Original Article

Treatment of postoperative nausea and vomiting after spinal anesthesia for cesarean delivery: A randomized, double-blinded comparison of midazolam, ondansetron, and a combination

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Abstract

Background: The antiemetic efficacy of midazolam and ondansetron was shown before. The aim of the present study was to compare efficacy of using intravenous midazoalm, ondansetron, and midazolam in combination with ondansetron for treatment of nausea and vomiting after cesarean delivery in parturient underwent spinal anesthesia.

Materials and Methods: One hundred thirty two parturients were randomly allocated to one of three groups: group M (n = 44) that received intravenous midazoalm 30 μg/kg; group O (n = 44) that received intravenous ondansetron 8 mg; group MO (n = 44) that received intravenous midazoalm 30 μg/kg combined with intravenous ondansetron 8 mg if patients had vomiting or VAS of nausea $\geq$ 3 during surgery (after umbilical cord clamping) and 24 hours after that. The incidence and severity of vomiting episodes and nausea with visual analog scale (VAS) > 3 were evaluated at 2 hours, 6 hours, and 24 hours after injection of study drugs.

Results: The incidence of nausea was significantly less in group MO compared with group M and group O at 6 hours postoperatively ($P = 0.01$). This variable was not significantly different in three groups at 2 hours and 24 hours after operation. The severity of nausea and vomiting was significantly different in three groups at 6 hours after operation ($P < 0.05$).

Conclusion: Our study showed that using intravenous midazolam 30 μg/kg in combination with intravenous ondansetron 8 mg was superior to administering single drug in treatment of emetic symptoms after cesarean delivery under spinal anesthesia.

Key Words: Anesthesia, cesarean section, midazoalm, ondansetron, postoperative nausea and vomiting, spinal

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INTRODUCTION

Nausea and vomiting during spinal anesthesia for elective cesarean delivery is a common finding and may occur in up to 66% of patients.[1] The usual drugs used for prevention or treatment of this important adverse effect have adverse effects such as intense sedation, dystonic

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reactions, restlessness, and extrapyramidal symptoms.[2]

Tarhan *et al.*[1] showed that administration of a subhypnotic dose of midazolam was as effective as the subhypnotic dose of propofol for prevention of nausea and vomiting in parturient candidates for cesarean delivery under spinal anesthesia. Ondansetron is a 5-HT3 antagonist that is also effective in reducing nausea in this setting.[4,5] Both IV ondansetron and IV midazolam have been used for preventing nausea and vomiting during cesarean delivery but to the best of our knowledge no study evaluated the efficacy of combined use of these drugs in comparison with each drug alone.

Therefore, we designed this randomized, double-blinded placebo controlled study to assess and compare efficacy of intravenous midazolam, intravenous ondansetron, and combination of two drugs for treatment of nausea and vomiting in the patient candidate for elective cesarean delivery under spinal anesthesia.

MATERIALS AND METHODS

One hundred thirty two American Society of Anesthesiologists (ASA) physical status I patients, aged 18--45 years, scheduled for elective cesarean delivery under spinal anesthesia and had vomiting or nausea visual analog scale (VAS) equal or more than three during surgery or after that, gave written informed consent to participate in the present study, which was approved by our institute Ethics Committee. Patients who had smoking habit, obstetric complications or any evidence of fetal compromise or patients who had history of motion sickness, previous postoperative emesis, gastrointestinal disease or administration of antiemetic medication in the previous 24 hours, with allergy to the study drugs, or any contraindication for spinal anesthesia were excluded from the study.

Before beginning spinal anesthesia, patients were instructed on the use of the visual analog scale (VAS = a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured; 0--10 cm: 0 = no pain, 10 = the worst pain possible) for pain and nausea (0--10 cm: 0 = no nausea, 10 = the worst nausea possible) evaluation. Monitoring included continuous ECG, noninvasive blood pressure, and pulse oximetry. Using a computer-generated list of random numbers, patients were allocated to one of three groups to receive intravenous midazolam 30 μg/kg (maximum 2 mg) (group M, n = 44), intravenous ondansetron 8 mg (group O, n = 44), intravenous midazolam 30 μg/kg plus intravenous ondansetron 8 mg (group MO) if patients had vomiting or VAS of nausea ≥ 3 during surgery (after umbilical cord clamping) and 24 hours after that. The dosage of study drugs were formulated based on the previous studies.[1,3] The study drugs were administered immediately after occurrence of vomiting or VAS of nausea ≥3.

An anesthesiologist prepared coded identical syringes with similar volume containing either the study medications for each subject. Administration of study drugs was done by another anesthesiologist who was not aware of the type of drugs used. After arrival of patients in the operating room and intravenous (IV) access, 15 ml/kg of Ringer solution was infused within 10 minutes before the initiation of the spinal block. Spinal anesthesia was done in sitting position with a 25-gauge Whitacare needle, using a midline approach at L4-5 interspace. Once free flow of CSF had been recognized, 10 mg of 0.5% bupivacaine was injected over 15 seconds.

The incidence of vomiting episodes and nausea with visual analogue scale (VAS) > 3 was evaluated at baseline (at the first time which patient had nausea with VAS > 3 or vomiting before administration of drugs), 2 hours, 6 hours, and 24 hours after injection of study drugs by resident of anesthesiology who was not aware of the group allocation. Nausea and vomiting after injection of the study drugs was evaluated in intervals of 2 hours, 6 hours, and 24 hours after its occurrence.

The severity of nausea was assessed by VAS (where mild = VAS 1--3; moderate = VAS 4--6; severe = 7--10). If patients had vomiting or nausea with VAS ≥ 3, metoclopromide 0.15 mg/kg was immediately administered intravenously and its total dose was recorded at intervals of 2 hours, 4 hours, and 24 hours after occurrence of its injection. Nausea was characterized as a subjectively unpleasant sensation associated with awareness of the urge to vomit, and vomiting was defined as the forceful expulsion of gastric contents from the mouth. For the purpose of data collection, retching (same as vomiting but without expulsion of gastric contents) was considered vomiting.

Sedation was assessed by the Ramsay sedation scale (where 1 = anxious or restless or both; 2 = cooperative, orientated and tranquil; 3 = responding to commands; 4 = brisk response to stimulus; 5 = sluggish response to stimulus; 6 = no response to stimulus)[6] before beginning surgery, 2 hours, 6 hours, and 24 hours after injection of study drugs. Postoperative pain was evaluated by using a visual analog scale (from 0 = no pain to 100 = worst pain imaginable) before beginning surgery, 2 hours, 6 hours, and 24 hours after administration of study drugs. If patients had pain with VAS ≥ 3, meperidine 0.4 mg/kg was administered

and its total dose was recorded.

The adverse effects of study drug administration including respiratory depression (respiratory rate less than 8 per minutes), headache, dizziness, and hiccup were recorded.

A power analysis showed that 44 patients per group would provide 80% power and a statistical significance of 0.05 to detect a 20% decrease in the incidence of nausea and vomiting among treatment groups. Statistical analysis was performed using SPSS 16 for Windows. Data were presented as mean ± standard deviation (SD), median or number (%). Patient demographics, duration of surgery and PACU stay time, rescue opioids, and metoclopromide dosage were analyzed by using one-way ANOVA and multiple comparison between pairs was performed by Scheffe's test. VAS scores were compared among groups by two-way analysis of variance for repeated measures. Nominal or ordinal variables were analyzed using the chi-square test. Fisher's exact test was used when appropriate. The median sedation level between groups was compared with the Kruskall--Wallis test. A P value less than 0.05 was considered to be significant.

RESULTS

One hundred thirty-two patients were included in the study. There were no patients excluded from the study due to existence of any problem [Figure 1]. The demographic data, duration of surgery, and PACU stay were not significantly different in the three groups as shown in Table 1.

The incidence of postoperative nausea (VAS > 3) and vomiting at baseline, 2 hours, 6 hours, and 24 hours is shown in Table 2. The incidence of nausea was significantly less in group MO compared with group M and group O at 6 hours postoperatively (P = 0.01). This variable was not significantly different in three groups at 2 hours and 24 hours after operation

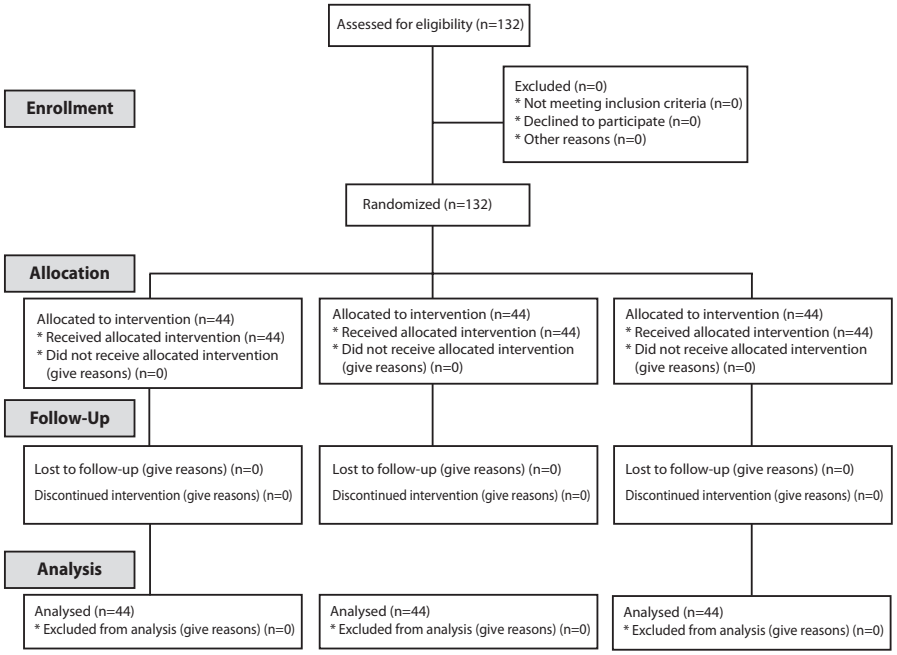

Figure 1: Flow diagram of randomized patients through trial

Table 1: Patient characteristics, duration of surgery, and PACU stay in three groups

Variable	Group M (n = 44)	Group O (n = 44)	Group MO (n = 44)
Age (yr)	29.6 ± 7.1	29.7 ± 7.2	29.4 ± 8.0
Weight (Kg)	73.1 ± 7.5	73.1 ± 8.7	74.3 ± 8.6
ASA (I/II)	27/17	29/15	37/7
Duration of surgery (min)	66.0 ± 7.8	64.6 ± 9.1	64.2 ± 7.3
Duration of PACU stay (min)	138.52 ± 46.1	141.93 ± 55.2	137.40 ± 55.3

Values are presented as mean ± SD or number. Group M = Intravenous midazolam group; group O = Intravenous ondans tron group; group MO = Combination of intravenous midazolam with the intravenous ondansetron group; PACU = Post anesthesia care unit. There were no significant differences between three groups; ASA: American Society of Anesthesiologists

[Table 2]. There was no significant difference between three groups with respect to the additional metoclopromide usage at 2 hours, 6 hours, and 24 hours after surgery [Table 2].

The severity of nausea was significantly different in three groups at 6 hours after operation ($P < 0.05$) [Table 3]. Analysis of data showed that the severity of nausea and vomiting was significantly less in group MO compared with group M or group O at 6 hours postoperatively ($P < 0.05$). This variable was not significantly different in three groups at 2 hours and 24 hours postoperatively ($P > 0.05$) [Table 3].

Table 2: The incidence of nausea (VAS > 3), vomiting and mean dosage of additional metoclopromide usage at baseline, 2 hours, 6 hours, and 24 hours after operation in three groups

Variable	Group M (n = 44)	Group O (n = 44)	Group MO (n = 44)	*P* value
Nausea				
Baseline	14 (31.8)	12 (27.3)	08 (18.2)	0.21
2h	32 (72.0)	27 (61.0)	25 (56.8)	0.27
6h	27 (61.4)	36 (81.8)	24 (54.5)	0.01
24h	18 (40.9)	20 (45.5)	19 (43.2)	0.91
Vomiting				
Baseline	30 (68.2)	32 (72.7)	36 (81.8)	0.33
2h	22 (50)	22 (50)	22 (50)	0.22
6h	26 (59.1)	27 (61.4)	19 (43.2)	0.17
24h	16 (36.4)	15 (34.1)	17 (38.6)	0.90
Additional dose of metoclopromide administered				
2h	0.45 ± 2.1	0.23 ± 1.5	0.0 ± 0.0	0.36
6h	1.82 ± 3.9	2.05 ± 4.08	3.21 ± 1.7	0.49
24h	1.60 ± 3.7	1.82 ± 4.50	1.60 ± 4.10	0.87

Values are presented as number (%) or mean ± SD. Group M = Intravenous midazolam group; Group O = Intravenous ondansetron group; Group MO = Combination of intravenous midazolam with the intravenous ondansetron group

Table 3: The incidence of vomiting and nausea based on it's severity at baseline, 2 hours, 6 hours, and 24 hours after operation in three groups

Severity of nausea	Group M (n = 44)	Group O (n = 44)	Group MO (n = 44)	*P* value
Baseline				
No nausea	01 (2.4)	04 (9.1)	04 (9.1)	
Mild	26 (61.9)	16 (36.4)	19 (44.2)	
Moderate	12 (28.6)	16 (36.4)	16 (36.4)	
Sever	03 (7.1)	07 (15.9)	04 (9.3)	
Vomiting	00 (0.0)	01 (2.3)	00 (00)	0.33
2h				
No nausea	10 (22.7)	10 (22.7)	13 (29.5)	
Mild	15 (34.1)	12 (27.3)	13 (29.5)	
Moderate	13 (29.5)	16 (34.6)	13 (29.5)	
Sever	2 (4.5)	3 (6.8)	1 (2.3)	
Vomiting	2 (9.1)	3 (6.8)	4 (9.1)	0.70
6h				
No nausea	15 (34.1)	5 (11.4)	22 (50.0)	
Mild	10 (22.7)	12 (27.3)	4 (9.1)	
Moderate	11 (25.0)	21 (47.7)	12 (27.3)	
Sever	7 (15.9)	5 (11.4)	4 (9.1)	
Vomiting	1 (2.3)	1 (2.3)	2 (4.5)	0.03
24h				
No nausea	37 (84.1)	33 (75.0)	34 (77.3)	
Mild	4 (9.1)	5 (11.4)	4 (9.1)	
Moderate	2 (4.5)	5 (11.4)	4 (9.1)	
Sever	1 (2.3)	0 (0.0)	2 (4.5)	
Vomiting	0 (0)	1 (2.3)	0 (0)	0.53

Values are presented as number (%). Group M = Intravenous midazolam group; Group O = Intravenous ondansetron group; Group MO = Combination of intravenous midazolam with the intravenous ondansetron group

Mean VAS scores of nausea were not significantly different at baseline, 2 hours, and 24 hours after operation in three groups ($P > 0.05$) [Table 4]. This variable was significantly different at 6 hours after operation among three groups ($P < 0.05$) [Table 4].

Mean VAS scores for evaluation of pain intensity were not significantly different in three groups at baseline (before beginning surgery), 2 hours, 6 hours, and 24 hours after operation [Table 5]. The additional dosage of meperidine administered was not significantly different in three groups at 2 hours, 6 hours, and 24 hours postoperatively [Table 5]. The median sedation scale was not significantly different among three groups at 2 hours, 6 hours, and 24 hours after operation. There was no significant difference between three groups regarding postoperative adverse effect ($P = 0.86$) [Table 6].

DISCUSSION

Our results showed that there was high incidence of nausea (73.6% 2 hours after operation) during spinal anesthesia for cesarean delivery. The emetic symptoms occur more frequently in parturient compared with nonparturient patients due to high level of progesterone that causes smooth muscle relaxation, increase in gastrin secretion, decrease in gastrointestinal motility, and lower esophageal sphincter tones.[7]

As our findings showed, the combination of midazolam 30 μg/kg with ondansetron 8 mg significantly decreased the incidence of nausea 6 hours after operation compared with using midazolam or ondansetron alone without occurrence of important side effects. Also, using combination of two drugs significantly

Table 4: The mean VAS score of nausea at baseline, 2 hours, 6 hours, and 24 hours after operation in three groups

Variable	Group M (n = 44)	Group O (n = 44)	Group MO (n = 44)	*P* value
Mean VAS				
Baseline	8.7 ± 2.4	9.0 ± 1.8	9.4 ± 1.5	0.22
2h	3.4 ± 2.9	3.7 ± 2.9	3.2 ± 2.9	0.76
6h	3.2 ± 3.0	4.1 ± 2.2	2.6 ± 3.0	0.04
24 h	0.6 ±1.5	1.1 ± 2.2	1.0 ± 2.1	0.40

Values are presented as mean ± SD or median. Group M = intravenous midazolam group; Group O = Intravenous ondansetron group; Group MO = Combination of intravenous midazolam with the intravenous ondansetron group

Table 5: The mean VAS score of pain and additional meperidine dosage administered at baseline, 2 hours, 6 hours, and 24 hours after operation in three groups

Variable	Group M (n = 44)	Group O (n = 44)	Group MO (n = 44)	*P* value
Mean VAS				
Before surgery	5.61 ± 1.9	5.82 ± 1.8	5.69 ± 1.94	0.86
2h	4.89 ± 2.0	4.91 ± 2.1	4.90 ± 2.2	0.99
6h	4.64 ± 2.2	4.90 ± 2.1	4.70 ± 2.3	0.88
24 h	3.70 ± 2.1	3.00 ± 1.7	3.64 ± 2.1	0.19
Additional dose of meperidine administered				
2h	5.80 ± 13.2	4.50 ± 12.4	5.11 ± 11.5	0.89
6h	9.90 ± 22.8	15.23 ± 17.6	17.05 ± 21.2	0.56
24h	20.90 ± 22.6	11.70 ± 17.7	18.70 ± 20.8	0.09
Median Sedation Scale				
Before surgery	3	3	3	0.42
2h	2	2	2	0.24
6h	2	2	2	0.77
24 h	2	2	2	1.00

Values are presented as mean ± SD or median. Group M = Intravenous midazolam group; Group O = Intravenous ondansetron group; Group MO = Combination of intravenous midazolam with the intravenous ondansetron group

Table 6: The incidence of postoperative adverse effects in three groups

Variable	Group M (n = 44)	Group O (n = 44)	Group MO (n = 44)
Without adverse effect	30 (68.2)	30 (68.2)	32 (72.7)
With adverse effect	14 (31.8)	14 (31.8)	12 (27.3)

Values are presented as number (%). Group M = Intravenous midazolam group; Group O = Intravenous ondansetron group; Group MO = Combination of intravenous midazolam with the intravenous ondansetron group. There were no significant differences between three groups ($P = 0.86$)

decreased the severity of nausea and vomiting 6 hours after operation in comparison with administration of each drug alone.

The risk factors of emetic symptoms in pregnancy are hormonal changes, smoking habit, age, pain, history of motion sickness or previous postoperative emesis, hypotension, surgical procedure, and anesthetic technique.[8] Our treatment groups were similar with regard to maternal demographic and operating management that considered being risk factors for postoperative emetic symptoms. Therefore, the difference in incidence and severity of nausea and vomiting among the study groups can be attributed to the study drug administration.

Many studies concerning antiemetic effect of midazolam were performed. Splinter and colleagues[9] showed that injection of midazolam 0.05 mg/kg after induction of anesthesia significantly reduced the incidence of nausea and vomiting similar to the same dose of droperidol in children undergoing strabismus. Bauer *et al*.[10] showed that preoperative administration of midazoam 0.04 mg/kg effectively decreased incidence of PONV while increased patient satisfaction. In another study performed by Unlugenc *et al*.[11] it was shown that midazolam was as effective as ondansetron in treating PONV without untoward adverse effects. The prophylactic administration of midazoalm was effective in control of vomiting after tonsillectomy in children.[9] Midazolam was effective as the antiemetic agent in patients had chemotherapy.[12] Tarhan *et al*.[1] showed that administration of a subhypnotic dose of midazoalm 1 mg/h was as effective as the subhypnotic dose of propofol 1 mg/kg/h for prevention of nausea and vomiting in parturient underwent cesarean delivery under spinal anesthesia. Safavi and colleagues,[13] found that midazolam 35 μg/kg administered intravenously 30 minutes before termination of surgery was more effective in decreasing the incidence of PONV than midazolam premeditation 35 μg/kg.

The mechanism of the antiemetic effect of midazolam has not been completely understood. It seems that midazoalm reduces dopamine input at the chemoreceptor trigger zone (CRTZ)[14] and decreases adenosine reuptake.[15] This causes reduction in synthesis, release, and postsynaptic action of dopamine at the CRTZ that mediated by adenosine. Also, adenosine reduces dopaminergic neuronal activity and 5-HT3 release by binding to the gamma-aminobutyric acid (GABA) receptor.[16] The mechanism of action of midazolam has not been fully understood. It is thought that midazolam decreases dopamine input at the chemoreceptor trigger zone (CRTZ)[14] and decreases adenosine reuptake.[15] This leads to an adenosine-mediated reduction in synthesis, release, and postsynaptic action of dopamine at the CRTZ.[14] It may also decrease dopaminergic neuronal activity and 5-HT3 release by binding to the gamma-aminobutyric acid (GABA) receptor.[16]

Ondansetron, a serotonin antagonist, selectively inhibits 5-HT3 receptors while is devoid of dopamine, histamine, cholinergic, or adrenergic receptor activity. 5-HT type serotonin receptors are present peripherally on vagal nerve terminals and centrally on the chemoreceptor trigger zone of the area postrema[17,18] which is known to be associated with nausea and vomiting. It is probable that the antiemetic effect of ondansetron is triggered by the effect on these sites. Pan *et al*.[4] showed that prophylactic ondansetron administration 8 mg was significantly more effective than placebo in reducing the incidence and severity of intraoperative emetic symptoms in patients underwent cesarean delivery under epidural anesthesia.

We used ondansetron with dose of 8 mg because the risk of emetic symptoms in cesarean delivery is high. Also, early efficacy studies of ondansetron were performed with using 8 mg. Pearman[19] showed that ondansetron 8 mg had more efficacy than 4 mg in females with a high risk of emetic symptoms. As our study showed, ondansetron was tolerated well without occurring significant adverse effect. Lee and colleagues[20] showed that treatment using ondansetron 4 mg for antiemetic prophylaxis did not provide a superior benefit compared to midazolam 2 mg in patients scheduled for minor gynecological or urological procedures planned to last 1--2 hours under sevoflurane anesthesia with spontaneous ventilation of the lungs via a laryngeal mask airway. The results of our study are in accordance with findings of Lee *et al*. study.

Combination of ondansetron with midazoam has significantly reduced the incidence and severity of nausea and vomiting 6 hours after operation without important side effects. No significant difference was noted in this regard at 2 hours and 24 hours after operation. As mentioned before, benzodiazepine binding to the $GABA_A$-benzodiazepine receptor complex reduces 5HT3 release.[1] It was shown that high doses of midazolam allosterically inhibit function of 5HT3 receptors.[21] It seems that the more efficacy of using midazolam-ondansetron combination on PONV arise from these mechanisms.

Our study has some limitations. Adding midazoalm to ondansetrone had no advantage for treatment of nausea vomiting in comparison with using each drugs alone at 2 hours and 24 hours after operation. This

could be due to low sample size. We had no control group because it was not ethical that we did not use any antiemetic drugs in patients developing emetic symptoms.

In conclusion, we have shown that intravenous administration of ondanstron 8 mg combined with midazolam 30 μg/kg after cord clamping were superior to using single drug in treatment of emetic symptoms after cesarean delivery under spinal anesthesia. This is the first study that evaluated combination therapy of midazolam and ondansetron for treatment of PONV in patients underwent cesarean delivery with intrathecal anesthesia. Further investigations must be done before final conclusion can be elicited.

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