Reports of Original Investigations

Effects of baricity of 0.5% or 0.75% levobupivacaine on the onset time of spinal anesthesia: a randomized trial

[Effets de la baricité de la lévobupivacaine à 0,5 % ou de 0,75 % sur le délai d'installation d'une rachianesthésie : une étude randomisée]

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Purpose: Levobupivacaine has been extensively evaluated for spinal anesthesia. Its pharmacologic properties are similar to those of bupivacaine, but differences in density between two commercially-available preparations of plain levobupivacaine might lead to different block profiles. We examined the characteristics of spinal anesthesia using the same dose of 0.5% and 0.75% plain levobupivacaine.

Methods: In this randomized, controlled, double-blind clinical trial, 60 ASA I–III patients, scheduled for hip fracture surgery, were randomly allocated to receive spinal anesthesia with 15 mg of either 0.5% (group Levo-0.5), or 0.75% (group Levo-0.75) plain levobupivacaine.

Onset time (primary outcome), sensory block height level by pinprick, motor block using a modified Bromage scale, and hemodynamic variables were recorded.

Results: In group Levo-0.5 ($n = 29$), surgical anesthesia was obtained within 15 (10–20) min, compared to 12 (7–21) min in group Levo-0.75 ($n = 31$) ($P = 0.409$). The highest sensory block level was T11 (T6–T12) in group Levo-0.5, and T10 (T8–T12) in group Levo-0.75 ($P = 0.759$). Mean duration of anesthesia was 285 (224–303) min in group Levo-0.5, and 318 (243–375) min in group Levo-0.75 ($P = 0.117$). The groups were similar in regards to the number of failed blocks requiring general anesthesia, and the number of patients requiring vasopressors.

Conclusions: In this population of elderly patients, spinal anesthesia with 15 mg of either 0.5% or 0.75% plain levobupivacaine resulted in similar onset of pharmacological actions, and

outcomes. Potential differences in baricity did not appear to be clinically relevant in this setting.

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Objectif : La lévobupivacaine en rachianesthésie a fait l'objet de nombreuses évaluations. Ses propriétés pharmacologiques sont semblables à celles de la bupivacaine, mais les densités différentes de deux préparations de lévobupivacaine simple disponibles sur le marché pourraient avoir pour conséquences des profils de blocs différents. Nous avons examiné les caractéristiques d'une rachianesthésie réalisée à l'aide d'une même dose de lévobupivacaine simple à 0,5 % ou à 0,75 %.

Méthode : Dans cette étude clinique randomisée, contrôlée et en double aveugle, 60 patients ASA I–III devant subir une chirurgie pour une fracture de la hanche ont été randomisés à recevoir une rachianesthésie avec 15 mg de lévobupivacaine simple, soit à 0,5 % (groupe Levo-0.5), soit à 0,75 % (groupe Levo-0.75). Le délai d'installation (résultat principal), le niveau du bloc sensitif mesuré à la piqûre, le bloc moteur mesuré par une échelle de Bromage modifiée et les variables hémodynamiques ont été enregistrés.

Résultats : Dans le groupe Levo-0.5 ($n = 29$), l'anesthésie chirurgicale a été réalisée en 15 (10–20) min, par rapport à 12 (7–21) min dans le groupe Levo-0.75 ($n = 31$) ($P = 0,409$). Le niveau de bloc sensitif le plus élevé était T11 (T6–T12) dans le groupe

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Levo-0.5, et T10 (T8-T12) dans le groupe Levo-0.75 ($P = 0,759$). La durée moyenne de l'anesthésie était de 285 (224–303) min dans le groupe Levo-0.5, et de 318 (243–375) min dans le groupe Levo-0.75 ($P = 0,117$). Le nombre de blocs non réussis ayant nécessité une anesthésie générale et le nombre de patients nécessitant des vasopresseurs étaient semblables dans les deux groupes.

Conclusion : *La rachianesthésie réalisée avec 15 mg de lévobupivacaine simple à 0,5 % ou 0,75 % chez une population de patients âgés provoque des réactions pharmacologiques semblables et donne des résultats similaires. Les différences possibles de baricité ne semblent pas avoir été pertinentes dans ce contexte.*

L EVOBUPIVACAINE [S(-)-bupivacaine] has been extensively evaluated for spinal anesthesia in obstetric and non-obstetric patients,¹ and clinical findings showed that levobupivacaine's spinal blockade is similar to that induced by the racemic mixture.²

Laboratory studies reported that there are significant differences in density between commercially-available preparations of 0.5% and 0.75% solutions of plain levobupivacaine.³ A generally-accepted definition of isobaricity is a mean density ± 3 SD, falling within 3 SD of the mean cerebrospinal fluid (CSF) density.^{4,5} Therefore, 0.75% levobupivacaine can be considered as an isobaric solution at 37°C,^{3,6,7} whereas 0.5% levobupivacaine behaves as either a hypo- or isobaric solution, depending on the examined population.³

Differences in the baricity of local anesthetics have the potential for influencing the evolution and clinical profile of spinal block.⁸ These differences can be even more marked in a population of elderly patients, such as those undergoing surgery for hip fracture repair, because of the reduced efficiency of compensatory mechanisms.⁹ Therefore, we conducted this prospective, randomized double-blinded study to compare the onset time of spinal anesthesia produced with the same dose of plain levobupivacaine (15 mg), when using either a 0.5% or 0.75% formulation, in patients undergoing spinal anesthesia for femur fracture repair. The effects on arterial blood pressure, heart rate (HR), and the time course of the spinal block, were studied as secondary outcome variables.

Methods

With Ethics Committee approval, patients undergoing gamma-nail fixation or hip hemiarthroplasty, for femoral fracture repair, were invited to participate in this trial, after having given written, informed consent. Eligible patients were > 18 yr of age, and of ASA

physical status I–III. Patients were excluded if they were unable to understand, to cooperate, and to communicate with the investigators. Any contraindication to spinal anesthesia or a known history of hypersensitivity to amide local anesthetics, also resulted in exclusion. Patients were approached for consent by an independent investigator who did not participate in the anesthetic management.

After standard monitors were applied, patients received 8 mL·kg⁻¹ of normal saline solution over 15 min., through a 16G intravenous cannula. Randomization was achieved using a computer-generated sequence of random numbers, and allocation concealment was ensured using sequentially numbered, sealed opaque envelopes. According to the randomization sequence, patients received a spinal block with 15 mg of levobupivacaine, either as a 0.5% plain solution [group Levo-0.5: 3 mL or 15 mg, density (3 SD) at 37°C: 1.00419 (0.00003) g·mL⁻¹],³ or as a 0.75% plain solution [group Levo-0.75: 2 mL or 5 mg, density (3 SD) at 37°C: 1.00482 (0.00002) g·mL⁻¹].³ The dose was chosen according to a previous report in which 0.5% levobupivacaine 15 mg produced similar spinal anesthesia to that induced by 0.5% bupivacaine 15 mg, the standard at our institution for spinal anesthesia for hip fracture repair surgery.¹⁰ Both preparations were aseptically aspirated from ampoules (Chirocaine®, Abbott SpA, Campoverde di Aprilia, Latina, Italy) at room temperature (20–22°C) into 5-mL syringes. Spinal anesthesia was performed with patients placed in the lateral decubitus position, lying on their non-operative side. Spinal puncture was performed with a 25G Whitacre spinal needle at the L3–L4 interspace, with the orifice of the needle oriented cephalad. After free CSF flow from the needle hub was observed, the assigned local anesthetic solution was injected over a 15–20 sec period, without further aspiration. Patients were then transferred to the supine position.

An independent observer, who was blinded to group allocation, recorded the following variables: HR, non-invasive blood pressure, level of sensory block, degree of motor block, time to maximum level of sensory block, and time to two-segment regression of sensory block. Sensory block was evaluated as loss of sharp prick sensation with a 24G needle. Motor block was evaluated, on the nonoperative limb, using a modified Bromage scale (0 = no motor block; 1 = hip blocked; 2 = hip and knee blocked; 3 = hip, knee, and ankle blocked). The time to achieve readiness for surgery, defined as a sensory block $\geq$ T12 with motor block ≥ 2 , was also recorded. Complete resolution of spinal block was defined as recovery of pinprick sensation at the S1 level, with complete recovery of motor function (Bro-

mage score = 0). Observations were performed every 2.5 min for the first 15 min, every five minutes until the start of surgery, and every ten minutes thereafter until the patient was discharged from the recovery area. All patients received a follow-up physical examination four hours, and 24 hr after completion of surgery. Clinically relevant hypotension, defined as a decrease in mean arterial pressure $\geq 30\%$ from baseline values, was treated with ephedrine 5 mg *iv*; bradycardia, defined as a decrease in HR < 50 beats·min⁻¹, was treated with atropine 0.5 mg *iv*. Intraoperative evaluations were performed on the non-operated limb. In the event of pain or inadequate anesthesia, analgesic supplementation with 100 µg fentanyl *iv* was given. If this proved to be ineffective to complete surgery, general anesthesia was administered.

Statistical analysis

The study was designed to test the hypothesis that the differing densities of the two anesthetic solutions might result in different onset times of surgical block. Thus, we based our hypothesis on a mean onset time for 0.5% levobupivacaine of 12 min, with a SD of six minutes, as previously reported.¹¹ As no information was available regarding the expected differences in onset time between 0.5% and 0.75% levobupivacaine, the required sample size was calculated according to a hypothetical effect size to standard deviation ratio of 0.8, accepting a two-tailed α error of 5% and a β error of 20%, for a final power of 80%.¹² Such effect size would be equivalent, for example, to a difference of four minutes with a SD of five minutes, or a difference of six minutes with a pooled SD of 7.5 min. According to our calculations, a minimum of 28 patients per group would be required; however, considering potential drop-outs, we included a total of 33 patients per group.

Statistical analysis was performed in SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). All relevant variables were analyzed for normal distribution using visual inspection of quantile-quantile distribution plots and the Kolmogorov-Smirnov test. Comparisons between numerical variables were made using Student's *t* test or the Mann-Whitney U test, accordingly. Pearson's Chi-square tests or Fisher's exact tests were used for categorical data.

To test for potential differences in onset profiles of the two concentrations, a repeated measures analysis of variance (ANOVA) was applied to the first 20 min after the injection of levobupivacaine. Basal values for systolic blood pressure, diastolic blood pressure, and HR were entered as covariates in the relevant models (ANCOVA). Group assignment was entered as the

TABLE I Anthropometric characteristics of patients

Variable	Group Levo-0.5 (n=29)	Group Levo-0.75 (n=31)
Age (yr)	66 (59–73)	65 (58–72)
Height (cm)	170 (167–173)	168 (165–171)
Weight (kg)	75 (70–80)	70 (65–74)
BMI (kg·m ⁻²)	25.9 (24.4–27.5)	24.7 (23.2–26.2)
Gender		
Male	14 (48%)	18 (58%)
Female	15 (52%)	13 (42%)

Data presented as mean (95% confidence intervals), median (1st – 3rd quartile), or count (% of group total), as appropriate. BMI = body mass index.

between-subject factor. The Greenhouse-Geisser correction for the denominator degrees of freedom was used if the assumption of sphericity did not hold. We chose to only consider results from the time $\times$ group interaction, to assess for possible differences in the time course of the sensory block.

Scalar variables are presented as mean (95% confidence intervals) or median (1st – 3rd quartile), as appropriate; categorical values are in the form of count (% of the group total). A $P < 0.05$ was considered significant.

Results

Enrolment took place at the University Hospital of Parma between May and July 2006. Eighty-three patients who met the enrolment criteria were approached for consent, and 66 consented to participate in the study. A total of 60 patients completed the observation period (29 in group Levo-0.5 and 31 in group Levo-0.75). Reasons for the six drop-outs were: withdrawal of consent, because of discomfort during the study protocol (three cases); pre-procedural anxiety requiring sedation and, as a result, impaired communication (one case); and unforeseen prolongation of surgery requiring elective general anesthesia (two cases).

Anthropometric data are presented in Table I. Patients in group Levo-0.5 achieved readiness for surgery in 16 (11–21) min compared to 12 (6–20) min in group Levo-0.75 (Table II). The mean difference in onset time between the Levo-0.5 and Levo-0.75 group was 4 (–4–12) min ($P = 0.409$). All patients had complete motor block at the time of readiness for surgery, except two in group Levo-0.75 (6.5%) who had a modified Bromage score of 2 ($P = 0.459$). One of these patients later received general anesthesia for inadequate sensory block during surgery. The duration of anesthesia was 285 (224–303) min in group Levo-0.5, and 318 (243–375) min in group Levo-0.75 ($P = 0.117$).

TABLE II Primary and secondary outcomes

Variable	Group Levo-0.5 (n = 29)	Group Levo-0.75 (n = 31)	P
Time to readiness for surgery (min)	16 (10–21)	12 (6–20)	0.409
Maximum height of the sensory block (dermatome)	T11 (T6–T12)	T10 (T8–T12)	0.759
Time to highest sensory block level (min)	21 (16–26)	20 (16–24)	0.350
Duration of anesthesia (min)	285 (224–303)	318 (243–375)	0.117
Hypotension (n)	13 (44.8%)	10 (32.3%)	0.430
Bradycardia (n)	3 (10.3%)	3 (9.7%)	1.000
Need for general anesthesia (n)	0 (0%)	2 (6.5%)	0.492

Duration of anesthesia was defined as the time from the injection of the local anesthetic to the regression of the sensory block to the S1 dermatome in the absence of motor block. Data are presented as mean (95% confidence intervals), median (1st – 3rd quartile), or count (% of group total), as appropriate.

FIGURE 1 Time course of the highest sensory block height during the first 35 min of observation. Error bars represent the 1st – 3rd quartile range.

The highest level of blockade was T11 (T6–T12) in group Levo-0.5, and T10 (T8–T12) in group Levo-0.75 ($P = 0.759$) (Figure 1). The highest sensory level was attained within 21 (16–26) min in group Levo-0.5, and 20 (16–24) min in group Levo-0.75 ($P = 0.350$). In the ANOVA for repeated measurements, there were no significant between-group differences in terms of arterial systolic and diastolic blood pressure (Figure 2), HR, and level of anesthesia

FIGURE 2 Summary of the time course of systolic blood pressure values over time. “Start” represents the beginning of surgery. Error bars represent 1st – 3rd quartile ranges. SBP = systolic blood pressure.

($P = 0.172$, $P = 0.390$, $P = 0.079$, and $P = 0.950$, respectively).

Two patients (6.5%) in group Levo-0.75 underwent general anesthesia due to discomfort during surgery, as opposed to no one in group Levo-0.5 ($P = 0.492$). Clinically relevant hypotension was reported in 13 patients of group Levo-0.5 (44.8%) and ten patients of group Levo-0.75 (32.3%) ($P = 0.430$). Bradycardia occurred in three cases in each group (10.3% vs 9.7%; $P = 1.000$). At the 24-hr follow-up visit, no patient complained of residual sensory deficits, difficult voiding (when not catheterized), or residual motor weakness.

Discussion

This prospective, randomized, blinded study shows that 0.5% and 0.75% solutions of plain levobupivacaine achieve a similar clinical profile, and evolution of spinal anesthesia, in elderly patients undergoing surgery for hip fracture repair. A direct comparison of the effects of these two concentrations of plain levobupivacaine has not previously been reported.

In comparing amide local anesthetics, with and without added dextrose, McLeod *et al.*³ reported a density of 1.00024 (0.00009) g·mL⁻¹ for plain 0.5% levobupivacaine, and 1.00056 (0.00010) g·mL⁻¹ for the 0.75% preparation [data measured at 37°C and presented here as mean (3 SD)]. Plain 0.75% levobupivacaine may thus be regarded as isobaric in all populations examined in recent studies,^{7,13,14} with the possible exception of pregnant women, in whom it may range between isobaricity and hyperbaricity.^{7,13} According to the report by Heller *et al.*,¹⁴ plain 0.5% levobupivacaine would be slightly hypobaric in elderly

men. In one data set, the mean measured density of 0.5% levobupivacaine is hypobaric in men and premenopausal women, and the lower bound of its density (i.e., mean – 3 SD) is hypobaric in all populations examined in this study.¹³ In contrast, 0.5% levobupivacaine is isobaric when compared to CSF densities measured in all patients by Lui *et al.*⁷

In laboratory studies, it has been shown that even small differences in density may significantly affect the spread of intrathecal anesthesia.¹⁵ Early reports about the apparent low predictability of the cephalad spread of 0.5% bupivacaine,¹⁶ as those about 0.5% levobupivacaine,¹¹ might be explained by hypobaricity of the solutions. However, the present study failed to show significant differences, in terms of cephalad spread or regression by two dermatomes, when comparing plain 0.5% levobupivacaine, presumably hypobaric in this setting, with the 0.75% preparation, an isobaric solution in the studied population. We cannot exclude that small clinical differences between the two formulations of levobupivacaine might, in theory, have been masked by the relatively large dose used in our study. The lack of difference, in terms of maximum cephalad spread of sensory block, has also been described when comparing hypo-¹⁷ or hyperbaric¹⁸ bupivacaine with the plain 0.5% solution.

The maximum sensory levels reported here for the Levo-0.5 group are lower than those found in previous studies evaluating 0.5% levobupivacaine, by about three segments.^{10,11} This difference might be explained by a higher puncture site in the former study, and a different injection speed in the latter. However, in light of the wide variations in sensory block level associated with hypo- and isobaric local anesthetic solutions, this disagreement might also be due to chance. This study has several limitations. As we did not measure CSF density in our patients, it is possible that, in our population, both levobupivacaine formulations were entirely within the range of isobaricity, as it would have been in patients studied by Lui *et al.*⁷ However, the aim of this investigation was to elucidate whether known differences in density translated into clinically apparent variations in the profile of the block in a clinical setting, where individual CSF density measurements are not feasible. A second limitation is the relatively high probability of β -error (20%) in our study, as it was not adequately powered to test the null hypothesis of equivalence. Our results translate to an effect size of 0.42 for a difference in onset time.¹² According to the present results, a formal equivalence study between 0.5% and 0.75% levobupivacaine would require between 121 and 159 patients per group, to obtain a power of 90–95% to detect differences of 4

four minutes in time to readiness for surgery. It is questionable whether such differences would have a significant clinical impact.

In conclusion, although the differences in density of the commercially available solutions of 0.5% and 0.75% levobupivacaine may result in different baricity, as compared to the density of CSF in elderly patients, results of this prospective, randomized double-blind trial did not demonstrate clinically relevant effects on the evolution and profile of spinal anesthesia with 15 mg of levobupivacaine.

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