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Intrathecal sufentanil (1.5μg) added to hyperbaric bupivacaine (0.5%) for elective cesarean section provides adequate analgesia without need for pruritus therapy

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Abstract
Purpose. We compared the effects of different doses of intrathecal sufentanil when administered together with hyperbaric bupivacaine for elective caesarean section.
Methods. This was a prospective, randomized, double-blind, controlled trial involving 100 pregnant women, American Society of Anesthesiologists (ASA) I-II, who were scheduled for elective caesarean section under spinal anesthesia. The patients were assigned to four groups according to the dose of sufentanil used: no sufentanil (group I; placebo) or 1.5, 2.5, or 5.0 μg sufentanil (groups 2–4, respectively). In every group, the local anesthetic used was hyperbaric bupivacaine 0.5% (12.5 mg), and the total volume of the solution was 3.5 ml. The duration of complete analgesia, maternal side effects, and maternal/fetal outcomes were recorded. The duration of complete analgesia was defined as the time from intrathecal injection to a vernal analogue score (VAS) of more than 0.
Results. No patient experienced intraoperative pain. The duration of complete analgesia was prolonged in all groups receiving opioids. The duration of the analgesia and the 0- to 6-h intravenous analgesic requirements were similar in the sufentanil groups. Moreover, the sufentanil groups had longer durations of complete analgesia than the placebo group. Pruritus was more frequent in the 2.5- and 5-μg sufentanil groups than in the 1.5-μg sufentanil and placebo groups. There were no differences among the groups in umbilical cord blood gases on in neonatal Apgar scores.
Conclusion. The addition of sufentanil 1.5 and 2.5 μg to hyperbaric bupivacaine provided adequate anesthesia for caesarean delivery and good postoperative analgesia. In addition, the incidence of pruritus was significantly lower in the 1.5-μg sufentanil group when compared with that in the 2.5- and 5-μg groups.

Key words Cesarean section · Intrathecal · Pruritus · Sufentanil

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Introduction

The lipophilic opioids fentanyl and sufentanil added to neuraxial local anesthetic improve analgesia and anesthesia quality, prolong sensory blockade, and reduce local anesthetic requirements [1–3]. However, in parturients, beneficial analgesia has to be balanced against fetal bradycardia and against known maternal effects, including respiratory depression, emetogenesis, and pruritus [4,5]. To prevent postoperative pruritus is a difficult and important problem for both the anesthesiologist and the patient in the postanesthetic care unit (PACU). Pruritus after intrathecal (IT) opioids is an undesirable side effect of opioids which can develop with a frequency ranging between 20% and 80% [6,7].

The mechanisms causing pruritus are complex [8–10] and may involve central or peripheral mechanisms. Both central opiate and serotonin receptors are involved. Naloxone is effective against pruritus arising from IT or epidural opioids, but may increase pain [5,8]. Recently, some studies have reported that reducing the dose of IT opioids reduced the incidence of pruritus, and the pruritic effect of sufentanil was dose-dependent [6,11,12]. Dahlgren et al. [6] observed that IT sufentanil 2.5 μg added to bupivacaine provided satisfactory analgesia, with a lower incidence of pruritus than that without bupivacaine.

We hypothesized that a 1.5-μg dose of sufentanil, when combined with 12.5 mg bupivacaine, would provide satisfactory analgesia with a lower incidence of pruritus than that without bupivacaine.

Methods

The study was conducted between January 2004 and May 2005 and was approved by the ethics committee of our university hospital. After obtaining the informed

consent of all patients, we conducted a prospective, double-blind, randomized, controlled trial with 100 American Society of Anesthesiologists (ASA) physical status I-II term pregnant women undergoing elective caesarean section. The exclusion criteria were patients with psychiatric illness, coagulation disorders, chronic pain, and allergy to opiates or local anesthetics.

The patients were distributed randomly into four groups of 25 patients each, using a computer-generated random number list. All groups received a 3.5-ml admixture of prepared solution as follows; group I (hyperbaric bupivacaine 0.5% 12.5 mg [2.5 ml], 1 ml preservative-free 0.9% physiological saline), group II (hyperbaric bupivacaine 0.5% 12.5 mg [2.5 ml], 0.7 ml preservative-free 0.9% physiological saline, sufentanil 1.5 μg [0.3 ml]), group III (hyperbaric bupivacaine 0.5% 12.5 mg [2.5 ml], 0.5 ml preservative-free 0.9% physiological saline, sufentanil 2.5 μg [0.5 ml]), and group IV (hyperbaric bupivacaine 0.5% 12.5 mg [2.5 ml], sufentanil 5.0 μg [1 ml]). Once the free flow of clear cerebrospinal fluid was obtained, the admixted solution was injected at the rate of approximately 0.2 ml·s^{-1}. With the spinal needle bevel facing cephalad, the anesthetic solution was injected without barbotage or aspiration.

We started the intravenous (IV) hydration process with Ringer's lactate solution (20 ml·kg^{-1}·h^{-1}) 1 h before the IT injection. With the patient in the right lateral position, a 25-gauge pencil-point needle was inserted in the subarachnoid space at the L2–3 or L3–4 interspaces. After the IT injection, the patient was returned to the supine position with a left lateral tilt for left uterine displacement. Intravenous boluses of 5–10 mg ephedrine and additional IV fluids were given to treat hypotension, which was defined as a systolic blood pressure below 90 mmHg or a decrease in systolic pressure of more than 20% of the baseline value. Blood pressures were recorded every 5 min, noninvasively, in the operating room. All patients were given oxygen 2–4 l·min^{-1} through a nasal cannula. Respiratory depression was defined as a respiratory rate less than 10 breaths·min^{-1} or oxygen saturation less than 95%.

Specific variables were evaluated every 15 min in the operating room or PACU for the first 90 min, then every 30 min. The following variables were evaluated: incidence, location, and severity (verbal analogue score [VAS]) of pruritus, postoperative pain; and any other problems. Pain and pruritus scores were obtained with a VAS, with 0 meaning none and 10 the worst pain or pruritus. Patients were treated with an analgesic or an antipruritic when their VAS was over 4. Pruritus was treated with diphenhydramine first and then with naloxone. If the pruritus VAS was more than 4, then up to two doses of diphenhydramine 25 mg were given IV every 2 h as necessary. If the pruritus did not improve, then naloxone, up to 1 μg·kg^{-1}, was given IV. In the intraoperative period fentanyl 1 μg·kg^{-1} IV was used for pain and metoclopramide 10 mg IV was used for nausea.

The surgical technique was uniform in all the patients and included exteriorization of the uterus. At delivery, blood samples were collected from the umbilical artery and vein for blood gas analyses. Apgar scores were evaluated at 1 and 5 min.

In the recovery room, the VAS for pain was used. Duration of effective analgesia was defined as the time to a VAS score of 4 or less. The duration of complete analgesia was defined as the time from the IT injection to a VAS score of more than 0. The duration of complete analgesia was monitored at 30-min intervals after the IT injection until the VAS score was more than 0. The patients were discharged to the ward approximately 6 h after anesthesia induction. Patients received IV tramadol 1–2 mg·kg^{-1} when the VAS score was more than 4. Analgesic requirements and side effects were recorded for 24 h after anesthesia induction.

Power analysis indicated that the minimum number of patients required for an 80% power was 23 patients per group to detect a 20% incidence of pruritus. We chose a value on the lower end of the expected range (20% to 80%). However, the actual incidence of pruritus was much less than expected, so that a post-hoc analysis showed that sample size was appropriate for excluding a type II error. Continuously distributed variables were analyzed using two-tailed analysis of variance (ANOVA), followed by Scheffé's test for comparisons between the groups. Frequency data were analyzed using the χ^2 test and Fisher's exact test. A P value of less than 0.05 was considered significant.

Results

One hundred women completed the study. There were no significant differences among the groups in patient height, weight, age, or surgical time. The duration of complete analgesia was longer in all the sufentanil groups compared with the placebo group, and the duration of analgesia was longer in the 5-μg sufentanil group than in the 1.5- and 2.5-μg sufentanil and placebo groups ($P < 0.05$; Table 1).

There were no cases of maternal respiratory depression. The hypotensive responses to the block, as well as the ephedrine requirements, were similar in all groups. Hypotension was observed in the placebo group (4 patients), the 1.5-μg sufentanil group (3 patients), the 2.5-μg sufentanil group (3 patients), and the 5-μg sufentanil group (2 patients). The incidence of nausea and vomiting was higher in the placebo group than in the sufentanil groups during the pre- and postoperative periods ($P < 0.05$). Intraoperatively, anti-emetic rescue

Table 1. Demographic data, surgical time, and duration of analgesia

	Group 1 (placebo)	Group 2 (sufentanil 1.5)	Group 3 (sufentanil 2.5)	Group 4 (sufentanil 5)
Height (cm)	157.5 ± 4.8	159.4 ± 6.4	161.3 ± 6.8	162.5 ± 7.1
Weight (kg)	82.3 ± 9.6	78.7 ± 7.3	81.3 ± 9.7	84.6 ± 7.5
Age (years)	27.8 ± 6.2	28 ± 5.5	30.4 ± 6.2	29.5 ± 6.4
Duration of complete analgesia (min)	193.5 ± 23	274 ± 36*	294 ± 37*	346 ± 50*;**
Surgical time (min)	56.8 ± 6.2	58.8 ± 8.8	57.9 ± 6.2	53.6 ± 7.1

* Significant difference ($P < 0.05$, Scheffé's test) from the placebo group; ** significant difference ($P < 0.05$ Scheffé's test) from the other groups
Values are means ± SD

Table 2. Side effects, and the number of patients requiring treatment intraoperatively and in the first 6 h postoperatively

	Group 1 (placebo)	Group 2 (sufentanil 1.5)	Group 3 (sufentanil 1.5)	Group 4 (sufentanil 5)
Nausea	10*	3	4	4
Vomiting	3	1	1	1
Mean maximal pruritus score (VAS)	2.04 ± 1.22	2.71 ± 1.29	4.27 ± 2.5**	5.62 ± 2.9**
Intraoperative pruritus (%)	0	4%	20%*	28%*
Postoperative pruritus (%)	0	4%	24%*	32%*
Pruritus rescue	0	0	4*	7*
Anti-emetic rescue	5***	1	1	1
Hypotension	4	3	3	2
Respiratory depression	0	0	0	0

* Significant difference ($P < 0.05$; Fisher's exact test) from the placebo group; ** significant difference ($P < 0.05$; Scheffé's test) from the placebo group; *** significant difference ($P < 0.05$; Fisher's exact test) from the other groups
Data values are numbers of patients

Table 3. Umbilical venous blood gases in the babies

	Group 1 (placebo)	Group 2 (sufentanil 1.5)	Group 3 (sufentanil 2.5)	Group 4 (sufentanil 5)
Ph	7.3 ± 0.1	7.3 ± 0.8	7.3 ± 0.4	7.3 ± 0.9
*P*O2	20.7 ± 9	20.9 ± 7	20.8 ± 8	20.9 ± 6
*P*CO2	46.5 ± 9.1	47.8 ± 9.4	46.8 ± 9.1	47.2 ± 9.3
HCO3	23.6 ± 1.6	23.3 ± 2.3	23.3 ± 1.9	23.3 ± 2.5
BE	(–2.5 ± 1.7)	(–3.3 ± 2.8)	(–3.1 ± 2.3)	(–3.0 ± 1.8)

was significantly higher in the placebo group than in the sufentanil groups ($P < 0.05$). Pruritus requiring treatment was predominant intraoperatively and postoperatively in the 2.5- and 5-µg sufentanil groups (Table 2).

The mean maximal pruritus scores (VAS) were 2.04 ± 1.22 in the placebo group; 2.71 ± 1.29 in the 1.5-µg sufentanil group, 4.27 ± 2.5 in the 2.5-µg sufentanil group, and 5.62 ± 2.9 in the 5-µg sufentanil group. Pruritus was not observed intra- or postoperatively in the placebo group. The frequency of pruritus was 4% intraoperatively and 4% postoperatively in the 1.5-µg sufentanil group, 20% intraoperatively and 24% postoperatively in the 2.5-µg sufentanil group, and 28% intraoperatively and 32% postoperatively in the 5-µg sufentanil group. The incidence of intra- and postoperative pruritus was significantly greater in the 2.5- and 5-µg sufentanil groups than in the 1.5-µg sufentanil and placebo groups ($P < 0.05$; Table 2).

The newborn infants had a mean gestational age of 39.33 ± 1.25 weeks and a mean birth weight of 3685 ± 420 g. No infant had a 5-min Apgar score of less than 7. Umbilical venous blood gases showed no significant differences among the groups (Table 3).

The 6-h postoperative tramadol requirements were 75 ± 20, 85 ± 25, 90 ± 30, and 125 ± 30 mg in the 5-, 2.5-, and 1.5-µg sufentanil and placebo groups, respectively. The amount of tramadol required in the placebo group was significantly higher than the amounts required in the 1.5-, 2.5-, and 5-µg sufentanil groups ($P < 0.05$; Fig. 1). The 6- to 24-h requirement for tramadol did not differ significantly among the groups.

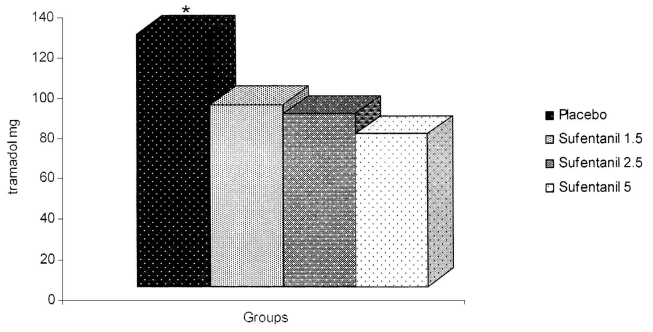

Fig. 1. Tramadol requirements of the patients in the first 6 hs postoperatively. * Significant difference ($P < 0.05$, Fisher's exact test) between placebo and all the sufentanil groups

Discussion

In this study, our purpose was to determine the lowest dose of sufentanil with hyperbaric bupivacaine that provided effective postoperative analgesia with the lowest incidence of pruritus. Our results were similar to those of others [6,12] and demonstrate that the addition of sufentanil 5.0 μg to hyperbaric bupivacaine significantly prolonged the duration of complete analgesia in comparison with that provided by bupivacaine alone, or bupivacaine with sufentanil 1.5 μg or 2.5 μg. In the 1.5- and 2.5-μg sufentanil groups, there was a significant increase in the duration of complete analgesia compared with the placebo group. However, these findings were different from those of the other studies noted above [6,12]. The authors of those studies found that the group receiving a 2.5-μg dose of sufentanil showed an insignificant increase in the duration of complete analgesia compared with the control group. Braga et al. [13] suggested that increasing the dose of sufentanil to more than 5 μg significantly increased the incidence of pruritus, without any advantage in terms of postoperative analgesia.

Dahlgren et al. [6] compared 5 μg versus 2.5 μg sufentanil at caesarean delivery and found a higher incidence of pruritus with the higher dose, but no significant difference in the duration of analgesia. In another study, 2.5, 5, and 7.5 μg sufentanil were compared, and pruritus was found to be more frequent in the 5- and 7.5-μg sufentanil groups [12]. Our study used 1.5, 2.5, and 5 μg sufentanil doses, and pruritus was more frequent in the 2.5- and 5-μg sufentanil groups. The duration of complete analgesia was prolonged in the 5-μg sufentanil group compared with the other groups, but there was no significant difference in the duration of complete analgesia between the 1.5- and 2.5-μg sufentanil groups. Although we observed a significantly longer duration of analgesia with 5 μg sufentanil than with the placebo or 1.5 μg sufentanil, there was no difference between 2.5 and 5 μg sufentanil.

Recently, sufentanil added to hyperbaric bupivacaine has been administered at different IT doses, and pruritus has been identified as the most common side effect, almost always being attributed to high doses of sufentanil [3,6]. The addition of sufentanil 10–20 μg to hyperbaric bupivacaine in the subarachnoid space significantly prolongs the duration of analgesia compared with bupivacaine alone. However, increasing the dose of IT sufentanil above 10 μg does not achieve a corresponding increase in the duration of analgesia [10]. The addition of sufentanil, at less than 10 μg, to IT hyperbaric bupivacaine has recently been used in caesarean delivery [6,12].

These results show that increasing the dose of sufentanil to 2.5 μg or more significantly increases the incidence of pruritus. In addition to pruritus, opioids delivered by the spinal route may produce nausea, vomiting, urinary retention, and respiratory depression, mainly owing to opioid action via μ and κ receptors [13].

The incidence of pruritus has been reported to range from 20% to 80% at different doses of IT sufentanil [4,6–14]. In our study, pruritus arising from sufentanil was not common, and it tapered when the dosage was reduced; the lowest frequencies, of 4% intraoperatively and 4% postoperatively, occurred in the 1.5-μg sufentanil group.

Dahlgren et al. [6] reported that pruritus treatment was required in the postoperative unit for one patient in their 2.5-μg sufentanil group and nine patients in their 5-μg sufentanil group. In our study, pruritus treatment was required in the postoperative unit for four patients in the 2.5-μg sufentanil group and seven patients in the 5-μg sufentanil group.

A reduction in intraoperative nausea has been observed with the addition of fentanyl and sufentanil to hyperbaric bupivacaine [6,15]. In our study, the incidence of nausea during the intraoperative period was lower in those groups that received sufentanil.

Like previous studies [6,12,16], this study also did not find differences in umbilical blood gases or neonatal Apgar scores among groups with different doses of sufentanil. It seems unlikely that there were any adverse neonatal effects related to the use of IT opioids.

In conclusion, the addition of sufentanil 1.5 and 2.5 μg to hyperbaric bupivacaine provided adequate anaesthesia for cesarean delivery and good postoperative analgesia. In addition, the incidence of pruritus was significantly lower in the 1.5-μg sufentanil group when compared with that in the 2.5- and 5-μg groups.

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