Prevention of Post-cesarean Nausea and vomiting by Intramuscular Metoclopramide: A Randomized Clinical trial

Jila Agah (MD)¹, Roya Baghany (MSc)², Seyed Mohammad Mireskandari (MD)³, Mohammad Hassan Rakhshani (PhD)⁴

¹ Assistant Professor, Department of Obstetrics and Gynecology, Faculty of medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran  
² MSc in midwifery, Faculty of Nursing and Midwifery, Sabzevar University of Medical Sciences, Sabzevar, Iran  
³ Associate professor in Anesthesiology, Department of Anesthesia and Intensive Care, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran  
⁴ MSc in Biostatistics, Department of Biostatistics, Faculty of Health, Sabzevar University of Medical Sciences, Sabzevar, Iran

Background & aim: Nausea and vomiting are considered as the main post-cesarean complications in women undergoing cesarean section. Therefore, the present study aimed to examine the efficacy of intramuscular metoclopramide before cesarean section to prevent post-cesarean nausea and vomiting.

Methods: Study population in the present study consisted of 617 women scheduled for cesarean section. The participants were randomly divided into intervention and control groups. The intervention group received 10 mg intramuscular metoclopramide prior to the surgery, compared to the control group taking an aquatic neutral placebo. Nausea, vomiting, feeling of hunger, and eating time were assessed postoperatively using a visual analog scale every 4 hour. Data were analyzed using the Chi-square test and t-test in SPSS software (version 17).

Results: During 12-hour postoperative observation, the incidence and intensity of nausea were lower in the metoclopramide group (P=0.005). Metoclopramide group clearly needed a less severe therapeutic approach for nausea (14% vs. 44%). Furthermore, participants in the intervention group showed a decline in vomiting; however, this decline was not significant (P=0.4). The metoclopramide group developed the feeling of hunger and eating sooner than those in the control group (P=0.003, P=0.002, respectively). None of the participants reported any side effects of this medication.

Conclusion: The intramuscular injection of 10 mg metoclopramide before cesarean section decreased the incidence and intensity of nausea as well as discharge time from the hospital. Metoclopramide is recommended as a safe, available, and inexpensive medication, which can result in a higher level of maternal health and shorter period of hospitalization.

Introduction

Nausea and vomiting are common distressing symptoms experienced commonly after surgeries, particularly abdominal surgeries. The incidence of postoperative nausea and vomiting (PONV) has not been fully known. However, the overall incidence rate of PONV has been reported as 20-30%, but increasing up to 80% in high-risk circumstances [1, 2]. The PONV can be more significant following cesarean, compared to other operations since the factors of age and gender heighten the risk of PONV. In addition, a reduction in gastrointestinal peristalsis leads to physiologic changes during pregnancy, which enhance the susceptibility to PONV [3, 4]. Other factors that can contribute to the PONV include hypoxia, hypotension, anesthetic regimen, use of nitrous oxide for analgesia, postoperative use of opiates, psychological factors, and the exteriorization of the uterus during cesarean. Past history of motion sickness or PONV has been

*Corresponding author: Agah J, Assistant Professor, Department of Obstetrics and Gynecology, Faculty of medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran. Tel: 00989153012952; Email: jilaagah@yahoo.com
known as risk factors while smoking accounts as a protective factor [5-7]. The PONV can lead to critical complications, such as dehydration, electrolyte imbalance, wound dehiscence, incisional hernia, and esophageal injury. However, it is a logical challenge to find an appropriate antiemetic agent. In recent decades, many researchers have tried to achieve a qualified agent or method for prophylactic antiemetic goals [4, 8-10]; however, there is still no consensus on this instance. There is no doubt that the best drug should be not only effective and safe but also available and inexpensive.

Metoclopramide is a chlorobenzamide derivative with an antidopaminergic effect, which decreases nausea and vomiting by the stimulation of chemoreceptors in the trigger zone of the brain. Although its effect on PONV treatment has been reported for over 50 years [11, 12], its impact on the prevention of PONV is still under debate [13-16]. A bulk of studies in the literature showed that the majority of the previous authors working on metoclopramide have intravenously examined the effect of this drug in common surgeries other than cesarean section. The distressing symptoms, which generally occur after cesarean, put the mother and her family into trouble and interfere with the mothers' ability of breastfeeding as well as mother-neonate interaction. Therefore, the present study aimed to investigate the effect of intramuscular injection of metoclopramide on the prevention of nausea and vomiting following a cesarean delivery.

Materials and Methods
This randomized controlled trial was conducted at Mobini Hospital (Sabzevar, Iran) from February 2014 to July 2015. The study was conducted after the approval of Institutional Ethics Committee (with ethical code number: medsat.rec.93.10 and trial registration number: ISRCTN/P32K7GM). A total number of 617 full-term pregnant women scheduled for elective or urgent cesarean section under general or neuraxial (spinal or epidural) anesthesia were enrolled in this study. After the written informed consent was obtained, the demographic data and past history of patients were recorded in a checklist by an interviewer.

The inclusion criteria were women’s willingness to participate in the study, single-fetus and full-term pregnancy, and no contraindications for intramuscular injection. The exclusion criteria included 1) a history of abdominal surgery other than cesarean, 2) administration of antiemetic drugs 12 h before the operation, 3) constipation or other gastrointestinal disorders, 4) peptic ulcer, 5) usculoskeletal disorders, 6) pancreatitis, 7) diabetes, 8) peritonitis, 9) pre-eclampsia, 10) hypothyroidism, 11) chronic use of opiates, 12) use of magnesium sulfate, 13) women with Parkinsonism and epilepsies, 14) pregnant women intolerant to metoclopramide, 15) complicated or prolonged cesarean section, and 15) postpartum massive hemorrhage.

Participants were divided into two groups of intervention and control using a simple random sampling technique. Women in the intervention group (n=286) were subjected to the intramuscular injection of 10 mg metoclopramide and those in the control group (n=260) received an intramuscular injection of an aquatic neutral agent as a placebo.

Based on the anesthesiologists' choice, all surgeries were performed under general or regional anesthesia. At the end of the surgery, all participants received 100 mg sodium diclofenac suppository and then the same dose was postoperatively injected every 8 h for 24 h. The events and complications concomitant with surgery were recorded while the non-eligible cases were excluded from the study. After cesarean section, post-operative nausea was assessed every 4 h through using a 5-point Likert scale visual analog ranging from lack of nausea to highly severe nausea. After the operation all participants were asked for the occurrence of nausea and vomiting, feeding of hunger, feeding condition, and adverse effects of metoclopramide. Patients with moderate to highly severe nausea and vomiting were intravenously treated with 4 mg ondansetron. The data collection was accomplished with the help of two assistant researchers who were blind to the study groups.

The collected data were analyzed by SPSS software (version 17). The Mann-Whitney U test, t-test, and the Chi-square test were employed to compare the two groups. P-value less than 0.05 was considered statistically significant.

Results
Among 617 participants who were scheduled for cesarean section, 546 participants were finally completed the study program (260 and 286 women were in the control and intervention groups, respectively [Figure1]). There was no significant difference between the two groups in terms of demographic characteristics, such as age, obstetrical history, body mass index fasting period educational level, duration of surgery, and type of anesthesia (Table 1).

![Consort diagram of the participants involved in clinical trial](image)

**Figure 1.** Consort diagram of the participants involved in clinical trial

**Table 1.** Demographic characteristics of the participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Metoclopramide group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in year*</td>
<td>27.2(4.30)</td>
<td>26.7(4.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Body mass index*(kg/m2)</td>
<td>25.6(2.5)</td>
<td>25.8(2.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Educational level**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary (%)</td>
<td>106(37%)</td>
<td>107(41%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Secondary (%)</td>
<td>152(53%)</td>
<td>124(48%)</td>
<td></td>
</tr>
<tr>
<td>University (%)</td>
<td>28(10%)</td>
<td>29(11%)</td>
<td></td>
</tr>
</tbody>
</table>
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The obtained results of Chi-square test indicated that the incidence of nausea was lower in metoclopramide group, compared to the control (17.14% vs. 21.16%, P=0.005) during 24 h after the surgery. The Mann-Whitney U test revealed that the severity of nausea was significantly lower in metoclopramide group than control group (P<0.001; Table 2).

Table 2. Incidence and severity of nausea expressed by participants using Visual Analogue Scale

<table>
<thead>
<tr>
<th>Nausea expressed by participants</th>
<th>Metoclopramide group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>population</td>
<td>Incidence rate</td>
<td>population</td>
</tr>
<tr>
<td>lack of nausea</td>
<td>237</td>
<td>82.86 %</td>
<td>205</td>
</tr>
<tr>
<td>mild</td>
<td>42</td>
<td>14.69 %</td>
<td>31</td>
</tr>
<tr>
<td>moderate</td>
<td>4</td>
<td>1.40 %</td>
<td>18</td>
</tr>
<tr>
<td>severe</td>
<td>3</td>
<td>1.05 %</td>
<td>3</td>
</tr>
<tr>
<td>highly severe</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

The participants, who needed antiemetic drugs to treat nausea, were fewer in the intervention group (15% vs. 44%). The obtained results of Chi-square test was indicative of a decline in vomiting of individuals in the metoclopramide group (4.54% vs. 6.15%); however, this decline was not significant (P=0.4). In metoclopramide group, the feeling of hunger was established sooner than the control group (P=0.003) and they tolerated eating sooner(p=0.002). In the present study, adverse effects of the drug were observed in none of the participants.

Discussion

The current study was performed on a large number of cases admitted to a crowded hospital. The obtained results of the study showed that an intramuscular injection of 10 mg prophylactic metoclopramide could significantly diminish the incidence of nausea following cesarean and subside its severity in case of occurrence. However, metoclopramide could spontaneously eliminate nausea in 85% of women in the intervention group, who expressed nausea at a mild level. Moreover, only 15% of cases who expressed nausea at a moderate level required treatment. In contrast, about 44% of women in the control group expressed nausea at a moderate level, which needed treatment. Furthermore, 13 and 16 cases in the intervention and control groups revealed the occurrence of vomiting at a low rate, respectively. The low incidence of vomiting could be due to the administration of ondansetron for participants who suffered from significant nausea mainly those in control group. Of note, the women who had received prophylactic metoclopramide clearly had more tolerance to feeding during the day after cesarean. A large number of many women undergo cesarean section daily worldwide, and based on the report, PONV is considered as the most disturbing complication [1, 4].

Metoclopramide eliminates nausea and vomiting through an antagonist action against the brain receptors of dopamine and serotonin. It can be administered orally, injected intravenously or intramuscularly, or sprayed
nasally. In theory, the effects of metoclopramide are permanent whenever the drug is intramuscularly injected due to its gradual absorption [11, 17]. Extrapyramidal reaction with a reported incidence of 0.2% is the prominent disadvantage of this drug. However, it is transient and promptly disappears by drug withdrawal and it is commonly observed in high doses of 30-40 mg not the low dose of 10 mg. Moreover, this drug has not showed any main side effect in pregnancy with such a low dose of administration [4, 11]. The obtained results of the present study indicated no side effects of this drug at the administered dose. It should be noted that extrapyramidal reaction can be observed after the administration of other antiemetic drugs, such as ondansetron [12, 18]. The obtained results of the current study are in line with the meta-analysis reported by Oliviera et al, who declared metoclopramide had a significant effect on the prevention of PONV and was highly effective for nausea [15]. Moreover, some researchers showed the preventive effects of metoclopramide for PONV in women undergoing cesarean section. Some reports regarded intravenous injection in regional anesthesia and the others examined intramuscular injection in general anesthesia, which supported the findings of the current study [2, 9, 14, 9]. In contrast, Fujii et al. declared metoclopramide was not effective for the prevention of PONV in general anesthesia [16]. Some researchers administered intravenous metoclopramide in combination with other drugs (e.g. triptasan or glycopyrrolate) which enhanced its efficiency to prevent PONV during the first 2 hours after the surgery [20]. Furthermore, a meta-analysis conducted by Mishriky et al. revealed that 10 mg of intravenous metoclopramide could be effective for the prevention of PONV in the first 4 h after an operation [13]. In the present study the efficacy of drug was remained up to 12 h of administration; however, other researchers found that its maximum effect could be up to 4 h. In contrast to other studies in which metoclopramide were intravenously administered, the administration of metoclopramide was intramuscular in the present experiment. It is probable that drug intramuscular injection may result in the longer establishment of the drug effects. On the other hand, most reports about metoclopramide and PONV were based on the data obtained from surgeries other than cesarean, which were different in nature. Firstly, cesarean section is not associated with the direct manipulation of gastrointestinal tract. Secondly, physiologic changes of pregnancy significantly affect the responses and reactions of the parturients to the surgical and pharmacological interventions. Other agents, such as granisetron, ondansetron, dexamethasone and gabapentin, have also been examined for PONV. Although these medications indicated relatively acceptable results, they could lead to side effects, such as headache and constipation [1, 8, 17, 21-23]. Some investigators examined herbal agents. However, it is worth mentioning that the herbal medicine may lead to probable allergic reaction which is not a matter of concern with metoclopramide. Ginger in the form of dry powder, which has been administered before cesarean, was not effective for the prevention of PONV [24]. Furthermore, the preventive effects of peppermint aromatherapy in PONV treatment have not been determined [25]. Non-pharmacological interventions, such as oxygen therapy, intravenous fluids, and acupuncture, may also lead to contradictory results and some technical problems [10, 26]. In comparison with the mentioned agents, metoclopramide is safe, available, cost-benefit, and user-friendly without the need to any special equipment or technical tools.

On the other hand, metoclopramide benefits from some valuable advantages with notable effects on the well-being of the mothers. The cholinergic effect of metoclopramide leads to an increase in the motility of gastrointestinal tract, which results in a decrease in esophageal reflux and ileus. As reported in the current study and the literature, the parturients who used metoclopramide before cesarean had lower risk of ileus and earlier defecation. They could also start eating and moving more quickly [4, 27]. Subsequently, they showed less severe complications, including thromboembolism, and could be discharged from hospital at a shorter time.

Conclusions
Metoclopramide is known as a safe, cost-effective, and available drug. The intramuscular administration of metoclopramide prior to cesarean as a low dose of 10 mg can significantly decrease the incidence and intensity of nausea during at least 12 h after the operation. Subsequently, this issue leads to the earlier establishment of parturient nutrition. As a result, these benefits not only improve maternal health, but also help the reduction of delivery expenses. Undoubtedly, more investigations are needed to confirm the obtained results.

Acknowledgments

The researchers find it obligatory to express their sincere appreciation to the Deputy of Research in Sabzevar University of Medical Sciences, Sabzevar, Iran, due to financial supports and also special thanks to the chief and the maternity care staff of Mobini Hospital, Sabzevar, Iran.

Conflicts of interest

The authors have no conflicts of interest.

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