ORIGINAL ARTICLE

Intrathecal low-dose levobupivacaine and bupivacaine combined with fentanyl in a randomised controlled study for caesarean section: blockade characteristics, maternal and neonatal effects

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Abstract

Background: Intrathecal combination of local anaesthetics with opioids produces a synergistic effect without intensifying motor and sympathetic blockades. It also enables successful anaesthesia with use of a low dose of local anaesthetic, which also results in more stable haemodynamics. We compared the characteristics of blockade and maternal–neonatal effects of low-dose levobupivacaine and low-dose bupivacaine combined with fentanyl used in spinal anaesthesia for caesarean section.

Methods: Seventy-two patients undergoing caesarean section with spinal anaesthesia received low-dose 0.5% levobupivacaine (7 mg) plus fentanyl 25 μg (group L) or low-dose 0.5% bupivacaine (7 mg) plus fentanyl 25 μg (group B). The time to achieve sensory blockade of T_6, the maximum spread of sensory blockade, time to S_2 regression, sensorial blockade levels and motor blockade at the beginning and end of surgery were the parameters assessed. Haemodynamic parameters (systolic and diastolic blood pressures, heart rate), neonatal effects (APGAR scores at 1. and 5. min, umblical-cord gas analyses) were recorded, as were side-effects.

Results: The qualities of sensory blockade were similar and clinically effective in both groups. Significantly more patients had complete motor blockade in group B than in group L at the beginning and end of surgery. Haemodynamic and neonatal parameters were similar between the two groups. Pruritis was a common side-effect in both groups.

Conclusion: In spinal anaesthesia for caesarean section, using low-dose levobupivacaine in combination with fentanyl elicits effective sensorial blockade and less motor blockade with similar haemodynamic and neonatal effects than usage of low-dose bupivacaine in combination with fentanyl. Hippokratia 2013; 17 (3): 262-267

Keywords: Local anaesthetics, levobupivacaine, bupivacaine, fentanyl, caesarean section

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Introduction

Spinal anaesthesia for caesarean section (CS) is a widely preferred type of regional anaesthesia because of its ease of placement and rapid onset. Careful prevention of potential complications must be sought to maintain a high safety profile because all procedures affect the mother and newborn. Unwanted cephalad extensions of the blockade occur as a result of physiological changes in epidural veins and cerebrospinal fluid (CSF) in pregnant women[1-3]. CS is also a relatively short-duration procedure that is often followed by early mobilisation of the patient, which increases the potential for late extension of the blockade.

Levobupivacaine is the pure S(–) enantiomer of racemic bupivacaine. It has a similar clinical profile and a lower potency for motor blockade but an enhanced safety profile when compared with bupivacaine: this is a major advantage in regional anesthesia and analgesia (especially in obstetrics)[4-7]. Levobupivacaine shows a lower risk of toxicity in the cardiovascular sysytem and central nervous system (CNS) than bupivacaine[8,9].

Neuraxial anaesthesia can be undertaken using local anaesthetics at different doses and baricity. Intrathecal opioids added to local anaesthetics produce a well-documented synergistic effect without intensifying motor and sympathetic blockades, and enable successful anaesthesia with the use of a low-dose local anaesthetic which results in more stable haemodynamics[10-12].

The aim of the present study was to evaluate the clinical effectiveness and blockade quality of low-dose levobupivacaine and to compare it with low-dose bupivacaine when they are combined with fentanyl in CS. The primary endpoint was the difference in motor blockade between the two groups. Other endpoints were the differences between the two groups with respect to the characteristics of sensory blockade, maternal haemodynamic and neonatal effects, and side effects.

Materials and Methods

The Ethics Committee of Sisli Etfal Training and Research Hospital (Approval date: 27.10.2008, number: 63) approved this prospective randomised, double-blind study. All patients provided written informed consent to participate in this study.

We studied 72 women (age, 18–42 years) of American Society of Anesthesiologists (ASA) physical status I–II who required elective CS at gestation >36 weeks for delivery of a singleton baby at term. The exclusion criteria were patients who would not accept spinal anaesthesia and those with: abnormal coagulation profiles; known hypersensitivity to amide local anaesthetics and/or opioids; skin infections; cardiac disease; hypertension; diabetes mellitus.

All patients were premedicated with intravenous (i.v.) 50 mg of ranitidine and 10 mg of metoclopyramide 2 h before surgery. Thirty minutes before the induction of spinal anaesthesia, we started the intravenous infusion of 10 $ml.kg^{-1}$ of crystalloid solution (Isolyte S™) to provide volume preload. Patients were randomised into two groups via a sealed-envelope method. A wedge was placed under the right hip of the women during the spinal anaesthesia procedure. In both groups, spinal anesthesia was performed by one anaesthesiologist using the same technique with the patient in the lateral position using a midline approach at L_3–L_4 or L_4–L_5 with a 25-G Quincke needle. After free flow of CSF was observed, patients in the levobupivacaine group (group L) received 7 mg (1.2 ml) 0.5% levobupivacaine + 25 μg fentanyl (0.5 ml), and the bupivacaine group (group B) received 7 mg 0.5% bupivacaine (1.2 ml) + 25 μg fentanyl (0.5 ml) at an injection interval of ≈30 s. Patients were moved to the supine lateral tilt position immediately after administration of the spinal blockade. The anaesthesiologist who performed spinal anaesthesia was blinded to the study groups. The study solutions used in the present study were prepared by another anaesthesiologist and used at room temperature (23°C).

All patients underwent non-invasive monitoring of systolic blood pressure (SBP) and diastolic blood pressure (DBP), measurement of blood oxygen saturation (SpO_2) using pulse oximetry, and electrocardiography for heart rate (HR) with a PETAS KMA-175 Monitor (PETAS, Istanbul, Turkey). A dedicated observer recorded these parameters before spinal anaesthesia, every 1 min for 15 min after spinal anaesthesia, every 3 min thereafter for 30 min, and every 5 min until the end of surgery. Supplementary oxygen (2 $ml.min^{-1}$) was given to all patients via a face mask.

Blockade characteristics were assessed by testing for sensory and motor blockade. Sensory blockade was monitored with the pin-prick test at 1-min intervals for the first 5 min, then every 2 min for 20 min, until the end of surgery. Surgery was allowed if the upper dermatome to the level of the loss of discrimination to a pin-prick was at least T_6. The time to achieve sensory blockade of T_6, maximum spread of sensory blockade, and time to S_2 regression (as well as sensorial blockade levels at the beginning and end of surgery) were recorded. Motor blockade was assessed based on a modified Bromage scale (0 = no paralysis, able to flex hips/knees/ankles; 1 = able to move knees, unable to raise extended legs; 2 = able to flex ankles, unable to flex knees; 3 = unable to move any part of the lower limbs) at 1-min intervals for the first 5 min, then every 2 min for 20 min, until the end of surgery. Bromage scores at the beginning and end of surgery were noted.

Perioperative maternal hypotension (SBP <20% of baseline or 90 mmHg) or episodes of bradycardia (heart rate <50 beats/min) were recorded and treated with boluses of fluid, or 5 mg ephedrine or 0.5 mg atropine given *via* the intravenous route. Any other side-effects (e.g. respiratory depression, nausea, vomiting and pruritus) were recorded.

Newborns were evaluated with APGAR scores at 1 min and 5 min by the same neonatologist and with umbilical-cord blood gas values.

Statistical analyses

Sample size was calculated to provide 80% power and $\alpha = 0.05$ to detect a 30-min difference according to the duration of motor blockade between the two groups. Statistical analyses were conducted using the Number Cruncher Statistical System 2007 (NCSS, Kaysville, UT, USA). Independent-sample *t*-tests for parametric data, Mann-Whitney U test for non-parametric data, Fisher's exact test and chi-square tests for frequency data were undertaken. $p<0.05$ was considered significant. Data are the mean ± standard deviation (SD), median (range), or the number of patients (n).

Results

There were no significant differences with regard to mean values of age, weight and gestational age among women as well as the duration of surgery in the two groups (Table 1). Values of SBP, DBP and heart rates were comparable and almost stable during surgery in both groups (Table 2).

The sensory and motor blockades characteristics' are

Table 1: Patients' demographics and duration of surgery in Levobupivacaine and Bupivacaine groups.

Variables	Group L	Group B
Age (years)	29.06 ± 6.2	28.61 ± 5.67
Weight (kilograms)	76.47 ± 10	78.67 ± 13.53
Gestational age (months)	37.4 ± 1.07	37.65 ± 0.82
Duration of surgery (minutes)	45.56 ± 11.13	48.61 ± 8.99

Data are expressed as Mean ± Standard Deviation (SD), Group L: Group Levobupivacaine, Group B: Group Bupivacaine.

Table 2: Sensorial block characteristics' of Levobupivacaine and Bupivacaine groups.

Variables	Group L	Group B
Time to achieve sensory block of T_6 (minutes)	8.33 ± 1.24	7.8 ± 1.06
Max spread of sensory block *	T5 (T4-T6)	T4 (T4-T6)
Time to S_2 regression (minutes)	69.05 ± 4.61	66.69 ± 5.48

Data are expressed as Mean ± Standard Deviation (SD), *: median (range), Group L: Group Levobupivacaine, Group B: Group Bupivacaine.

Table 3: Sensorial block level and motor block degree of Levobupivacaine and Bupivacaine groups.

Variables	Group L	Group B
Sensorial block level at the beginning of the surgery (T4 / T4-T6 / T6)	14 (38.9) / 1 (2.8) / 21 (58.3)	20 (55.6) / 3 (8.3) / 13 (36.1)
Sensorial block level at the end of the surgery (T4 / T4-T6 / T6)	5 (13.9) / 8 (22.2) / 23 (63.9)	10 (27.8) / 6 (16.7) / 17 (47.2)
Bromage scores at the beginning of the surgery (0 - 1/2/3)	0 - 0 / 33 (91.7) / 3 (8.3)	0 - 0 / 26 (72.2) / 10 (27.8) *
Bromage scores at the end of the surgery (0 - 1/2/3)	0 - 17 (47.2) / 19 (52.8) / 0	0 - 9 (25) / 21 (58,3) / 6 (16.7) *

Data are expressed as number of patients (n) - %, *: $p<0.05$ compared with Group L, Group L: Group Levobupivacaine, Group B: Group Bupivacaine.

shown in Tables 3 and 4. The qualities of sensory blockade were similar and clinically effective in both groups (Tables 3 and 4). At the onset of surgery, 10 patients in group B and 3 patients in group L had a Bromage score of 3. At the end of surgery, 6 patients in group B had a Bromage score of 3, but none of the patients had a Bromage score of 3 in group L. These differences were significant ($p=0.032$ and $p=0.014$, respectively) (Table 4).

The number of patients having episodes of hypotension and bradycardia were comparable between the two groups. The prevalence of hypotension was 30,5% in group L and 25% in group B. Three patients in group L and 5 patients in group B had an episode of bradycardia. Patients responded to intravenous boluses of fluid and ephedrine treatment. Atropine was used in 1 patient in group B. A total of 11.1% of patients in group L and 13.8% of patients in group B had pruritis.

Neither APGAR scores at 1 min and 5 min (Table 5) nor umblical-cord gas analyses (Table 5) had any significant changes between the two groups. These data were within physiological ranges in group L and group B.

Discussion

In this present study, low-dose levobupivacaine and low-dose bupivacaine combined with fentanyl produced a similar quality of sensorial blockade as well as maternal haemodynamic and neonatal effects in CS under spinal anaesthesia. Combination of fentanyl with low-dose levobupivacaine induced less motor blockade than low-dose bupivacaine when administered via the intrathecal route.

The efficacy of neuraxial local anaesthetics is enhanced by the addition of intrathecal opioids. Such combinations are usually associated with improved anaesthesia and analgesia. It also allows the use of very low doses of local anaesthetic, which contributes to more stable haemodynamics[13-15]. In the study by Parpaglioni et al[16], the addition of sufentanil via the intrathecal route reduced the minimum local anaesthetic dose (MLAD) of spinal levobupivacaine and ropivacaine. It did not affect their potency ratio significantly, and resulted in enhanced spinal anaesthesia. Intrathecal fentanyl added to low-dose local anaesthetics produces a synergistic effect without increasing sympathetic blockade or delaying discharge from hospital[17].

Lee et al study[18] was published as the first study on the intrathecal use of 0.5% levobupivacaine with fentanyl. They concluded that 2.3 ml of 0.5% levobupivacaine with fentanyl (15 μg) was as effective as 2.6 ml of 0.5% levobupivacaine alone in spinal anaesthesia for urological surgery. Significant differences were not observed

Table 4: Haemodynamic parameters of the Levobupivacaine and Bupivacaine groups.

Time	**SBP** (mmHg)		**DBP** (mmHg)		**HR** (bpm)	
	Group L	**Group B**	**Group L**	**Group B**	**Group L**	**Group B**
Bazal	123.97 ± 15.05	125.89 ± 14.98	73.44 ± 11.16	73.92 ± 9.63	90.64 ± 15.39	91.94 ± 11.05
After preloading	128.42 ± 13.55	130.67 ± 17.5	76.25 ± 11.27	78.31 ± 13.83	94.86 ± 14.63	95.06 ± 11.84
After spinal anaesthesia	120.72 ± 11.97	125.78 ± 17.56	69.44 ± 14.22	76.08 ± 17.54	97.94 ± 16.28	98.36 ± 15.52
1.min ASpA	115.61 ± 12.45	119.39 ± 13.79	66.94 ± 13.02	71.31 ± 14.48	98.72 ± 17.8	97.92 ± 17.85
2.min ASpA	111.89 ± 17.69	116.06 ± 18.15	66 ± 14.93	68.89 ± 17.66	97.69 ± 18.43	95.03 ± 19.67
3.min ASpA	107.42 ± 16.91	114.94 ± 21.04	60.69 ± 15.68	66.06 ± 16.88	95.72 ± 19.26	101.94 ± 24.29
4.min ASpA	104.61 ± 15.37	111.56 ± 24.72	59.25 ± 14.92	67.03 ± 19.27	96.36 ± 19.84	101.81 ± 22.77
5.min ASpA	101.58 ± 22.94	107.25 ± 22.73	58.06 ± 14.31	63.44 ± 15.88	95.61 ± 20.34	101.03 ± 21.34
10.min ASpA	108.56 ± 20.11	109.03 ± 24.21	59.14 ± 14.07	62.53 ± 17.34	94.36 ± 14.9	97.25 ± 17.16
20.min ASpA	115.53 ± 14.64	116.5 ± 15.92	60.69 ± 12.28	64 ± 14.07	92.69 ± 13.5	96.42 ± 15.31
30.min ASpA	115.29 ± 14.36	119.42 ± 17.6	62.89 ± 11.33	65.06 ± 16.57	93.28 ± 14.22	94.43 ± 14.56
60.min ASpA	119 ± 8.8	123.6 ± 12.92	62.72 ± 10.83	64.78 ± 15.67	80.33 ± 14.83	82.5 ± 5.32

Data are expressed as Mean ± Standard Deviation (SD), Group L: Group Levobupivacaine, Group B: Group Bupivacaine, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, bpm: beat per minute, ASpA: after spinal anaesthesia.

Table 5: APGAR Scores and Blood gas analyses (of the newborns from umblical cord) in Levobupivacaine and Bupivacaine groups.

		Group L	**Group B**
APGAR Scores	**1.min**	8.36 ± 0.49	8.56 ± 0.50
	5.min	9.42 ± 0.50	9.61 ± 0.49
Blood gas analyses	**pH**	7.3 ± 0.05	7.29 ± 0.05
	PCO_2	44.83 ± 7.44	46.65 ± 7.06
	PO_2	22.72 ± 7.03	22.07 ± 6.08
	HCO_3	21.6 ± 2.25	21.91 ± 2.04

Data are expressed as Mean ± Standard Deviation (SD), Group L: Group Levobupivacaine, Group B: Group Bupivacaine.

between the two groups with respect to haemodynamic changes and the quality of sensory and motor blockades. In a recent study by Cuvas et al[19], addition of fentanyl 15 μg (0.3 ml) to 0.5% levobupivacaine (2.2 ml) produced a shorter duration of motor blockade than pure 0.5% levobupivacaine (2.5 ml solution) in spinal anaesthesia, whereas both regimens were effective for transurethral resections. Akcaboy et al[20] and Erbay et al[21] compared the effectiveness of low doses of 0.5% levobupivacaine and 0.5% bupivacaine (5 mg and 7.5 mg, respectively) when combined with fentanyl (25 μg). These regimens were shown to be effective in spinal anaesthesia for transurethral resection of the prostate (TURP) if used in higher doses. In both studies, levobupivacaine plus fentanyl resulted in effective sensorial blockade with less motor blockade than bupivacaine plus fentanyl.

Studies have demonstrated the effect of a combination of local anaesthetic and opioid for regional anaesthesia in CS[5,22-25]: different results with regard to the characteristics of sensorial blockade between levobupivacaine and bupivacaine have been observed. However, most of these studies have concluded that there was less motor blockade with levobupivacaine than with bupivacaine. The only study comparing the combination of fentanyl and low-dose levobupivacaine *versus* bupivacaine in CS is that of Bremerich et al[7]. They compared fixed doses of intrathecal hypertonic 0.5% levobupivacaine (10 mg) and 0.5% bupivacaine (10 mg) combined with intrathecal fentanyl (10 and 20 μg), or sufentanil (5 μg) in terms of the characteristics of sensory and motor blockade in parturients undergoing elective CS with spinal anaesthesia. In that study, levobupivacaine produced a significantly shorter and less pronounced motor blockade than racemic bupivacaine regardless of the type and dose of opioid added. In the present study, we preferred to use 7 mg of 0.5% levobupivacaine and 0.5% bupivacaine as a low dose in combination with 25 μg fentanyl for spinal anaesthesia for patients undergoing CS. Levobupivacaine

produced adequate and comparable sensorial blockade with bupivacaine but induced less motor blockade than bupivacaine, a result consistent with previous studies.

Gunusen et al[24], concluded that levobupivacaine (7.5 mg) combined with fentanyl (15 µg) was suitable for combined spinal-epidural anaesthesia in elective CS. In other studies focusing on the optimal dose of levobupivacaine in combination with opioids, the median effective dose (ED_{50}) was 6.2 mg and the dose required for the desired effect in 95% of the population exposed to it (ED_{95}) was 12.9 mg in the study by Bouvet et al[25]. The MLAD was 4.73 mg in the study by Parpaglioni et al[16] for CS. In the present study, a low-dose of levobupivacaine (7 mg), which was in-between the doses mentioned above, combined with fentanyl produced effective anaesthesia for CS.

In the present study, decreases in SBP and DBP as well as changes in heart rate were in acceptable ranges. Erdil et al[26] noted, in spinal anaesthesia, better haemodynamic stability associated with low-dose levobupivacaine plus fentanyl compared with that seen with low-dose bupivacaine plus fentanyl. Coppejans et al[22] compared equipotent doses of bupivacaine, levobupivacaine and ropivacaine combined with sufentanil in patients undergoing elective CS with combined spinal–epidural anaesthesia. They found that haemodynamic values were comparable between the three groups (although a trend towards better SBPs and a lower prevalence of severe hypotension were noticed with levobupivacaine). In the present study (and not in accordance with the studies above), maternal haemodynamic changes were comparable between levobupivacaine and bupivacaine.

Hypotension is a frequent side-effect that can be seen in 18-84% in parturients during spinal anaesthesia[27-29]. In pregnant women, engorgement of epidural veins from aortocaval compression with displacement of CSF may contribute to unwanted cephalad extensions of the blockade, which can be associated with an increased risk of hypotension. In the present study, the relatively lower prevalence of hypotension in both groups was thought to be a result of volume preloading before spinal anaesthesia and lowering of the local anaesthetic dose in combination with an opioid. Pruritis was also recorded in both groups in the present study. Pruritis is a common adverse effect of intrathecal use of fentanyl which has been reported by other investigators[20,30].

In the present study, the neonatal effects of levobupivacaine and bupivacaine in combination with fentanyl were similar. In a study by Lirk et al[31], intrathecal bupivacaine, ropivacaine and levobupivacaine used for CS produced similar effects on neonates (as evaluated by APGAR scores and the pH of arteries in the umbilical cord). In another study[22], after combination of sufentanil with bupivacaine, ropivacaine and levobupivacaine, Apgar scores and the pH of arteries in the umbilical cord in neonates did not differ: our results are consistent with that study.

One limitation of our study is that not evaluating the time to full recovery of sensory block, which can also be related with analgesia time or time to first analgesic request. In the literature there is conflicting results of this data showing shorter time to full recovery of sensory block[21] or longer time to first analgesic request[5] with intrathecal bupivacaine compared to levobupivacaine in combination with opioids. This can be assess in a future study.

In conclusion: in CS, spinal anaesthesia with 7 mg levobupivacaine plus 25 µg fentanyl provided less motor blockade with effective sensorial blockade compared with that seen with 7 mg bupivacaine plus 25 µg fentanyl. Such induced motor blockade offers the advantage of early mobilisation. Both agents produced similar maternal and neonatal effects with a negligible side-effects.

Conflict of interest

None.

References

1. Barclay DL, Renegar OJ, Nelson EW Jr. The influence of inferior vena cava compression on the level of spinal anesthesia. Am J Obstet Gynecol. 1968; 101: 792-800.
2. Jawan B, Lee JH, Chong ZK, Chang CS. Spread of spinal anaesthesia for caesarean section in singleton and twin pregnancies. Br J Anaesth. 1993; 70: 639-641.
3. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Igarashi T. Soft tissue anatomy within the vertebral canal in pregnant women. Br J Anaesth. 1996; 77: 153-156.
4. Vercauteren MP, Hans G, De Decker K, Adriaensen HA. Levobupivacaine combined with sufentanil and epinephrine for intrathecal labor analgesia: a comparison with racemic bupivacaine. Anesth Analg. 2001; 93: 996-1000.
5. Gautier P, De Kock M, Huberty L, Demir T, Izydorczic M, Vanderick B. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for Caesarean section. Br J Anaesth. 2003 ; 91: 684-689.
6. Camorcia M, Capogna G, Berritta C, Columb MO. The relative potencies for motor block after intrathecal ropivacaine, levobupivacaine, and bupivacaine. Anesth Analg. 2007; 104: 904-907.
7. Bremerich DH, Fetsch N, Zwissler BC, Meininger D, Gogarten W, Byhahn C. Comparison of intrathecal bupivacaine and levobupivacaine combined with opioids for Caesarean section. Curr Med Res Opin. 2007; 23: 3047-3054.
8. McClellan KJ, Spencer CM. Levobupivacaine. Drugs. 1998; 56: 355-362.
9. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1998; 46: 245-249.
10. Ben-David B, Solomon E, Levin H, Admoni H, Goldik Z. Intrathecal fentanyl with small-dose dilute bupivacaine: better anesthesia without prolonging recovery. Anesth Analg. 1997; 85: 560-565.
11. Kuusniemi KS, Pihlajamäki KK, Pitkänen MT, Helenius HY, Kirvelä OA. The use of bupivacaine and fentanyl for spinal anesthesia for urologic surgery. Anesth Analg. 2000; 91: 1452-1456.
12. Ben-David B, Frankel R, Arzumonov T, Marchevsky Y, Volpin G. Minidose bupivacaine-fentanyl spinal anesthesia for surgical repair of hip fracture in the aged. Anesthesiology. 2000; 92: 6-10.
13. Choi DH, Ahn HJ, Kim MH. Bupivacaine-sparing effect of fentanyl in spinal anesthesia for cesarean delivery. Reg Anesth Pain Med. 2000; 25: 240-245.
14. Ben-David B, Miller G, Gavriel R, Gurevitch A. Low-dose

bupivacaine-fentanyl spinal anesthesia for cesarean delivery. Reg Anesth Pain Med. 2000; 25: 235-239.
15. Chen X, Qian X, Fu F, Lu H, Bein B. Intrathecal sufentanil decreases the median effective dose (ED50) of intrathecal hyperbaric ropivacaine for caesarean delivery. Acta Anaesthesiol Scand. 2010; 54: 284-290.
16. Parpaglioni R, Baldassini B, Barbati G, Celleno D. Adding sufentanil to levobupivacaine or ropivacaine intrathecal anaesthesia affects the minimum local anaesthetic dose required. Acta Anaesthesiol Scand. 2009; 53: 1214-1220.
17. Goel S, Bhardwaj N, Grover VK. Intrathecal fentanyl added to intrathecal bupivacaine for day case surgery: a randomized study. Eur J Anaesthesiol. 2003; 20: 294-297.
18. Lee YY, Muchhal K, Chan CK, Cheung AS. Levobupivacaine and fentanyl for spinal anaesthesia: a randomized trial. Eur J Anaesthesiol. 2005; 22: 899-903.
19. Cuvas O, Basar H, Yeygel A, Turkyilmaz E, Sunay MM. Spinal anesthesia for transurethral resection operations: levobupivacaine with or without fentanyl. Middle East J Anesthesiol. 2010; 20: 547-552.
20. Akcaboy EY, Akcaboy ZN, Gogus N. Low dose levobupivacaine 0.5% with fentanyl in spinal anaesthesia for transurethral resection of prostate surgery. J Res Med Sci. 2011; 16: 68-73.
21. Hakan Erbay R, Ermumcu O, Hanci V, Atalay H. A comparison of spinal anesthesia with low-dose hyperbaric levobupivacaine and hyperbaric bupivacaine for transurethral surgery: a randomized controlled trial. Minerva Anestesiol. 2010; 76: 992-1001.
22. Coppejans HC, Vercauteren MP. Low-dose combined spinal-epidural anesthesia for cesarean delivery: a comparison of three plain local anesthetics. Acta Anaesthesiol Belg. 2006; 57: 39-43.
23. Guasch E, Gilsanz F, Díez J, Alsina E. [Maternal hypotension with low doses of spinal bupivacaine or levobupivacaine and epidural volume expansion with saline for cesarean section]. Rev Esp Anestesiol Reanim. 2010; 57: 267-274.
24. Gunusen I, Karaman S, Sargin A, Firat V. A randomized comparison of different doses of intrathecal levobupivacaine combined with fentanyl for elective cesarean section: prospective, double-blinded study. J Anesth. 2011; 25: 205-212.
25. Bouvet L, Da-Col X, Chassard D, Daléry F, Ruynat L, Allaouchiche B, et al. ED_{50} and ED_{95} of intrathecal levobupivacaine with opioids for Caesarean delivery. Br J Anaesth. 2011; 106: 215-220.
26. Erdil F, Bulut S, Demirbilek S, Gedik E, Gulhas N, Ersoy MO. The effects of intrathecal levobupivacaine and bupivacaine in the elderly. Anaesthesia. 2009; 64: 942-946.
27. Siddik SM, Aouad MT, Kai GE, Sfeir MM, Baraka AS. Hydroxyethylstarch 10% is superior to Ringer's solution for preloading before spinal anesthesia for Cesarean section. Can J Anaesth. 2000; 47: 616-621.
28. Yorozu T, Morisaki H, Kondoh M, Zenfuku M, Shigematsu T. Comparative effect of 6% hydroxyethyl starch (containing 1% dextrose) and lactated Ringer's solution for cesarean section under spinal anesthesia. J Anesth. 2002; 16: 203-206.
29. Ko JS, Kim CS, Cho HS, Choi DH. A randomized trial of crystalloid versus colloid solution for prevention of hypotension during spinal or low-dose combined spinal-epidural anesthesia for elective cesarean delivery. Int J Obstet Anesth. 2007; 16: 8-12.
30. Hamber EA, Viscomi CM. Intrathecal lipophilic opioids as adjuncts to surgical spinal anesthesia. Reg Anesth Pain Med. 1999; 24: 255-263.
31. Lirk P, Kleber N, Mitterschiffthaler G, Keller C, Benzer A, Putz G. Pulmonary effects of bupivacaine, ropivacaine, and levobupivacaine in parturients undergoing spinal anaesthesia for elective caesarean delivery: a randomised controlled study. Int J Obstet Anesth. 2010; 19: 287-292.