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ORIGINAL ARTICLE

Preoperative Use of 10-mg Metoclopramide and 50-mg Dimenhydrinate in the Prophylaxis of Postoperative Nausea and Vomiting in Elective Caesarean Births: A Prospective Randomized Clinical Study

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Abstract

Background The purpose of this study was to assess the efficacy and outcomes of preoperative prophylactic metoclopramide and dimenhydrinate use in elective cesarean births.

Methods Participants ($n = 84$) scheduled for elective cesarean births were randomized equally into placebo (10 cc 0.9 % NaCl), 10-mg metoclopramide or 50-mg dimenhydrinate groups. Oral alimentation was prohibited 8 h before the surgery; however, patients continued drinking water until 4 h before surgery. Placebo and antiemetics were administered 1 h before the anticipated procedure in a 5-ml syringe. In metoclopramide and dimenhydrinate group, an ampoule of the agents was completed to 5 ml by adding 0.9 % NaCl. In the control group 5 ml of 0.9 % NaCl was used. All prophylactic agents were administered intramuscularly. All patients received a general anesthesia. The placebo group (control group) was compared with the metoclopramide and dimenhydrinate groups.

Results Demographic data including maternal age, height, weight, body mass index, gravidity, parity, miscarriage, induced abortion, the number of offspring, and the medical history did not show significant differences among the three groups. Postoperative nausea, vomiting, and the use of rescue medication ratios were significantly lower in metoclopramide and dimenhydrinate groups compared with the placebo group ($p < 0.05$); however, the difference

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between the metoclopramide and dimenhydrinate groups was not significant ($p > 0.05$).

Conclusion Dimenhydrinate and metoclopramide significantly decrease postoperative nausea, vomiting, and the need for rescue antiemetic medication. Both agents have similar efficacy and may be used as an alternative to each other.

Keywords Anesthesia · Cesarean section · Dimenhydrinate · Metoclopramide · Postoperative nausea and vomiting · Surgical procedures · Elective

Introduction

Intra- and postoperative nausea and vomiting (IONV and PONV) are common in most of operations, and varied incidences of nausea and vomiting with rates up to 60–80 % were reported in the medical literature [1, 2].

Intra- and postoperative nausea and vomiting associated with pregnancy originate from multiple factors. Progesterone-induced lowering of the lower esophageal sphincter pressure, elevation of the intra-gastric pressure by the elevated uterus [3], hypotension, extra-abdominal manipulation of the uterus, visceral stimulation, decrease in gastric motility and elevated intra-abdominal pressure, and the use of opioids are among the suspected etiological factors [1]. All these factors can cause serious morbidity in patients undergoing caesarean delivery under general anesthesia.

Within the first 24 h of a surgical procedure more than 25 % of patients experience PONV [4, 5]. Despite the fact, prophylaxis against PONV was not found cost-effective in many publications. Although some authors suggest the prophylactic use of antiemetic therapy for high-risk patients and rescue antiemetic treatment during episodes of PONV, the optimal PONV management is unclear to many clinicians [6, 7] and high risk patients are not easily eliminated in most cases. In addition, patients' concern about PONV is higher than their concern about the postoperative pain [8].

Dimenhydrinate is an inexpensive histamine H1 receptor antagonist with moderate to high antiemetic properties available as an IV or IM long-acting formulation. In addition, its antiemetic effect in patients with motion sickness makes its use desirable in patients after surgery [9]. Its use during pregnancy was found safe in animal studies [10].

Metoclopramide as an inexpensive antiemetic used in the management of anesthesia-associated nausea and vomiting has multiple sites of action. It increases the tone of the lower esophageal sphincter and also has antidopaminergic and anti-serotonergic activity [11, 12]. At a dose of 10 mg, it is safe for the parturient and is not associated with adverse fetal/neonatal effects [1, 3, 13].

In some parts of the world, both drugs, dimenhydrinate and metoclopramide, are routinely used in the prophylaxis and treatment of intra- and postoperative nausea and vomiting in patients undergoing elective caesarean births. However, the accumulated medical literature lacks a comparative study with a higher level of evidence about their use in elective caesarean births [7]. We, therefore, designed this randomized prospective study to assess the efficacy and outcomes of these agents undergoing elective caesarean deliveries under general anesthesia.

Methods

The local Institutional review board of Kafkas University School of Medicine approved the study, and all participants gave written informed consents. We conducted the study between December 2010 and June 2011 with the collaboration of the departments of Obstetrics and Gynecology and Anesthesia and Reanimation of Kafkas University School of Medicine.

More than a quarter of patients experience PONV within the first 24 h of surgery [4, 5] and the rate of PONV may increase up to 80 % in high risk patients [14]. Since female gender, pregnancy, laparotomy, non-smoking status, and intraoperative opioid use increase the risk of PONS [1, 3, 6, 7], we used the highest rate of PONS risk for power analysis. Power analysis indicated that in order to achieve a 25 % risk reduction in the PONV rate at one side alpha of 0.05, at least 28 participants were needed in each group. Thus, in each group we included 28 women undergoing elective caesarean births.

The participating pregnant women scheduled for elective caesarean births were randomized using a computer-generated randomization table, in a stratified manner, according to their participation in placebo (10 cc 0.9 % NaCl), 10-mg metoclopramide or 50-mg dimenhydrinate groups in order to study the efficacy of metoclopramide and dimenhydrinate to prevent postoperative nausea and vomiting.

All participants had a consultation by an anesthesiologist at least 1 day prior to the scheduled operations. Women presenting to elective caesarean section were invited to participate in the study. On the morning of the surgery, the women were admitted to the obstetrics and gynecology department and assigned into one of the groups by the nurse responsible for the follow-up. In case where a woman changed her mind to participate or receive regional anesthesia, the next woman was assigned into the same group in the same order and received the same protocol number.

We included singleton pregnancies with 39 or more gestational weeks. Gestational age was established by the

first date of the last menstrual period and confirmed by first trimester ultrasound. Exclusion criteria included the women with rupture of membranes, placental insertion anomalies, active labor, and the history of nausea and vomiting. Maternal or fetal complications also resulted in exclusions. Maternal complications included hypertensive pregnancy disorders, gestational or pre-gestational diabetes, maternal vascular disease, urinary tract infections, and any known chronic illness. Fetal complications included rupture of membranes, congenital malformations, intra-uterine growth restriction, and an abnormal non-stress test or biophysics profile.

Oral alimentation was prohibited 8 h before the surgery; however, the women were allowed to drink water until 4 h before surgery. All three agents were administered 1 h before the anticipated procedure. All study drugs were prepared in a 5-ml syringe. In metoclopramide and dimenhydrinate group, an ampoule of the agents was completed to 5 ml by adding 0.9 % NaCl and a 5 ml of 0.9 % NaCl was used in the control group. All agents were administered intramuscularly. Patients were blinded to the medication they received.

All patients received a general anesthetic with endotracheal intubation and ventilation. Anesthesia was induced with propofol 1.5–2.5 mg/kg, and intubation was facilitated with rocuronium 0.4–0.6 mg/kg. Oxygen supplementation was maintained before and after intubation at 100 and 50 % (mixed with the operative theatre's air) rates, respectively. Anesthesia was maintained with sevoflurane 2 %, and fentanyl 50 μg. We used 0.9 % NaCl or Ringer's lactate solution at 10 ml/kg on IV insertion to replace existing fluid deficit and maintained the hydration at 2 ml/kg/h. In case of unexpected bleeding, the blood loss was supplemented by adding a crystalloid solution at a rate of 3 ml/kg/h. Neuromuscular blockade was reversed using atropine 1–1.2 mg IV. Intramuscular meperidine at 50 mg was injected at the end of the surgery. Beginning from the postoperative 8th hour oral paracetamol 500 mg with 8 h intervals was given. In case of a need for a rescue analgesic, intravenous metamizole sodium 1 g/2 ml was given.

Demographic data including maternal age, height, weight, body mass index, gravidity, parity, miscarriage, induced abortion, the number of offspring, and the medical history were gathered upon patient enrolment. In the postoperative first 24 h, the symptoms of nausea and vomiting with their frequencies, pain scores, and the rate of rescue medication use for PONS were recorded. As a rescue medication, metoclopramide and dimenhydrinate groups received a repeat dose of their own groups' drugs; however, the placebo group received a four mg of ondansetron hydrochloride. Rescue medications were used for all vomiting; however, the participating women decided the use of a rescue medication just for nausea. The severity of the nausea was determined as follows: None = 0; Mild = 1; Moderate = 2; and Severe = 3. Visual analogue scale (VAS) was used to score the pain intensity. On a 100-mm VAS, 0 and 100 mm were considered as no pain and intolerable pain, respectively.

Statistical analyses were performed using SPSS version 16.0 software (SPSS Inc, Chicago, IL). Shapiro–Wilk test was used to assess the distribution of the variables. The placebo group (control group) was compared with the metoclopramide and dimenhydrinate groups. We used analysis of variance (ANOVA) test for the normally distributed variables and Kruskal–Wallis test for the non-normally distributed variables. In the post hoc analysis of the significantly different variables, we used Bonferroni correction and Mann–Whitney test to compare the three groups for normally and non-normally distributed variables, respectively. The correlation analysis was performed using the Spearman's correlation test. A p value < 0.05 was considered statistically significant.

Results

Of the 95 women invited to participate, 11 did not participate in the study. Three of them did not want to participate in the study and eight of them changed their mind in the operative theatre and received regional anesthesia (Fig. 1).

Demographic data including maternal age, height, weight, body mass index, gravidity, parity, miscarriage, induced abortion, the number of offspring, and the medical history did not show significant differences among the three groups ($p > 0.05$). Table 1 summarizes the comparison of the demographic data of the groups.

Postoperative nausea, vomiting, the severity of vomiting, and the use of rescue antiemetic rates were significantly lower in the metoclopramide and dimenhydrinate groups compared with the placebo group ($p < 0.05$); however, the difference between the metoclopramide and dimenhydrinate groups was not significant ($p > 0.05$). In addition, the duration of the operations was not significantly different among the three groups ($p > 0.05$).

Postoperative pain scores and the rate of rescue analgesic use were not significantly among groups ($p > 0.05$). Table 2 summarizes the comparison of the intra- and postoperative findings of the placebo, metoclopramide, and dimenhydrinate groups.

The characteristics of the women included in the study were analyzed for correlations. Maternal age, gravidity, parity, miscarriages, and the offspring number positively correlated with each other ($p < 0.05$). Although the weight of the women correlated with the height and body mass index of the women, the height of the women correlated only with the weight of the women ($p > 0.05$). These three parameters did not correlate with any of the other parameters of the study.

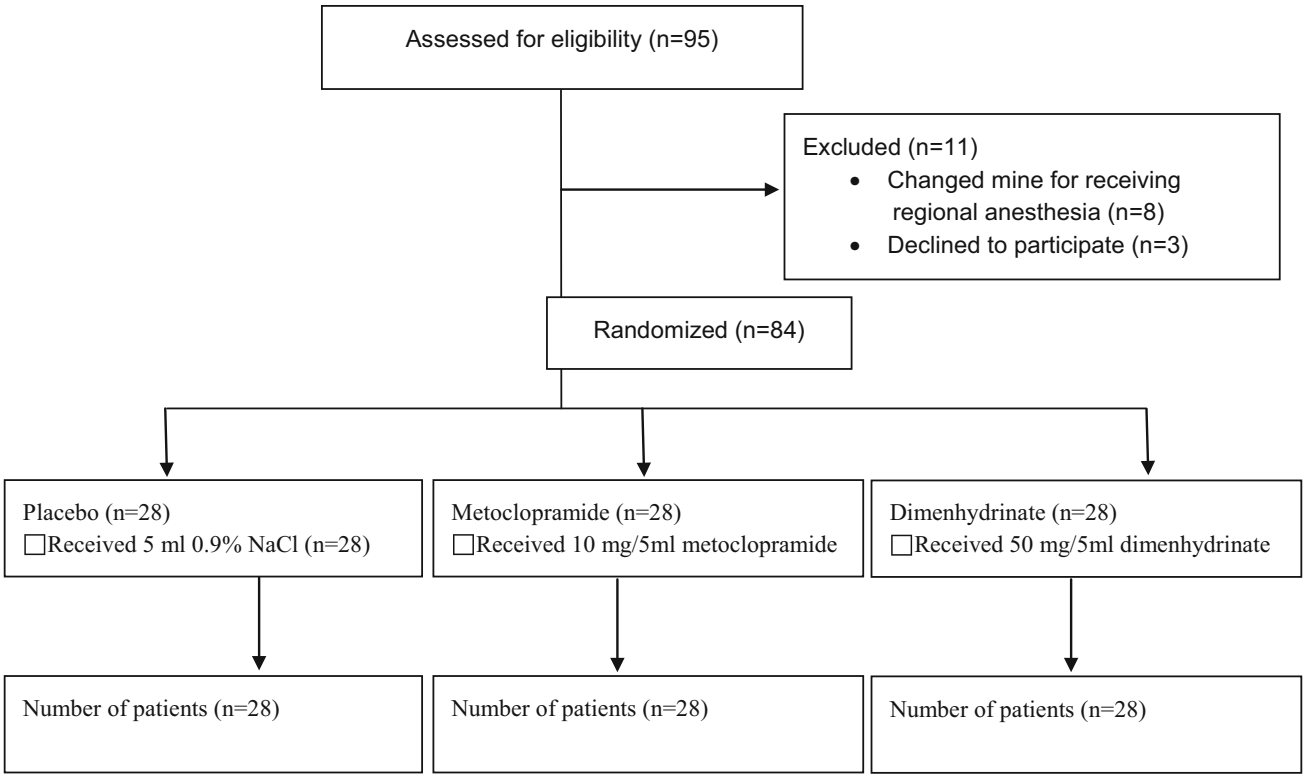

Fig. 1 The flow chart shows the study profile

Table 1 Demographics of the women included in the study

	NaCl (Placebo) (5 ml, IM) ($n = 28$)	Metoclopramide (10 mg IM) ($n = 28$)	Dimenhydrinate (50 mg IM) ($n = 28$)	p value
Maternal age	30.46 ± 3.25	30.78 ± 3.96	29.50 ± 6.27	0.624*
Height (m)	1.64 ± 0.05	1.64 ± 0.06	1.62 ± 0.05	0.330**
Weight (kg)	79.08 ± 11.27	77.39 ± 10.69	78.09 ± 11.39	0.849**
BMI (kg/m^2)	29.41 ± 4.05	28.58 ± 3.32	29.63 ± 4.13	0.562**
Gravidity	2	2	2	0.512*
Parity	1	1	1	0.609*
Miscarriages	0	0	0	0.960*
Induced abortions	0	0	0	0.132*
Offspring	1	1	1	0.452*

The data were presented with median ± standard deviation or median values

IM intramuscular administration

* Kruskal–Wallis test (for non-normal distribution)

** Analysis of variance (ANOVA) test (for normal distribution)

The variables including the rates of nausea and vomiting, the severity of nausea, and the need for rescue antiemetic use correlated with each other ($p < 0.05$). The duration of the operations positively correlated with the rates of nausea, severe nausea, vomiting, and the need for the rescue medication ($p < 0.05$).

Discussion

The principal finding of the study is that intramuscular use of 50 mg of dimenhydrinate and 10 mg of metoclopramide 1 h before the anticipated elective caesarean section causes significant decreases in the rates of postoperative nausea,

Table 2 Comparison of the intra- and postoperative findings of the placebo, metoclopramide, and dimenhydrinate groups

	NaCl (Placebo) (5 ml, IM) ($n = 28$)	Metoclopramide (10 mg IM) ($n = 28$)	Dimenhydrinate (50 mg IM) ($n = 28$)	p value*
Nausea	15/28 (53)	3/28 (11)	5/28 (18)	0.001
Vomiting	10/28 (36)	2/28 (7)	2/28 (7)	0.004
Rescue antiemetic use in first 24 h	14/28 (50)	2/28 (7)	3/28 (11)	<0.001
Severity of nausea	1.53 ± 1.50	0.21 ± 0.69	0.39 ± 0.96	<0.001
Operative time	42.50 ± 9.38	40.07 ± 9.94	40.50 ± 9.81	0.295
VAS 1st hour	5.71 ± 1.38	6.18 ± 1.61	6.07 ± 1.98	0.625
VAS 4th hour	4.10 ± 1.45	4.75 ± 1.86	3.96 ± 0.64	0.443
VAS 8th hour	3.68 ± 1.09	3.78 ± 1.17	3.21 ± 0.83	0.262
VAS 12th hour	3.46 ± 0.84	3.46 ± 0.74	3.03 ± 0.92	0.093
VAS 24th hour	2.89 ± 1.06	2.96 ± 0.69	2.71 ± 0.94	0.593
Rescue analgesic use in first 24 hour	23/28 (82)	22/28 (78)	19/28 (68)	0.430

The data were presented as observed number/total group number (percent) or mean ± standard deviation

VAS visual analogue scale representing the mean postoperative pain scores

* Kruskal–Wallis test

vomiting, and the need for rescue medication. In addition, both drugs have similar efficacy.

Strengths and Limitations

Both drugs are routinely used in the prophylaxis and treatment of intra- and postoperative nausea and vomiting in women undergoing elective caesarean sections. However, to our knowledge, this is the first study comparing the agents with placebo and each other. Although the effectiveness of the drugs for nausea and vomiting of pregnancy was well established [15], the effectiveness of their preoperative use was not well studied in PONS following elective caesarean sections.

There are many different agents used in the induction and maintenance of general anesthesia. In our study, the agents were administered 1 h before the anticipated surgery; thus, the data reflects the results of an individual study protocol. However, the agents are generally administered just before the induction of anesthesia or as a rescue medication at the time of the symptoms. Thus, we cannot argue about the efficacy of the agents in a different anesthesia protocol. In addition, the use of spinal or epidural anesthesia with various agents may alter the results. We used the highest published PONS incidence ratio to adjust the needed sample size; however, lower risk groups may need a larger sample size.

Comparisons with Other Studies

Cesarean section rates have increased for the last two decades, particularly in developed countries [16–18]. Between 1965 and 2007, the caesarean section rate increased from 4.5 to 32 % in the United States, and the global rate rose from about 5 % in developed countries in the early 1970s to more than 50 % in some regions in 2000s [16–22]. Thus, more women and clinicians have to confront with the risks of the caesarean section. PONV effecting more than 25 % of patients within the first 24 h of surgery [4, 5] may increase the postoperative mortality, including aspiration pneumonitis, hematoma formation, suture dehiscence, and esophageal rupture [6]. In addition, many patients concern about PONV more than the postoperative pain [8]. However, the optimal PONV management is unclear to many clinicians [6]. Moreover, universal PONV prophylaxis was not found cost-effective. From this point of view, determination of the prophylactic effects of two inexpensive and popular agents was reasonable. In our study, both metoclopramide and dimenhydrinate decreased significantly the rates of nausea, severe nausea, vomiting, and the need for rescue medication ($p < 0.05$).

There are some risk factors for PONS: female gender, non-smoking status, history of PONV/motion sickness, use of volatile anesthetics within 0–2 h, use of nitrous oxide, use of intra- and postoperative opioids, longer operative times, and the type of the surgery (e.g., laparotomy) [14, 23]. In our study, all patients were non-smoker females; there was no history of PONV/motion sickness; we used propofol for anesthesia induction and sevoflurane as a volatile anesthetics; we did not use nitrous oxide at any stage of the anesthesia; we did not use any opioid other than 50-mg meperidine at the end of the surgery, and all operations were performed by laparotomy. In addition, the operation durations correlated with the incidence of nausea, vomiting, and the need for rescue medication ($p < 0.05$). Although the rates of rescue analgesic use were high in all

groups (ranged between 68 and 82 %), the mean pain scores were not significantly different. The high ratios might have been resulted from the study protocol in which we applied the rescue analgesic in every patient with a VAS score of more than four.

There are some strategies to reduce the baseline risk for PONS like the use of regional anesthesia, propofol for anesthesia induction and maintenance, intraoperative supplemental oxygen, hydration, and avoidance of nitrous oxide and volatile anesthetics, and minimization of neostigmine, intra- and postoperative opioids [6, 24, 25]. Although we used general anesthesia, we used propofol, hydration, and intraoperative oxygen supplementation. In addition, we used only a 50-mg intramuscular dose of meperidine at the end of the surgery. Neostigmine was completely avoided in our study.

The optimal timing of the use of the antiemetic agent was studied in several studies. The consensus guidelines for managing PONS [4] included the optimal timing for several agents; however, it lacks the optimal timing of metoclopramide and dimenhydrinate. In a recent systematic review, the authors concluded that metoclopramide in a dose of 10 mg was effective and safe for the prophylaxis against IONV and early PONV in parturient undergoing caesarean delivery. However, the review included only the operations performed under spinal or epidural anesthesia [26], and metoclopramide was used either during the operations or after the delivery. Dimenhydrinate use 1 h before the anticipated gynecological operation was effective in reducing postoperative nausea but not vomiting in a study published in 2004; however, the agent was used orally with 30 ml of water [27]. In our study, we used both agents from the intramuscular route 1 h before the anticipated surgery and all the women received general anesthesia.

The optimal effective and safe dose of metoclopramide and dimenhydrinate varied according to the published data. The consensus guidelines for managing PONV suggested the use of the lowest effective doses. According to the published data, the use of a 1–2 mg/kg of dimenhydrinate was suggested; however, the suggestion lacks the optimal dose for the pregnant women [4]. In most of the studies, the optimal dose of dimenhydrinate ranged between 50 and 100 mg [27–29]. Although some publications provided evidence for the effectiveness of metoclopramide in PONS [3, 29] (the dose of metoclopramide was 20 mg in the 2nd study), the consensus guidelines concluded that metoclopramide was ineffective in standard clinical 10-mg IV doses and most of the members of the panel did not recommend metoclopramide as an antiemetic [4]. In contrast, we used 10 mg of metoclopramide and 50 mg of dimenhydrinate intramuscularly one hour before the surgery and found that each agent was significantly and similarly effective in preventing PONV in women undergoing elective caesarean section compared with placebo. The contrast may originate from the timing and administrative route of the agents.

Although both agents were effective in reducing the rates of PONS in our study, the optimal management of PONS in women undergoing elective caesarean sections is still not clear. Further studies including the comparison of the coast-effectiveness, availability, administrative time, dose, route, and results of various antiemetics are needed.

In conclusion, the inexpensive antiemetics, dimenhydrinate, and metoclopramide significantly decrease postoperative nausea, vomiting, and the need for rescue antiemetic medication. Both agents have similar efficacy and may be used as an alternative to each other.

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Compliance with Ethical Requirements and conflict of interest "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards." Both authors, Hüseyinoğlu Ürfettin and Ülker Kahraman, declare no conflict of interest.

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