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Is there an advantage in using low-dose intrathecal bupivacaine for cesarean section?

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Abstract
Purpose. Spinal anesthesia for cesarean section is associated with a high incidence of maternal hypotension. The aim of this study was to assess the efficacy of low-dose bupivacaine with fentanyl to reduce the incidence of hypotension in spinal anesthesia for cesarean section.
Methods. Forty pregnant women undergoing elective cesarean section were randomly allocated to two groups; those receiving 10 mg bupivacaine to group B (n = 20) and those receiving 4 mg bupivacaine plus 25 µg fentanyl to group BF (n = 20); the agents were given intrathecally with patients in the sitting position, with a combined spinal-epidural technique.
Results. Sensory block was adequate for surgery in all patients. Hypotension occurred in all patients in group B (100%) and in 15 patients in group BF (75%). The incidence of hypotension, number of ephedrine treatments, and need for ephedrine were significantly greater in group B than group BF. Three patients in group BF required i.v. fentanyl supplementation after delivery. In 1 of these patients, i.v. fentanyl was not adequate, and epidural supplementation of 1% lidocaine was required.
Conclusion. The development of hypotension after spinal block in subjects undergoing cesarean section was not prevented despite low-dose (4 mg) bupivacaine plus 25 µg fentanyl, but the severity of maternal hypotension, and the number of ephedrine treatments and the total dose of ephedrine were decreased.

Key words Analgesics, fentanyl · Local anesthetics, bupivacaine · Anesthetic techniques, spinal · Cesarean section · Complication, hypotension

Introduction

Spinal anesthesia for cesarean section is associated with a high incidence of maternal hypotension. The commonly used methods to prevent or treat such hypotension include preloading with fluids, avoidance of aortocaval compression, and administration of vasopressor drugs [1,2].

The combination of intrathecal fentanyl with bupivacaine has been shown to improve the quality of spinal anesthesia for cesarean delivery without untoward effects. The use of intrathecal fentanyl provided a more intense sensory block and allowed lower bupivacaine doses. Limiting the bupivacaine dose has been advocated, with the goals of decreasing maternal hypotension, vasopressor requirements, nausea, and time to discharge from the post-anesthesia care unit (PACU) and improving maternal satisfaction [3].

The present study was designed to evaluate the efficacy of reducing the bupivacaine dose with the addition of fentanyl in spinal anesthesia for cesarean section. Therefore, we conducted a prospective, double-blinded, controlled study in which mothers were allocated randomly to two groups, bupivacaine or low-dose bupivacaine with fentanyl. Our hypothesis predicted that administration of low-dose bupivacaine with fentanyl would lead to a decrease in the incidence of maternal hypotension. The secondary outcome measures we compared were sensory block, neonatal outcome, and necessity for vasopressor treatment.

Patients and methods

The approval of the institutional Human Studies Committee was given for the study, and signed written informed consent was obtained from all participating patients. Patients with diabetes, infection at the injection site, pregnancy-induced hypertension, hypersensitivity to amide local anesthetics or fentanyl, mental disturbance, coagulation disorder, or neurologic disease were excluded from the study.

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All patients were premedicated with oral sodium citrate (30 ml) and i.v. metoclopramide (10 mg) before arrival at the operating room. Electrocardiogram, noninvasive blood pressure, and peripheral oxygen saturation were monitored, and baseline values of systolic arterial pressure (SAP; mmHg), and heart rate (HR; beats·min^{-1}) were calculated as the mean of three successive measurements taken at intervals of 1 min that had a difference of no more than 10%. All patients had an intravenous catheter inserted in a peripheral arm vein and 500 ml lactated Ringer's solution was administered 15 min before anesthesia. Based on a computer-generated random sequence, 40 patients were allocated randomly to two groups. The patients in group B ($n = 20$) received 10 mg of plain bupivacaine 0.5% intrathecally, and those in group BF ($n = 20$) received 4 mg of plain bupivacaine plus 25 μg of fentanyl, also intrathecally. To make a total volume of 2 ml, normal saline was added to the spinal anesthetic solution in group BF. The drugs given intrathecally were prepared by an investigator and administered by a second investigator who remained blinded to the contents. The patients were also blinded to the study drugs that had been administered to them.

For anesthesia, a combined spinal-epidural set (Espocan; B. Braun, Melsungen, Germany) was used, with the patient in the sitting position. By using an 18-gauge Tuohy needle and the loss of resistance to air technique, the epidural space was identified at the L2–3 or L3–4 interspace. Then, a 27-gauge spinal needle was passed through the epidural needle, and 2 ml of the study solution prepared previously by another investigator was injected intrathecally, in a double-blinded manner, over a period of 10 s. The direction of the needle aperture was cranial during the injection. The spinal needle was then removed and an epidural catheter was inserted 2.5–3 cm into the epidural space and secured with tape, but no medication was injected via this catheter. The patient was then placed in the supine position with 15° left table tilt. The table was returned to an almost horizontal position before the skin incision was made.

Blood pressure and heart rate were monitored every 2 min until the baby was delivered and then every 5 min until completion of surgery. Hypotension (SAP < 90 mmHg or 30% decrease from the baseline) and bradycardia (HR < 45 beats·min^{-1}) were treated with intravenous bolus of ephedrine 5 mg i.v. Maternal hypotension, number of ephedrine treatments, and the total dose of ephedrine used for each patient were recorded.

Sensory block was tested frequently by pinprick until the block reached T6, when surgical incision was allowed. After the sensory block reached the level of T6, the level of sensory block was measured at 2-min intervals during the first 10 min and then at 5-min intervals during the operation, and the peak level of sensory block and time to peak sensory level were also recorded. If a bilateral T6 sensory level was not attained within 15 min after the time of intrathecal drug administration, epidural supplementation would be given; this situation was accepted as anesthesia failure, and the patient would be excluded from the study. The degree of motor block was assessed by using a modified Bromage scale (0, no paralysis; 1, unable to raise the extended leg; 2, unable to flex knee; 3, unable to flex ankle). The legs of the patient were not fastened and the motor block was measured at 5-min intervals during the operation. When motor blockade reached the maximum level and remained unchanged during 20 min, the maximum Bromage scale was recorded. The sedation level was recorded, using the Ramsay sedation scale, at 5-min intervals from the beginning of spinal anesthesia until the two-segment regression of sensory block was determined, and the maximum sedation scores of the patients were taken for statistical analysis (1, anxious, agitated, restless; 2, eyes open, cooperative, oriented, tranquil; 3, patient drowsy but responsive to commands; 4, patient asleep but with a brisk response to a light glabellar tap or loud auditory stimulus; 5, patient asleep with a sluggish response to a light glabellar tap or loud auditory stimulus; 6, patient asleep with no response). After the operation, the sedation score and the level of sensory block were measured at 5-min intervals during the postoperative period until the two-segment regression of sensory block was determined.

The surgical technique was uniform in all patients and included exteriorization of the uterus. Pain was evaluated with a 10-cm linear visual analog scale (VAS), with 0 corresponding to no pain and 10 to the worst pain imaginable. The use of the VAS was explained to each patient before surgery. Pain evaluation was carried out by asking about the patient's pain state frequently during the operation. When the VAS exceeded 3 and the patient complained of pain, firstly fentanyl 50 μg i.v. was given. If pain had still continued, 7 ml of 1% lidocaine would be administered epidurally, but the patient would not be excluded from the study.

Intraoperative nausea, vomiting, pruritus, shivering, and respiratory depression (respiratory rate per minute < 8 or Sp_{O_2} < 92 percent) were recorded when the side effects occurred. After delivery, the Apgar scores were assessed at 1 and 5 min. On arrival in the postanesthesia care unit (PACU), sensory level was assessed by pinprick; the time required from the spinal injection until two-segment regression was recorded. Also, patients were asked about their satisfaction with the anesthetic (on a satisfaction scale of 0, very bad; 1, bad; 2, good; 3, very good).

Power analysis revealed that 20 cases were required for each group for an α level of 0.05 and a β level of 0.1 to show a decrease in the incidence of hypotension from 94% to 50%, as was shown in the study by Ben-David et al. [3]. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (release 9.0, Standard Version; SPSS, Chicago, IL, USA). Demographic data, hemodynamic variables, spinal injection-to-delivery time, duration of surgery, and two-segment regression times were analyzed using analysis of variance. The Kruskal-Wallis test was used to analyze the Bromage, sedation, and Apgar scores. The χ^2 test was used to compare the frequency of side effects. Data were expressed as means (SD), medians [ranges], or numbers (percentages) as appropriate, and P values of less than 0.05 were interpreted as statistically significant.

Results

The two groups were comparable with respect to age, height, weight, parity, gestational age, spinal injection-to-delivery time, and duration of surgery (Table 1). Sufficient sensory blockade (T6 or higher) was obtained in all patients. Three patients in group BF required i.v. fentanyl supplementation after delivery. In one of these patients, i.v. fentanyl was not adequate, and epidural supplementation with 7 ml of 1% lidocaine was required and given via the epidural catheter. This dose was enough to complete the operation without pain. There was no statistically significant difference with regard to i.v. fentanyl administration. Two-segment regression of the sensory block was significantly longer in group B. Motor block was significantly lower in group BF compared with group B. Hypotension occurred in all patients in group B (100%) and in 15 patients in group BF (75%). The incidence of hypotension, number of ephedrine treatments, and total dose of ephedrine were all significantly lower in group BF (Table 2). Apgar scores at 1 and 5 min were similar in the two groups. There were no significant differences in maternal satisfaction with anesthesia between the two groups (Table 2). The incidence of pruritus was significantly higher in group BF, and the incidences of nausea and vomiting were

Table 1. Physical characteristics of patients, spinal block-to-delivery time, and duration of surgery

	Group B (n = 20)	Group BF (n = 20)
Age (years)	28.15 (4.9)	27.25 (6.3)
Weight (kg)	79.5 (7.7)	79.4 (5.3)
Height (cm)	161.9 (2.6)	161.3 (1.8)
Primipara/Multipara	3/17	2/18
Gestational age (weeks)	37.7 (0.9)	37.4 (0.6)
Spinal block-to-delivery time (min)	8.45 (1.5)	9.0 (1.3)
Duration of surgery (min)	39.6 (11.3)	41.4 (13.4)

Values are means (SD) or n

Table 2. Study results

	Group B (n = 20)	Group BF (n = 20)
Time of block to T6 (min)	2.45 (1.05)	2.4 (1.09)
Peak sensory level	T2 [T1–T4]	T2 [T2–T6]
Time to peak sensory level (min)	5.3 (1.87)	6.8 (4.3)
Two-segment regression (min)	59.8 (17.9)	42.3 (14.2)***
Maximum Bromage score	2 [1–3]	0.5 [0–3]**
Incidence of hypotension	20 (100%)	15 (75%)*
Ephedrine total dose (mg)		
Range [min-max]	20 [5–45]	10 [0–30]***
Mean (SD)	19.5 (8, 7)	10.3 (9.2) ***
No of ephedrine treatments	3.9 (1.7)	2.1 (1.8) ***
No of patients given i.v. fentanyl	0	3
No of patients given epidural supplementation	0	1
APGAR 1-min	7 [4–8]	8 [5–9]
APGAR 5-min	9 [8–9]	9 [8–9]
Maximum sedation score	1 [1–2]	1 [1–2]
Satisfaction scale 0, 1, 2, 3	0, 0, 4, 16	0, 1, 2, 17

* $P < 0.05$, Significantly different from group I; ** $P < 0.001$, significantly different from group I; *** $P < 0.005$, significantly different from group I
Values are means (SD), medians [ranges], or numbers (percentages)

Table 3. Incidence of side effects

	Group B ($n = 20$)	Group BF ($n = 20$)
Nausea	17 (85%)*	5 (25%)
Vomiting	6 (30%)*	1 (5%)
Pruritus	0 (0%) *	15 (75%)
Headache	1 (5%)	0 (0%)
Shivering	10 (50%)	8 (40%)

Values are numbers of patients (percentages)
* Significantly different from the other group, $P < 0.05$

significantly higher in group B (Table 3). No respiratory depression was detected.

Discussion

We preferred a 4-mg bupivacaine dose with fentanyl, because we had institutional experience with this dose for cesarean section, and our observations suggested that low-dose bupivacaine (4 mg) with fentanyl would entail a lower incidence of maternal hypotension and less necessity for ephedrine than bupivacaine doses of 10 or 12.5 mg. Maternal hypotension developed in all the patients in group B in the present study, and only five patients in group BF did not need treatment for hypotension. This study showed that the use of 4 mg plain bupivacaine with 25 μg fentanyl could not completely prevent the maternal hypotension associated with spinal anesthesia. The incidence of hypotension was 75% in group BF, and total ephedrine doses were significantly lower than those in group B. In the study of Ben-David et al. [3], 31% of the patients in the low-dose plain bupivacaine (5 mg) with fentanyl (25 μg) group required treatment for hypotension versus 94% of the patients in the plain bupivacaine (10 mg) group. More recently Van de Velde et al. [4] demonstrated that the incidences of hypotension with 9.5 mg and 6.5 mg intrathecal bupivacaine were 68% and 16%, respectively. Teoh et al. [5] also reported that hypotension occurred at incidences of 73% and 14% with 9 mg and 3.75 mg intrathecal bupivacaine, respectively.

The prevention and treatment of maternal hypotension associated with spinal anesthesia for cesarean section remains a difficult problem, with no consensus as to the optimal mode of management. This lack of consensus is probably due to the causes of hypotension. As hypotension is predominantly due to venous, arterial, and arteriolar vasodilation secondary to sympathetic blockade, the dose of local anesthetic is an important part of the etiology of the hypotension [6]. It has been reported that increasing the dose of local anesthetic increased maternal hypotension [7]. Intrathecal opioids enhance analgesia without altering the degree of sympathetic blockade when added to subtherapeutic doses of local anesthetics [8–10]. However, the causes of hypotension are multifactorial, with factors such as high levels of preganglionic sympathetic blockade, aortocaval compression, and blockage of cardioaccelerator fibers being involved. Several strategies, such as volume loading, left uterine displacement, wrapping of lower limbs, preemptive vasopressor administration, and vasopressor infusion regimens have been used to decrease the incidence of hypotension [11].

In our study, we could not reduce the incidence of hypotension, as in the other studies mentioned above, though the dose of bupivacaine was lower. In these studies, patients were positioned from supine to 15° left lateral tilt after the injection of drugs [3–5]. To position the table in left lateral tilt at greater angles makes the patient uncomfortable, and an additional person is needed to support the patient [12]. Although positions allowing left deviation of the uterus can reduce the incidence of hypotension, and pregnant women are recommended to avoid the supine position [12], a left lateral tilt of 15° could not be maintained throughout our study, because the surgeons found this position unacceptable and the patients felt as if they were falling. The table was initially positioned at 15° left lateral tilt for all patients, but by the beginning of the operation, we repositioned the table to almost horizontal, because a table angle below 12° left lateral tilt is not beneficial [12]. We think that uterine aortocaval compression may have influenced the development of hypotension and this may have been a reason for our inability to achieve a reduction in the incidence of hypotension similar to the extent obtained in other studies.

It is generally accepted that the level of sensory blockade has to be T5 or higher for cesarean section. However, Ginosar et al. [13] suggested that 10 min to achieve a T6 sensory level is a period of time consistent with the realities of a busy operating suite and the occasional demands for urgent cesarean delivery. The level of sensory blockade in the patients in both groups in our study was higher than T6 before 10 min in all patients. Ben-David et al. [3] reported no anesthesia failures when anesthesia failure was defined as patient pain requiring conversion to general anesthesia. Although one of the patients in our study required epidural supplementation near the end of the operation, we think that spinal anesthesia with low-dose bupivacaine (4 mg) plus fentanyl (25 μg) can provide adequate surgical anesthesia for cesarean section.

Lower motor blockade scores were reported in previous studies, similar to our results, when fentanyl and bupivacaine were coadministered for spinal anesthesia [3, 9]. It may be thought that insufficient motor blockade observed in our low-dose bupivacaine group is a drawback for delivery. However, there was no difference between our two groups in spinal anesthesia-to-

delivery time. We did not investigate the positive effects of low motor blockade, such as early mobilization. New studies may be planned to investigate these effects of low-dose bupivacaine-fentanyl spinal anesthesia in cesarean section.

Intrathecal fentanyl-associated side effects could be regarded as a drawback, but previous studies have also shown that intrathecal fentanyl at a dose of 25 μg can be safely used in parturients [3,14]. In the present study, pruritus was the most common adverse effect in the group receiving high-dose intrathecal fentanyl, as previously reported by other investigators [9,10]. However, none of the patients needed treatment. We did not observe respiratory depression or deep sedation even in patients who received concurrent i.v. fentanyl. The incidences of other side effects, i.e., nausea and vomiting, were significantly lower in the bupivacaine-fentanyl group than in the bupivacaine-only group. These data are consistent with the study of Manullang and colleagues [15]. They suggested that 20 μg intrathecal fentanyl was superior to 4 mg intravenous ondansetron for the prevention of perioperative nausea during cesarean delivery performed with bupivacaine spinal anesthesia [15].

At the beginning, our expectation from the study was that the incidence of maternal hypotension could be prevented in at least half of the patients, but low-dose bupivacaine did not reduce maternal hypotension sufficiently. However, bupivacaine with fentanyl could be used at a low dose (4 mg) for spinal anesthesia in cesarean section, and this low dose was associated with significantly less hypotension and vasopressor requirements. By adding 25 μg intrathecal fentanyl, the bupivacaine dose can be reduced as low as 4 mg, and it can be used with a single-shot spinal anaesthesia technique, but we suggest that a combined spinal epidural technique may be preferable to the single-shot spinal anesthesia technique, because the inserted epidural catheter can be activated without conversion to general anesthesia, if the spinal anesthesia is inadequate.

In conclusion, the development of hypotension after spinal block in subjects undergoing cesarean section was not prevented despite the low dose of bupivacaine, but the severity of maternal hypotension, the number of ephedrine treatments, and the total dose of ephedrine may be decreased by using low-dose (4 mg) intrathecal bupivacaine plus 25 μg intrathecal fentanyl for cesarean section.

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