



Preventing Nausea and Vomiting Using Ondansetron and Metoclopramide-Phenylephrine in Cesarean Section Using Spinal Anesthesia

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Abstract

Objectives: The present study evaluated the effect of combining 2 drugs, namely, ondansetron and metoclopramide-phenylephrine on intra- and postoperative nausea and vomiting (PONV) in patients who selectively underwent cesarean section (C-section) surgery using spinal anesthesia.

Materials and Methods: This randomized double-blind clinical trial controlled with placebo was conducted on 110 patients with class I and II ASA who underwent C-section with spinal anesthesia. Patients within the age range of 20-30 years were divided into 2 groups including 55 subjects. The first group received 10 mg IV metoclopramide while the second group received 10 and 0.4 mg bolus of the metoclopramide-phenylephrine combination before the spinal anesthesia and after closing the umbilical cord, respectively. Prophylactic phenylephrine was injected after the spinal anesthesia. In addition, the patients were anesthetized using bupivacaine 10 mg plus fentanyl 10 mg. Hemodynamic was monitored every 3 minutes. Further, intraoperative and postoperative complications, nausea and its intensity, cut-off point, sedation score, and epinephrine were recorded.

Results: No significant difference was found regarding demographic characteristics. ($P > 0.05$). The incidence and severity of nausea and vomiting were significantly lower in metoclopramide-ondansetron group compared to the metoclopramide group ($P=0.033$ & $P=0.03$, respectively). As regards the phenylephrine infusion, there were no significant differences in blood pressure, heart rate, and ephedrine consumption between the 2 groups. Furthermore, the incidence of other complications like shivering and pruritis was similar in both groups.

Conclusions: Generally, it was revealed that combination therapy with metoclopramide and ondansetron along with prophylaxis of the hypotension with phenylephrine can significantly reduce intra and PONV and its severity in patients undergoing C-section surgery during spinal anesthesia.

Keywords: Metoclopramide, Ondansetron, Nausea-vomiting, Cesarean section, Spinal anesthesia

Introduction

Spinal anesthesia is considered a rapid, easy, and safe technique for cesarean section (C-section) surgery (1). Although this method may have complications along with intraoperative nausea and vomiting (IONV), these complications are observed in 66% of the patients (2,3).

Different factors can lead to IONV during spinal anesthesia including increased vagal activity, hypotension, and opioids administration. Moreover, other causes encompass surgical stimulation, visceral peritoneum traction with exteriorization of the uterus, intraoperative bleeding, using agents like antibiotics or uterotonics, and the patient's motion at the end of the surgery (4, 5).

One of the most important factors responsible for nausea and vomiting is hypotension which can cause brainstem ischemia and activate vomiting centers in the medulla due

to cerebral hypoperfusion (1). Additionally, hypotension leads to intestinal ischemia and resultant release of the emetogenic agents such as serotonin from gastrointestinal system. Therefore, any prevention including preloading, lateral positioning, and any prophylactic use of vasopressors such as phenylephrine infusion was found to significantly reduce the intraoperative hypotension (6,7).

In addition, emesis causes abrupt diaphragmatic contractions which may result in protruding the abdominal viscera, increasing the risk of visceral injuries, discomforting the patient, and making the surgery more difficult. Further, aspiration is an additional hazard if the patient's stomach is full (8). Therefore, prevention of aspiration during surgeries under the spinal anesthesia including C-section seems more advisable. Based on previous studies, different antiemetic drugs like



metoclopramide and droperidol can reduce nausea and vomiting. However, each of these antiemetic drugs has some side effects such as restlessness, sedation, and extrapyramidal symptoms (8,9).

Recently, combination therapy with antiemetic agents such as serotonin receptor antagonists (5-HT₃), antihistamines, corticosteroids, and metoclopramide was used to prevent IONV and postoperative nausea and vomiting (PONV) which has limited prophylactic effect when used alone (8-10).

Metoclopramide, among others, is a prokinetic agent that increases the lower esophageal sphincter tone. Furthermore, it has an antidopaminergic action and is reported to be safe in parturients despite crossing the placental barrier (9).

Ondansetron is a selective 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist, as well as an effective antiemetic for prophylaxis and treatment of nausea and vomiting. However, its use can appropriately decrease the occurrence of nausea and vomiting, but not completely, during C-section when used alone (10). Accordingly, combinations of different antiemetic agents are useful for preventing or treating intra and PONV since these symptoms occur by different mechanisms (11,12).

Materials and Methods

The present randomized double-blind and placebo-controlled clinical trial was approved by the Ethics Committee of Tabriz University of Medical Sciences and performed in Alzahra Obstetrics and Gynecology Educational Hospital of Tabriz. A number of 110 parturients with ASA physical status of I and II whose age varied from 20-38 years and who underwent spinal anesthesia for the elective C-section were randomly allocated to one of the case or control groups. Moreover, the sample size was calculated based on the study by Fujii (4). A power analysis was performed using PONV as the primary outcome. The results of this analysis indicated that a sample size of 48 patients/group was necessary. Therefore, 55 patients were recruited for each group in order to allow for the potential drop-outs. All patients provided informed written consents to participate in this study. Exclusion criteria were pregnant patients with ASA class III or higher, any gastrointestinal problems, antiemetic therapy in the last 24 hours, sensitivity to ondansetron or metoclopramide, patients on tricyclic antidepressants or monoamine oxidase inhibitor (MAOI) therapy, and any contraindication for performing spinal anesthesia. Additionally, all the patients were given a ranitidine 150 mg tablet as premedication 90 minutes before the operation in order to prevent the risk of aspiration. Ringer's 20 mg/kg solution combined with hyperbaric 0.5% bupivacaine 10 mg (2 mL) and fentanyl 10 µg were used for all patients before the spinal anesthesia. Analgesia in T₄-T₅ dermatomes was obtained by intravertebral infusion into the L₃-L₄ space using a

25 mL anesthesia syringe. In addition, patients were put into the lateral position and given 5 L/minute oxygen by a facial mask for avoiding the pressure on the aortocaval area. Systemic blood pressure (BP) was measured and monitored at 2-minute intervals until childbirth and at 5-minute intervals thereafter. Patients were randomly administered metoclopramide (n = 55) as group M, and ondansetron-metoclopramide (n = 55) as group M/O. The prophylactic vasopressor (phenylephrine 500 µg in 500 mL saline 0.9 % at maximum rate on the infusion pump, 999 mL/h) infusion was started as soon as all the patients in both groups were injected spinally. Infusion of phenylephrine was stopped 10 minutes after the delivery. Patients in group 1 received metoclopramide 10 mg intravenously before the spinal anesthesia and placebo (saline) after the delivery. Further, Metoclopramide 10 mg was used before the spinal block and ondansetron 4 mg intravenously was administered instantly upon clamping of the umbilical cord for patients in group 2. Randomization was performed using random numbers in a computer. Furthermore, syringes were prepared and put into packages by a nurse anesthetist who was not aware of the study purpose. Moreover, post-delivery IONV was monitored and recorded by an anesthetist who was unaware of the study purpose. Finally, nausea and vomiting were evaluated using the Bellville scoring (13), that is, the following values were assigned to the factors: no symptom = 0, nausea = 1, gagging = 2, vomiting = 3.

Statistical Analysis

ANOVA and chi-square tests were employed to analyze the demographic data and quantitative variables. Additionally, Fisher exact test was used to analyze the frequency of patients without vomiting and those with nausea, gagging, and vomiting. In addition, the intensity of nausea and vomiting was measured by means of Mann-Whitney test. The significance level was considered $P < 0.05$.

Results

A total of 116 patients were enrolled in this study and randomly assigned to metoclopramide (n=55) and metoclopramide/ondansetron groups (n=55). Six patients (four from group M and 2 from group M/O) were excluded from the study due to technical difficulty or failure of the block. Finally, 110 patients' data were recorded and reviewed for the analysis. There were no significant differences in demographic data including age, weight, height, ASA physical class, time of delivery, and overall operation time between the groups ($P > 0.05$). Demographic data of the population under investigation are provided in Table 1. All patients had an adequate sensory level of spinal the block for surgery (T₃-T₅ sensory level).

Basic systolic, diastolic, as well as mean arterial BP and heart rates, were evaluated 10 minutes after the spinal

Table 1. Demographic Data of the Population Under Study

Variable	Phenylephrine/Metoclopramid (n = 55), Mean ± SD	Phenylephrine/Metoclopramid Ondansetron (n = 55), Mean ± SD	P Value*
Age (y)	30.45 ± 5.81	28.78 ± 5.94	0.139
Height (cm)	161.18 ± 9.81	163.04 ± 4.76	0.211
Weight (kg)	80.48 ± 8.7	79.20 ± 13.57	0.586
Gravid	2.1 ± 0.81	1.9 ± 0.78	0.001
Duration of surgery (min)	57.60 ± 9.32	56.18 ± 11.78	0.485
Time to delivery (min)	11.55 ± 2.91	10.45 ± 1.47	0.015

*P < 0.05 is significant between the groups.

anesthesia. No significant differences were observed in hemodynamic changes between the 2 groups regarding the above-mentioned variables ($P = 0.12$, $P = 0.85$, $P = 0.54$, & $P = 0.09$). However, systolic BP and heart rates were decreased ten minutes after the spinal block compared to the basic values in each group ($P < 0.001$).

The incidence of nausea and vomiting were 29.09 % (16 out of 55 patients) in group M while the patients of group M/O experienced significantly fewer episodes of nausea and vomiting (10.9%, 6 patients) than group M ($P = 0.033$). Further, based on the results of Table 2, the severity of nausea and vomiting was higher in group M compared to group M/O. Therefore, more patients in group M received rescue treatment for severe nausea and vomiting during and/or after the surgery ($P = 0.01$). The data related to the number of patients and mean ephedrine dose consumption in each group are presented in Table 3. There were no significant differences in other complications including a headache, purities, or agitation between both groups ($P > 0.05$).

Discussion

The results of the present study demonstrated that prophylactic combination of Metoclopramide and Ondansetron was more effective in preventing the intra and PONV during C-section under spinal anaesthesia than metoclopramide alone.

IONV during abdominal surgeries with spinal

anaesthesia are related to multifactorial origin like gender (female), anxiety, manipulation of abdominal viscera, arterial hypotension, and hypoperfusion of the brain stem (14).

Furthermore, pregnant women are vulnerable to the occurrence of nausea and vomiting due to the high level of progesterone and intraabdominal pressures. Accordingly, multimodal antiemetic prophylaxis has a preventive effect against nausea and vomiting in these group of patients who underwent spinal anaesthesia (15,16). All the contributing factors in both groups of the current study were similar. Moreover, prophylactic phenylephrine was infused to maintain BP changes in the range of 20% from the baseline in order to avoid the influence of hypotension on nausea and vomiting. Based on the results, no significant differences were found between the groups regarding the hemodynamic changes. However, hypotension in the range of 20% from the baseline was observed in the tenth minute BP measurement after the spinal anesthesia in both groups. Negan et al indicated that infusing the phenylephrine during C-section under spinal anesthesia can prevent IONV when arterial blood pressure is maintained around 10% of basic values (7).

Additionally, Mishriky and Habib in a meta-analysis reviewed the effect of Metoclopramide administration for prophylaxis of nausea and vomiting and resulted that administering 10 mg IV metoclopramide before the spinal block can significantly prevent nausea and vomiting in

Table 2. The Severity of Nausea and Vomiting Between the 2 Groups

Group	Severity of Nausea & Vomiting (Bellville Scoring)				
	0	1	2	3	4
Phenylephrine/metoclopramide (n = 55)	39 (70.9)	7 (12.7)	8 (14.5)	1 (1.8)	55 (100)
Phenylephrine/metoclopramide ondansetron (n = 55)	49 (89.1)	6 (10.9)	0 (0)	0 (0)	55 (100)
Total	88 (80 %)	13 (11.8)	8 (7.3)	1 (0.9)	110 (100)

Data are summarized as numbers (%).

Table 3. Number of Patients and Mean Ephedrine Dose Consumption in Each Group

Group	Number of Patients	Mean Ephedrine Dose (mg) Mean ± SD	Percent
Phenylephrine/metoclopramide (n = 55)	8	9.2 ± 1.8	14.5
Phenylephrine/metoclopramide ondansetron (n = 55)	5	5.8 ± 1.9	9.1%

The result is significant at *P < 0.05.

pregnant patients who underwent spinal anesthesia for C-section surgery (9). In the present study, the incidence of nausea and vomiting was 29.9% in metoclopramide group which is relatively low although it was higher than that of the group who received the combination therapy. In addition, Garcia-Miguel et al investigated the prophylactic effect of metoclopramide and ondansetron on IONV and compared the impact of these 2 drugs with that of the placebo. They indicated that the occurrence of nausea and vomiting during caesarean with spinal block were lower in both metoclopramide and ondansetron groups compared to the placebo. However, such an occurrence was not different between the patients who received metoclopramide or ondansetron (3).

Further, Habib et al used the combination of ondansetron and metoclopramide and compared it with metoclopramide alone and the placebo in their study. Furthermore, they infused phenylephrine in order to prevent hypotension during the spinal block and concluded that the severity and incidence of nausea and vomiting were decreased in patients who received combination therapy during and after the caesarean (17). Similar results were obtained by Voigh et al who used multimodal therapy with the combination of prophylactic tropisetron and metoclopramide in one group and dimenhydramine and dexamethasone in another group. Then, they compared these 2 groups with Tropisetron alone and placebo and demonstrated that the risk of PONV was lower in the combination group compared to the placebo but not different with tropisetron alone (5). However, Demirhan et al compared the combined therapy with ondansetron and dexamethasone and each drug when used alone in three groups. They found that dexamethasone and ondansetron had different mechanisms in preventing nausea and vomiting. However, no difference was observed with regard to the incidence of nausea and vomiting between the patients receiving combination therapy and those who received dexamethasone or ondansetron alone (16).

The findings of the current study revealed that patients who received the combination of metoclopramide-ondansetron experienced a lower incidence of intra and PONV compared to the group receiving the metoclopramide alone (5). Moreover, the severity of nausea and vomiting were lower in the MO group. Additionally, the rescue antiemetic treatment used for severe nausea or vomiting was significantly low in combination and high metoclopramide groups.

Conclusions

Generally speaking, considering the varying mechanisms of nausea and vomiting in patients undergoing C-section operation with spinal anesthesia, the combination of ondansetron and metoclopramide with different anticonvulsant effects can be used both intraoperatively and postoperatively in order to prevent nausea and vomiting without any significant side-effects.

Ethical Issues

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethics No. 91202). Moreover, the study was registered in the Iranian Registry of Clinical Trials website (identifier: [IRCT2013042210765N2](https://www.irct.ir/IRCT2013042210765N2)).

Conflict of Interests

None.

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