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Lornoxicam and ondansetron for the prevention of intrathecal fentanyl-induced pruritus

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Abstract

Purpose. In this randomized, double-blind study, we aimed to compare the effectiveness of lornoxicam and ondansetron for the prevention of intrathecal fentanyl-induced pruritus in patients undergoing cesarean section.

Methods. One hundred and eight parturients (American Society of Anesthesiologists [ASA] I-II status) requesting neuraxial analgesia by a combined spinal-epidural (CSE) technique were recruited for this study. A CSE technique was performed and anesthesia was achieved with fentanyl 25 µg and hyperbaric bupivacaine 12 mg. Patients were randomly allocated to three groups, each with 36 participants. Immediately following delivery, patients received either lornoxicam 8 mg IV (group L; $n = 36$), ondansetron 8 mg IV (group O; $n = 36$), or normal saline 2 ml IV (group P; $n = 36$). Pruritus, pain, and nausea and vomiting scores were recorded during the initial 24 h postoperatively.

Results. The incidence of pruritus was significantly lower in group O from 4 to 12 h postoperatively when compared to that in group L and group P. According to the pruritus grading system we used, the number of patients without pruritus was significantly higher in group O when compared to that in group L and group P. The number of patients experiencing moderate pruritus was significantly lower in group O when compared to that in group P.

Conclusion. We observed that the administration of 8 mg IV lornoxicam failed to prevent intrathecal fentanyl-induced pruritus in parturients. Also, our data confirmed that ondansetron is likely to attenuate intrathecal fentanyl-induced pruritus.

Key words Intrathecal · Fentanyl · Pruritus · Ondansetron · Lornoxicam

Introduction

Parturients appear to be the group of patients most susceptible to pruritus after neuraxial opioid administration. While the incidence of pruritus after neuraxial opioid administration varies from 30% to 100% in nonpregnant patients, it has been reported to be between 60% and 100% in parturients [1]. The underlying mechanism of postoperative pruritus after intrathecal or epidural opioids appears to be complex. Possible mechanisms include the cephalad spread of the drug in the cerebrospinal fluid; the action of the neuroaxial opioids on $5HT_3$ receptors [2]; a possible link with the pain pathway, which suggests that pain and pruritus are transmitted by the same population of sensory neurones and small unmyelinated nerve fibers (C-fibers) [3]; and the release of prostaglandins (PGE_1 and PGE_2), which may enhance C-fiber transmission to the central nervous system.

Various drugs have been used in attempts to prevent neuraxial opioid-induced pruritus in the setting of regional anesthesia; however, almost all of these have been linked to certain limitations, such as an increase in postoperative pain with naloxone [2], cardiac dysrhythmias with droperidol, [2] and limited efficacy in the setting of obstetric anesthesia with propofol [1].

Ondansetron (Zofran; Glaxo Wellcome, Wiltshire, England) is a selective $5HT_3$ receptor antagonist. Several investigators have examined the effectiveness of ondansetron for the prevention of pruritus, with contradictory results [2]. Nonetheless, a $5HT_3$ receptor antagonist such as ondansetron should be regarded as the drug of choice for the prevention of pruritus, with respect to efficacy as well as the minimal side effects [1].

Nonsteroidal anti-inflammatory drugs (NSAIDs), which have a well-recognized role in the relief of postoperative pain, inhibit cyclooxygenases and decrease the formation of prostaglandins [3,4]. NSAIDs, tenoxicam in particular, have been used in attempts to control

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postoperative pain as well as pruritus [4,5]. Lornoxicam (Xefo; Nycomed, Roskilde, Denmark) (chlortenoxicam) has been shown to exert cyclooxygenase inhibitory activity that is approximately 100 times more powerful than that of tenoxicam. Besides, lornoxicam has a short plasma half-life, which may translate into a better tolerability profile [6,7].

To date, the effect of lornoxicam on postoperative pruritus has not been investigated. Therefore, the purpose of this study was to evaluate the effectiveness of lornoxicam, in comparison to ondansetron, in preventing fentanyl-induced pruritus in patients undergoing cesarean section.

Patients and methods

After obtaining the approval of the institutional ethics committee, 108 parturients (American Society of Anesthesiologists [ASA] I-II status) scheduled for elective cesarean delivery who had requested neuraxial analgesia by a combined spinal-epidural (CSE) technique, were enrolled in the study. Written informed consent was obtained from all of the patients. Patients with preterm gestation and a history of a disorder associated with pruritus, patients in whom cerebrospinal fluid could not be identified at the time of spinal needle insertion, and patients who were allergic to any of the study drugs were excluded. Patients needing epidural top-ups were also excluded from the study.

After electrocardiography, noninvasive blood pressure and oxygen saturation (SpO_2) monitoring and intravenous cannulation was applied and all parturients were hydrated with 500 to 1000 ml normal saline before the administration of CSE anesthesia. The block was then performed by the needle-through-needle technique, using an 18-gauge Touhy needle (Perican; B. Braun, Melsungen, Germany) at either the L3-4 or the L4-5 interspace. After reaching the epidural space by the loss-of-resistance method, spinal anesthesia was performed using a 27-gauge pencil-point spinal needle (Espocan; B. Braun). Anesthesia was achieved using fentanyl 25 µg and hyperbaric bupivacaine 0.5% (12 mg). Following the placement of a catheter in the epidural space, the parturients were immediately placed in the supine position, and supplemental oxygen was delivered through a face mask, at $4 l \cdot min^{-1}$. If the anesthesia level did not reach T5 at 15 min, the epidural catheter was tested with lidocaine 2% and epinephrine and epidural top-ups were administered as needed.

Maternal ECG and oxygen saturation were monitored, and noninvasive blood pressure was measured every 2 min until the birth of the child, and every 5 min subsequently until the patient was moved to the postanesthesia care unit (PACU). IV fluids and ephedrine were administered as needed to maintain the systolic blood pressure within 20% of its preoperative value. The surgical technique was uniform for all patients and included exteriorization of the uterus. After the delivery, 5 IU oxytocin was administered IV and Apgar scores were recorded.

From a random number table, an allocation table was made to distribute the 108 patients into three groups. Five minutes after the delivery, patients received either lornoxicam 8 mg IV (group L; $n = 36$), ondansetron 8 mg IV (group O; $n = 36$), or normal saline 2 ml IV (group P; $n = 36$). The study drugs were prepared by an anesthesiologist who did not participate in the care and evaluation of the patients. The patients were not aware of the drug they received. Pruritus, pain, and nausea or vomiting were assessed by the same clinician who cared for the patients in the perioperative and postoperative periods. Patients were assessed every 2 h for 24 h after the induction of spinal anesthesia and at least once a day subsequently until discharge from the hospital. Pruritus was classified as absent, mild (restricted to one area such as face or arms, not troubling the patient, often reported only after prompting), moderate (affecting a larger area such as face and arms or face and anterior surface of thorax, not disturbing the patient, therefore not requiring treatment), or severe (extensive or generalized, often disturbing the patient to the point of necessitating treatment). Patients who continued to have severe pruritus were treated with 25 mg diphenhydramine IV. Postoperatively, for 24 h, pain was evaluated by the patients on a visual analog scale (VAS) with scores ranging from 0, no pain, to 10, worst imaginable pain. Patients with a VAS score higher than 3 received bupivacaine through the epidural catheter with patient controlled analgesia (PCA) for postoperative analgesia. The bolus was set at 5 ml bupivacaine 0.125%, with a lockout time of 30 min and a $10 \cdot ml \cdot h^{-1}$ background infusion. Patients were also asked to evaluate their nausea or vomiting according to a three-point scale, with 0, no nausea or vomiting; 1, mild to moderate nausea or vomiting not necessitating treatment; and 2, severe nausea or vomiting necessitating treatment. Nausea and vomiting were treated with metoclopramide 10 mg IV as needed.

Statistical analysis

Prior to the initiation of the study, a power analysis was performed. A minumum of 34 patients were required in each group to detect a decrease from 80% to 30% with a power of 80% and a significance level of 95%. Statistical analysis was performed using the 11.0 version of SPSS for Windows software package (SPSS, Chicago, IL, USA). Within the groups, normality for continued variables was determined using the Shapiro-Wilk test. The groups were compared with respect to age, height,

Table 1. Demographic data, Apgar scores, and durations of operations in the three groups

	Group L ($n = 36$)	Group O ($n = 36$)	Group P ($n = 36$)
Age (years)	30.04 ± 4.94	30.45 ± 0.90	30.20 ± 0.97
Weight (kg)	75.7 ± 12.2	74.6 ± 9.03	75.6 ± 9.7
Height (cm)	161.8 ± 3.9	162.0 ± 4.2	162.9 ± 4.5
Apgar 1-min	8 (5–10)	8 (5–10)	8 (6–10)
Apgar 5-min	10 (7–10)	10 (7–10)	10 (6–10)
Surgery (min)	36 ± 9	38 ± 10	39 ± 9

Values are presented as means ± SD or medians (ranges)
There were no significant differences between the groups

Table 2. Patients with pruritus in groups, stratified by time

	Group L ($n = 36$)	Group O ($n = 36$)	Group P ($n = 36$)
0–4 h	18 (50)	18 (50)	24 (66.7)
4–12 h	9 (25)	2 (5.6)*	9 (25)
12–24 h	1 (2.8)	0	3 (8.3)

* $P < 0.05$ versus group L and group P
Values are presented as numbers of patients and percentages

weight, and duration of the operation, using analysis of variance (ANOVA). Between the groups, comparisons of the incidence and severity of pruritus were done using the χ^2 test. A P value of less than 0.05 was considered to be statistically significant.

Results

The demographic data, Apgar scores of the babies, and the duration of the operations were similar in the three groups (Table 1). One patient in each group was excluded from the analysis because they required epidural top–ups. None of the patients required general anaesthesia due to a failed block. Within the first 4 h postoperatively, the incidence of pruritus was similar for group L, group O, and group P ($P > 0.05$). From 4 h until 12 h postoperatively, the incidence of pruritus was significantly lower for group O when compared to that in group L and group P ($P < 0.05$). From 12 h until 24 h postoperatively, the incidence of pruritus was similar for group L, group O, and group P ($P > 0.05$). The incidence of pruritus, stratified by time, is shown in Table 2.

According to the pruritus grading system we used, the number of patients experiencing no pruritus was significantly higher in group O when compared to that in group L and group P ($P < 0.05$). The number of patients experiencing moderate pruritus was significantly lower in group O when compared to that in group P ($P < 0.05$). On the other hand, the number of patients experiencing severe pruritus was similar in group L and group O ($P > 0.05$). Pruritus scores are shown in Fig. 1.

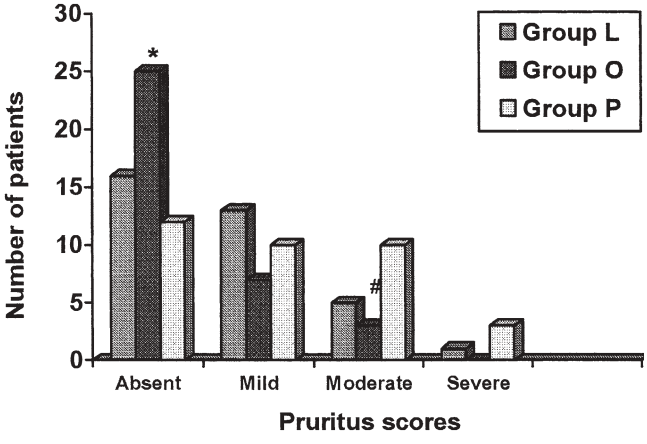

Fig. 1. According to the pruritus grading system used in the study, the number of patients experiencing no pruritus was significantly higher in group O when compared to that in group L and group P ($P < 0.05$; *asterisk*). On the other hand, the number of patients experiencing moderate pruritus was significantly lower in group O when compared to that in group P ($P < 0.05$; *hatch symbol*)

The incidence of nausea and vomiting, the severity of nausea and vomiting, and the time to reach a VAS score of 3 were similar in the three groups (Table 3). The VAS scores in all of the postoperative evaluation periods were also similar.

Discussion

The recommended dose for the intrathecal administration of fentanyl in the setting of cesarean sections ranges

Table 3. The incidence and severity of nausea and vomiting, and the time to reach a VAS = score of 3 in the three groups

	Group L ($n = 35$)	Group O ($n = 35$)	Group P ($n = 35$)
Nausea/vomiting	2/0	2/0	3/1
Nausea or vomiting: no/mild/severe	33/2/0	33/2/0	31/3/1
Time to reach VAS score of 3 (min)	116.2 ± 31.2	116.4 ± 32.9	108.2 ± 35.3

Values are presented as numbers or means ± SD
There were no significant differences between the groups

from 10 to 25 μg [8–12]. Within the recommended dose range, treatment of pruritus resulting from higher doses of intrathecal fentanyl is likely to be of benefit when $5HT_3$ receptor antagonists are used. On the other hand, the lack of efficacy of $5HT_3$ receptor antagonists such as ondansetron in the clinical scenario of lower doses of intrathecal fentanyl may be explained by the absence of the cephalad migration of fentanyl in the cerebrospinal fluid (CSF). Korhonen et al. [13] have suggested that small doses of fentanyl (such as 10 μg) may not reach the trigeminal nucleus in the spinal cord, where the center for pruritus is probably located. Therefore, the selection of 25 μg as the dose for the intrathecal administration of fentanyl in the present study enabled the authors to exploit all of the possible mechanisms towards the prevention of pruritus.

In the present study, lornoxicam did not reduce the incidence or the severity of fentanyl-induced pruritus for the initial 24 h postoperatively. However, the administration of 8 mg ondansetron IV resulted in a significant reduction in the number of patients experiencing pruritus, as well as a significant reduction in the severity of pruritus in patients who received fentanyl by the intrathecal route. Our study failed to demonstrate any significant antipruritic or analgesic effect of lornoxicam 8 mg within the first 24 h postoperatively. The reason for the lack of effectiveness of lornoxicam in our study may have been the use of a single dose of 8 mg. Had we administered lornoxicam at the recommended maximum daily dose of 24 mg, we could have better observed its effectiveness in alleviating pruritus. Due to the existing link between pain and pruritus pathways, the ineffective pain control may also explain the inadequate antipruritic effect. The timing of lornoxicam dosing may also have affected the results. It is possible that lornoxicam may have been more effective if it had been used prior to, rather than following, the intrathecal administration of fentanyl, in attempting to inhibit the generation of the prostaglandins that are involved in the mechanism of neuraxial opioid-induced pruritus. However, due to licensing regulations which prevent the use of lornoxicam prior to delivery since the drug may cross the placenta and affect the fetus, it was not possible for the authors to administer lornoxicam prior to the administration of fentanyl.

Another possible explanation for the lack of effectiveness of lornoxicam in the present study may be the altered drug metabolism during pregnancy. Throughout pregnancy, the albumin-to-globulin ratio falls [14] and increased plasma volume and changes in protein binding may alter the apparent volume of distribution (Vd) of drugs [15]. Furthermore, the metabolism of lornoxicam, which is catalyzed by select cytochrome P450 (CYP) isoenzymes (such as CYP3A4, CYP2D6 and CYP2C9), may change during pregnancy [15].

Colbert et al. [4] demonstrated that, in patients undergoing abdominal surgery for whom epidural fentanyl was administered, tenoxicam significantly decreased both the incidence and the severity of pruritus for 24 h postoperatively. In our study, lornoxicam did not reduce the incidence of pruritus. The difference between lornoxicam and tenoxicam regarding their effectiveness in the treatment of pruritus may be explained by the comparatively short half-life of lornoxicam.

Prophylactic IV administration of ondansetron has also been investigated for a possible anti-pruritic effect in intrathecal fentanyl-induced pruritus. In a recent study, Gurkan and Toker [16] showed that ondansetron 8 mg IV significantly reduced the incidence of pruritus, from 68% to 39%, in patients undergoing elective surgery. Likewise, Yeh et al. [17] and Charuluxananan et al. [18] demonstrated that ondansetron significantly reduced the incidence of intrathecal morphine-induced pruritus after cesarean section, from 85% to 25% and from 80% to 36%, respectively. Our results are consistent with these studies. Although there is no comparative study comparing the effects of ondansetron on opioid-induced neuroaxial pruritus in pregnant and non-pregnant patients, these studies suggested that the effect of ondansetron on pruritus did not change during pregnancy. On the other hand, some authors have demonstrated that the prophylactic IV administration of ondansetron did not decrease the incidence or the severity of pruritus [13,19]. Yazigi et al. [19] reported that the failure of ondansetron to prevent pruritus in their study may have been related to the fact that ondansetron could not reach $5HT_3$ receptors in the spinal cord before the highly lipophilic drug sufentanyl reached these receptors.

In conclusion, we observed that the administration of 8 mg IV lornoxicam failed to prevent intrathecal fentanyl-induced pruritus in parturients. Also, our data confirmed that ondansetron is likely to attenuate intrathecal fentanyl-induced pruritus.

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