Ondansetron Versus Metoclopramide in the Treatment of Postoperative Nausea and Vomiting

Enrico Polati, MD*, Giuseppe Verlato, MD, PhD†, Gabriele Finco, MD*, Walter Mosaner, MD*, Salvatore Grosso, MD*, Leonardo Gottin, MD*, Anna M. Pinaroli, MD*, and Stefano Ischia, MD, PhD*

Institutes of *Anesthesiology and Intensive Care and †Medical Statistics, University of Verona, Verona, Italy

In this prospective, randomized, double-blind study, we compared the efficacy and safety of ondansetron and metoclopramide in the treatment of postoperative nausea and vomiting (PONV). One hundred seventy-five patients with PONV during recovery from anesthesia for gynecological laparoscopy were treated intravenously with either ondansetron 4 mg (58 patients), metoclopramide 10 mg (57 patients), or placebo (60 patients). Early antiemetic efficacy (abolition of vomiting within 10 min and of nausea within 30 min from the administration of the study drugs with no further vomiting or nausea episodes during the first hour) was obtained in 54 of 58 patients (93.1%) in the ondansetron group, in 38 of 57 patients (66.7%) in the metoclopramide group, and in 21 of 60 patients (35%) in the placebo group ($P < 0.001$). This difference was still significant when controlling for age, body weight, history of motion sickness, previous PONV episodes, duration of anesthesia, and intraoperative fentanyl consumption using a logistic model. Early antiemetic efficacy was inversely related to the amount of fentanyl administered during anesthesia, regardless of treatment. According to the Kaplan-Meier method, the probability of remaining PONV-free for 48 h after a successful treatment was 0.59 (95% confidence interval 0.45–0.71) in the ondansetron group, 0.45 (0.29–0.60) in the metoclopramide group, and 0.33 (0.15–0.53) in the placebo group ($P = 0.003$). In conclusion, ondansetron 4 mg is more effective than metoclopramide 10 mg and placebo in the treatment of established PONV.

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Postoperative nausea and vomiting (PONV) occurs often after both general and regional anesthesia (1,2). Nonpharmacological techniques and many different antiemetic drugs are available for the prevention and treatment of PONV (1,2).

Drugs known to block dopamine (D$_2$), histamine (H$_1$), and muscarinic cholinergic receptors have antiemetic effects (1,2). Selective antagonists at the 5-hydroxytryptamine 3 (5-HT$_3$) receptor have potent antiemetic activity, and ondansetron is the prototype of these compounds (3). The site of action of ondansetron is thought to be the 5-HT$_3$ receptor on neurons located in the visceral afferent vagus and in the area postrema (4).

In the current literature, many reports assess the efficacy and safety of ondansetron, metoclopramide, or placebo (5–17) in the prevention of PONV, but few studies compared ondansetron with placebo (18–21) in its treatment. No article has so far compared ondansetron with other antiemetic drugs in the treatment of established PONV. Moreover, it has not yet been evaluated whether any of the identified risk factors for PONV (22–24) also affect the efficacy of the antiemetic treatment.

The aim of this study was to compare the efficacy and safety of ondansetron with metoclopramide or placebo in the treatment of PONV and to establish whether the benefits of treatment are blunted by any of the risk factors for PONV.

Methods

This was a prospective, randomized, double-blind, single-dose, parallel groups study. After approval of the local ethical committee, written, informed consent to participate in the study was obtained from 400 inpatients who were aged 18–66 yr, classified as ASA physical status I or II, and scheduled for elective gynecological laparoscopic surgery. Exclusion criteria were age <18 or >70 yr, pregnancy, breastfeeding, renal or liver disease, psychological illness, a positive

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Address correspondence and reprint requests to Enrico Polati, MD, Istituto di Anestesiologia e Rianimazione, Ospedale Policlinico, via delle Menegone, 37134 Verona, Italy.

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history for alcoholism or opioid addiction, body mass index (weight/height$^2$, Kg/m$^2$) greater than 30, consumption of antiemetic drugs during the 3 days preceding the intervention, occurrence of nausea or vomiting in the same period, and conditions associated with delayed gastric emptying, such as gastrointestinal obstruction, pyloric stenosis, chronic cholecystitis, diabetes mellitus, and neuromuscular disorders. A standardized anesthetic technique consisting of intramuscular diazepam (0.15 mg/kg) plus atropine (0.01 mg/kg) 1 h before the induction of anesthesia as premedication, intravenous (IV) thiopental (5 mg/kg) plus fentanyl (2.5 µg/kg) plus vecuronium (0.1 mg/kg) for the induction, and nitrous oxide/oxygen 60/40 plus isoflurane 0%–1% for the maintenance of anesthesia was used. Supplementary boluses of fentanyl and vecuronium were used if needed. Reversal of neuromuscular blockade was achieved in all patients with neostigmine and atropine at the end of the surgical procedure. The placement of a nasal or oral gastric tube during surgery was not permitted.

These criteria were met by 378 of 400 patients because 22 of the 400 patients dropped out because of deviation from the surgical plan (19 patients) or from the anesthesiologic protocol (3 patients). In this patient population, 193 of 378 patients (51%) experienced persistent nausea (lasting more than 10 min) with at least one emetic episode within 4 h of recovery. These patients were randomly assigned to one of the following treatment groups: 64 patients received ondansetron 4 mg IV (ondansetron group), 64 patients received metoclopramide 10 mg IV (metoclopramide group), and 65 patients received normal saline 20 mL IV (placebo group).

The randomization list was made, specifying the group to which each prospective patient would be assigned upon entry into the study. On the basis of this list, a nurse who was not involved in the study prepared the anonymous syringes containing either the drugs diluted to 20 mL with normal saline or 20 mL of normal saline. The solutions were administered IV over 2 min. Follow-up was conducted by anesthesiologists blinded to the treatment for 48 h: during the day, physicians visited the patient hourly, while they were contacted by nurses whenever PONV recurred during the night.

Patients who presented with fever (body temperature more than 38.5°C), hypotension (mean arterial pressure more than 33% below the preoperative values), or pain intensity greater than 3 on a visual analog scale from 0 to 10 in spite of a postoperative analgesia treated with nonopioid analgesics during the follow-up dropped out. Patients who underwent reintervention or who received opioid analgesics during the study period were also eliminated from the study.

Early antiemetic efficacy was defined as abolition of vomiting within 10 min and of nausea within 30 min from the administration of the study drugs with no further vomiting or nausea episodes during the first hour. Patients in whom vomiting and nausea persisted or recurred during the follow-up period could be treated with a rescue antiemetic, the choice of which was left to the anesthesiologists conducting the follow-up according to their clinical experience. The administration of a rescue antiemetic outside this protocol eliminated the patient from this study.

As regards the safety, we reported all drug-related side effects, and we collected the vital signs (blood pressure, heart rate, respiratory rate) before and 15 min after treatment.

Significance of the differences among groups was evaluated using analysis of variance for continuous variables and $\chi^2$ test for categorical variables. A multiplicative logistic model (25) was applied to compare the early antiemetic efficacy of different treatments both before and after adjustment for some reported risk factors for the occurrence of PONV (potential confounders): age, body weight, history of motion sickness (0 = absent, 1 = present), previous PONV episodes (0 = no previous anesthetic experience, 1 = previous anesthetic experience without PONV, 2 = previous anesthetic experience with PONV), duration of anesthesia, and intraoperative fentanyl consumption. The significance of the interactions between antiemetic treatment and each of the potential confounders was also tested. Results of the analysis were synthesized through the odds ratios. Calculation of the odds ratios for continuous variables (age, body weight, duration of anesthesia, and intraoperative fentanyl consumption) was based on an increase in the values of 1 sd. Recurrence of PONV in patients with early efficacy of antiemetic treatments was analyzed by means of Kaplan-Meier probability curves and a log-rank test (25). Changes in vital signs (diastolic and systolic blood pressure, heart rate, and respiratory rate) induced by the different treatments were analyzed using analysis of variance for mixed design. A significance level of 0.05 was chosen.

Results

After the study began, 18 patients were excluded because they were given opioid analgesics for adequate control of postoperative pain (12 patients) or rescue antiemetic separately from the protocol (2 patients), or they underwent reintervention (3 patients) or presented with fever (1 patient) during the follow-up period. At the time of the exclusion, we did not know to which group the patients belonged, but once the randomization list was consulted, we found that six patients were from the ondansetron group, seven were from the metoclopramide group, and five were
Table 1. Demographic and Clinical Characteristics of Patient Population (N = 175)

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Age (yr)</th>
<th>Body weight (kg)</th>
<th>History of motion sickness</th>
<th>History of PONV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron (58)</td>
<td>34 ± 10</td>
<td>58 ± 11</td>
<td>18</td>
<td>NPAE = 16</td>
</tr>
<tr>
<td>Metoclopramide (57)</td>
<td>36 ± 10</td>
<td>56 ± 8</td>
<td>19</td>
<td>PAEP = 24</td>
</tr>
<tr>
<td>Placebo (60)</td>
<td>35 ± 12</td>
<td>56 ± 10</td>
<td>21</td>
<td>PAENP = 18</td>
</tr>
</tbody>
</table>

Age and body weight data are presented as mean ± sd. History of motion sickness and PONV data are presented as the number of patients. PONV = postoperative nausea and vomiting, NPAE = no previous anesthetic experience, PAEP = previous anesthetic experience with PONV, PAENP = previous anesthetic experience without PONV.

from the placebo group. Thus, data analysis was performed on 58, 57, and 60 patients in the ondansetron, metoclopramide, and placebo groups, respectively.

The main demographic and clinical characteristics of the patients under investigation were not significantly different among the three groups (Table 1). Moreover, duration of anesthesia (88 ± 38, 81 ± 33, and 79 ± 25 min in the ondansetron, metoclopramide, and placebo groups, respectively; mean ± sd) and fentanyl consumption (418 ± 178, 399 ± 164, 394 ± 134 μg in the ondansetron, metoclopramide, and placebo groups, respectively) were not significantly different in the three groups.

Early antiemetic efficacy was obtained in 54 of 58 patients (93.1%) in the ondansetron group, in 38 of 57 patients (66.7%) in the metoclopramide group, and in 21 of 60 patients (35%) in the placebo group.

Early antiemetic efficacy was significantly different in the three groups (P < 0.001) (Table 2). Ondansetron proved to be more effective in abolishing nausea and vomiting than metoclopramide, which in turn proved to be more effective than placebo. These differences were even greater when controlling for potential confounders (age, body weight, history of motion sickness, previous PONV episodes, duration of anesthesia, and intraoperative fentanyl consumption). Moreover, early antiemetic efficacy was inversely related to the amount of fentanyl administered during anesthesia, irrespective of the type of treatment. Other variables did not exert an independent effect on the efficacy of the antiemetic regimen. The efficacy of the antiemetic regimen tended to decrease with increased duration of anesthesia (P = 0.079), but this effect completely disappeared after controlling for the amount of opioids given.

In a separate analysis, we evaluated whether the early antiemetic efficacy of the different treatments was modulated by any of the risk factors considered. We found a significant interaction between the efficacy of the three different treatments and body weight (P = 0.023): early antiemetic efficacy decreased with increasing body weight in the ondansetron and metoclopramide groups, while there was no clear trend with body weight in the placebo group.

Among the patients who were successfully treated, 22 of 54 patients (40.7%) in the ondansetron group, 21 of 38 patients (55.3%) in the metoclopramide group, and 14 of 21 patients (66.7%) in the placebo group had recurrence of PONV, so that at the end of the follow-up period, the treatment was effective in 32 of 58 patients (55.2%) in the ondansetron group, in 17 of 57 patients (29.8%) in the metoclopramide group, and in 7 of 60 patients (11.7%) in the placebo group. According to the Kaplan-Meier method, probability of remaining PONV-free for 48 h after a successful treatment was 0.59 (95% confidence interval 0.45–0.71) in the ondansetron group, 0.45 (0.29–0.60) in the metoclopramide group, and 0.33 (0.15–0.53) in the placebo group. These differences are statistically significant (P = 0.003). As shown in Figure 1, the antiemetic efficacy of ondansetron fully persisted for the first 2–3 h after injection, whereas recurrence of vomiting was recorded in half of the placebo-treated patients and in nearly none of the ondansetron-treated patients. Later on, this difference decreased since sporadic cases of vomiting were still observed after 6 h in the ondansetron group but not in the placebo group.

As regards the safety, one patient in the ondansetron group reported a moderate, transient headache after the treatment (lasting 3 h and requiring treatment with a nonsteroidal antiinflammatory drug); its relationship with drug administration was judged probable. With regard to the vital signs, no significant variations of blood pressure, heart rate, or respiratory rate, compared to the basal values, were recorded in any group during the study.

**Discussion**

The main finding of this single-dose study is that ondansetron 4 mg is more effective than metoclopramide 10 mg, which in turn is more effective than
Table 2. Odds Ratio (95% Confidence Interval) of One-Hour Efficacy of Antiemetic Regimen in 175 Patients Undergoing Gynecologic Surgery Before and After Adjustment for All Other Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nonadjusted</th>
<th>Adjusted</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (sd 10.8 yr)</td>
<td>0.85 (0.62–1.15)</td>
<td>1.02 (0.66–1.57)</td>
<td>0.927</td>
</tr>
<tr>
<td>Body weight (sd 9.6 kg)</td>
<td>0.78 (0.57–1.06)</td>
<td>0.67 (0.43–1.06)</td>
<td>0.080</td>
</tr>
<tr>
<td>Motion sickness (present versus absent)</td>
<td>1.19 (0.61–2.32)</td>
<td>1.85 (0.75–4.56)</td>
<td>0.175</td>
</tr>
<tr>
<td>Past history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAEP versus NPAE</td>
<td>0.51 (0.24–1.11)</td>
<td>0.51 (0.18–1.49)</td>
<td>0.151</td>
</tr>
<tr>
<td>PAENP versus NPAE</td>
<td>1.35 (0.55–3.27)</td>
<td>1.31 (0.38–4.55)</td>
<td></td>
</tr>
<tr>
<td>Duration (sd 32.5 min)</td>
<td>0.76 (0.56–1.03)</td>
<td>1.07 (0.60–1.93)</td>
<td>0.812</td>
</tr>
<tr>
<td>Fentanyl (sd 159 µg)</td>
<td>0.56 (0.41–0.78)</td>
<td>0.33 (0.17–0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron versus metoclopramide</td>
<td>6.75 (2.13–21.4)</td>
<td>17.8 (3.97–79.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo versus metoclopramide</td>
<td>0.27 (0.13–0.58)</td>
<td>0.18 (0.07–0.45)</td>
<td></td>
</tr>
</tbody>
</table>

Odds ratios were derived from a logistic regression model. Odds ratios for continuous variables were computed on the basis of an increase in the values of 1 sd.
NPAE = no previous anesthetic experience, PAEP = previous anesthetic experience with postoperative nausea and vomiting, PAENP = previous anesthetic experience without postoperative nausea and vomiting.

*P values were computed controlling for all other variables.

Figure 1. Kaplan-Meier estimates of probability of remaining PONV-free after a successful treatment (113 patients).

ondansetron
metoclopramide
placebo

Ondansetron 4 mg can be considered the optimal dose for the treatment of PONV (20); on the other hand, metoclopramide 10 mg is a conventional antiemetic drug, largely and safely used at this dose in adults for both prevention and treatment of PONV (1). Although its antiemetic efficacy is under debate, some controlled trials performed during gynecological and obstetric procedures (16,17,26,27), as well as our own data, showed that metoclopramide 10 mg is effective and safe. We are not able to say whether larger doses of metoclopramide could be more effective and equally safe in the treatment of established PONV. This should be investigated by further, differently designed studies.

The etiology of PONV is multifactorial, and patient-related factors (age, gender, body weight, history of PONV or history of motion sickness, gastroparesis), surgical-related factors (type of surgery), anesthesia-related factors (premedication drugs, anesthetic technique, duration of anesthesia, type and doses of anesthetic drugs), and postoperative period-related factors (pain, hypotension, use of opioids analgesics) may influence its occurrence (1,28). There are no studies that evaluate whether any of these factors may also affect the treatment outcome. In this study, we standardized some of these factors (gender, absence of conditions associated with delayed gastric emptying, type of surgery, anesthetic technique, premedication drugs, induction of anesthesia, type of anesthetics used for the maintenance of anesthesia, postoperative period-related factors), and when applying a multiplicative logistic model, we found that among the studied factors, only intraoperative fentanyl consumption affected the treatment outcome, being inversely related to the early antiemetic efficacy, irrespective of the type of treatment.

placebo, in abolishing PONV. Ondansetron not only abolished PONV in a higher percentage of patients than metoclopramide and placebo but also prevented or delayed the recurrence of these symptoms after successful treatment. Indeed, the antiemetic efficacy of ondansetron remained maximal for the first two to three hours after injection.

As regards the safety study, the incidence of adverse effects due to the drug administration was negligible in our patients and did not significantly differ among the three groups. The treatment did not significantly alter the vital signs (blood pressure, heart rate, respiratory rate) compared with the basal values in the three groups.

To compare the antiemetic efficacy of ondansetron with metoclopramide in the treatment of established PONV, we used two active, fixed-dose treatments: ondansetron 4 mg and metoclopramide 10 mg IV.
In the anesthesiologic setting, prevention of PONV may be particularly important when its occurrence may represent a risk to the patient (for instance, in the presence of a depressed level of consciousness or after oral surgery, when the jaw is wired) (2) or when it can result in additional cost-related consequences (for instance, in outpatients undergoing ambulatory surgery) (29). Patients at high risk of PONV should receive special consideration with respect to the prophylactic use of antiemetic drugs (1). In most cases, however, it is not justified to routinely use antiemetics preoperatively (1,2), and physicians should also consider the direct treatment. The present study shows that ondansetron 4 mg IV has a greater efficacy/safety ratio than metoclopramide 10 mg IV and placebo when used to treat established PONV.

References