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Combination of intrathecal and intravenous fentanyl for cesarean delivery

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Introduction

Intrathecal opioid, a useful adjunct to prolong analgesic effects, potentiates spinal anesthesia [1]. However, the clinical relevance of intrathecal fentanyl in cesarean section is still debated [2,3]. Several studies reported the advantages of additional intrathecal fentanyl over plain local anesthetic solution in cesarean section patients [4,5]. These investigations indicated that intrathecal fentanyl significantly prolonged the duration of analgesia and protected patients from intraoperative nausea caused by surgical manipulation. Recently, Siddik-Sayyid et al. [6] reported that intrathecal fentanyl provided better intraoperative analgesia and prolonged the duration of a subarchnoid block compared with intravenous fentanyl. However, the impact of intrathecal fentanyl on early postoperative pain control remains somewhat unclear. In this prospective randomized study, we tested the hypothesis that a combination of intrathecal and intravenous fentanyl would provide better postoperative pain control than intravenous fentanyl alone in patients undergoing elective cesarean section.

Subjects and methods

The study protocol was approved by the institutional ethics committee and written informed consent was obtained from each participant. Thirty-six otherwise healthy pregnant women who were scheduled for elective cesarean section were enrolled in this study. Premedication consisted of 75 mg oral roxatidine, a histamine H_2 receptor antagonist, and 0.5 mg of intramuscular atropine sulfate. The drug, which was composed of 2 ml of 0.3% hyperbalic dibucaine with either 10 μg of fentanyl or the same volume of saline, was prepared by an anesthesiologist who did not participate in the anesthetic management or subsequent data collection. A subarachnoid block was performed with a 25 G pencil-point spinal needle (Beckton Dickinson, Franklin Lakes, NJ, USA) at the L3-4 interspace with the patient in a right decubitus position, and patients were randomly allocated to receive one of the medications described above (n = 18 each) according to computer-generated random numbers. The sensory block was frequently tested with cold stimulation, and block height at 5 min after intrathecal injection and at the end of surgery was recorded. Standard perioperative care, including crystalloid administration and left uterine displacement, was provided. Five milligrams of intravenous ephedrine was administered to maintain systolic blood pressure over 100 mm Hg and repeated if necessary. Nausea and vomiting were initially treated by correcting hypotension, if present. If nausea and vomiting persisted in the face of stable blood pressure (maternal systolic blood pressure >100 mm Hg), 0.5 mg of intravenous droperidol was injected. The neonatal Apgar score was recorded at 1 and 5 min after delivery. Thereafter, intravenous midazolam (1 mg) and fentanyl were injected. Ninety micrograms fentanyl was intravenously administered to the patients who had received intrathecal fentanyl (IT + IV group), and 100 μg fentanyl was administered to those who did not receive intrathecal fentanyl (IV group). Therefore, the total intraoperative dose of fentanyl was 100 μg in both groups.

In the postoperative period, all evaluation was done by ward nurses, who were blinded to the medication. The nursing staff was asked to make frequent postoperative rounds and to assess the regression of the

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analgesic area and postoperative symptoms such as nausea/vomiting and respiratory depression. Additionally, the patients were instructed to report to the nurses when they first felt pain. Postoperative pain, according to the Prince Henry pain scale, was recorded every hour until 4 h after surgery and then every 4 h until 24 h postoperatively. Either 15 mg of pentazocine or 1 mg of butorphanol was intramuscularly administered when the patient reported pain with a Prince Henry pain scale score of 3 points or higher. The duration of complete analgesia (time from subarachnoid injection to the first report of pain), effective analgesia (time from subarachnoid injection to first administration of parenteral opioid), and time to sensory regression to T12 were recorded. The incidence of hypotension, nausea, vomiting, and respiratory depression, which was defined as a respiratory rate of less than 10 breaths/min or $S_{pO_2} < 90\%$ under room air, was recorded, and each event was categorized into intraoperative, early (to 4 h) postoperative, and late (4–24 h) postoperative periods.

Sample size was determined by power analysis with $\alpha = 0.05$ and $\beta = 0.2$ to detect a 30% elongation of duration of effective analgesia between the two study groups [7]. Data were expressed as mean ± SD unless otherwise specified. The differences between the two groups were analyzed with an unpaired *t*-test or χ-squared test as appropriate. The scores of the postoperative Prince Henry pain scale were statistically analyzed with two-way analysis of variance (ANOVA) with repeated measures. $P < 0.05$ was considered statistically significant.

Results

Patient demographics were summarized in Table 1. There were no significant differences between the two study groups. A sensory block at T4 level was achieved at 5 min after subarachnoid injection in both groups. At the end of surgery, all patients in the IT + IV group and 11 patients in the IV group showed sensory block at T4 level, and the other 7 patients in the IV group showed sensory block at T6 level. Table 2 shows the durations of complete analgesia and effective analgesia, and time to sensory regression to T12 level. No statistical difference was found between the two groups. The incidences of several perioperative side effects are summarized in the Table 3. Ten patients in the IT + IV group and nine patients in the IV group were treated with a single dose of intravenous ephedrine. All these events occurred within 10 min after subarachnoid injection, and the incidence was not statistically different between the groups. Twelve patients in the IT + IV group and ten patients in the IV group reported nausea intraoperatively (Table 3). Most of these symptoms occurred coincidently with hypotension after intrathecal injection, and no patients reported discomfort during uterine manipulation or intraabdominal exploration after delivery. In addition, one patient in each group reported nausea in the early postoperative period. No incidence of postoperative respiratory depression was found in this study. Neonatal condition was similar in both groups with Apgar scores more than 7 at 1 min and always more than 8 at 5 min for the infant of every study subject. The postoperative

Table 1. Patient characteristics

	IT + IV fentanyl ($n = 18$)	IV fentanyl ($n = 18$)
Age [years]	30 ± 4	30 ± 4
Height [cm]	158 ± 4	156 ± 5
Weight [kg]	63 ± 10	62 ± 6
Gestational weeks	38 ± 2	38 ± 1
Gravidity[primigravida/multigravida]	8/10	5/13
Parity [nullpara/multipara]	18/0	14/4
Duration of operation [min]	43 ± 7	41 ± 11

Data are expressed as mean ± SD
IT, intrathecal; IV, intravenous

Table 2. Postoperative analgesia

	IT + IV fentanyl ($n = 18$)	IV fentanyl ($n = 18$)
Duration of complete analgesia [min]	199 ± 69	187 ± 110
Duration of effective analgesia [min]	408 ± 196	326 ± 161
Time to T12 regression [min]	147 ± 47	155 ± 52

Data are expressed as mean ± SD

Table 3. Perioperative incidence of hypotension and nausea/vomiting

	Number of patients		
	Intraoperative	Early postoperative	Late postoperative
Nausea/vomiting			
IT + IV fentanyl	12	1	0
IV fentanyl	10	1	0
Hypotension			
IT + IV fentanyl	10	0	0
IV fentanyl	9	0	0
Shivering			
IT + IV fentanyl	0	0	0
IV fentanyl	2	0	0

Early postoperative period, 0–4 h; late postoperative period, 4–24 h

pain scores are summarized by Fig. 1. The scores on the postoperative Prince Henry pain scale were not different between the two study groups.

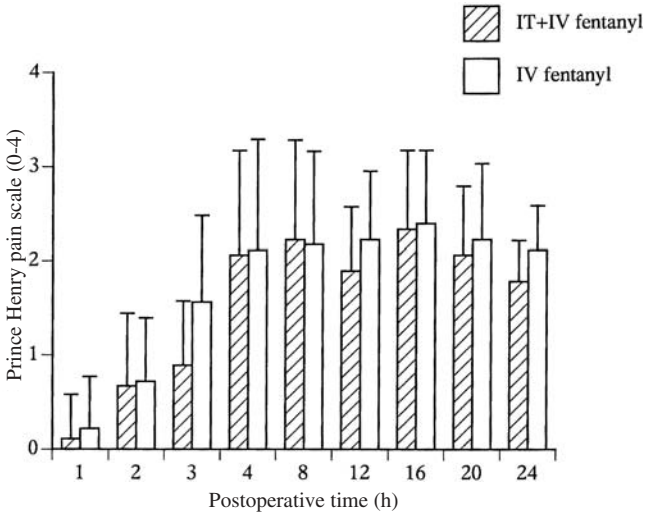

Fig. 1. Postoperative pain was assessed on the Prince Henry pain scale by blinded observers. Data are expressed as mean ± SD. Scores did not differ significantly between the IT + IV fentanyl group (n = 18, shaded bar) and the IV fentanyl group (n = 18, open bar) by two-way analysis of variance with repeated measures. *IT*, intrathecal; *IV*, intravenous

Discussion

This study demonstrated that a combination of intrathecal and intravenous fentanyl provided no significant potentiation of analgesia compared with intravenous fentanyl alone in terms of intra- and postoperative pain control and the incidence of side effects in patients undergoing cesarean section. Effects on the neonates were comparable between these two analgesic regimens.

Several studies have investigated the beneficial effects of intrathecal fentanyl administration in patients receiving cesarean section. Most reports agree with the following two points: First, intrathecal fentanyl provides better intraoperative analgesia compared with plain local anesthetic solution [4,8–10]. Second, the incidence and degree of perioperative nausea and vomiting are reduced with the addition of intrathecal fentanyl [10,11]. However, the effect of intrathecal fentanyl is limited mostly to the intraoperative period, and from this perspective, the clinical usefulness of intrathecal fentanyl in cesarean section remains controversial [2,12]. Based on these previous investigations, we hypothesized that a combination of intrathecal and intravenous fentanyl would potentiate the effect and provide better analgesia. This study demonstrated that intrathecal plus intravenous fentanyl did not provide superior analgesia compared with intravenous fentanyl.

Several factors may account for this rather disappointing result. First, the effect of intrathecal fentanyl may depend on the choice and amount of local anesthetic. Indeed, previous studies have reported that the beneficial effect of intrathecal fentanyl was more evident when either a reduced amount of bupivacaine was employed to prevent unwanted side effects such as hypotension [13,14] or when lidocaine was used [5,15]. Compared to these reports, our choice of intrathecal medication (6 mg of dibucaine) may have produced a more effective block and partially eliminated any possible favorable effects of intrathecal fentanyl. The longer duration of complete and effective analgesia found in our study supports this speculation. Second, the dose of fentanyl may have considerably affected the outcome. Hunt et al. [4] reported that 6.25 μg of fentanyl enhanced the subarachnoid block, and Belzarena [8] reported a dose-dependent increase of intraoperative sedation. The intrathecal fentanyl dose that we used in this investigation was within the effective and clinically

feasible dose range. Siddik-Sayyid et al. [6] showed that intrathecal fentanyl provided better intraoperative and early postoperative analgesia than the same amount administered intravenously. However, it seems obvious that a much larger dose is necessary for systemic fentanyl to produce an analgesic effect equipotent to that of intrathecal fentanyl. A larger intravenous fentanyl dose might be necessary for clinically meaningful comparison.

The incidence of side effects such as hypotension and nausea/vomiting and postoperative pain scores did not differ between the two study groups. This finding agrees with a previous review showing that intrathecal fentanyl has little impact on postoperative pain management [2]. Interestingly, these findings were in contrast to those of Siddik-Sayyid et al. [6] who reported reduced incidence of intraoperative hypotension and nausea/vomiting. Since they administered fentanyl intravenously immediately after intrathecal administration of bupivacaine, the timing of intravenous fentanyl administration may have a significant impact on the incidence of intraoperative nausea.

In summary, in this prospective randomized study, we compared the analgesic effects of intrathecal plus intravenous fentanyl and intravenous fentanyl in 36 cesarean section patients. There were no differences between the two methods in the duration of analgesia and motor block, postoperative pain scale scores, or the frequency of side effects such as nausea/vomiting and hypotension.

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