A comparison of different densities of levobupivacaine solutions for unilateral spinal anaesthesia

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Received 31 May 2014; accepted 7 August 2014
Available online 26 November 2014

KEYWORDS
Hyperbaric levobupivacaine; Unilateral spinal anaesthesia; Arthroscopic knee surgery

Abstract
Background and objectives: The aim of the study was to compare the block characteristics and clinical effects of dextrose added to levobupivacaine solutions at different concentrations to provide unilateral spinal anaesthesia in lower extremity surgery.
Methods: This prospective, randomised, double-blind study comprised 75 ASA I–II risk patients for whom unilateral total knee arthroscopy was planned. The patients were assigned to three groups: in Group I, 60 mg dextrose was added to 7.5 mg of 0.5% levobupivacaine, in Group II, 80 mg and in Group III, 100 mg. Spinal anaesthesia was applied to the patient in the lateral decubitus position with the operated side below and the patient was kept in position for 10 min.
Results: The time for the sensorial block to achieve T12 level was slower in Group I than in Groups II and III (p < 0.05, p < 0.00). The time to full recovery of the sensorial block was 136 min in Group I, 154 min in Group II and 170 min in Group III. The differences were statistically significant (p < 0.05). The mean duration of the motor block was 88 min in Group I, 105 min in Group II, and 139 min in Group III and the differences were statistically significant (p < 0.05). The time to urination in Group I was statistically significantly shorter than in the other groups (p < 0.00).
Conclusions: The results of the study showed that together with an increase in density, the sensory and motor block duration was lengthened. It can be concluded that 30 mg mL⁻¹ concentration of dextrose added to 7.5 mg levobupivacaine is sufficient to provide unilateral spinal anaesthesia in day-case arthroscopic knee surgery.
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http://dx.doi.org/10.1016/j.bjane.2014.08.009
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PALAVRAS-CHAVE
Levobupivacainha hiperbárica; Raquianestesia unilateral; Artroscopia do joelho

Uma comparação das diferentes densidades das soluções de levobupivacaina para raquianestesia unilateral

Resumo
Justificativa e objetivos: O objetivo deste estudo foi comparar as características do bloqueio e os efeitos clínicos da adição de dextrose às soluções de levobupivacaina em diferentes concentrações para proporcionar raquianestesia unilateral em cirurgia de extremitade inferior. Métodos: Estudo prospectivo, randômico e duplo-cego conduzido com 75 pacientes, estado físico ASA I–II, programados para artroplastia unilateral total do joelho. Os pacientes foram divididos em três grupos: no Grupo-I, 60 mg de dextrose foram adicionados a 7,5 mg de levobupivacaina a 0,5%; no Grupo II, 80 mg e no Grupo III, 100 mg. A raquianestesia foi aplicada ao paciente posicionado em decúbito lateral, com o lado operado abaixo, e o paciente foi mantido em posição durante 10 minutos. Resultados: O tempo para o bloqueio sensorial atingir o nível T12 foi mais lento no Grupo-I que nos grupos II e III (p < 0,05, p < 0,00). O tempo de recuperação total do bloqueio sensorial foi de 136 minutos no Grupo-I, 154 minutos no Grupo-II e 170 minutos no Grupo III. As diferenças foram estatisticamente significativas (p < 0,05). A média da duração do bloqueio motor foi de 88 minutos no Grupo-I, 105 minutos no Grupo-II e 139 minutos no Grupo-III, e as diferenças foram estatisticamente significativas (p < 0,05). O tempo de micção foi significativamente menor no Grupo-I que nos outros grupos (p < 0,00). Conclusões: Os resultados do estudo mostraram que, junto com um aumento da densidade, a duração dos bloqueios sensorial e motor foi prolongada. Pode-se concluir que uma concentração 30 mg mL⁻¹ de dextrose adicionada a 7,5 mg de levobupivacaina é suficiente para proporcionar raquianestesia unilateral para artroscopia do joelho em regime ambulatorial.
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Introduction

In vitro studies have shown that differences in the specific densities of local anaesthetic solution can significantly affect the clinical presentation of spinal block. Better control of the block level is provided with hyperbaric solutions compared to isobaric solutions and therefore, fewer side effects, such as hypotension and uncontrollable block height, are expected. Other advantages of hyperbaric forms are that a unilateral block can be created and there is a lower rate of failed blocks.

Previous studies have compared the hyperbaric form of levobupivacaine with the isobaric form and other hyperbaric local anaesthetics. It has been reported in literature that a hyperbaric solution is obtained by adding dextrose at different concentrations to levobupivacaine. However, to the best of our knowledge, there is no previous comparative study on the most appropriate dextrose content for unilateral spinal anaesthesia.

The hypothesis of this study was that with the lowest dextrose content to achieve unilateral block, more stable haemodynamics and shorter duration of sensory and motor block can be obtained. With the aim of testing this hypothesis, in this prospective, randomised, double-blind study, a comparison was made of the block characteristics of levobupivacaine mL forms containing 30, 40 and 50 mg dextrose for unilateral spinal anaesthesia in lower extremity surgery and their suitability for day procedure anaesthesia.

Methods

After Ethics Committee approval and Clinical Trials registration (NCT01938759), 75 ASA I–II risk patients, aged 18–65 years, for whom elective unilateral knee arthroscopy was planned were included in the study. The Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting randomised, controlled clinical trials were followed (Fig. 1). Informed consent was obtained from all the patients. Exclusion criteria were contraindication for spinal anaesthesia, severe systemic disease, allergy to local anaesthetic, peripheral neuropathy, body mass index (BMI) >35 kg m⁻², psychiatric disorders and chronic pain treatment.

Premedication was not applied and after transfer to the operating room, ECG, non-invasive blood pressure, peripheral O₂ saturation (SpO₂) monitoring was made and an infusion of 10 mL kg⁻¹ lactated Ringer’s solution was started. The study was conducted in a double-blind method with the local anaesthetic solution to be used for spinal anaesthesia prepared by an anaesthetist other than the one who applied the spinal anaesthesia and monitored the patient. Using a computer generated sequence of numbers and a sealed envelope technique, patients were randomly divided into three groups. For all the patients, 7.5 mg (1.5 mL) 0.5% concentration of levobupivacaine was used as local anaesthetic. In addition, by adding in Group I (n = 25), 0.3 mL 20% dextrose (60 mg) and 0.2 mL distilled water, in Group II (n = 25), 0.4 mL 20% dextrose (80 mg) and 0.1 mL distilled water, in
water and in Group III (n = 25), 0.5 mL 20% dextrose (100 mg)
a total amount of 2 mL was defined. The densities measured at 37 °C of the levobupivacaine with 30 mg mL⁻¹, 40 mg mL⁻¹
and 50 mg mL⁻¹ dextrose were 1.008, 1.014 and 1.019 g L⁻¹, respectively. Measurements were made with IQ200 (Iris Diagnos-
tics, Chatsworth, CA).

Spinal anaesthesia was applied with a midline approach
from the 3rd and 4th intervertebral space with the patient
in the lateral decubitus position with the side to be operated
on below. A Quinke tipped 25 G spinal needle (Spinocon, B.
Braun, Melsungen, Germany) was used with the tip facing
downwards and, without barbotage, the anaesthetic solu-
tion was administered to all the patients at the rate of
0.1 mL s⁻¹. Patients were kept in position for 10 min and
then moved into a supine position and 0.03 mg kg⁻¹ iv mida-
zolam was administered. When the sensory block achieved
T12 level on the operation side, the operation was started.

The sensory and motor block of the patients was evalu-
ated every 5 min starting from the time of application (0 min)
by a researcher blind to the group distribution. The sen-
sory block was evaluated with the pinprick test with a 22 G
hypodermic needle touching the dermatomes on the mid-
clavicular line bilaterally and the motor block was evaluated
with the modified Bromage scale (0 = no motor block, 1 = only
the knee and foot can be moved, 2 = only the foot can be
moved, 3 = full motor block). At the end of the operation,
the block levels were checked at 15-min intervals until the
block was completely removed.

At the times of sensory and motor block evaluations, the
haemodynamic data were recorded. According to the pre-
operative value, a drop of 30% in mean arterial pressure
(MAP) was accepted as hypotension and rapid iv fluid infu-
sion (200 mL lactated Ringer’s solution) was administered
and in cases where no response could be achieved, 5 mg
iv ephedrine was planned. Heart beat rate falling below
50 bpm was accepted as bradycardia, for which it was
planned to administer 0.01 mg kg⁻¹ iv atropine. The qual-
ity of the spinal block anaesthesia was evaluated according
to the need for iv sedative or analgesia support. 8 Suf-
cient spinal block = no requirement for sedative or analgesia
until the surgery was completed, insufficient spinal block = a
requirement for additional analgesia (1 mcg kg⁻¹ iv bolus
fentanyl) or sedative (1 mg kg⁻¹ iv bolus propofol) for com-
pletion of surgery, failed spinal block = general anaesthesia
required to complete surgery. Additional to the spread of
the block, a record was made of the time to full recovery
of the sensory block (evaluated as no remaining feeling of
numbness in the leg), time to duration of the motor block
(time of Bromage = 0) and the time of the first urination.
Postoperative analgesia consisted of 75 mg im diclofenac
sodium (Diclofed, Abdi Ibrahim, Istanbul, Turkey) every 12 h
on request on the operation day.

Power analysis

The calculation of the required sample size was based on
mean and standard deviation of complete regression of
spinal block after anaesthesia with hyperbaric levobupiva-
caine reported in previous investigations: 25 patients
per group were required to detect a 20 min difference in time for
complete regression of spinal anaesthesia with an expected
**Table 1** Patients characteristics and duration of surgery. Data are presented as mean ± SD or frequencies.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 24)</th>
<th>Group II (n = 25)</th>
<th>Group III (n = 24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>36.1 ± 8.3</td>
<td>36.0 ± 8.4</td>
<td>35.8 ± 8.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>25.2 ± 3.3</td>
<td>24.7 ± 3.4</td>
<td>24.5 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>14/10</td>
<td>12/13</td>
<td>13/11</td>
<td>NS</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>15/9</td>
<td>18/7</td>
<td>17/7</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>38.5 ± 6.5</td>
<td>38.6 ± 5.8</td>
<td>37.2 ± 6.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant; BMI, body mass index; F/M, female/male; ASA, American Society of Anesthesiologist.

The operative side degree of motor block was significantly less in the Group I compared with the Group III in the minutes 10, 30, 45, and 120. Grade 3 motor block was not observed on the nonoperative side of the cases in all groups. The duration of motor block was significantly different among the three groups (Table 2). The first urination time was significantly shorter in Group I compared to other groups (Table 2).

Cardiovascular changes were minimal in groups. MAP levels of all measurement sequences were decreased significantly when compared to preoperative values which were obtained in three groups. In comparisons among the groups, there were statistical differences between the Groups II and III at the minute 5, between the Groups I and III at the minute 210 (Fig. 4). Initial HRs were decreased during the follow-up period (Fig. 5). There were no statistical differences among the three groups in incidence of hypotension or bradycardia. The adverse events during the study period are shown in Figure 3.

**Figure 2** Median level of operative side sensory block in groups.

**Figure 3** Median level of nonoperative side sensory block in groups.

**Statistical analysis**

Statistical analysis was performed using the program SPSS 20.0 (IBM SPSS Statistics, Chicago, IL, USA). Continuous variables are presented as mean ± SD or as median (range); categorical data are presented as number (%). Kruskal–Wallis test and Mann–Whitney U test were used to assess the demographic data, maximum sensorial block level, time to reach maximum sensorial block level and time to reach maximum motor block level. The Wilcoxon test was used for repeated measurements in groups. ASA classifications, gender, Bromage scale, number of hypotension and bradycardia episodes in groups were assessed with the chi-square test. Value of $p < 0.05$ was considered as a statistically significant.

**Results**

A total of 73 patients were enrolled in the study (Fig. 1). Patients who were required general anaesthesia (1 patient in Group I and 1 in Group III) as a result of technical failure were excluded from the study. Additional doses of fentanyl and propofol were administered to three patients in Group I and one patient in Group II during surgery. No statistically significant differences were observed among the three groups.

The groups were comparable with regard to age, sex, BMI, ASA status and duration of surgery (Table 1). The onset time of T12 level of sensorial block was more rapid in Group II and Group III compared to Group I ($p = 0.03$ and $p = 0.003$ respectively). No significant difference was observed between Group II and Group III. Maximum sensorial block height was significantly different between Group I and Group III ($p = 0.02$). The time to reach maximum sensorial block level and two-segment regression times of sensorial block did not differ significantly among all groups (Table 2).

In Group III, at the minute 150, the operative side sensorial block level was significantly higher than in Group I ($p = 0.043$). No significant difference between groups was observed for the operative side sensorial block levels at the other time points (Fig. 2). The nonoperative side sensorial block did not significantly differ among the three groups at the all time points (Fig. 3). In Group I, the time to full recovery of sensorial block was significantly shorter than other groups and Group II significantly shorter than Group III (Table 2).

effect size to standard deviation ratio of 0.9 accepting a two-tailed $\alpha$ error of 5% and a $\beta$ error of 20%.

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in Table 3. There were no significant differences among all groups for any of the adverse events.

**Discussion**

As a result of this study comparing levobupivacaine solutions with differing dextrose contents for unilateral spinal anaesthesia, shorter sensory and motor block durations and time to first urination were determined with a 30 mg mL⁻¹ dextrose content.

Levobupivacaine hydrochloride is an 5(−) enantiomer of racemic bupivacaine which is less toxic on the heart and central nervous system. Clinical studies have shown both agents to be effective at equal doses in spinal anaesthesia. In a study which compared 5, 7.5, 10 and 12.5 mg doses of 0.5% bupivacaine for unilateral spinal anaesthesia in knee arthroscopy, the optimal dose was

![Figure 4](image1.png) **Figure 4** Mean arterial blood pressure changes in groups (mmHg). Data are presented as mean. *p = 0.02 Group II vs III. †p = 0.04 Group I vs III.

![Figure 5](image2.png) **Figure 5** Heart rate changes in groups (bpm, beats per minute). Data are presented as mean.
reported to be 7.5 mg.\textsuperscript{39} Therefore, the same dose was used in the current study.

The difference in density between cerebrospinal fluid (CSF) and local anaesthetic is an important factor in determining the distribution of the solution in the subarachnoid area. Local anaesthesia density reduces with increased temperature and increases with an increase in glucose concentration.\textsuperscript{20-22} At 37°C the mean density of CSF is 1.0003 g L\textsuperscript{-1}, ranging from 1.0000 to 1.0006 g L\textsuperscript{-1} (±2SD).\textsuperscript{23} Solutions at a density below 0.9990 can be accepted as hypobaric and those above 1.0010 as hyperbaric.\textsuperscript{21} On the commercial market, the only hyperbaric form available is bupivacaine containing 8% dextrose. It has been reported that solution containing dextrose at a higher concentration than 8% will have hyperbaric behaviour.\textsuperscript{25} This unnecessarily high concentration of 8% has been reported to allow the usage of low dose and additional adjuvants.\textsuperscript{7} However, in literature, local anaesthetics containing dextrose at 8% concentration are often used for unilateral spinal anaesthesia.\textsuperscript{5,10,24} In the current study, the density of the solution containing 3% concentration dextrose in Group I was measured as 1.008 g L\textsuperscript{-1} at 37°C. From the results of the study, it was determined that this difference from CSF in density was sufficient to form a unilateral block.

Local anaesthesia which is used to provide unilateral spinal block depends on dose, density and the duration of the lateral decubitus position.\textsuperscript{9} It has been reported that the best result for unilateral block is achieved with 10–20 min waiting in the lateral decubitus position after using a low dose of local anaesthesia.\textsuperscript{25} In the current study, a 10 min waiting period after the procedure was preferred. Following the 10 min waiting period, Grade 3 motor block was not seen in any patient on the nonoperative side. This can be considered to be due to the use of a low dose of local anaesthetic.

At the end of the current study, a sufficient level of unilateral spinal anaesthesia was achieved without leading to any serious side effects with levobupivacaine solutions containing dextrose at rates of 3%, 4% and 5% (30, 40 and 50 mg mL\textsuperscript{-1}, respectively). In Group I with the lowest dextrose content, the time to sensory block onset was longer compared to the other groups and the maximum block level was lower than that in Group III. In literature it has been reported that an increase in local anaesthesia solution density has the effect of accelerating onset\textsuperscript{6,9,26,27} and causes an increase in maximum block level.\textsuperscript{9,27}

In the current study, the time to full recovery of both sensory and motor blocks was shorter in Group I. There have been various studies on the effect of an increase in local anaesthetic solution density on the duration of sensory and motor block. In a study by Janik et al.,\textsuperscript{26} comparing bupivacaine solutions containing glucose at 8% and 5%, higher glucose content was reported to significantly lengthen the duration of sensory block. Similarly, in the current study, the resolution of the motor block was delayed. Bannister et al.\textsuperscript{29} compared 0.5% bupivacaine solutions containing different concentrations of glucose and determined a longer sensory block duration in the group with the solution containing 8% glucose.

In a study by Sanansilp et al.,\textsuperscript{30} isobaric and hyperbaric solutions of levobupivacaine were compared in spinal anaesthesia and no difference was determined in the regression times of the motor and sensory block. However, Sen et al.\textsuperscript{39} compared intrathecal isobaric and hyperbaric levobupivacaine in urology surgery and the duration of the motor and sensory block was found to be longer in the hyperbaric group. It can be concluded that the current study differed from that of Sanansilp in not using the isobaric form and was also different from these studies in that unilateral spinal anaesthesia was provided. Similar results to those of the current study were reported by Janik and Bannister where local anaesthesia solutions containing different concentrations of dextrose were used.\textsuperscript{28,29}

It has been reported that hyperbaric solutions can lead to an increase in the incidence of cardio respiratory side effects depending on the concentration of dextrose in the solution.\textsuperscript{23,31} Critchley et al.\textsuperscript{32} compared the haemodynamic effects of bupivacaine solutions, plain and containing 8% and 4% dextrose and reported that in the group with the solution containing 8% dextrose, haemodynamic changes started significantly more quickly. There was a similar rapid onset of sensory block but the maximum sensory block level was determined to be similar in all the groups. The haemodynamic data of the current study were similar. In 1 patient in Group I and 2 patients in Group III, hypotension developed and ephedrine was administered. It is known that in unilateral spinal anaesthesia low dose local anaesthesia can be used and more stable haemodynamics are presented because of the selective blockage created on the operative side.\textsuperscript{25,33,34}

In day-case surgical procedures, the time of first urination and time to mobilisation are important in respect of hospital discharge. Postoperative mobilisation time can be affected by some surgical characteristics. The most frequently encountered factor restricting the meeting of discharge criteria has been reported to be the return to spontaneous urination.\textsuperscript{6} Therefore, in the current study, the time to return of spontaneous urination was taken as a criterion rather than time of discharge. In Group I this time was 128 min, which was significantly shorter than the times of both Group II and Group III. In a study by Cappelleri et al.,\textsuperscript{8} in which hyperbaric forms of levobupivacaine and ropivacaine were compared in unilateral spinal anaesthesia for knee arthroscopy, this period was reported as 238 min in the group with 7.5 mg levobupivacaine including 8.2% glucose. The time to discharge of this group was defined as the time of first urination.

In a study by Luck et al.,\textsuperscript{11} comparing hyperbaric forms of bupivacaine, levobupivacaine and ropivacaine containing 30 mg dextrose in spinal anaesthesia, the time of first urination of the levobupivacaine group was determined as 347 min. This result can be thought to be due to the high dosage of levobupivacaine (15 mg) and the bilateral nature of the spinal block. In patients to whom unilateral spinal anaesthesia is applied, a more rapid return to bladder function has been reported due to unilateral blocking of the sacral parasympathetic efferent ligaments which innervate the detrusor muscle.\textsuperscript{35} In a study by Mulroy et al.,\textsuperscript{11} it was reported that neuroaxial blocks applied with short-term effect drugs for day-case surgical procedures carry a low risk of urinary retention.\textsuperscript{36} However, it was also stated that more extensive studies are required to confirm this result.
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The main limitation of the current study is that no comparison was made of the times to mobilisation and actual discharge. The reason for this is that mobilisation and discharge of the patients may be affected by patient or surgery-related factors that are independent of the anaesthesia. In this study, which compared levobupivacaine solutions containing 3%, 4% or 5% dextrose for unilateral spinal anaesthesia, while successful unilateral spinal block was provided in all three groups together with a low side-effect profile, extended duration of both sensory and motor block was determined with an increase in density. For unilateral spinal anaesthesia in day-case arthroscopic knee surgery, the addition of 30 mg mL⁻¹ dextrose to 7.5 mg levobupivacaine can be considered sufficient.

Conflicts of interest
The authors declare no conflicts of interest.

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