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Effect of fentanyl on nausea and vomiting in cesarean section under spinal anesthesia: a randomized controlled study

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Abstract

Objective: Although opioids may induce nausea and vomiting, they possess sedative effects and can reduce intraoperative nausea and vomiting (IONV). This study assessed the effect of adding fentanyl to midazolam on sedation levels and IONV during cesarean section under spinal anesthesia.

Methods: Eighty parturients scheduled for elective cesarean section were enrolled in the study. Following fetal delivery, patients were administered 0.05 mg/kg of midazolam plus 0.03 mL/kg of normal saline (M group) or 0.05 mg/kg of midazolam plus 1.5 μg/kg of fentanyl (MF group). The primary outcome was the incidence of IONV. The secondary outcomes were incidence of post-operative nausea and vomiting (PONV), intraoperative sedation level, and five-point patient satisfaction score (PSS).

Results: The IONV incidence was significantly lower in the MF group compared with the M group (5% [2/40] vs. 25% [10/40]). The PONV incidence did not differ significantly between the groups. The intraoperative sedation level tended to be deeper in the MF group. The 5-point PSS was significantly higher in the MF group. There was a strong correlation between the sedation level and IONV incidence.

Conclusions: Adding fentanyl to midazolam is effective for sedation and to prevent IONV in women who are undergoing cesarean section under spinal anesthesia.

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Introduction

Spinal anesthesia is widely used for cesarean section. Although hypotension is a common adverse effect, the technique offers the advantages of a fast onset, high block density, and a high success rate. Compared with general anesthesia, spinal anesthesia has few adverse effects, and it is associated with good maternal and fetal outcomes.[1] Spinal anesthesia provides the mother with the opportunity to see her child immediately after delivery, in a state of awareness. This alertness, however, can cause mental stress in the mother because she is unable to move her legs and may experience tremors because of both a decreased body temperature and nausea and vomiting. Patients frequently experience these discomforts during cesarean section under spinal anesthesia,[2,3] and they may reduce patient satisfaction with the procedure.[4]

Intraoperative nausea and vomiting (IONV) is a complex multifactorial problem that results from anesthetic and non-anesthetic factors. Its major causative factor is hypotension, but it is also produced by various factors such as surgical stimuli, uterotonic agents, and increased vagal activity.[5] Concomitant sudden contractions of the diaphragm associated with IONV may reduce patient satisfaction and result in damage to the abdominal organs. IONV must, therefore, be controlled to prevent the aspiration of vomit.[5] The incidence and severity of IONV can be controlled using sedative drugs such as midazolam and propofol.[6–8] While these agents differ in their manner of use, they generally have similar effects.[9]

The sedative effect of benzodiazepine drugs may be increased by the concomitant administration of narcotic analgesics. Administration of a combination of midazolam and fentanyl immediately before spinal anesthesia has been found to result in maternal comfort, without neonatal adverse effects.[10] Although opioids are a risk factor for postoperative nausea and vomiting (PONV), the relationship between IONV and PONV is unclear, especially with respect to the amount and type of analgesic administered, as well as the timing of injection.[11,12]

We hypothesized that, compared with midazolam alone, sedation with a combination of fentanyl and midazolam would reduce the incidence of IONV in mothers who are undergoing cesarean section under spinal anesthesia, an outcome that may be the result of more effective sedation.

Materials and methods

This prospective, double-blind, randomized controlled trial was approved by the institutional review board at Gumi Cha Hospital (Gumi, South Korea; approval No.16-07). The study was conducted at Gumi Cha Hospital between April and December 2016. Written informed consent was obtained from each parturient or care giver. The trial was registered with the Clinical Research Information Service (KCT0002424).

The study included parturients aged 20 to 40 years, with American Society of

Anesthesiologists (ASA) classification I to II, who were scheduled for elective cesarean section. Parturients were excluded if they had significant pre-existing maternal or fetal medical problems, chronic pain, insulin-dependent diabetes mellitus, hypertensive disease of pregnancy, a body mass index >39 kg/m^2 (morbid obesity), or a low sensory level, or if they refused sedation. Typical indications for a scheduled cesarean section included a history of prior cesarean delivery and fetal malpresentation.

Randomization and blinding

Randomization sequences of blocks of four subjects created by a computer were saved in Redcap (redcap.cnuh.co.kr). This randomization function in Redcap was accessible only to researchers who were preparing study drugs. These researchers were not involved in patient monitoring or outcome analyses, and prepared identical 3-mL syringes with either fentanyl (Myungmoon Pharm. Co., Ltd., Seoul, Korea) (MF group) or normal saline (M group). Following administration of spinal anesthesia and confirmation of a proper level of anesthesia, the subjects were randomized in a 1:1 ratio to either the M group or the MF group.

Intraoperative management

All parturients were treated with Ringer's lactate solution (10 mL/kg) for 10 to 20 minutes to prevent hypotension. Spinal anesthesia for subjects with a base height of 155 cm consisted of 1.8 mL heavy bupivacaine (0.5%; Mitsubishi Tanabe Pharm Korea Co., Ltd., Seoul, Korea) with 0.1 mL added or subtracted for every 5 cm difference in height. Bupivacaine was injected intrathecally into the L3–4 or L4–5 intervertebral space using a 26-gauge Quincke spinal needle (Taechang Industrial Co., Ltd., Seoul, Korea). The parturient was placed in the left tilt position to prevent hypotension resulting from aortocaval compression, and oxygen was supplied at a rate of 5 L/minute through a facial mask. Oxygen saturation, electrocardiogram (EKG), and automated noninvasive blood pressure were monitored continuously. If the blood pressure decreased >20% from baseline or if the systolic blood pressure decreased below 90 mmHg, 4 mg of ephedrine was injected, with the administration repeated if the blood pressure did not recover. Surgery was initiated following identification of the anesthetized segment using a pinprick test. Immediately following delivery, fetal aspiration was assessed, Apgar scores were assigned, and the neonate was shown to the mother. Patients were subsequently administered 0.05 mg/kg midazolam (Bukwang Pharm Co., Ltd., Seoul, Korea) plus 0.03 mL/kg normal saline (M group) or 0.05 mg/kg midazolam plus 1.5 μg/kg fentanyl (MF group). Midazolam was administered after examining the neonate, with fentanyl or saline administered 2 to 3 minutes later to prevent apnea and hypotension.

Data collection

The primary outcome was the incidence of IONV. To exclude nausea and vomiting that result from hypotension that was experienced immediately after spinal anesthesia, assessment of IONV was based on symptoms occurring from the injection of the study drug to the end of the surgery because the injection of the study drug took place after delivery of the neonate.

The secondary outcomes were the incidence of PONV, intraoperative modified Ramsay Sedation Scale (mRSS) score, and five-point patient satisfaction score (PSS).

Blood pressure, pulse rate, oxygen saturation, mRSS score, and nausea and vomiting score (Bellville score) were measured before and after administration of spinal anesthesia, immediately after fetal delivery,

5 and 15 minutes after administration of midazolam plus fentanyl or saline, and at the end of the procedure. mRSS scores ranged from 1 to 6, with 1 indicating anxiety, agitation, and restlessness; 2 indicating awake, cooperative, oriented, and tranquil; 3 indicating semi-asleep but responsive to commands; 4 indicating asleep but with brisk response to a glabellar tap or loud auditory stimulus; 5 indicating asleep with sluggish or decreased response to glabellar tap or loud auditory stimulus; and 6 indicating no response. Scores from 4 to 6 on the mRSS were deemed to be associated with no nausea symptoms because of the deep sedation levels. Nausea and vomiting scores ranged from 0 to 3, with 0 indicating no symptoms, 1 indicating nausea, 2 indicating retching, and 3 indicating vomiting. Patients with nausea and vomiting scores ≥ 2 or more than two episodes of nausea were treated with 10 mg of metoclopramide. Satisfaction with sedation and anesthesia before transfer to the ward was assessed using satisfaction scale scores, which ranged from 5 to 1, with scores of 5, 4, and 3 indicating, respectively, definite agreement, agreement, and possible agreement on the part of the patient to undergo spinal anesthesia the next time; 2 indicating the patient was unlikely to undergo repeat spinal anesthesia; and 1 indicating refusal to repeat spinal anesthesia.

Statistical analysis

In a pilot study, IONV occurred in four of ten (40%) midazolam-treated patients. The effect size was calculated such that administration of fentanyl would reduce the incidence of IONV by 10%. The sample size for each group was calculated as 36, assuming a power of 0.8 and a two-sided alpha of 0.05. Because of an expected dropout rate of 10%, 80 patients were recruited into this study.

Normality was assessed using the Shapiro–Wilk test. Continuous variables were recorded as the mean $\pm$ standard deviation (SD) or median (upper and lower quartiles), and differences were analyzed using independent *t*-tests or Mann–Whitney *U*-tests, depending on the results of normality testing. Quantitative variables were reported as the number (%) and compared using χ^2 tests or Fisher's exact tests. The Cramer's V was used to evaluate the correlation between categorical variables.[13] Repeated measurements (e.g., blood pressure, heart rate) were analyzed using repeated measures analysis of variance. P values <0.05 were considered to be statistically significant. All statistical analyses were performed using R software version 3.4.2 (R Project for Statistical Computing, Vienna, Austria).

Results

Initially, the study included 82 parturients; however, two did not wish to undergo sedation and were subsequently excluded. Eighty parturients were randomly assigned to one of two groups, with 40 parturients assigned to the M and 40 parturients assigned to the MF group. Data from all participants were analyzed (Figure 1). Body weight was significantly higher in the MF group compared with the M group ($P = 0.012$), but other demographic data were similar (Table 1). Among the 80 patients, 12 (15%) experienced IONV: two (5%) of 40 in the MF group and ten (25%) of 40 in the M group ($P = 0.012$, relative risk 0.79, 95% confidence interval [0.65–0.96]). The incidence of PONV in the MF (5% [2/40]) and M (20% [8/40]) groups did not differ significantly. The antiemetic agent metoclopramide was administered to nine (22.5%) patients in the M group, compared with no patients in the MF group, which was statistically

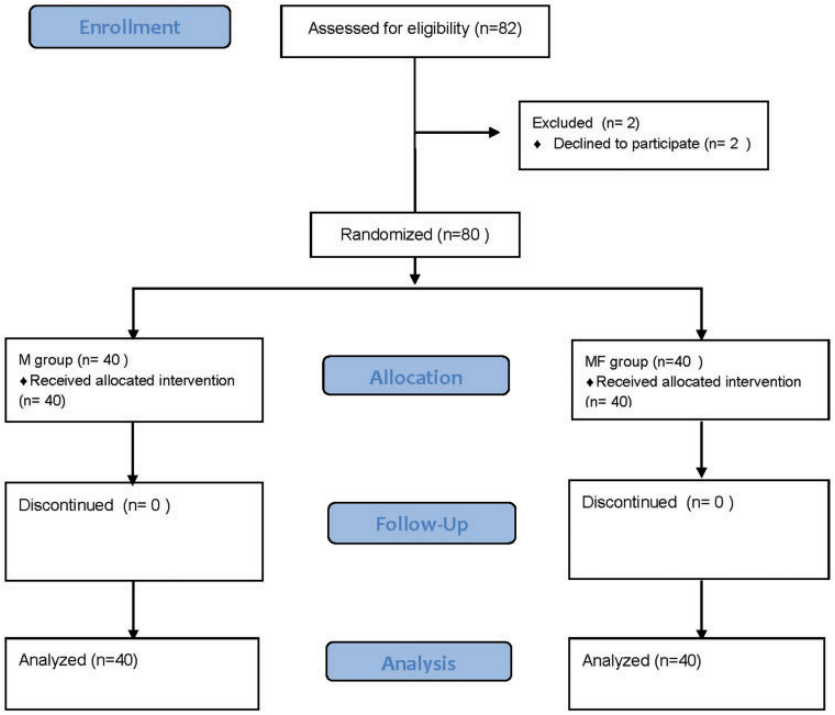

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

Table 1. Demographic characteristics of the M and MF groups.

	M (n = 40)	MF (n = 40)
Age (years)	33.0 [30.5;35.5]	32.5 [31.0;35.5]
Height (cm)	160.2 ± 4.1	161.7 ± 4.2
Weight (kg)	68.8 ± 9.7	75.2 ± 12.5
Surgery time (minutes)	51.5 [45.0;56.0]	55.0 [46.0;67.5]
Pregnancy period (days)	267.0 [264.0;270.0]	268.0 [265.0;270.5]
Sensory level		
T4	32 (80%)	37 (92.5%)
T5	8 (20%)	3 (7.5%)

Data are expressed as the mean ± standard deviation, median [quartile], or number (%).
Abbreviations: M, midazolam; MF, midazolam plus fentanyl.

significant ($P = 0.005$). Patient satisfaction immediately after surgery was significantly higher in the MF compared with the M group (4.2 ± 0.7 vs. 3.4 ± 0.9, $P < 0.001$; Table 2).

During surgery, the mRSS score was higher in the MF compared with the M group (Table 3). IONV occurred mainly at low mRSS scores, and the correlation between IONV and mRSS

Table 2. Primary and secondary outcomes of patients in the M and MF groups.

	M (n = 40)	MF (n = 40)	p
Intraoperative N/V	10 (25.0%)	2 (5.0%)	0.028
N/R/V	8/1/1	2/0/0	
Postoperative N/V	8 (20.0%)	2 (5.0%)	0.091
N/R/V	8/0/0	2/0/0	
Use of antiemetics	9 (22.5%)	0 (0%)	0.005
Intraoperative/Postoperative	8/1	0/0	
Patients with ephedrine injected	17 (42.5%)	13 (32.5%)	0.488
Ephedrine (mg)	3.8 ± 4.9	3.0 ± 4.8	0.460
Five-point satisfaction score	3.4 ± 0.9	4.2 ± 0.7	<0.001

Data are expressed as the mean ± standard deviation, number of patients (n), or n (%).
Abbreviations: M, midazolam; MF, midazolam plus fentanyl; N, nausea; R, retching; V, vomiting.

Table 3. Modified Ramsay Sedation Scale score during operation in the M and MF groups.

	M (n = 40)	MF (n = 40)	P
After delivery and study drug injection			0.603
1	1 (2.5%)	1 (2.5%)	
2	39 (97.5%)	38 (95.0%)	
4	0 (0.0%)	1 (2.5%)	
5 minutes after study drug injection			<0.001
2	13 (32.5%)	0 (0.0%)	
3	13 (32.5%)	8 (20.0%)	
4	14 (35.0%)	27 (67.5%)	
5	0 (0.0%)	5 (12.5%)	
15 minutes after study drug injection			<0.001
2	18 (45.0%)	2 (5.0%)	
3	16 (40.0%)	11 (27.5%)	
4	6 (15.0%)	26 (65.0%)	
5	0 (0.0%)	1 (2.5%)	
End of operation			0.009
2	38 (95.0%)	28 (70.0%)	
3	2 (5.0%)	6 (15.0%)	
4	0 (0.0%)	6 (15.0%)	
After entering recovery room			1.000
2	39 (97.5%)	40 (100.0%)	
3	1 (2.5%)	0 (0.0%)	

Data are expressed as the number of patients (n), or n (%). Abbreviations: M, midazolam; MF, midazolam plus fentanyl.

scores using Cramer's V was very strong (Cramer's V: 0.372 and 0.442 at 5 and 15 minutes, respectively, after study drug injection).[13]

The hemodynamic data measured before and after anesthesia induction, immediately after delivery, 5 and 15 minutes after study drug administration, and at the end of

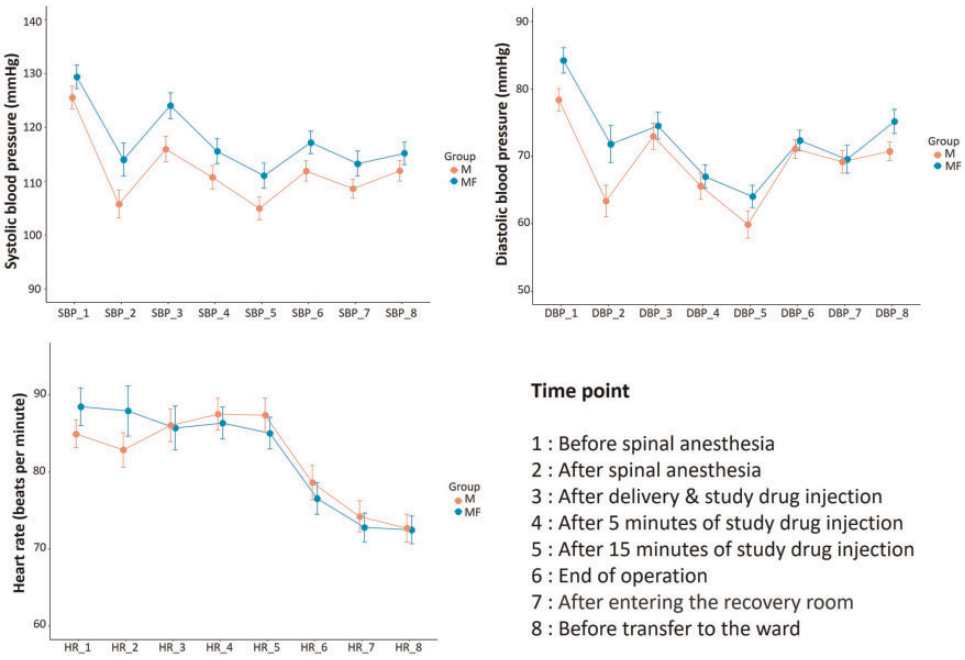

Figure 2. Hemodynamic changes during surgery. There were changes over time but there was no interaction between time and group.

surgery varied over time, but there were no between-group differences (Figure 2).

Discussion

In this study, the frequency of IONV was significantly lower in the MF compared with the M group. The combination of fentanyl and midazolam resulted in an additive sedative effect and a reduction in IONV.

Spinal anesthesia reduces an observer's assessment on the alertness/sedation scale and on the self-sedation visual analogue scale scores, with greater sedation in patients who were administered the combination of spinal anesthesia and fentanyl in the spinal cord compared with those receiving spinal anesthesia alone.[3] Although opioids are frequent causes of PONV,[11] fentanyl injected into the spinal cord and epidural space reduces rather than increases IONV.[14,15] However, it remains unclear whether increased nausea and pruritus are typical side effects of intrathecal opioids,[16] making it necessary to examine the effects of the amounts and types of opioids.[12]

IONV can cause abdominal organ damage because of sudden contraction of the diaphragm, and it can also increase the risk of pulmonary aspiration. Because progesterone relaxes smooth muscles, increases gastrin secretion, reduces gastrointestinal motility, and lowers esophageal sphincter tone, IONV is more frequent in progesterone-enhanced parturients.[17] However, other causative factors can also play a role in nausea and vomiting, including smoking status, age, sex, previous history of septicemia, history of PONV, hypotension, surgical methods, and hormonal changes.[11,18] Patients with low anesthesia levels that could cause anxiety or pain were excluded from this study, and no patients were anesthetized at or lower

than T6. Hypotension is an important factor in the development of IONV. Our study also showed a slight decrease in blood pressure after anesthesia, but there were no differences between the two groups with respect to this variable, and no difference in the number of ephedrine-treated patients. The incidence of PONV was similar in the two groups. The number of patients who received metoclopramide during surgery was significantly higher in the M group, suggesting that this treatment may have decreased the incidence of PONV.

The degree of anxiety and sedation during surgery can affect nausea and vomiting. Propofol is an intravenous anesthetic that can induce deep sedation and has anti-vomiting activity. Induction and maintenance of anesthesia with propofol was found to reduce the incidence of PONV and prevent early PONV, and results similar to those observed with ondansetron 4 mg.[19] Propofol can also be used as an antiemetic agent in the recovery room, with a bolus dose of 20 mg considered appropriate.[20] However, propofol has direct antiemetic properties, as well as acting to some extent as a serotonin receptor (5-HT3) antagonist.[21] It remains unclear, therefore, whether the propofol-induced reduction in vomiting is a sedative effect. The degree of sedation during certain procedures has been associated with a greater degree of satisfaction.[22] In the present study, satisfaction was significantly higher in the MF group, in which patients experienced a higher degree of sedation, compared with the M group. Administration of 1.5 μg/kg of fentanyl enhances the sedative effects of midazolam, with high-quality sedation reducing IONV and increasing patient satisfaction with surgery. Fifteen minutes after injection of the study drug, 27 (67.5%) and six (15%) patients in the MF and M groups, respectively, had mRSS scores $\geq$4, and sedation levels were higher in the MF compared with the M group. IONV was more frequent, and satisfaction scores were lower, in the M group compared with the MF group. These findings suggest that proper sedation during surgery under spinal anesthesia is essential. The addition of opioids to sedatives may, therefore, be indicated.

All patients in both groups in this study received 0.05 mg/kg of midazolam. Midazolam has anti-anxiety and sleep-inducing effects, but also has an antiemetic effect. Although its mechanism of action is not clear, midazolam is thought to reduce anxiety and lower the excretion of dopamine into the chemoreceptor trigger zone.[23,24] A comparison of midazolam with metoclopramide in parturients undergoing cesarean section under spinal anesthesia found that midazolam was more effective than metoclopramide in preventing nausea and vomiting.[25] In the present study, about 25% of parturients in the M group experienced IONV, a result that differed from the low incidence of IONV that was observed in other studies.[8,9] This discrepancy likely results from our administration of a single bolus injection rather than the continuous infusion that was administered in other studies. In the MF group, fentanyl was administered only as a single bolus, along with midazolam, but intravenous sedation was maintained properly, and IONV was also decreased.

In conclusion, treatment with fentanyl with midazolam is effective for sedation and to prevent IONV in women undergoing cesarean section under spinal anesthesia.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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