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Comparison of Two Different Doses of Fentanyl Combined With Levobupivacaine For Elective Cesarean Section

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Abstract

Objectives: In this prospective, randomized, double-blind, controlled study, we compared the effects of two different doses of fentanyl (10 μg or 25 μg) given intrathecally in addition to 0.5% levobupivacaine for cesarean section.

Methods: Eight hundred, ASA I-II parturients, who were scheduled for elective cesarean section, were enrolled in the study. They were randomly allocated into three groups. Group I received 0.5% levobupivacaine; Group II received 0.5% levobupivacaine plus 15 μg fentanyl; Group III received 0.5% levobupivacaine plus 25 μg fentanyl intrathecally. Ephedrine was administered as a bolus dose (0.1 mg/kg), and then the continuous infusion was initiated. The rate of infusion was maintained with respect to baseline systolic blood pressure until umbilical cord clamping. We recorded maternal sistolic blood pressure, heart rate, total ephedrine dose, fetal Apgar scores (at 1st and 5th min), and umbilical cord blood parameters. Other side effects, such as hypotension, nausea/vomiting, bradycardia, etc. were also noted.

Results: Bolus, infusion and total ephedrine doses were significantly lower in Group III when compared with the other groups ($P<0.05$). The incidences of hypotension in the I, II, and III groups were 17.30%, 13.38%, and 11.63%, respectively. There was no significant difference between the three groups regarding the Apgar scores at the 1st or 5th min, umbilical arterial or venous pH. There was no difference in the incidence of other side effects among the three groups.

Conclusion: We conclude that the addition of 25 μg fentanyl to adjusting the dose of levobupivacaine to a patient's height decreases the ephedrine requirement without additional side effects and adverse neonatal outcomes when compared with the other groups. The levobupivacaine doses as determined by the length of the patients' and the use of the appropriate fluid resuscitation therapy with an infusion of ephedrine can be used effective methods.

Keywords: Spinal anesthesia; Cesarean; Levobupivacaine; Fentanyl; Ephedrine

Introduction

Spinal anesthesia is a widely used technique for cesarean sections, because it provides a fast and efficient blockade. However, hypotension is the most frequently encountered complication. If maternal hypotension is severe and sustained, it may cause harmful effects for both mother (nausea, vomiting, dizziness, faintness), and baby (fetal hypoxia, acidosis, and neurological injury) [1]. Therefore, the measures should be taken for the prevention, and its treatment should be done rapidly when it occurs.

Although numerous methods have been investigated for the prevention and the treatment of the hypotension, it remains to be a common critical problem [2]. Ephedrine is a sympathomimetic agent with an impact both on the alpha and beta receptors. It was reported that the use of ephedrine as an infusion followed by a bolus dose may reduce the incidence of hypotension.

The addition of opioids to local anesthetics intrathecally produces a synergistic analgesic effect without intensifying motor and sympathetic blockades, and ensures successful anesthesia with the use of a low-dose local anesthetic which results in more stable haemodynamics [1].

Levobupivacaine is a pure S (-) enantiomer of racemic bupivacaine, and is less toxic to the heart and central nervous system [3]. The use of the levobupivacaine and opioid combinations for obstetric anesthesia has become popular in recent years [4-9].

In the literature, there are numerous studies that compared to bupivacaine with levobupivacaine [4,6-9], but there are few studies in which the use of levobupivacaine and various opioid combinations is compared to its use without opioids in spinal anesthesia for cesarean section [10-13].

In this prospective, randomized, double-blind, controlled study, we aimed to compare the effects of adding two different doses of fentanyl (10 μg or 25 μg) to 0.5% levobupivacaine intrathecally on ephedrine requirement. We also evaluated maternal hemodynamic parameters, neonatal effects, and side effects.

Methods

After approval of the Local Ethics Committee of Zekai Tahir Burak Hospital, informed consent forms were obtained from each patients. This prospective, double-blinded, randomized study was performed from February 2009 to March 2010, on 800 pregnant female patients presented to our hospital for delivery by cesarean section with spinal anesthesia.

The full-term (gestational age 37 to 42 week) parturients with singleton pregnancies, aged between 18-45 years, classified as American Society of Anesthesiologists (ASA) I or II with normal coagulation profile, weight between 60 and 90 kg and height between 155 and 170 cm were enrolled in the study.

Patients with a history of allergic reactions to any study drug, with any contraindication to regional anesthesia, with pre-eclampsia, eclampsia, gestational hypertension, diabetes mellitus, cardiac problems or bleeding diathesis were excluded.

The patients were randomly allocated into three groups according to a computer-generated randomization table: Group I received levobupivacaine, Group II received levobupivacaine along with 10 μg fentanyl, Group III received levobupivacaine along with 25 μg fentanyl.

Each woman received 2, 2.2 or 2.4 ml (depending on the patient's height: 2 ml (10 mg), if 155-160 cm; 2.2 ml (11 mg), if 161-165 cm; 2.4 ml (12 mg), if 166-170 cm) levobupivacaine 0.5% (Chirocaine, Abbott Laboratories, Istanbul, Turkey). In Group II, fentanyl 10 μg, and in Group III, fentanyl 25 μg were added to the local anesthetic. The study drugs were diluted to 3.0 ml with normal saline.

To facilitate blinding, spinal blocks were performed by one anesthetist, who was unaware of patient assignment, and the study solution were prepared immediately before injection by another anesthetist who did not involve with subsequent patient assessments. Neither the anesthetist performing the block nor the patient herself was aware of the drug combination.

On arrival to the operating room, the electrocardiogram (ECG), pulse oximetric saturation (SpO_2), and non-invasive blood pressure measurement instruments were set up for monitorization, and a 18-G catheter was utilized for vein cannulation. All parturients were given 15 ml/kg Ringer's lactate solution infusion in 10-15 min before spinal anesthesia, and the infusion was maintained at 8-10 ml/kg/h throughout the operation.

Spinal anesthesia was performed in sitting position. Quincke needle was inserted at the L3-4 or L4-L5 spinal interspace (with a median approach), and after confirming free flow of cerebrospinal fluid, the spinal solutions were injected over approximately 20 seconds.

Immediately after blockade, the patients were placed in the left lateral position, and oxygen nasal cannula was used 2 L/min. All patients received a bolus 0.1 mg/kg of ephedrine, and followed by continuous intravenous infusion with a syringe pump. Ephedrine infusion was maintained until birth by monitoring systolic blood pressure (SBP) in reference to the baseline values as follows:

- Infusion was discontinued, if SBP value reached >100% of the baseline value,
- Infusion was maintained at 10 μg/kg/min, if SBP value was between 80% and 100% of the baseline value,
- Infusion was maintained at 20 μg/kg/min, if SBP value was <80% of the baseline value,
- In addition to 5 mg bonus administration, infusion was maintained at 20 μg/kg/min, if SBP value was <90 mmHg.

Infusion was maintained until umbilical cord clamping. The level of sensory block was assessed by loss of pinprick sensation. The surgery was allowed to start after the sensorial blockade reached T4-5. If the upper level failed to reach T4-5 after 10 minutes, it became necessary to convert to general anesthesia; the patient was excluded from the study. The time from blockade to skin incision, and extraction of fetus were recorded.

Maternal heart rate (HR) and SBP values were recorded before the initiation of the Ringer lactate solution (baseline), immediately after the induction of spinal anesthesia, every two minutes until incision, every four minutes from incision to birth and then every five minutes until the operation was concluded. Side effects, such as hypotension, nausea and/or vomiting, bradycardia, shivering, pruritus, tachycardia, or reactive hypertension were also recorded and treated. Umbilical artery and vein pH values were measured for the newborn. The weights of the newborns as well as one-minute and five-minute Apgar scores were recorded. At the conclusion of the operation, bolus, infused and total ephedrine doses were calculated.

Statistical analysis

Data were expressed as mean ± standard deviation (SD), or number (%) of patients, as appropriate. For the statistical analysis, SPSS version 13.0 (SPSS Inc. Illinois) was used. A one-way analysis of variance was used to compare the continuous variables among the groups. If a significant difference was noted, to know which group differs from which others, post hoc Tukey was used. Categorical variables were analyzed using the chi-square test or Fisher exact test, as appropriate. P value of less than 0.05 was considered statistically significant. The Bonferroni Correction was applied for all possible multiple comparisons controlling Type I error.

Results

In the present study, a total of 800 parturients were approached for this study, and 787 parturients were included in the final analysis. Seven parturients (4 of them in Group I, 2 in Group II, and 1 in Group II) failed spinal anesthesia and changed to general anesthesia, and two parturients eventually changed to general anesthesia because the surgery was complicated and lasted for 4 hours. Four parturients were excluded due to insufficient samples of blood collected from the umbilical cord.

No statistically significant differences were observed in the groups in terms of demographical characteristics as well as the data regarding anesthesia and surgery (Table 1). The alterations in SBP and HR during the perioperative period are given in Figure 1 and Figure 2. Intra-group and inter-group differences are also marked on the figures.

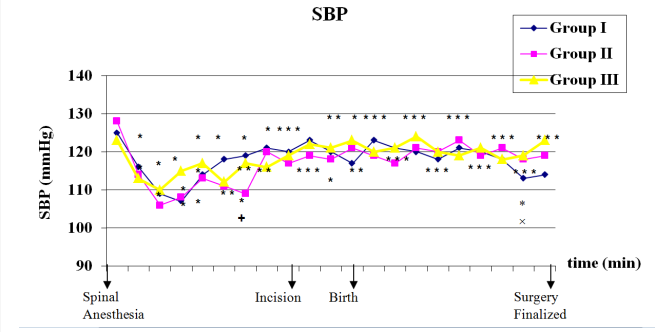

Figure 1: Maternal systolic blood pressure. *P<0.05 *vs.* baseline (Group I), **P<0.05 *vs.* baseline (Group II), ***P<0.05 *vs.* baseline (Group III), +P value <0.05 *vs.* Group I and Group III, ×P value <0.05 *vs.* Group II and Group III.

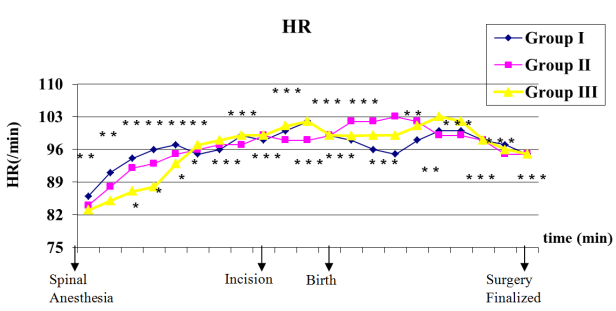

Figure 2: Maternal heart rate. *P<0.05 *vs.* baseline (Group I), **P<0.05 *vs.* baseline (Group II), ***P<0.05 *vs.* baseline (Group III).

Bolus, infusion and total ephedrine doses were significantly lower in Group III when compared with the other groups (P<0.05). There was no significant difference between the three groups regarding the Apgar scores at the 1st or 5th minute, umbilical arterial or venous pH (Table 2).

There was no significant difference of the incidence of side effects, such as hypotension, nausea and/or vomiting, bradycardia, shivering, pruritus, tachycardia, or reactive hypertension (Table 3).

	Group I (n=260)	Group II (n=269)	Group III (n=258)
Age (years)	27.83 ± 4.87	28.35 ± 5.20	29.12 ± 6.47
Weight (kg)	75.54 ± 9.80	78.05 ± 10.10	80,10 ± 9.15
Height (cm)	162.32 ± 5.85	160.54 ± 4.47	159.82 ± 3.85
Gestational age (weeks)	38.75 ± 0.87	39.05 ± 0.92	39.10 ± 1.12
Weight of the newborn (g)	3295.6 ± 345	3157.2 ± 286	3210.4 ± 263
Blockade-skin incision (min)	7.13 ± 1.05	6.75 ± 1.48	6.05 ± 1.16
Blockade-birth (min)	12.30 ± 2.13	11.35 ± 2.15	10.44 ± 2.04
Duration of surgery (min)	50.45 ± 11.15	46.72 ± 13.85	48.88 ± 14.70
Data are represented as mean ± SD.			

Table 1: Demographical and surgical data.

	Group I (n=260)	Group II (n=269)	Group III (n=258)
Maternal data			
Ephedrine bolus dose (mg)	9.85 ± 8.25	8.68 ± 5.95	4.95 ± 4.10*
Ephedrine infusion dose (mg)	16.22 ± 7.55	15.73 ± 6.85	9.84 ± 5.22*
Total ephedrine dose (mg)	26.07 ± 16.39	24.41 ± 12.95	14.79 ± 9.40*
Neonatal data			
Apgar score (1st min)	8.65 ± 0.45	8.28 ± 0.38	8.71 ± 0.57
Apgar score (5th min)	9.30 ± 0.55	9.64± 0.71	9.45 ± 0.63

Umbilical arterial pH	7.29 ± 0.02	7.28 ± 0.03	7.27 ± 0.04
Umbilical venous pH	7.34 ± 0.06	7.31 ± 0.05	7.32 ± 0.08
The ratio of cases with umbilical artery pH value of <7.2 (%)	28 (% 10.76)	25 (% 9.29)	19 (% 7.36)
Data are represented as mean ± SD or number (%). *P value <0.05; *vs.* Group I and Group II.			

Table 2: Ephedrine doses, and neonatal data.

	Group I (n=260)	Group II (n=269)	Group III (n=258)
Hypotension	45 (17.30)	36 (13.38)	30 (11.63)
Nausea and/or vomiting	50 (19.23)	35 (13.01)	25 (9.69)
Bradycardia	30 (11.54)	18 (6.69)	15 (5.81)
Shivering	46 (17.69)	42 (15.61)	32 (12.40)
Pruritus	15 (5.76)	25 (9.29)	31 (12.01)
Tachycardia	28 (10.77)	25 (9.29)	21 (8.14)
Reactive hypertension	20 (7.69)	18 (6.69)	15 (5.81)
Data are expressed as the number and proportion (%) of patients in each group.			

Table 3: Side effects.

Discussion

Spinal anesthesia is commonly preferred over general anesthesia for cesarean section due to its lower mortality and morbidity rates [14]. However, it is known that the most critical problem after spinal anesthesia for cesarean delivery is hypotension. Cyna et al. [2] reviewed trials carried out with a total of 4624 women and reported that 70% of women had been noted with hypotension when no precautions had been taken. Hypotension occurring during spinal anesthesia can have serious implications such as nausea-vomiting and depressed uterine blood flow (fetal acidosis) [15].

Therefore, a number of methods, such as patient position, administering various fluid protocols (coloading or preloading, with crystalloid or colloid), and vasopressors in various modalities (bolus or infusion) or decreasing the dose of the local anesthetic agent used, have been investigated for preventing and treating of hypotension, but none of them alone is not effective for preventing hypertension [2].

Ephedrine, phenylephrine and metaraminol have widely been used to prevent hypotension during spinal anesthesia. Of those, ephedrine has been the most commonly utilized agent since 1982 [2,14]. Ephedrine is a sympathomimetic agent demonstrating both alpha and beta receptor activity, leading to elevated cardiac output and heart rate [15].

In recent years, researches have reported that the use of sympathomimetics along with the various fluids protocols can be an effective method [16-18]. Khooshiden and Heidari [18] compared combination of crystalloid and ephedrine to crystalloid alone. They found that combination of crystalloid and ephedrine was better. Cyna et al. [2] reported that the ephedrine infusion administered with perioperative fluid had been effective in preventing hypotension. Gunusen et al. [16] compared the effects of fluid preload (crystalloid or colloid) and crystalloid co-load plus ephedrine infusion. They reported that the group administered with ephedrine infusion had lower incidence of hypotension and vomiting, while no differences were established between the groups in terms of umbilical artery and vein pH values.

Although ephedrine is an excellent choice in preventing maternal hypotension, its high doses are associated with reactive hypertension, tachycardia and fetal acidosis caused by impaired fetal perfusion [19]. Furthermore, it is slow acting and its effect lasts longer. Therefore, its higher doses may lead to the depletion of presynaptic noradrenaline stores and tachyphylaxis may occur as a result of persistent blockage of adrenergic receptors.

Consequently, ephedrine has been recommended to be administered by infusion by monitoring mean artery pressure values in order to avoid high doses and prevent adverse events in clinical use [2].

In this current study, we administered ephedrine first as a prophylactic bolus dose (0.1 mg/kg), then initiated an infusion to maintain SBP at 80%-110% of the baseline value.

Many articles suggest that the addition of different opioids can enhance local anesthesia and allow the reduction of local anesthetics doses with more stable hemodynamics for cesarean section [1-4]. In recent years, the use of levobupivacaine in combination with opioids has become widespread for spinal anesthesia during cesarean delivery.

Parpaglioni et al. [20] reported a minimum intrathecal levobupivacaine dose of 10.58 mg in cesarean section. Bouvet et al. [11] reported that the ED95 dose of intrathecal levobupivacaine combined with intrathecal morphine 100 mg and intrathecal sufentanil 2.5 mg for elective cesarean delivery anesthesia was 12.9 mg. In their study comparing addition of 5 mg sufentanil and 10 and 20 μg fentanyl to 10 mg levobupivacaine and 10 mg bupivacaine during spinal anesthesia, Bremeric et al. reported that the hemodynamic data of both groups were similar, with no differences regarding side effects. They recommended 10 mg levobupivacaine for parturients undergoing elective cesarean section with spinal anesthesia. Gunusen et al. [13] demonstrated that the addition of 10 μg fentanyl to 10 mg levobupivacaine increased the incidence of hypotension, whereas lower doses of levobupivacaine led to insufficient anesthesia and analgesia.

In light of all these studies, in this study, levobupivacaine was administered at determined doses according to the patient height (10-12 mg), and 15 μg or 25 μg doses of fentanyl was added.

In our study, bolus, infusion and total ephedrine doses were significantly lower in Group III. Although there is no statically significant, hypotension, nausea and/or vomiting, and bradycardia

were more frequent in Group I. We did not see that the negative effects neither of ephedrine nor on maternal and neonatal.

The limitation of this study is that our study is a single center, and it was failure to do follow-up of post-operative pain. The other limitation is that the satisfaction scores could not be assessed neither the patients nor surgeons.

Conclusion

The addition of 25 μg fentanyl to levobupivacaine for cesarean sections reduces the use of ephedrine doses without additional side effects, and adverse neonatal outcomes.

If the levobupivacaine doses as determined by the length of the patients', and the use of the appropriate fluid resuscitation therapy co-administered with an infusion of ephedrine can be used safely for the prevention and the treatment of maternal hypotension.

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