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Effects of epidural fentanyl and intravenous flurbiprofen for visceral pain during cesarean section under spinal anesthesia

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Abstract

Purpose. Despite adequate levels of sensory blockade, patients sometimes complain of abdominal pain during cesarean section performed under spinal anesthesia. The aim of this study was to evaluate the effects of epidural fentanyl and intravenous flurbiprofen on visceral pain during cesarean section in patients having spinal anesthesia.

Methods. Thirty ASA physical status I and II patients undergoing elective cesarean section were studied. Spinal-epidural anesthesia was performed in all groups. Group A received no additional analgesics, group B received epidural fentanyl 100 μg, and group C received flurbiprofen 50 mg i.v. immediately after the delivery. Postdelivery, intraoperative visceral pain was evaluated by using the visual analog scale. Incidence and visual analog scale scores of visceral pain and incidence of intraoperative nausea and vomiting were obtained from each patient.

Results. Visual analog scale scores of pain were significantly lower in group B than in the other groups ($P < 0.05$). The incidence of nausea was comparable in all groups. The incidence of intraoperative vomiting was lower in group C than in the other groups ($P < 0.05$).

Conclusion. Epidural fentanyl, but not intravenous flurbiprofen, decreases the incidence and severity of visceral pain during cesarean section.

Key words Visceral pain · Cesarean section · Fentanyl · Flurbiprofen

Introduction

Even when sensory blockade spreads over the fourth thoracic dermatome level, patients sometimes complain of abdominal pain, nausea, and vomiting during cesarean section performed under spinal anesthesia. This pain is thought to be visceral pain [1] transmitted by unmyelinated C-fibers. To reduce visceral pain, doses of spinal local anesthetics [2,3], spinal opioids [4,5], and spinal clonidine [6] have been investigated. These treatments were performed before delivery. However, the effects of postdelivery uses of epidural fentanyl and intravenous nonsteroidal anti-inflammatory drugs (NSAIDs) on visceral pain during cesarean section have not been studied.

The aim of the present study was to evaluate whether epidural fentanyl or intravenous flurbiprofen given immediately after delivery could decrease the incidence and severity of visceral pain during cesarean section.

Methods

This study was approved by our institutional review board, and informed consent was obtained from all patients. Healthy women scheduled to undergo cesarean section under combined spinal-epidural anesthesia were recruited for this prospective, randomized, single-blind study. Exclusion criteria included patients receiving any systemic analgesics or sedatives other than epidural fentanyl and flurbiprofen during the operation, and a fetus with suspected medical or congenital abnormalities.

None of the patients were premedicated. The patients were given 500 ml of acetate Ringer's solution and were then placed in the lateral position for initiation of the spinal-epidural procedure. First, the epidural catheter was inserted via an 18-gauge Tuohy needle at the T12-L1 vertebral interspace, using a midline approach and loss of resistance technique and advanced 5 cm cephalad. Then, spinal anesthesia was performed with a 1.8–2 ml hyperbaric mixture of 0.24% dibucaine, 0.12% t-caine, and 0.2 mg epinephrine at the L2–3 interspace. Sensory blockade was assessed by the complete loss of cold perception to ice water at each dermatomal level. When the blockade was extended to T4, the operation

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was started. If the sensory blockade was not obtained to T4, supplemental 2% lidocaine was administered through the epidural catheter. Hypotension was treated with an increased infusion rate of acetated Ringer's solution and 5 mg of i.v. ephedrine. Nausea and vomiting unrelated to hypotension were treated by metoclopramide 10 mg i.v.

Immediately after umbilical cord clamping, the patients were randomly allocated to one of three groups. Group A received no additional analgesics, group B received epidural fentanyl 100 μg, and group C was given flurbiprofen 50 mg i.v. just after umbilical cord clamping. Pain associated with exteriorization of the uterus and traction of peritoneum was defined as visceral pain. Standard 10-cm visual analog scales (VAS) were used to evaluate pain levels. Incidence and VAS scores of visceral pain were assessed when the patients complained of visceral pain. We also investigated the incidence of intraoperative nausea and vomiting and the postoperative anesthetic level. Severe nausea was defined as patient complaints of nausea more than twice after the delivery.

Patients' age, height, weight, parity, duration of operation and anesthesia, blood loss volume, and gestational age were compared using one-way analysis of variance followed by post hoc Bonferroni's correction. Comparisons of VAS data and postoperative anesthetic level among groups were performed by the Kruskal-Wallis test. If a significant result was obtained, Wilcoxon's rank-sum test and Bonferroni's correction were used to determine which groups differed significantly. The incidence of nausea and vomiting was analyzed by the chi-square test. $P < 0.05$ was considered statistically significant.

Results

Thirty patients were enrolled in this study. The patients' age, height, weight, parity, gestational age, duration of anesthesia, and duration of operation were not statistically different among the three groups. In all patients, a T4 level of anesthesia was established by spinal anesthesia. Therefore, supplemental epidural injection was not performed. Blood loss volume was comparable among the three groups (Table 1). The identities of the study drugs were blinded from the obstetricians, and they could not tell which patients had received flurbiprofen.

Visceral pain associated with peritoneal traction and exteriorization of the uterus after delivery was present in 7 of 10 patients in group A, 2 of 10 patients in group B, and 7 of 10 patients in group C (Table 2). The incidence of visceral pain was lower in group B than in other groups ($P < 0.05$). No patient complained of pain before delivery. The efficacy of fentanyl and flurbiprofen in the treatment of visceral pain is presented in Fig. 1. VAS scores were significantly lower in group B than in the other groups ($P < 0.05$). The postoperative anesthetic level was similar in all groups (Fig. 2).

Table 1. Patient characteristics[a]

Characteristic	Group A ($n = 10$)	Group B ($n = 10$)	Group C ($n = 10$)
Age (yr)	31 ± 3	30 ± 4	32 ± 6
Height (cm)	158 ± 5	155 ± 6	154 ± 6
Weight (kg)	60 ± 9	61 ± 9	57 ± 7
Gestational age (weeks)	37 ± 4	34 ± 5	37 ± 1
Duration of anesthesia (min)	121 ± 15	126 ± 27	130 ± 12
Duration of operation (min)	69 ± 7	76 ± 21	79 ± 9
Blood loss (g)	1237 ± 704	1073 ± 333	1192 ± 549
Parity			
Nulliparous	7	5	5
Multiparous	3	5	5

[a] Values are mean ± SD or number. There were no differences among the groups. Group A, control group; group B, fentanyl group; group C, flurbiprofen group

Table 2. Incidence of visceral pain, nausea, and vomiting[a]

Event	Group A ($n = 10$)	Group B ($n = 10$)	Group C ($n = 10$)	Chi-square P-value
Pain	7	2*	7	0.05
Nausea	7	7	5	NS
Vomiting	4	6	1*	0.05

[a] Values numbers of patients in whom visceral pain, nausea, or vomiting occurred. *$P < .05$ compared with the other groups. Group A, control group; group B, fentanyl group; group C, flurbiprofen group

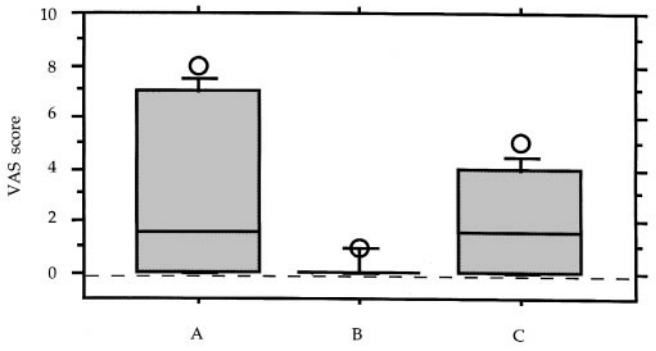

Fig. 1. Visual analog scale (*VAS*) scores in the three groups. Data are presented as box and whisker plots. The *box* represents the 25th and 75th percentiles, and the median is represented by the *solid line*. The *extended bars* represent the 10th and 90th percentiles. The *open circles* indicate out of 10th and 90th percentiles of each data set. The VAS scores were lower in group B than in the other groups. *A*, Control group; *B*, fentanyl group; *C*, flurbiprofen group

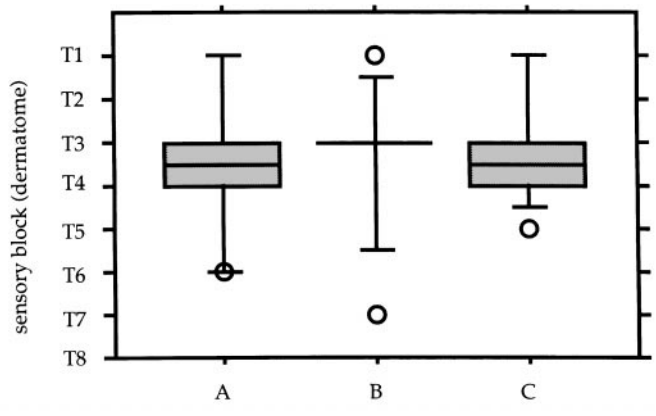

Fig. 2. Segmental levels of anesthesia at the end of the operation in three groups. Data are presented as box and whisker plots. The *box* represents the 25th and 75th percentiles, and the median is represented by the *solid line*. The *extended bars* represent the 10th and 90th percentiles. The *open circles* indicate out of 10th and 90th percentiles. The anesthesia levels were not different among the three groups. *A*, Control group; *B*, fentanyl group; *C*, flurbiprofen group

The incidence of nausea was comparable in all groups (Table 2). Although severe nausea was noted frequently in group A, the difference in severity was not statistically significant. The incidence of vomiting was lower in group C than in groups A and B ($P < 0.05$, Table 2). Nausea and vomiting seemed to have occurred on peritoneal traction and exteriorization of the uterus.

Discussion

In this study, we demonstrated that epidural fentanyl 100 μg, but not i.v. flurbiprofen 50 mg, effectively relieved pain during cesarean section. The present results indicate that epidural fentanyl may be favorable to relieve visceral pain at cesarean section.

We often encounter visceral pain during cesarean section performed under spinal or epidural anesthesia. Relief of visceral pain is necessary for anesthetic management. Several clinical studies have shown that increasing doses of local anesthetics [2,3], intrathecal fentanyl [4], and intrathecal combination of clonidine-fentanyl [6] improved analgesia during cesarean section under spinal anesthesia. These procedures were performed before delivery. Fentanyl and flurbiprofen have molecular weights of less than 500 and relatively high lipid solubilities, and hence they rapidly cross the placenta. Intravenous use of fentanyl during labor has been reported to be associated with temporary depressant effects on fetal biophysical parameters, such as body movements between uterine contractions, breathing, and fetal heart rate [7]. Furthermore, visceral pain develops after delivery [2]. Therefore, it may be preferable to administer analgesics after delivery.

Sensory blockade to the fourth thoracic dermatome is necessary for cesarean section. In the present study, pain was noted despite adequate levels of anesthesia. We usually assess anesthetic level by using the loss of sensation to cold or pinprick methods. However, those methods evaluate blockade of Aδ fibers but not C-fibers [8]. Thus, we could not assess the anesthetic level for C-fibers. Myelinated axons are blocked by a lower average concentration of lidocaine than unmyelinated axons [9]. Therefore, an adequate level of anesthesia for C-fibers might have not been achieved. Because visceral pain is transmitted by C-fibers, drugs with analgesic effects for C-fibers may be profitable. Opioids such as morphine [10] and fentanyl [11] have been reported to depress C-fiber-mediated responses. In addition, spinal μ- and δ-opioid receptors have a significant role in the modulation of visceral nociception [12]. Some studies have shown that spinal opioids may be beneficial in the control of visceral pain [4,6]. Therefore, spinal or epidural use of opioids may improve visceral pain during cesarean section.

Visceral pain was associated with peritoneal traction and exteriorization of the uterus immediately after delivery. Thus, the interval between delivery and the onset of visceral pain was short. Because we gave analgesics after delivery, rapid-onset opioids should be advantageous. The analgesic effect of epidural fentanyl is rapid in onset compared with that of epidural morphine. Epidural fentanyl produces analgesia by a primary spinal action [13]. In addition, analgesia from epidural fentanyl is more rapid in onset and more complete than analgesia from intramuscular fentanyl [14]. Therefore, we gave fentanyl via the epidural route.

Kusuhara and coworkers [15] showed that prostaglandins were synthesized after visceronociceptive stimulation. Other investigators [16] reported the involvement of prostaglandins in visceral pain induced by peritoneal irritation in rats. Inhibition of synthesis of prostaglandins may be beneficial for the management of visceral pain. NSAIDs impair the synthesis of prostaglandins by inhibiting cyclooxygenase. Flurbiprofen has been reported to be a potent analgesic in the treatment of postoperative pain [17], and it can be given intravenously. Analgesia by intravenous administration of flurbiprofen should be more rapid in onset than analgesia by rectal application. Furthermore, the antinociceptive action of flurbiprofen is more effective on visceral pain than on somatic pain [18]. Therefore, we used intravenous flurbiprofen to relieve visceral pain. However, in the present study, flurbiprofen failed to induce analgesia during cesarean section. Ohmori and coworkers [18] demonstrated that a dose of $30\,mg \cdot kg^{-1}$ flurbiprofen produced a powerful antinociceptive effect on visceral pain. In the present study, the dose of flurbiprofen was approximately $0.8\,mg \cdot kg^{-1}$. The flurbiprofen dosage we used may have been too small to provide satisfactory analgesia for visceral pain, although 50 mg flurbiprofen should have been sufficient to relieve postoperative pain [19]. Flurbiprofen produces significant dose-related antinociception [20]. Further study would be needed to clarify the optimal dose of flurbiprofen for the relief of visceral pain.

Because prostaglandins are suggested to be mediators of uterine contraction [21], using flurbiprofen during cesarean section may impair uterine contraction. On the contrary, a recent paper showed that NSAIDs did not interfere with uterine contraction [22]. In the present study, the intraoperative blood loss was similar in the three groups. The results indicate that flurbiprofen 50 mg may not affect uterine contraction significantly.

Hirabayashi and coworkers [3] reported that visceral pain was accompanied by nausea and vomiting. In agreement with their study, the present study showed that nausea and vomiting were associated with visceral pain in the control group. Nausea and vomiting have been shown to be reduced by epidural fentanyl [23]. On the contrary, the present study demonstrated that nausea and vomiting occurred without the development of visceral pain in the epidural fentanyl group. They occurred on peritoneal traction and exteriorization of the uterus. The uterus and peritoneum are widely innervated with vagal nerves. Abdominal vagal afferents have been reported to play a role in inducing emesis [24]. In the present study, vagal nerves were not blocked by spinal-epidural anesthesia. The vagal nerves may be involved in nausea and vomiting during cesarean section.

The present study showed that the incidence of vomiting was lower in the flurbiprofen group than in the other groups. Prostaglandins used in pregnant women have caused nausea and vomiting [25]. In addition, prostaglandins and/or dopamine have been regarded as possible mediators of radiation-induced emesis [26]. Those reports and our results indicate that prostaglandins may be involved in intraoperative vomiting during cesarean section under spinal anesthesia.

In summary, epidural fentanyl, but not intravenous flurbiprofen, reduced the incidence and severity of visceral pain during cesarean section. Since nausea and vomiting still persist despite adequate pain control with epidural fentanyl, concomitant use of antiemetic drugs may be necessary for better anesthetic management.

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