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# Assessment of the Effect of Intrathecal Low Dose Levobupivacaine or Bupivacaine Combined with Fentanyl in Patients Undergoing Cesarean Section

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## Abstract

In our study, we evaluated the effects of fentanyl added to intrathecal levobupivacaine or bupivacaine on the level of motor-sensory block, analgesia duration, patient satisfaction and newborn's well being in patients undergoing elective cesarean section.

The study was designed as a prospective, randomized and double-blind study. The patients were randomly allocated into two groups, so that patients in Group C received intrathecal isobaric 7.5 mg 0.5% levobupivacaine (1.5 ml) and 20 µg fentanyl (0.4 mL), while the ones in Group B had intrathecal isobaric 7.5 mg 0.5% bupivacaine (1.5 mL)and 20 µg fentanyl (0.4 mL). Following spinal anesthesia, hemodynamic parameters, onset and recovery time of sensorial and motor block, side effects, Apgar scores of the newborns, blood gas levels of the umblical artery, pain scores (VAS) of the patients, surgeon, patient and anesthesiologist satisfaction were recorded.

The onset time for sensorial block and the requirement of ephedrine were similar in both groups. The recovery time of block to T10 and the initial analgesic requirement time were detected to be significantly longer in Group C. Duration of motor block was significantly longer in Group B (p=0,017).

The intratechal fentanyl added to levobupivacaine or bupivacaine had similar effects both on the mother and the newborn.

**Keywords:** Spinal anaesthesia; Levobupivacaine; Bupivacaine; Fentanyl

## Introduction

Intrathecal anesthesia in caesarean sections has become an established technique, and various local anesthetics and opioids have been used, either alone or in combination. Smaller doses of local anesthetics supplemented by intrathecal opioids have been recommended for spinal anesthesia in parturients undergoing cesarean section delivery [1,2].

Levobupivacaine is relatively recently introduced amino amide local anesthetic that is structurally similar to bupivacaine. Clinical studies all indicate that levobupivacaine is well tolerated and has an efficacy equivalant to bupivacaine for anesthesia and analgesia [3]. Levobupivacaine has been associated with less central nervous system and cardiac toxicity relative to bupivacaine when equal concentrations were compared [4,5]. Bupivacaine, an amide type of local anesthetic, has high potency and long duration of action (1.5-2 h). Its most serious side effect is cardiotoxicity and pregnant women are more susceptible to this side effect [4].

The addition of low doses of opioids to local anesthetics used in spinal anesthesia, reduces the dose of local anesthetic used. The incidence of adverse effects is reduced. Additionally, it may shortenthe onset time and prolong the duration of postoperative analgesia [6].

The aim of this study was to compare spinal anesthesia effects (hemodynamic changes, motor and sensorial block level, analgesia durations and neonetal outcome) of low-dose levobupivacaine (7.5 mg) or bupivacaine (7.5 mg) combined with fentanyl (20 µg) for elective cesarean section.

## Materials and Methods

The protocol was approved by the hospital ethics committe (Atatürk Training Hospital, Ankara, Turkey) and written informed consent was obtained from each patient. 60 ASA I-II parturients age 18-40 yr, weight less than 110 kg with uncomplicated singleton pregnancy between 37-42 weeks undergoing elective Caesarean section were enrolled in the study. Exclusion criteria were any contraindication to spinal anesthesia, allergy to local anesthetics of the amide type and communication difficulties that would prevent reliable assesment and those women with diabetes mellitus, pre-eclampsia, psychiatric disease or history of drug abuse. All patients received ranitidine 150 mg orally 2h before the operation. In the operating room, all parturients received oxygen (4 litre $min^{-1}$) via a facemask and an i.v. infusion of 20 ml $kg^{-1}$ lactated Ringer's solution was administered over approximately 15 min. Oxygen saturation, electrocardiography and blood pressure were monitored. All parturients received a spinal technique in the left lateral decubitis position. All parturients were allocated into one of the two groups (n=30 per group) in a double- blind, randomized, prospectivepattern so that the first group (Group B) (n=30) received 1.5 ml 7.5 mg isobaric bupivacaine (Marcaine, AstraZeneca) and 20 µg fentanyl (0.4 ml) and the second group (Group C) (n=30) received 1.5 ml 7.5 mg isobaric levobupivacaine (Chirocaine, Abbott Laboratories) and 20 µg fentanyl (0.4 ml). The study drug was prepared by an anesthesiologist who was

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not involved in the parturient assesment. The subarachnoid space was located using 25-gauge Quincke needle at the L4-L5 interspace. When a free flow of clear cerebrospinal fluid was obtained in the needle, the study drug was injected into the intrathecal space, over 10-15s. Immediately after the spinal injection, the patient was placed in the supine position, with left lateral tilt. Maternal heart rate and systolic and diastolic blood pressure were noninvasively recorded prior to induction of anesthesia and every 5 min from the time injection of local anesthetic until the patient arrived in the recovery room.

The level of sensory anesthesia to pinprick was assessed bilaterally at midaxillary line. Motor block was asssessed using a modified Bromage scale, where 1=complete block, unable to move feet or knees; 2=ability to move feet only; 3=just able to move knees; 4=detectable weakness of hip flexion; 5=full flexion of hips and knees while supine. These tests were performed at baseline, and then every 5 min thereafter. Surgery was allowed to start when at least the T5 dermotomal level was obtained. For assesment of the onset of anesthesia, the time for sensory block to develop to maximum block height and the time to achieve maximum Bromage score were recorded. To assess the duration of the sensory block, the two- segment regression time from the maximum block height and time for regression to T10 were used. During this time the parturients were observed for side effects such as hypotension, bradycardia, nause (0=no, 1=yes) and vomiting (0=no, 1=yes). Nause and vomiting were treated with metoclopramide. Hypotension was defined as a 20% decrease in the mean arterial blood pressure when compared with the baseline values and treated, if necessary, with 5 mg IV boluses of ephedrine. Bradycardia (defined as heart rate <50/min) was treated with 0.5 mg atropine. Neonatal welfare was evaluated by Apgar scores at 1, 5 and 10 min after delivery and umbilical arterial blood-gas analysis was also performed.

Pain was assessed with a 10 cm linear visual analogue scale (VAS) at surgical incision, birth and peritoneal closure and at 15 min intervals after surgery. The duration of analgesia was documented from the beginning of intrathecal injection time until time of request for additional analgesia. During the procedure, the surgeons evaluated muscle relaxation according to a four-point scale (1=poor, 2=fair, 3=good, 4=excellent). After the surgery, parturients were questioned about the quality of their anesthesia (1=poor, 2=fair, 3=good, 4=excellent).

| Variables | Group C | Group B | p |
|---|---|---|---|
| Age (year) | 27,6 ± 3,4 | 27,9 ± 4,3 | 0,740[a] |
| Weight(kg) | 75,6 ± 13,0 | 73,6 ± 10,3 | 0,498[a] |
| Height(cm) | 159,3 ± 5,7 | 160,8 ± 5,3 | 0,295[a] |
| BMI (kg/m$^2$) | 29,8 ± 5,1 | 28,4 ± 3,3 | 0,209[a] |
| Gestational age (week) | 38,3 ± 1,0 | 38,3 ± 1,1 | 0,655[b] |
| Duration of surgery (min) | 42,5 (25-65) | 42 (25-70) | 0,969[b] |
| Duration of anesthesia (min) | 50 (30-70) | 50 (25-76) | 0,395[b] |

[a]Student's t test.
[b]Mann Whitney U test.
(Mean ± SD), (min.-maksimum), Duration of surgery and anesthesia (min-max)

**Table 1:** Demographic data.

| Variables | Group C | Group B | p[a] |
|---|---|---|---|
| Sensory block onset time (min) | 2,0 (1,0-6,0) | 2,0 (1,0-4,0) | 0,036 |
| Time to reach max cephalic blok (dk) | 7,5 (3,0-20,0) | 7,0 (3,0-17,0) | 0,799 |
| 2 Segment regression time (min) | 70,0 (45,0-130,0) | 75,0 (40,0-110,0) | 0,649 |
| T 10 regression time (min) | 160,0 (130,0-210,0) | 140,0 (70,0-170,0) | <0,001* |

[a]Mann Whiyney U test.
*p<0,001intergroup comparison.

**Table 2:** Comparision between intergroups.

| Variables | Group C (n=30) | Group B (n=30) | P |
|---|---|---|---|
| **APGAR Score** | | | |
| 1.min | 7 (6-9) | 7 (5-9) | |
| 5.min | 9 (8-10)[a] | 9 (7-10)[a] | |
| 10.min | 9 (7-10)[a] | 9 (6-10)[a] | |
| **Umbilical venous blood values** | | | |
| pH | 7,33 (7,28-7,43) | 7,35 (7,16-7,41) | 0,237[b] |
| $pCO_2$ (mmHg) | 47,3 ± 5,7 | 46,6 ± 6,9 | 0,686[c] |
| $pO_2$ (mmHg) | 17,1 (4-38) | 16,9 (5-47) | 0,807[b] |
| Base excess (BE) (mmol/lt) | -1 (-3 – 2) | -0,8 (-7 – 2) | 0,882[b] |

[a]Correction of Bonferroni (p<0,008).
[b]Mann Whitney U test.
[c]Student's t test.

**Table 3:** Neonatal APGAR Scores and Umbilical venous blood values.

## Statistical Analysis

Data were analysed using a statistical software package (SPSS). The patients personal and obstetric data were represented as mean( SD) and median ( interquartile range) as appropriate. Statistical evaluation was performed using $\chi^2$ test, the Mann-Whitney *U*-test, Freidman test, Bonferroni Correction, Wilcoxon signed rank test, Repeated Measure Variance Analysis, Shapiro Wilkas appropriate. Significance was set at the $p<0.05$ level. Power was given at 90% with a level of significance of 0.05.

## Results

60 parturients were recruited in the study. None of the parturients experienced an inadequate block. There were no differences in the parturients' demographic data, duration of anesthesia and surgery between the two groups (Table 1). There were no differences in maternal blood pressure and heart rate values between the two groups. Block characteristic are demonstrated in Table 2. There were no statistically significant differences between treatment groups in mean time to onset of sensory block, time totwo- segment regression time and time to reach the maximum block height (p>0.05). The time for regression to T10 was significantly longer in Group C than Group B (p=0.036). There were no significant differences in groups for the maximum level of sensory block achieved (T4) and degree of motor block. The recovery time of motor block was prolonged in Group C compared to Group B (p=0.017). There was no difference in pain scores (VAS), or in the incidence of inadequate anesthesia between the two groups. The time to first analgesic request was also significantly longer in Group C (p=0.013) [Group C, median 170 (120-240) min, Group B, median 150 ( 80-210) min]. The incidence of hypotension, consumption of ephedrine, episodes of nausea and vomiting, were similar between two groups.Neonates had similar Apgar scores being 9 or more at 5 minutes. Blood gas values did not differ between groups. Mean umbilical arterial pH values were 7.33 (7.28-7.43) in the levobupivacaine group and 7.35 (7.16-7.41) in the bupivacaine group (Table 3). When considering the parturients, surgeon and anesthesiologist evaluation of analgesia (scores of quality), no significant differences were noted.

## Discussion

Spinal anesthesia, providing an effective surgical anesthesia and postoperative analgesia by ensuring minimal maternal and neonatal side effects, has been reported to be more advantageous than general anesthesia for caesarean operations [7,8].

Bupivacaine is a preferred agent in obstetric anesthesia due to its

long lasting action and lower levels of placental transition; however, its most serious side effect is cardiotoxicity, which makes pregnant women, more sensitive to this effect. Levobupivacaine is a more favorable local anesthetic agent in terms of safety profile with similar pharmacokinetic properties to racemic bupivacaine [9]. However, trials have reported that the cardiovascular and central nervous system-related side effects of levobupivacaine are less than those of bupivacaine, though the onset and duration of action, hemodynamic changes after spinal anesthesia are the same for levobupivacaine and bupivacaine [10,11].

In our study, in parallel to the clinical studies, we also observed thesimilar efficacy of the two local anesthetics with equal efficacy in epidural and spinal analgesia practices [12-14].

Although a slight decrease was seen in the mean arterial pressure and heart rate in the studies using intrathecal hyperbaric bupivacaine, ropivacaine and levobupivacaine in caesarean operations, no hemodynamic difference was found between the groups, in our study [11,13,15].

In the study of Glaser et al. in which 3.5 ml 0.5% isobaric levobupivacaine and 0.5% isobaric bupivacaine were used in orthopedic hip prosthetic surgery, no statistically significant difference was reported in the mean arterial pressure and heart rate values between the groups, but they stated that intragroup values were below the baseline value after intrathecal drug administration [13]. The results of our study were also consistent with the study of Glaser, and similarly MAP and HR were decreased in both groups after intrathecal administration. This reduction did not differ between groups. Lee et al. have achieved similar results in their study using 2.6 ml of 0.5% bupivacaine and levobupivacaine [14]. However, in the study of Copperjans et al. comparing 6.6 mg of bupivacaine supplemented with 3.3 μg of sufentanil, 6.6 mg of levobupivacaine and 10 mg of ropivacaine, they found a better value of systolic blood pressure in the levobupivacaine group, and they also detected a low rate of hypotension [16]. In another study, intrathecally administrated 0.5% hyperbaric 8 of mg bupivacaine, 8 mg of levobupivacaine and 12 mg of ropivacaine were compared respectively in cesarean operations, and although there was no statistical difference between the three groups, a minimum rate of hypotension was reported in the bupivacaine group [17].

The incidence of hypotension was reported to be 45% in spinal anesthesia practices in caesarean operations, and fluid overload, positioning the patient to the left and the use of vasoconstrictor agents were recommended to prevent hypotension [18,19]. Ephedrine used for this purpose may lead to maternal reactive hypertension, tachycardia, tachyphylaxis, and fetal acidosis with a reduction in uterine blood flow. In our study, the number of patients to whom we administered ephedrine due to hypotension (more than 20% reduction in MAP) was 60% in Group C and 40% in Group B, and there was no statistically significant difference between the two groups. Ephedrine-related side effects and fetal acidosis were not observed in either group.

The addition of opioids to local anesthetic agents reduces the dose and the incidence of side effects of local anesthetics, due to the synergistic effects of opioids with local anesthetics, without causing a sympathetic block [16,20]. It also ensures the occurrence of the effect in a shorter time and prolongs the duration of postoperative analgesia [21,22]. Use of local anesthetic agent alone was reported to be inadequate in preventing visceral pain and nausea during uterine manipulation and closure of the visceral peritoneum [23,24]. The addition of intrathecal opioid produces an antinociceptive effect in visceral and somatic pain [25]. The addition of lipophilic opioids to the local anesthetics in spinal anesthesia increases the quality of the anesthesia without prolonging the duration of the motor block. The disappearance rate of a motor block increases with such combinations [26].

In the study of Glasser et al. the onset time of sensory block was found to be 11 ± 6 minutes in the 3.5 ml of 0.5% isobaric levobupivacaine group and 13 ± 8 minutes in the 3.5 ml of isobaric 0.5% bupivacaine group, and they reported that there was no statistically significant difference between them [13]. Although, no statistical data can be given, we have trials using bupivacaine and levobupivacaine solely, in our daily practice. In this study, the onset time of sensory block of isobaric bupivacaine and levobupivacaine, and the maximum duration of cephalic spread were similar in both groups. But we have found a shorter onset time of sensory block and a shorter duration of cephalic spread due to the addition of 20 μg fentanyl. Higher levels of sensory block were similar in both groups (T4). It was increased to T2 level in one patient in the levobupivacaine group only. Lee et al. measured the time to reach T10 as 10 ± 6 minutes for levobupivacaine, and 8 ± 4 minutes for bupivacainein urologic surgeries using 2.6 ml of isobaric levobupivacaine and bupivacaine without fentanyl, and reported that there was no statistically significant difference between them [14].

Mısırlıoglu et al. used 25 μg fentanyl added to the local anesthestics. They found similar results. However, when the patient group is mother, and the fetus, we think that 20 μg fentanyl (a lower dose) might be important. That's why we chose a lower dose of added opioid for clinical investigation. Nevertheless, we believe, these small differences could be more important in larger group sizes to be more meaningful [27].

Choi et al. used 8 mg, 10 mg and 12 mg of 0.5% intrathecal hyperbaric bupivacaine in caesarean section operations and compared their effects. They reported that 12 mg of hyperbaric bupivacaine provided the most effective analgesia, rarely caused an increase in the level of sensory block, and provided an adequate postoperative analgesia. In the study done by adding 10 μg fentanyl to these doses, they reported that adding 10 μg of fentanyl to 8 mg of hyperbaric bupivacaine could be preferred, because it provided long-term postoperative analgesia without delaying the recovery of the motor block [1]. Choi tried to find the lowest dose of bupivacaine and fentanyl added to it. Similarly, we also chose similar dose of bupivacaine, however, the added fentanyl dose was higher in our study. Besides, we wanted to compare the efficicacy of bupivacaine with levobupivacaine with the addition of the same dose of fentanyl. Thus, the studies may seem si milar, but actually are different in the way of methodology. In our study, the lower dose of (7.5 mg) 0.5%isobaric bupivacaine and levobupivacaine, to which we added 20 μg of fentanyl, provided adequate analgesia.

In our study, The duration of decline to T10 was statistically significantly longer in the levobupivacaine group. Thus, the first analgesic requirement was detected later in the levobupivacaine group.

There was no difference in the maximum duration to reach motor block between the groups in our study, as is the case in many other studies [28-30]. A study conducted by Lacassie et al. showed that a motor block with shorter duration and at a lower depth occurred after application of epidural levobupivacaine [29]. Camorcia et al. estimated the power rate of motor block to be 0.71 for levobupivacaine/bupivacaine used without the addition of intrathecal opioids in pregnant women undergoing caesarean section operation with spinal anesthesia [30].

Also, in the study of Aydin using hyperbaric bupivacaine, ropivacaine and levobupivacaine, the bupivacaine group was found to create a more powerful motor block. When we compared the Bromage score values in our study, they were found to be 3 in 70% of

the patients in the levobupivacaine group and in 85% of the patients in the bupivacaine group, respectively. The average recovery time of the motor block was 102.5 min in the bupivacaine group and 80 min in the levobupivacaine group in our study, and the presence of a short-lasting motor block in the levobupivacaine group was similar to other studies [28,29,31]. Lower affinity of levobupivacaine to A-α fibers (somatic motor fibers) than that of bupivacaine may have resulted in a lesser motor block.

The use of low-dose bupivacaine causes a lower incidence of hypotension as a result of lesser sympathetic blockade. Fentanyl supplementation reduces the incidence of extremely high-block formation, and accelerates the compilation of the motor block. Side effects of intrathecal opioids may include respiratory depression in the mother, nausea, vomiting, and itching [32,33]. Respiratory depression was not observed in any of our patients. No significant difference was found in the other side effects (nausea, vomiting, itching, chest discomfort, allergic reactions) between the groups. Antiemetics were required in only two patients in each group.

Blood pH and acid-base balance of the umbilical cord is an objective indicator for the evaluation of the newborn. Bupivacaine and levobupivacaine do not show fetal toxicity depending on the pharmacological profiles. Although Bremerich et al. also obtained similar results in their study, short-term respiratory distress requiring ventilator support was observed in three newborns among the patients receiving 10 mg of levobupivacaine + 20 μg of fentanyl and 10 mg of bupivacaine + 20 μg fentanyl [34]. In our study, no statistically significant difference was found in the APGAR scores (1st, 5th, and 10th min.) and umbilical cord venous blood gas values (pH, $pO_2$, $pCO_2$, $HCO_3$, BE, and Sat%) between the two groups. Hemodynamics and respiratory parameters remained within normal limits in all newborns.

In conclusion, in our study, we found that the addition of 20 μg of fentanyl in low doses of intrathecal 7.5 mg of 0.5% isobaric levobupivacaine and 7.5 mg of 0.5% isobaric bupivacaine in elective caesarean section operations provided sufficient analgesia for surgery, and this had no negative effect on the mother or the baby. We believe that levobupivacaine + fentanyl can be an alternative to bupivacaine + fentanyl in caesarean section operations because the first analgesia is required at a later stage, motor blockade disappears earlier and early mobilization is ensured.

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