

Comparison of the effect of Dexamethasone - Metoclopramide combination and ondansetron in the prevention of nausea and vomiting in cesarean section under spinal Anesthesia

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Original Article

Abstract

Introduction: Nausea and vomiting is one of the complications of spinal anesthesia in cesarean section. The aim of this study was to compare the effects of dexamethasone-metoclopramide with ondansetron on preventing nausea and vomiting during spinal Anesthesia for cesarean section.

Methods: In this study 212 pregnant women (17-45 years old) candidate for elective cesarean section with an ASA I-II were subjected to a randomized double blind clinical trial. Before spinal anesthesia was applied the first group received 8 milligram dexamethasone and 10 milligram metoclopramide intravenously, the second group received 8 milligram ondansetron intravenously.

Results: There were no significant differences between the two groups regarding the demographic variables, and also heart rate, systolic and diastolic blood pressures at before neuroaxial block and at 1, 3, 5 and 10 minutes after block. ($P > 0.05$). The Apgar score between the two groups was significantly different at the first ($P = 0.028$), fifth ($P = 0.001$) and twentieth minute ($P = 0.019$). The overall incidence of nausea was 11.3% with no significant difference between the groups ($P = 0.665$). No patient in the dexamethasone-metoclopramide group experienced any vomiting and in the ondansetron group only 5 patients (4.7%) had vomiting ($P > 0.05$).

Conclusion: The combination of dexamethasone and metoclopramide is effective in preventing nausea and vomiting during cesarean section in women who have no other pregnancy related complications.

Key words: Metoclopramide, Vomiting, Ondansetron, Spinal Anesthesia

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Introduction:

Spinal anesthesia is a quick, easy, low-risk and widely-used method for cesarean section leading to reduced mortality among pregnant women who

need this operation (1). Nausea and vomiting are one of the most common and unpleasant problems of spinal anesthesia for cesarean section, which may cause damages to abdominal organs, the prevalence

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of which has been reported as 50 to 80 percent (2-5).

In studies conducted in North America and Europe, it has been observed that patients are willing to spend large sums to get rid of this problem. Therefore, it is obvious that prevention of Intra-Operative Nausea and Vomiting (IONV) increases the satisfaction of patients (6).

Ondansetron is used to prevent nausea and vomiting after chemotherapy and radiotherapy. They are also effective on postoperative nausea and vomiting; however, less-expensive drugs such as dexamethasone and metoclopramide have the similar preventive effects too (7,8).

Metoclopramide is a derivative of para-aminobenzoic acid (PARA) with gastokinetic and antiemetic effects. Metoclopramide exerts its prokinetic effect by antagonizing dopamine mediated relaxation effect on gastrointestinal smooth muscle. This enhances the response of the gastrointestinal smooth muscle to cholinergic stimulation, thereby leading to an increase of gastric emptying into the intestines. Metoclopramide may also strengthen the lower esophagus sphincter, thereby preventing acid reflux. This agent antagonizes D2 dopamine receptors in chemoreceptive trigger zone (CTZ) of the medulla, thereby preventing nausea and vomiting but due to this it causes severe side effects; for which anticholinergic agents are effective in treating these conditions (9).

Ondansetron Hydrochloride is a selective, competitive serotonin 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist with antiemetic and anti-vertigo effects. Although its mechanism of action has not been fully characterized, ondansetron appears to competitively block the action of serotonin at 5HT₃ receptors peripherally in the gastrointestinal tract as well as centrally in the area postrema of the CNS, where the chemoreceptor trigger zone (CTZ) for vomiting is located (10,11).

Dexamethasone is a long-acting glucocorticoid with immunosuppressant and anti-inflammatory activity. This agent can be used for the treatment of allergic reactions, inflammatory conditions, adrenal insufficiency, treatment of nausea and vomiting associated with chemotherapy and tuberculosis meningitis, and facial pains caused by temporal arteritis (9,12).

Different ways have been used so far to prevent nausea and vomiting during spinal anesthesia for cesarean section with different results. Numerous studies have evaluated the simultaneous effects of several antiemetic drugs for the prevention and treatment of nausea and vomiting perioperatively. The use of dexamethasone along with 5-HT₃ receptor antagonists (Ondansetron and Granisetron) causes an augmented antiemetic effect with favorable results (3).

In a study by Miguel et al., for the prevention of nausea and vomiting during cesarean section showed that the incidence of nausea and vomiting during caesarean section in the group of metoclopramide and ondansetron was significantly lower than that of normal saline; and no significant difference was observed between Metoclopramide and Ondansetron groups (13). The aim of our study was to compare the effect of dexamethasone in combination with metoclopramide and ondansetron in preventing nausea and vomiting in cesarean section under spinal anesthesia.

Methods:

The study was approved by the ethical committee of Hormozgan University of Medical Sciences (HUMS.REC.1394.127). Calculating Expected Ratio/Prevalence rate as 1% in the first group and 6.8% in the second group, and with regard to power: 0.8 and α : 0.05 using SPSS power analyzing test, the minimum sample size of 106 was calculated for each group. In this study, a total number of 281 pregnant women 17 to 45 years old, with ASA I and II, who were candidates for elective cesarean section under spinal anesthesia were recruited for this study (Figure 1).

A random number was drawn from a box of random numbers for each patient. Sampling and randomization was continued until the number of samples in each group; the dexamethasone-metoclopramide group (D-M group) and ondansetron group (O group), reached to 106 patients. After withdrawals and drop outs a total number of 212 patients were analysed. All patients were examined and evaluated by an anesthesiologist a day before operation. A written informed consent was obtained from all patients.

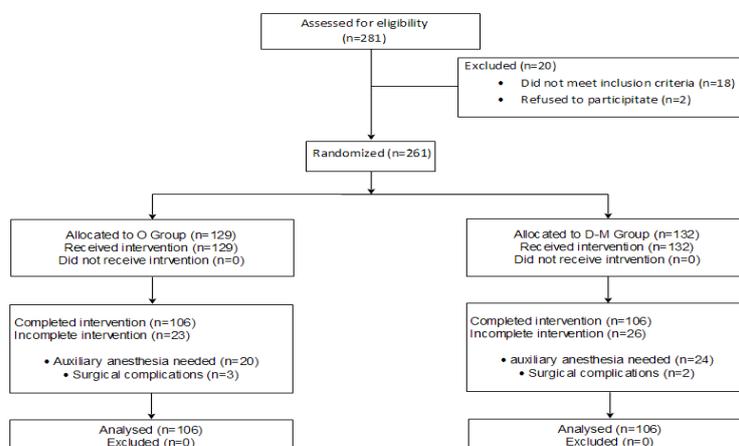


Figure 1. Consort diagram

Exclusion criteria included: preeclampsia, hypertension, hyperemesis gravidarum, the use of anti-emetic drugs, a history of peptic acid disease and motion sickness, spinal anesthesia contradictions, a history of allergy to study drugs (dexamethasone, metoclopramide, ondansetron), mechanical ileus, diabetes mellitus (e.g. gestational diabetes mellitus), renal failure, Pheochromocytoma, and suffering from complications such as bleeding, severe hypotension, surgery plan change (hysterectomy), prescription of sedative and analgesic medications during operation or high spinal block.

Standard monitoring devices including NIBP cuff, ECG, and pulse oximetry were applied to all patients entering the operating room; then their basic vital signs were recorded. Prior to anesthesia, all patients received a dose of 500ml of Ringer's lactate solution. Then, they were randomly assigned to one of two following groups:

Patients belonging to the D-M group received a dexamethasone 8mg, and metoclopramide 10mg, in two separate syringes A and B, each having a volume of 2ml over 5 minutes before receiving spinal anesthesia. Patients belonging to O group received intravenous ondansetron 8mg, and normal saline 2ml, in 2 separate syringes A and B.

Medicines were prepared by an anesthesia nurse and blinding was performed based on the received code.

Then patients were anesthetized in the sitting position using Quincke type spinal needle 25G, from the inter-vertebral space between L3-L4 or L4-L5 using midline method. Upon entering the inter-vertebral space and seeing clear CSF, 12.5mg Marcaine Hyperbaric 0.5% (2.5ml) was injected in the subarachnoid space.

Then, patients were quickly placed in supine position and tilted 15 degrees to the left side of the bed and six liters per minute of oxygen was used for each patient. The systolic and diastolic blood pressure and heart rate of all patients were measured immediately after blocks and during the first, third, fifth and tenth minutes after anesthesia. After that, they were measured and recorded every 5 minutes until the end of operation. The level of anesthesia was continuously assessed; and when it was reached to the level of T4-T6, cesarean section was started by the surgeon. Systolic blood pressure below 90mmHg or more than 20% drop in the initial blood pressure were considered as hypotension and treated by intravenous ephedrine (5 mg). Also, symptomatic bradycardia (HR < 60

beat/min) or heart rate below 50 beats per minute was treated by intravenous atropine (0.6 mg).

The frequency of vomiting during surgery was classified according to a well-defined vomiting scale (5-7) as follows:

- No vomiting: complete Control
- One to two vomiting: near complete control
- Three to five vomiting: incomplete control
- More than five vomiting: lack of control

For more than two times vomiting, metoclopramide (which is an antiemetic drug) was used as a rescue treatment. The presence of nausea was recorded based on the patient's statement. The Apgar score of the newborn was also checked and recorded by the doctor in charge during the first, fifth and tenth minutes.

Patients were monitored and data recorded by another researcher, who was unaware of the drugs applied to study groups. Collected data were recorded on a questionnaire, the first part of which was related to the demographic variables of age, weight and physical class (ASA) and the second part was related to the research findings. The data were compiled in SPSS 20 and analyzed.

Parameters were tested for normality using the Kolmogorov-Smirnov test ($P > 0.05$). Repeated measures were used to analyze hemodynamic data, and chi-square and independent-t tests were used for the analysis of nausea and vomiting in the two groups. A $P < 0.05$ was considered significant

Results:

In this clinical trial research, 212 pregnant women were included and studied in two groups, D-M group and O group, consisted of 106 patients. Patients in D-M group received dexamethasone and patients in O group received ondansetron.

Demographic variables:

The mean age of all participants was 28.04 ± 5.5 , while minimum age was 17 years and maximum was 43 years. In the D-M group, the average age was 27.74 ± 5.44 years, (min. 17 years-max. 40 years age). In the O group, the average age was 28.33 ± 5.73 years, (min. 18

years-max. 40 years age). The first and second groups were not significantly different in terms of age ($P = 0.440$). A total of 182 patients (85.8%) had ASA I and 30 patients (14.2%) had ASA II; that is, 95 patients in the first group (89.6%) and 87 patients (82.1%) in the second group had ASA I; and 11 patients in the first group (10.4%) and 19 patients in the second group (17.9%) had ASA II. The first and second groups were not significantly different in terms of physical class. ($P = 0.126$)

The main variables:

Mean heart rate before anesthesia in the D-M group was equal to 89.5 ± 15.57 beats per minute and in the O group was equal to 92.37 ± 16.93 beats per minute. The heart rate at one minute after anesthesia in the D-M group was equal to 92.12 ± 17.53 beats per minute and in the O group was equal to 92.37 ± 16.93 beats per minute. Mean heart rate in other times has been shown in Table 1. Comparison of the heart beat at times before anesthesia, and one minute, 3 minutes, 5 minutes and 10 minutes after anesthesia, has had a pattern with similar changes; and there was no significant difference between the two groups. ($P > 0.05$)

Mean systolic blood pressure before anesthesia in the D-M group was equal to 128.06 ± 13.84 mm Hg, and in the O group was equal to 127.9 ± 15.49 mm Hg. At one minute after anesthesia, it was equal to 118.77 ± 17.51 mm Hg in the D-M group and 118.52 ± 19.5 mm Hg in the O group. The mean systolic blood pressure at other times has been shown in the table 2. Comparison of systolic blood pressure, at times before anesthesia, and one minute, 3 minutes, 5 minutes and 10 minutes after anesthesia had a pattern with similar changes. There was no significant difference between the two groups. ($P > 0.05$).

The mean diastolic blood pressure before anesthesia in the D-M group was equal to 80.68 ± 13.87 mm Hg and in the O group was equal to 82.39 ± 12.24 mm Hg. At one minute after anesthesia, it was equal to 72.16 ± 14.5 mm/Hg in the D-M group and 73.55 ± 15.31 mm Hg in the O group. Mean diastolic blood pressure at other times has been shown in the table 3.

Table 1. Mean heart rate of mothers in both groups at different times of measurement

Group / time (heart beat)	Dexamethasone+metoclopramide		Ondansetron		Test statistic	P-value
	Mean	SD	Mean	SD		
Before anesthesia (baseline)	89.5	15.57	90.11	16.93	-0.298	0.766
1 min after anesthesia	92.12	17.53	92.37	16.93	-0.108	0.914
3 min after anesthesia	95.16	18.89	92.49	19.16	1.025	0.307
5 min after anesthesia	94.57	18.89	92.02	19.20	0.988	0.324
10 min after anesthesia	92.38	18.23	94.95	18.97	-0.830	0.407
Test statistic			0.062			
P-value			0.804			

Table 2. Mean systolic blood pressure of mothers in both groups at different times of measurement

Group / time (Systolic blood pressure)	Dexamethasone+metoclopramide		Ondansetron		Test statistic	P-value
	Mean	SD	Mean	SD		
Before anesthesia (baseline)	128.06	13.84	127.9	15.48	0.079	0.937
1 min. after anesthesia	118.77	17.51	118.52	19.5	0.096	0.923
3 min. after anesthesia	110.23	18.24	107.41	21.03	1.081	0.281
5 min. after anesthesia	110.30	18.52	111.58	17.02	-0.525	0.600
10 min. after anesthesia	117.29	15.65	115.79	19.59	0.616	0.539
Test statistic			0.176			
P-value			0.675			

Table 3. Mean diastolic blood pressure of mothers in both groups at different times of measurement

Group / time (Systolic blood pressure)	Dexamethasone+metoclopramide		Ondansetron		Test statistic	P-value
	Mean	SD	Mean	SD		
Before anesthesia (baseline)	80.68	13.87	82.39	12.24	-0.950	0.343
1 min. after anesthesia	72.16	14.5	73.55	15.31	-0.682	0.496
3 min. after anesthesia	65.45	14.59	64.33	16.43	0.521	0.603
5 min. after anesthesia	65.9	15.67	66.45	14.33	-0.265	0.791
10 min. after anesthesia	69.7	15.83	70.62	13.98	-0.446	0.656
Test statistic			0.236			
P-value			0.628			

Table 4. Average Apgar score, at different times of measurement

Group / time (heart beat)	Dexamethasone+metoclopramide		Ondansetron		Test statistic	P-value
	Mean	SD	Mean	SD		
Apgar, at min. 1	8.9	0.62	8.6	0.096	-2.204	0.028
Apgar, at min. 5	9.8	0.040	9.5	0.059	-3.194	0.001
Apgar at min. 20	9.8	0.035	9.7	0.052	-2.351	0.019
Test statistic		167.41			156.750	
P-value		<0.001			<0.001	

Table 5. Frequency of nausea and vomiting in the two groups

Group / Vomiting and Nausea	Dexamethasone+metoclopramide		Ondansetron		P-value
	Number	Percent	Number	Percent	
Vomiting	Yes	00	00	5	0.060
	No	106	100	101	
Nausea	Yes	11	10.4	13	0.665
	No	95	89.6	93	

Table 6. Frequency of the severity of vomiting in the two groups

Group / Vomiting	Dexamethasone+metoclopramide		Ondansetron		P-value
	Number	Percent	Number	Percent	
Zero	106	100	101	95.3	0.060
1-2 times	0	0	5	4.7	
3-5 times	0	0	0	0	
More than 5 times	0	0	0	0	

Comparison of diastolic blood pressure before anesthesia, and one minute, 3 minutes, 5 minutes and 10 minutes after anesthesia had a similar pattern for changes and there was no significant difference between the two groups. ($P > 0.05$).

There was a significant difference between the groups in terms of Apgar score which was lower in the Ondansetron group. This difference was observed at all times, including 1 minute ($P=0.028$), five minutes ($P=0.001$) and ten minutes ($P=0.019$) after operation. Also, a significant difference was observed within the two groups at different times in terms of Apgar score, which indicates with the increase in time, the Apgar score also increases (Table 4).

Of 106 patients in the dexamethasone - metoclopramide group, no one developed vomiting; and of 106 patients in the ondansetron group, only 5 patients (4.7%) developed vomiting. There was no significant difference between the two groups of dexamethasone-metoclopramide and ondansetron ($P=0.060$) (Table 5).

Only 2.4% of all 212 patients developed vomiting; all of them were related to the group receiving ondansetron and complete control was observed in the group receiving dexamethasone-metoclopramide. Only 1-2 episode of vomiting was observed (near-complete control) and there was no incomplete control or lack of control. Fisher's exact test showed no difference between the two groups in terms of the number of vomiting (Table 6). About 11.3% of patients developed nausea which was not significantly different in the two groups ($P=0.665$) (Table 5).

Conclusion:

Nausea and vomiting is a common problem during and after the surgery under spinal anesthesia. IONV (4) is an unpleasant experience for all patients, and many consider it worse than the pain and are concerned about the risk of nausea and

vomiting. In fact, IONV is one of the main reasons for their dissatisfaction during the postoperative period (8). Nausea and particularly vomiting during cesarean section is a common complication. Vomiting during operation is associated with the risk of damages to the organs, long duration of operation and possible aspiration. It can cause stress in patients and disturbance in the surgical procedure (7). In studies conducted in North America and Europe, it has been observed that patients are willing to spend large sums to get rid of this problem (6). So, it is obvious that prevention from IONV increases the satisfaction of patients (6).

Although the incidence of vomiting in the group receiving ondansetron was equal to 2.4% compared to zero in the group receiving dexamethasone-metoclopramide the difference in terms of the incidence of vomiting was not significant. Although the intensity of vomiting was mild in the O group. In a study conducted by Miguel et al., in 2000 in Spain (13), the incidence of nausea and vomiting after cesarean section in the group receiving metoclopramide and in the group receiving ondansetron was significantly lower than that of the group receiving normal saline. There was no significant difference between the group receiving metoclopramide and the group receiving ondansetron which is consistent with the results of the present study. But in the study conducted by Tavasoli et al., in 2011 in Mashhad (14), the incidence of vomiting was equal to zero in the group receiving ondansetron and equal to 7.5% in the group receiving metoclopramide-dexamethasone which is inconsistent with the results of this study. This inconsistency could be due to either the difference in the type of surgery, which was an elective cesarean in this study and a gynecologic laparoscopy in the study conducted by Tavasoli et al. or the prescription of drug which was administered prior to spinal anesthesia in the present study, and was administered after induction

of anesthesia in the study conducted by Tavasoli et al.. In the study conducted by Ghanei et al. in 2014 (15), the incidence of vomiting was equal to 8% in the group receiving ondansetron, and 27.2% in the group receiving placebo. Rates of nausea and vomiting in the group receiving ondansetron group in this study were closer to the results obtained in the present study. The difference in the rate of nausea and vomiting in the group receiving metoclopramide could be because of the fact that metoclopramide and dexamethasone were examined together in this study; while in the study conducted by Ghanei, metoclopramide and dexamethasone were studied separately (15).

In the study by Arif et al., conducted in 2012 in Egypt (16), the incidence of postoperative vomiting was equal to 30% in the group receiving dexamethasone-metoclopramide, 35% in the group receiving ondansetron, and 75% in the group receiving placebo which was not consistent with the results of the our study and the reason for this inconsistency could be related to the differences in the type of surgery, which was laparoscopic cholecystectomy surgery in Arif et al. study.

In the study conducted by Tobi et al. in Nigeria in 2013 (17), the incidence of postoperative vomiting in the group receiving dexamethasone was equal to 40%, in the group receiving metoclopramide was equal to 29.97%, and in the group receiving dexamethasone-metoclopramide was equal to 10%, which was similar with the results of the present study. The incidence of vomiting was higher in the D-M group of Tobi et al. study compared to ours this may be due to the fact that their study was applied to myomectomy patients.

In the study by Tabari et al. (18) in the City of Mashhad, Iran, in 2014, the incidence of postoperative vomiting in the group receiving dexamethasone was equal to 23.6%, in the group receiving metoclopramide was equal to 25%, and in the group receiving dexamethasone-metoclopramide was equal to 10.4%. Despite the fact that the patients had undergone Laparoscopic Cholecystectomy, their D-M group had a lower incidence of vomiting, meaning that the combination of dexamethasone-metoclopramide had a greater antiemetic affect than the drugs alone which was consistent with our findings too.

Given the differences that exist in the findings of the present study and other studies, it seems that the type of surgery, the time of prescribing antiemetic drugs (prior to anesthesia, close to the operation or after operation) and dosage of antiemetic drugs are effective in reduced nausea and vomiting. Comparing the variations in heart rates at times before anesthesia, and one minute, 3 minutes, 5 minutes and 10 minutes after anesthesia a similar pattern was observed; and there was no significant difference between the two groups. In a study by Hasan Neseb et al., in 2010 in the city of Babol (19) and the study by Tobi et al. in Nigeria (17) in 2013, a significant relationship was observed between the two groups in terms of heart rate, which is consistent with the results of the present study.

Variations of systolic and diastolic blood pressure in different time points had a similar pattern; and there was no significant difference between the two groups. In a study by Hasan Neseb et al. in 2010 in the city of Babol (19), no significant relationship was observed between the two groups in terms of systolic and diastolic blood pressure which was consistent with the results of the present study. In the study conducted by Tobi et al., in Nigeria in 2013 (17), systolic and diastolic blood pressure in the group receiving metoclopramide was higher than other groups which is inconsistent with the results of the present study.

There was a significant difference between the two groups and within each group, separately for each time, in terms of the Apgar scores, indicating that with increase in the time, the Apgar score also increases. In a study by Hassannasab et al., in the city of Sari in 2011 (20), no significant relationship was found between Apgar score at different times which was inconsistent with the results of this study (20). As a suggestion for future studies, it is better to search among similar studies conducted in terms of different combinations, and to have a larger study through increasing the groups of patients into more than two groups. Also, it is possible to consider other centers and placebo control studies. A suitable recommendation is to identify risk factors predictive of nausea in the spinal anesthesia.

In this case, it is possible to limit the interventions and not to apply unnecessary pharmacological interventions on patients with no

potential risk factors. In addition to evaluating nausea and vomiting during surgery, it is possible to study the patient satisfaction from surgery. Evaluating the frequency of nausea and vomiting and the ability to take care of the baby in the first 24 hours after cesarean section can be a subject for feature studies. Additionally the indications for the cesarean section can be considered as a confounding variable in nausea and vomiting which can also be studied. Finally, this study had some limitations including:

- Not mentioning other drugs received by the patients during operation such as atropine and ephedrine
- Not examining other complications of spinal anesthesia
- Not examining postoperative nausea and vomiting
- Not examining other complications of spinal anesthesia
- Not considering the control group
- Not measuring the weight of patients

The results of the present study indicate that the combination of metoclopramide and dexamethasone prevented intraoperative vomiting during cesarean section. The rate of nausea, as compared to ondansetron, was reduced, but it was not statistically significant. At least, it can be said that the combination of dexamethasone-metoclopramide is as effective as ondansetron.

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