes), 6 mg (10 minutes), and 8 mg (15 minutes) before being placed in a supine position for evaluation of the parameters studied and beginning of surgery.

Assessment of sensory and motor block was performed by another professional who was blinded to the patient's group allocation. The level of sensory block, defined as the lack of pinprick sensation, was assessed bilaterally at the midclavicular line, while motor block was assessed by modified Bromage scale¹³: 0 = free movement of lower limbs (LL), 1 = inability to raise the limbs extended, 2 = inability to flex knees, 3 = inability to move the ankles. Sensory and motor block were assessed in both limbs according to studied groups at 5, 10, and 15 minutes after surgery and comparison of involved and noninvolved limb was performed, as well as between groups. In case of blockade failure, another spinal anesthesia would be performed with 10 mg of 0.5% hyperbaric bupivacaine. In

case of insufficient time for the procedure, general anesthesia would be performed with a laryngeal mask. Hypotension (decreased SBP > 30% ward pressure) was treated with intravenous etilefrine (2 mg) and bradycardia (heart rate < 45 bpm) was treated with intravenous atropine (0.50 mg).

Duration of analgesia was determined by the time for sensation return to dermatome corresponding to the puncture site. Hemodynamic parameters were evaluated with 5 minutes interval throughout the procedure. Information regarding the blockade recovery time, surgical time, need for bladder catheterization, pain and treatment administered were recorded by an investigator. The time to begin ambulation was guided by the surgeon, and postoperative analgesia consisted of plexus blockade with peripheral nerve stimulator of lumbar or sacral nerve with 50 mL of 50% enantiomeric excess levobupivacaine at 0.2%, according to site of operation, and ketoprofen (100 mg) and dipyrone (3 g) administered intravenously. Blockade and the first analgesic dose were performed at end of surgery in the operating room. It was not part of the study to evaluate the quality of postoperative analgesia.

Upon leaving the operating room, patients were asked to record their opinion about the technique. The alternatives were optimal, satisfactory or poor. Patients were followed-up for three days postoperatively in order to gather information about headache, transient neurologic symptoms (TNS) or back pain. Headache was classified as post-dural puncture if presented with worsening at sitting position, occipital or frontal location, increased with coughing, straining or sneezing. Back pain was considered TNS if the patient experienced pain and/or dysesthesia in the back, buttocks, and legs after recovery with resolution within 72 hours.

The three treatment means were compared by analysis of variance. Probabilities of patient's level of satisfaction were compared by chi-square test and when it could not be used, Fisher's exact test was used. The Median Test was used to compare the medians of the three groups. The level of significance was $\alpha = 0.05$.

RESULTS

Regarding patients' demographic data, height showed a significant difference among the three groups (Table I). Blockades were sufficient for the procedures performed and there was no need for additional general anesthesia.

The onset of analgesia was rapid and comparable between groups. The dose used did not influence the onset of sensory block, defined as latency time (Table II). There was difference between groups receiving 4 mg and 8 mg regarding duration of surgery (p-value = 0.031) and between groups regarding duration of blockade in different groups, showing increasing duration with increased dosage (4 mg < 6 mg < 8 mg) (Table II). Development of hypotension showed significant correlation with increased dosage (p-value = 0.122, Fisher's exact test) (Table II).

The spread of analgesia in the operated limb was different between the three groups in the first evaluation (Figure 1). The sensory level evaluated by the median test was lower in

Table I – Patient Data

	4 mg	6 mg	8 mg	p
Age (years)	40.57 (13.57)	41.22 (9.72)	38.65 (11.31)	0.591*
Weight (kg)	62.82 (15.04)	68.80 (8.99)	67.50 (13.45)	0.093*
Height (cm)	164.12 (6.69)	168.17 (6.19)	165.50 (8.40)	0.040*
Sex (M/F)	19/21	23/17	21/19	0.530**

Mean (SD); M: male; F: female; Height: difference between groups 4 mg and 6 mg (p = 0.038). (*) 1-Factor ANOVA, (**) X² test.

Table II – Assessed Parameters

	4 mg	6 mg	8 mg	p-value
Latency (min)	1:46 (0:22)	1:41 (0:17)	1:39 (0:14)	0.196*
Surgery duration (min)	54 (8)	58 (8)	59 (8)	0.036*
Block duration (min)	75 (8)	117 (9)	174 (14)	< 0.001*
Hypotension	0	2	4	0.122**

(*) 1-Factor ANOVA; (**) Fisher's Exact Test.

the 4 mg group, which was lower than 6 mg group, which was lower than 8 mg group (Figure 1). The mode for T₁₂ was 4 mg, T₁₀ 6 mg, and T₈ 8 mg. The 2 mg increase in dosage corresponded to a significant increase of two segments in mode between the three doses (Figure 1).

The time spent in lateral decubitus position according to dose reflected a selective unilateral blockade in 38 patients receiving 4 mg (95%), 32 receiving 6 mg (80%), and 24 receiving 8 mg (65%). The increase in dosage corresponded to a significant decrease unilaterally (p-value = 0.001) (Table III). At the end of surgery, there was an increase in unilateral block with all doses, which was 100% with 4 mg, 85% with 6 mg, and 75% with 8 mg.

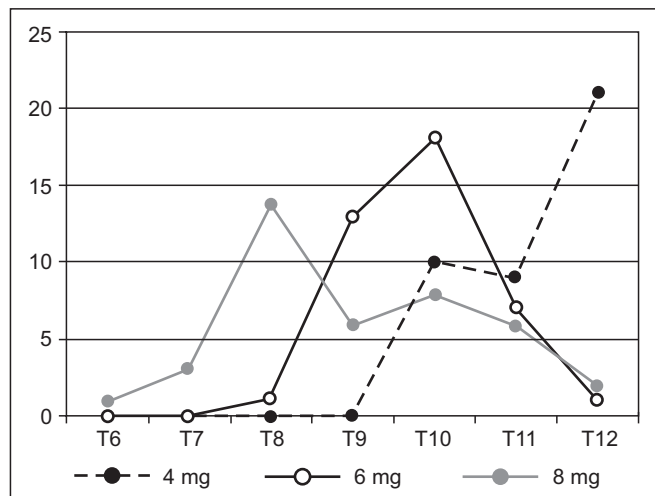


Figure 1 – Cephalad Spread on Operated Limb in the First Evaluation.
The mode was T₁₂ with 4 mg, T₁₀ with 6 mg, and T₈ with 8 mg.

Table III – Incidence of Unilateral Blockade According to Dose Used in the First Evaluation and at the End of Surgery

	4 mg	6 mg	8 mg	p
1st Evaluation				0.001*
Yes (%)	38 (95%)	32 (80%)	24 (65%)	
No (%)	2 (5%)	8 (20%)	16 (35%)	
End of Surgery				0.004*
Yes (%)	40 (100%)	34 (85%)	30 (75%)	
No (%)	0	6 (15%)	10 (25%)	

(*) Fisher's Exact Test.

At the initial evaluation, complete motor block (grade 3) in operated limb occurred in 31 patients (77.5%) receiving 4 mg, 38 patients receiving 6 mg (95%), and 40 patients receiving 8 mg (100%) (Figure 1). There is significant difference between doses (p-value < 0.001). At the end of the procedure, no patient showed grade 3 motor block with 4 mg, versus 32 patients with 6 mg and 34 with 8 mg.

In the contralateral limb, absence of motor block (grade 0) at the beginning of surgery occurred in 38 patients with 4 mg versus 32 with 6 mg and none with 8 mg (Figure 3), confirming that the lower dose results in a higher incidence of unilateral blockade. At the end of surgery, no motor block was present in all patients with 4 mg, in 34 patients with 6 mg, and in 26 patients with 8 mg.

Patients who developed hypotension (2 with 6 mg and 4 with 8 mg) required only one dose of the vasopressor. There was no bradycardia in patients of all groups. All patients had an optimal satisfaction with the technique used. No patient had post-dural puncture headache or urinary retention. There were no complaints of back pain or pain in the buttocks or legs during the three subsequent days.

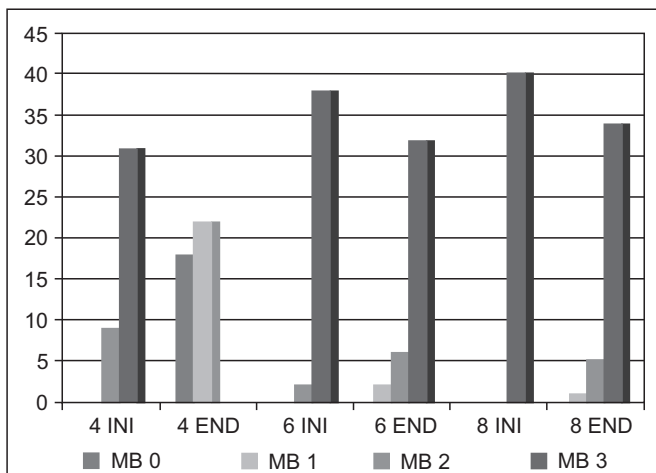


Figure 2 – Motor Block of Operated Limb in the First Evaluation and at the End of Surgery.
INI: Initial; END: Final.

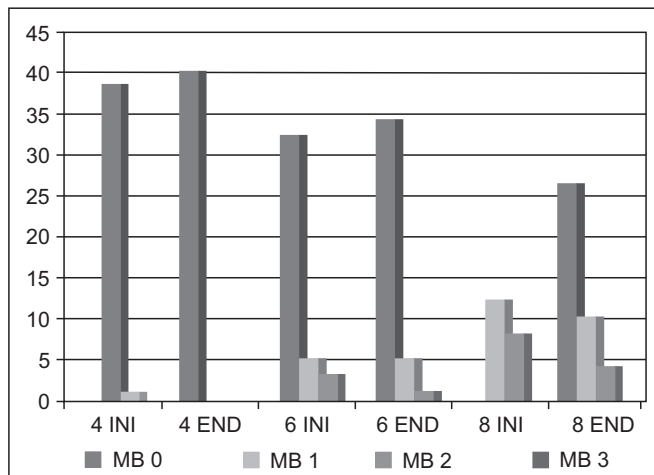


Figure 3 – Motor Block of Contralateral Limb in the First Evaluation and at the End of Surgery. INI: Initial; END: Final.

DISCUSSION

In this study, appropriate levels of anesthesia were achieved for surgeries of a single lower limb, using 4 mg, 6 mg, or 8 mg of 50% enantiomeric excess levobupivacaine at 0.4% hyperbaric. The 4 mg dose (1 mL) provided only unilateral blockade in 95% of patients, 6 mg (1.5 mL) in 80%, and 8 mg (2 mL) in 65%, showing that selectivity is dependent on the mass of injected anesthetic into the subarachnoid space. The rapid onset of action was no difference between doses, and duration of action was dose dependent.

Unilateral spinal anesthesia may result in sensory and motor hemiblock preferably on one side. The purpose of applying spinal anesthesia restricted to one of lower limbs is to minimize the extent of the blockade on the side to be operated, as well as obtaining surgical anesthesia throughout the procedure. This goal was achieved in 78.3% of patients in the first assessment and 86.6% of patients at the end of surgery.

The drugs evaluated for use in anesthesia depend on the national pharmacopoeia regulation and commercial factors. Enantiomeric excess levobupivacaine (S75: R25) at 0.5% was marketed only in isobaric formulation. In a previous study, a protocol was designed to evaluate the drug in hyperbaric solution at 0.4% in 5% glucose with different volumes, showing that it can easily replace the 0.5% solution¹², a fact confirmed in this study.

Hyperbaric bupivacaine is prepared with the addition of glucose, and additions of glucose were tested at 5% and 10%, with the 8% concentration presenting less variation in the extent of blockade. The use of bupivacaine 0.75% in 8% glucose showed no advantage over the 0.5% concentration¹⁴. Between 2 and 4 mL, the increased volume produced no change in dispersion, but produced an increase in duration of action, which is related to dose increase¹⁴. In children, hyperbaric bupivacaine with 0.9% or 8% glucose produced similar spinal anesthesia regarding success, cephalad spread of block, re-

covery, and side effects¹⁵, showing that there is no need for high doses of glucose to make the anesthetic hyperbaric. In a previous study with the same 0.4% solution with 5% glucose, and volumes ranging from 2.5 and 5 mL, there was greater cephalad spread, as well as increased duration of action with increasing dose¹². In this study, the same result was achieved with low doses for unilateral spinal anesthesia, showing that unilateral blockade was higher with the lower dose and inversely proportional to the dose used.

Obtaining a selective unilateral blockade depends on the anesthetic, dose, and time spent in the lateral decubitus position. High doses of bupivacaine (12-20 mg) show significant blockade migration, even after 1 hour in the lateral decubitus position¹⁶, while small doses of bupivacaine (5-8 mg) result in a restricted blockade after 10-15 minutes in the lateral decubitus position¹⁷. The best outcome for unilateral blockade occurred when low doses of hyperbaric or hypobaric bupivacaine were used and the patient remained in the lateral decubitus position for 10-20 minutes⁶. In this study, the patient was maintained in the lateral decubitus position with time depending on the dose used showing that the lowest dose (4 mg) required less time than moderate (6 mg) or high doses (8 mg). This resulted in a higher selectivity with the lowest dose (95%) compared with the higher dose (65%).

By definition, baricity is the relationship between the density of injected solution and the density of CSF. Mean baricity of CSF is $1.00059 \pm 0.00020 \text{ g.mL}^{-1}$ ¹⁸. The baricity of local anesthetics may be increased by the addition of glucose. The baricity of 0.4% enantiomeric excess hyperbaric levobupivacaine (S75: R25) is 1.0107 g.mL^{-1} at 37°C, thus hyperbaric in all patients. This fact was confirmed when 94 of 120 patients (78.3%) had pure unilateral blockade (only in a single limb), when anesthetized in lateral decubitus position, and only 26 patients (21.7%) had some degree of blockage in the non-operated limb. Large variations in volume and concentration of local anesthetic have little role in its spread to the leptomeningeal channel¹⁹ while the total amount of molecules injected into the spinal canal has a more important role. In this study with dose ranging from 4 to 8 mg, the highest dose resulted in a greater spread of anesthesia and lower selectivity.

The duration of spinal anesthesia is not only dependent on the choice of anesthetic, but also on the dose. The use of 6, 8, and 10 mg of 0.75% hyperbaric bupivacaine and the patient remaining in the lateral decubitus position resulted in a mean duration of analgesia of 93, 123, and 147 minutes, respectively²⁰. The recovery time using 5 mg of 5% hyperbaric bupivacaine was 2h30min², which was similar to 5 mg of 0.15% hypobaric bupivacaine (2h32min)¹ and 5 mg of 0.5% isobaric bupivacaine (2h34min)²¹. The study of different doses of 0.4% enantiomeric excess levobupivacaine (S75: R25) for infraumbilical surgeries reflected in a dose-dependent duration of action¹². In this study with the same solution and in the same concentration, low doses of 4, 6 and 8 mg provided recovery times of 75, 117, and 174 minutes, respectively, with positive correlation between doses.

The use of hyperbaric anesthetic at low doses (5 mg)² yielded only two unilateral block (without contralateral motor or sympathetic blockade), resulting in great cardiocirculatory sta-

bility without hypotension and bradycardia. In the present study at doses ranging from 4 to 8 mg of 0.4% hyperbaric enantiomeric excess levobupivacaine (S75, R25), excellent cardiocirculatory stability was seen with the onset of hypotension in two patients with 6, four with 8 mg and none with 4 mg.

The use of 0.4% enantiomeric excess hyperbaric levobupivacaine in different doses proved to be safe to avoid the onset of TNS¹². In the present study, there was no case of TNS at doses of 4-8 mg in the same concentration. Another factor that may have contributed to the non-emergence of TNS in our study was the lack of complete blockade of the lower limbs.

Similar to other study¹⁵, the addition of 5% glucose to enantiomeric excess levobupivacaine (S75, R25) showed that there is no need for a high concentration of glucose to make the anesthetic hyperbaric. There is much consistency in the

finding that the usual concentration of 8% glucose for hyperbaric spinal anesthesia is exaggerated, thus allowing the addition of adjuvant analgesics (opioids or not) to the lower dose of local anesthetic and conservation of hyperbaricity. Thus, many other studies can be performed with hyperbaric spinal anesthesia in the context of multimodal analgesia. Likewise, the results obtained by reducing the concentration to 0.4% enantiomeric excess levobupivacaine (S75, R25) are similar to results from other studies obtained with hyperbaric bupivacaine.

In conclusion, 0.4% enantiomeric excess hyperbaric levobupivacaine (S75: R25) with 5% glucose provided a rapid onset of sensory and motor block-level, block duration and patients' dose-dependent satisfaction. Permanence time is dose-dependant. The lower dose yielded the highest incidence of selectivity in both analgesia and motility.

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