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ORIGINAL ARTICLE

Effect of flurbiprofen, metoclopramide and droperidol for nausea and emesis during cesarean section under spinal anesthesia

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Abstract
Purpose Nausea and emesis frequently arise during cesarean section performed under spinal or epidural anesthesia, particularly after delivery. We have evaluated the treatment effects of flurbiprofen, metoclopramide and droperidol on nausea and emesis during cesarean section in patients under combined spinal and epidural anesthesia.
Methods The patient cohort comprised 361 patients with American Society of Anesthesiologists (ASA) physical status I or II who elected to undergo cesarean section. All patients received combined spinal–epidural anesthesia. After delivery, nausea and emesis was assessed using a 4-point scale as: 1, excellent, with no complaints; 2, mild nausea; 3, severe nausea; 4, emesis. Patients who experienced severe nausea or emesis were randomly assigned to receive one of the following intravenous drugs: Group A, flurbiprofen (50 mg); Group B, metoclopramide (10 mg); Group C, droperidol (1.25 mg). Effects on nausea and emesis were assessed at 5, 10 and 15 min after drug administration using a 4-point scale as: 1, obviously improved; 2, improved; 3, unchanged; 4 worsened.
Results Among the patients, 151 reported nausea or emesis. These patients experienced a longer duration of surgery and anesthesia and lost more blood than patients with no complaints. The frequency of improvement in the flurbiprofen group was significantly higher than that in the metoclopramide group at 5, 10 and 15 min ($p < 0.05$) after administration, and of that in the droperidol group at 15 min after administration ($p < 0.05$).
Conclusion Intravenous flurbiprofen improves nausea and emesis after delivery by cesarean section more effectively than metoclopramide or droperidol.

Keywords Flurbiprofen · Nausea and emesis · Cesarean section · Spinal anesthesia

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Introduction

Nausea and emesis during regional anesthesia for elective cesarean delivery is widespread, with a reported occurrence of 17–80% of patients experiencing a nausea and/or emesis event [1–11]. Metoclopramide and droperidol are commonly administered to reduce nausea and emesis in patients undergoing spinal anesthesia for cesarean section [1–3, 12]. Intraoperative nausea and emesis occur more often among patients taking opioid analgesics than among those taking nonsteroidal anti-inflammatory drugs (NSAIDs) [13]. Based on our clinical experience, we have considered the possibility that the administration of NSAIDS itself might have an effect on nausea and vomiting after cesarean section. However, the effectiveness of NSAIDs in improving nausea and emesis during caesarean section has not been determined. In the study reported here, we have compared the effects of flurbiprofen, metoclopramide and droperidol on nausea and emesis during cesarean section in patients under spinal anesthesia.

Methods

The institutional review board of Kiryu Welfare Hospital, Gunma University Hospital approved this study, and written, informed consent was obtained from all participating

patients. Healthy women ($n = 361$) scheduled for cesarean section under combined spinal and epidural (SE) anesthesia between January 2005 and October 2007 were recruited for this prospective, randomized, single-blind study. Randomization was performed with a random number table. Subjects were blinded to the administered drugs. Exclusion criteria included patients receiving systemic analgesics or sedatives other than intravenous (i.v.) flurbiprofen, metoclopramide and droperidol during the procedure.

None of the patients were premedicated, and all received 500 ml of acetate Ringer's solution before being placed in the lateral position to start the SE procedure. An epidural catheter was inserted via an 18-gauge Toughy needle at the L1–2 or L2–3 intervertebral space using a median or paramedian approach and the loss-of-resistance technique, and then advanced 5 cm cephalad. Spinal anesthesia was then achieved by injecting 2–2.6 ml of hyperbaric bupivacaine (0.5%) at the L3–4 or L4–5 intervertebral space using a 25-gauge pencil-point spinal needle. The dose was determined at the discretion of the anesthesiologist. Ten minutes after intrathecal injection and at the end of the surgery, the sensory blockade was assessed as the complete loss of cold perception to iced water at each dermatomal level.

Patients were administered 4–8 mg of i.v. ephedrine if the systolic blood pressure was <100 mmHg. After delivery of the baby and cord clamping, patients were i.v. administered 0.2 mg of methylergometrine maleate, 100 μg of epidural fentanyl and 2 ml of ropivacaine (0.2%).

The anesthesiologist asked the patients at 5-min intervals whether they felt nauseous and observed whether or not they vomited after delivery. According to the reported feeling of the patient, nausea and emesis were assessed on a 4-point scale as: 1, excellent, without complaints; 2, mild nausea; 3, severe nausea; 4, emesis. Any patient assessed as 3 or 4 on the scale was randomly assigned to groups administered i.v. with one of the following drugs: Group A, flurbiprofen 50 mg; Group B, metoclopramide 10 mg; Group C, droperidol 1.25 mg. Subsequent feelings of nausea and emesis were assessed at 5, 10 and 15 min after drug administration on a 4-point scale by a research assistant, who was blinded to which drug had been administered, as: 1, obviously improved; 2, improved; 3, unchanged; 4 worsened. If emesis was unchanged or worsened at 15 min after drug administration, another rescue antiemetic (metoclopramide 10 mg or droperidol 1.25 mg) was administered.

Data were analyzed at a later time by an individual who was also blinded to the treatment regimens. Sample sizes were calculated prior to the start of the study protocol as follows. Based on the incidence of expected improvement by metoclopramide and droperidol [12–14], we determined that 40 members in each group would be required to provide 80% power to detect a 20% difference among three groups. Taking into account the known incidence of nausea [5], we recruited a total of 361 patients for the study. Age, height, weight, duration of anesthesia and operation, blood loss volume, and total ephedrine consumption were compared between patients complaining of nausea or emesis and those with no complaints using the unpaired Student's t test, and among the three treatment groups using one-way analysis of variance (ANOVA). Sensory block level was analyzed between patients complaining of nausea or emesis and those with complaints using the Mann–Whitney U test, and among the three treatment groups using the Kruskal–Wallis test. The incidence of the effect was analyzed using two-way repeated-measures ANOVA followed by the Kruskal–Wallis test at each measurement time. If a significant results was obtained, the Mann–Whitney U test with Bonferroni correction was used to determine which groups differed significantly. Values of $p < 0.05$ were considered to be statistically significant.

Results

We excluded 16 patients from a final enrollment of 361, among whom 151 (43.8%) complained of nausea or emesis. Twenty-two patients assessed as 2 (mild nausea) on the nausea/emesis scale were followed closely without treatment. The drugs were administered to 129 patients who were assessed as 3 (severe nausea) and 4 (emesis) on the nausea/emesis scale. Another rescue antiemetic was provided after 15 min to 17 patients with unchanged or worsened emesis.

Age, height, weight, total ephedrine consumption and level of sensory block before and after delivery did not significantly differ among the non-treatment group and the three treatment groups (Tables 1, 2). The duration of surgery and anesthesia was longer for patients who complained of nausea or emesis, and these patients also lost more blood than those with no complaints ($p < 0.05$). However, duration of surgery and anesthesia and blood loss did not significantly differ among the three treatment groups.

The effects of the three treatments were significantly different ($p < 0.05$). Flurbiprofen was significantly more effective than metoclopramide in improving nausea and emesis at 5, 10 and 15 min (all $p < 0.05$), and more effective than droperidol at 15 min after administration ($p < 0.05$; Figs. 1, 2, 3). The effects on nausea and emesis did not significantly differ between the metoclopramide and droperidol groups at 5, 10 or 15 min (Figs. 1, 2, 3).

Discussion

Intraoperative emetic symptoms during cesarean section under regional anesthesia are problematic and can interfere

Table 1 Patient characteristics according to the presence or absence of nausea or emesis

Characteristic	Nausea and/or emesis ($n = 151$)	No complaints ($n = 194$)
Age (years)	31.1 ± 5.4	31.5 ± 4.3
Height (cm)	157.2 ± 5.8	157.0 ± 5.2
Weight (kg)	64.1 ± 8.9	64.5 ± 10.0
Duration of anesthesia (min)	79.3 ± 18.7*	73.9 ± 16.6
Duration of operation (min)	58.8 ± 16.7*	53.6 ± 14.3
Blood loss including amniotic fluid (g)	1204 ± 630*	1056 ± 641
Total ephedrine consumption (mg)	7.8 ± 8.8	7.7 ± 9.3
Sensory block level before delivery	Th4 (Th1–Th7)	Th4 (Th1–Th7)
Sensory block level after delivery	Th4 (C7–Th8)	Th4 (C7–Th8)

* $p < 0.05$ compared with the other group

Values are shown as mean ± standard deviation (SD) or as the median with the range in parenthesis

Table 2 Patient characteristics according to antiemetic treatment group

Characteristic	Group A ($n = 42$)	Group B ($n = 47$)	Group C ($n = 40$)
Age (years)	30.3 ± 5.6	31.7 ± 5.4	30.3 ± 4.7
Height (cm)	156.5 ± 6.6	156.2 ± 4.9	157.5 ± 5.8
Weight (kg)	62.0 ± 8.5	63.2 ± 9.3	67.3 ± 9.1
Duration of anesthesia (min)	79.6 ± 16.8	77.1 ± 15.1	79.1 ± 22.1
Duration of operation (min)	57.5 ± 14.2	57.0 ± 16.7	60.6 ± 20.0
Blood loss including amniotic fluid (g)	1241 ± 632	1222 ± 762	1168 ± 470.1
Total ephedrine consumption (mg)	6.8 ± 7.6	8.1 ± 8.8	8.2 ± 9.5
Sensory block level before delivery	Th4 (Th1–Th6)	Th4 (Th2–Th7)	Th4 (Th1–Th6)
Sensory block level after delivery	Th4 (Th1–Th7)	Th4 (Th1–Th8)	Th4 (C7–Th8)

Values are shown as the mean ± SD or as the median, with the range in parenthesis. There were no significant differences among groups

Group A, flurbiprofen; Group B, metoclopramide; Group C, droperidol

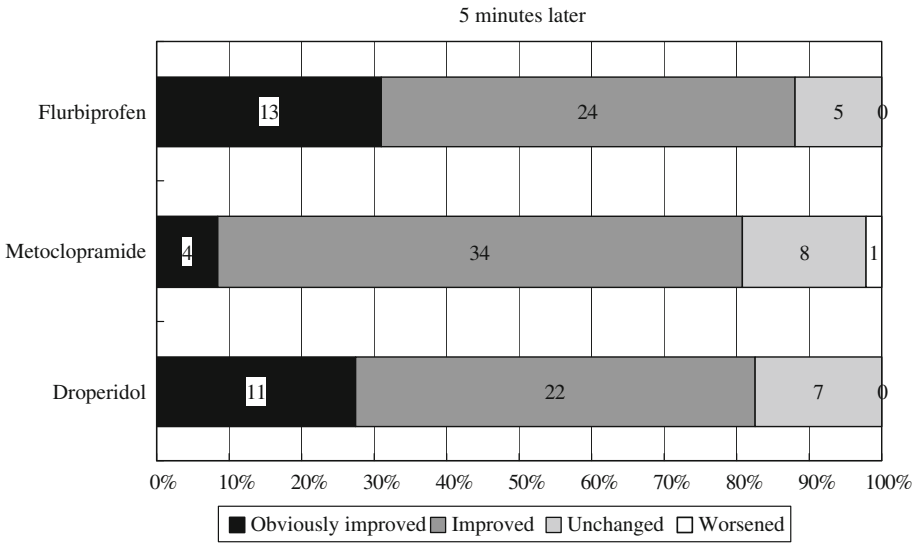

Fig. 1 Incidence of obvious improvement, improvement, no change and worsening in nausea and emesis 5 min post-administration of drug. Flurbiprofen was significantly more effective in improving nausea and emesis than metoclopramide after 5 min ($p < 0.05$). Effects on nausea and emesis did not significantly differ between flurbiprofen and droperidol, and between metoclopramide and droperidol

with the procedure. The incidence of intraoperative post-delivery emetic symptoms was lower in our study (43.8%) than that reported by Fujii et al. (63%) [10], but higher than that reported by Baliki et al. (17%) [11]. The overall incidence of intraoperative nausea and emesis during regional anesthesia for cesarean section is extremely variable and can reach 79%, depending on the anesthetic technique used and the preventive and therapeutic

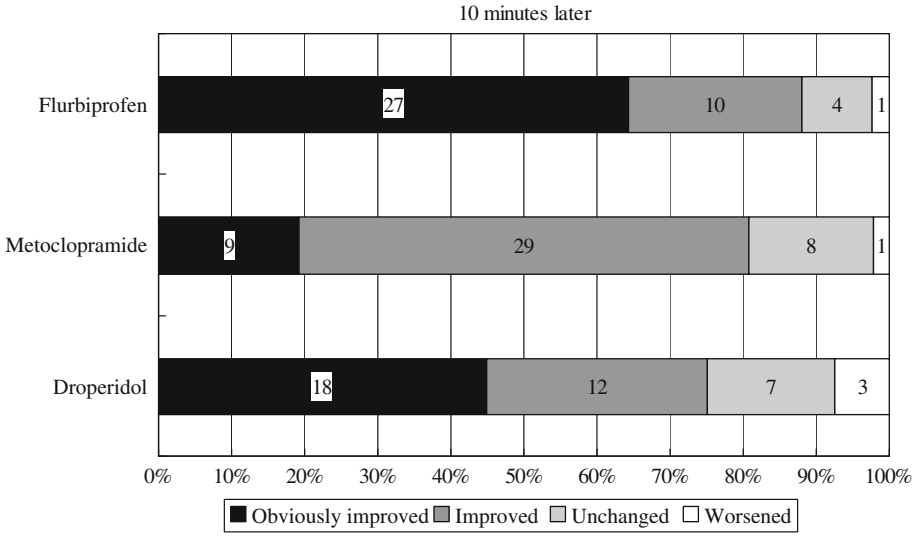

Fig. 2 Incidence of obvious improvement, improvement, no change and worsening in nausea and emesis 10 min post-administration of drug. Flurbiprofen was significantly more effective in improving nausea and emesis than metoclopramide after 10 min ($p < 0.05$). Effects on nausea and emesis did not significantly differ between flurbiprofen and droperidol, and between metoclopramide and droperidol

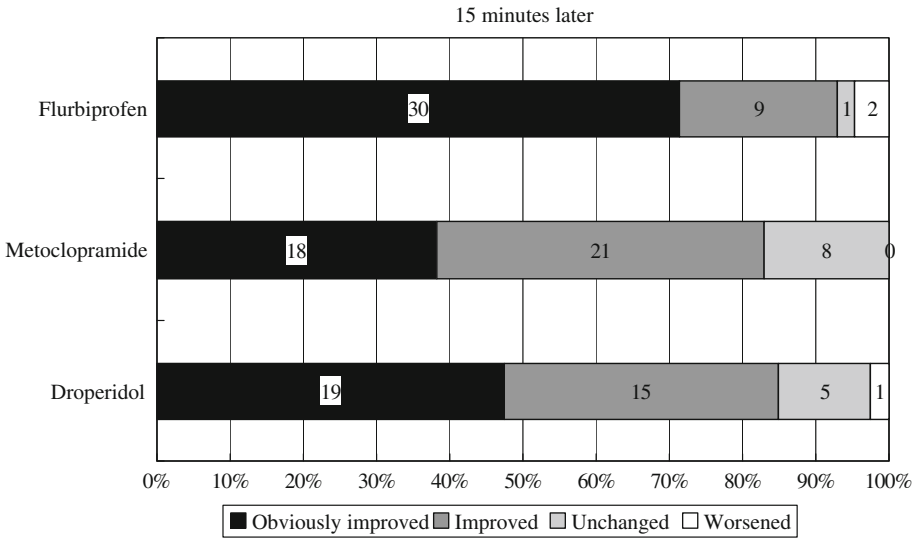

Fig. 3 Incidence of obvious improvement, improvement, no change and worsening in nausea and emesis 15 min post-administration of drug. Flurbiprofen was significantly more effective in improving nausea and emesis than metoclopramide and droperidol after 15 min ($p < 0.05$). Nausea and emesis did not significantly differ between metoclopramide and droperidol groups

measures applied [1–11]. Emetic symptoms have a complex and multifactorial etiology and can be influenced by age, gender, pain, operative procedure and anesthetic technique. This study and those reported by others involved a similar age group with one gender (female), with minimal pain under same anesthetic technique (regional anesthesia) for a single procedure (cesarean section). However, the reported incidence of nausea and emesis during cesarean section is extremely variable, possibly due to the differences in detailed surgical techniques and anesthetic procedure among these studies.

Maternal hypotension following the induction of spinal anesthesia is related to an increased incidence of intraoperative, post-delivery emetic symptoms [15]. We prevented hypotension using rapid fluid infusion, left uterine displacement and ephedrine as required. Total ephedrine consumption did not significantly differ among the non-treatment group and the three treatment groups.

Antiemetic therapy that is effective for one group of surgical patients may not be as effective for others undergoing a different surgical procedure or anesthetic technique. In our study, we focused on the antiemetic effects of flurbiprofen, metoclopramide and droperidol during cesarean section, and these agents were administered following the appearance of emetic symptoms. The dose of metoclopramide applied herein was based on a clinical investigation by Chestnut et al. [3] who reported that 0.15 mg/kg of metoclopramide administered after cord clamping during cesarean section under epidural anesthesia reduced the incidence of intraoperative nausea from 36 to 12% and emesis from 15 to 0%. Lussos et al. [2] reported significant reductions in the incidence of intraoperative

nausea from 81 to 14% and emesis from 43 to 5% when 10 mg of metoclopramide was administered before spinal anesthesia was initiated for cesarean section. The dose of droperidol applied to our patients was based on a clinical investigation by Fujii et al. [10] who reported that 1.25 mg of droperidol administered after clamping of the fetal umbilical cord in patients undergoing cesarean section under spinal anesthesia reduced the incidence of intraoperative nausea and emesis from 63 to 17%.

Our results demonstrate that i.v. flurbiprofen improved nausea and emesis after delivery during cesarean section more effectively than either metoclopramide or droperidol.

Wislicki [16] reported that prostaglandins administered to pregnant women can cause nausea and emesis. Prostaglandins and/or dopamine have also been regarded as possible mediators of radiation-induced emesis [17]. However, the exact mechanisms through which flurbiprofen improves emetic symptoms remain unclear. One possibility is that the NSAID flurbiprofen might improve nausea and emesis during cesarean section by inhibiting cyclooxygenase, which impairs prostaglandin synthesis.

Hirabayashi et al. [18] reported that visceral pain, which is associated with peritoneal traction and exteriorization of the uterus after delivery, is accompanied by nausea and emesis. Siddiqui et al. [19] showed that the incidence of intraoperative nausea and emesis was higher when the uterus was repaired while exteriorized than while remaining in situ (38 vs. 18%). In our study, in situ uterine repair was adopted for all patients. We found that patients complaining of nausea or emesis endured longer surgery and anesthesia and lost more blood than patients with no complaints. This difference may be explained by the possibility that lengthy surgery is associated with more forceful peritoneal traction.

Fujii et al. [10] demonstrated that droperidol reduced the rate of emetic symptoms during cesarean section from 63% in a placebo group to 17%, and that metoclopramide reduced symptoms to a rate of 20%. We found that the rate of intraoperative post-partum emetic symptoms was 43.8%. The incidence of nausea and emesis remained at 61.7 and 52.5% in the metoclopramide and droperidol groups, respectively, at 15 min post-administration. If these drugs were preemptively administered to all of our patients, the estimated incidence of emesis would have been 27.0% (determined by multiplying 43.8% by 61.7%) in the metoclopramide group and 23.0% (determined by multiplying 43.8% by 52.5%) in the droperidol group, which would be similar to the results reported by Fujii et al [10].

In our stuy, the effects of metoclopramide and droperidol on nausea and emesis did not significantly differ (Figs. 1, 2, 3), which supports the findings of others [14].

To the best of our knowledge, this is the first published study demonstrating that i.v. flurbiprofen is more effective than metoclopramide or droperidol in improving post-partum nausea and emesis during cesarean section under spinal anesthesia. However, we are not going to recommend single use of flurbiprofen for nausea and emesis because emetic symptoms have a complex and multifactorial etiology.

The Japanese Ministry of Health and Welfare has not yet approved ondansetron for perioperative nausea and emesis, so we could not compare our findings with the effects of this drug. The short study period (15 min) is a limitation of our study. Further studies are thus required to compare the effects of flurbiprofen with other antiemetics, such as ondansetron, for a long period.

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