Double-blind, Randomized Comparison of Ondansetron and Intraoperative Propofol to Prevent Postoperative Nausea and Vomiting


Background: Breast surgery is associated with a high incidence of postoperative nausea and vomiting. Propofol and prophylactic administration of ondansetron are associated with a lower incidence of postoperative nausea and vomiting. To date no comparison of these two drugs has been reported. A randomized study was done to compare the efficacy of ondansetron and intraoperative propofol given in various regimens.

Methods: Study participants included 89 women classified as American Society of Anesthesiologists physical status 1 or 2 who were scheduled for major breast surgery. Patients were randomly assigned to one of four groups. Group O received 4 mg ondansetron in 10 ml 0.9% saline and groups PI, PIP, and PP received 10 ml 0.9% saline before anesthesia induction. Group O received thiopental, isoflurane, nitrous oxide–oxygen, and fentanyl. Postoperative pain relief was provided with morphine administered by a patient-controlled analgesia pump. The incidence of nausea and vomiting, requests for rescue antiemetic and sedation, pain scores, and hemodynamic data were recorded for 24 h.

Results: Within 6 h of surgery, groups O and PP had a lower incidence of nausea compared with groups PI and PIP (P < 0.05). Fewer patients in group PP (19%) vomited during the 24-h period compared with groups O (48%), PI (64%), and PIP (52%) (P < 0.05). The incidence of antiemetic use was also less in group PP (P < 0.05). Patients in group PP had lower sedation scores at 30 min and at 1 h (P < 0.05). There were no differences among the groups in pain scores, blood pressure, heart rate, respiratory rate, and incidence of pruritus.

Conclusions: Propofol administered to induce and maintain anesthesia is more effective than ondansetron (with thiopental–isoflurane anesthesia) in preventing postoperative vomiting and is associated with fewer requests for rescue antiemetic and sedation in the early phase of recovery. It is equally effective in preventing postoperative nausea as ondansetron in the first 6 h after operation. Propofol used only as an induction agent or for induction and at the end of surgery was not as protective against postoperative nausea and vomiting. (Key words: Anesthetics, volatile; isoflurane. Anesthetics, intravenous: propofol. Surgery; breast. Antiemetics; ondansetron; propofol. Side effects: nausea; vomiting.)

POSTOPERATIVE nausea and vomiting (PONV) still occurs with a high frequency and is distressing to patients and potentially detrimental to their postoperative recovery. Breast surgery is associated with a high incidence of PONV. Propofol as an induction and maintenance agent has been associated with a lower incidence of PONV. More recently, propofol in subhypnotic doses has been shown to be effective against chemotransduction–induced nausea and vomiting and PONV. Ondansetron is a 5HT-3 antagonist and has been shown to be an effective antiemetic compared with placebo, metoclopramide, and droperidol. However, no study directly comparing propofol and ondansetron in various regimens.

Materials and Methods

We enrolled 89 women classified as American Society of Anesthesiologists physical status 1 or 2 who were 18 to 70 y old and scheduled for major breast surgery...
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(mastectomy, breast reconstruction, and insertion of breast implants). We obtained institutional review board approval and patients gave their informed consent. Patients who had received drugs with an antiemetic effect within 24 h before initiation of anesthesia, had received an investigational drug within the past 30 days, had vomited or retched within the preceding 24 h, or were twice their ideal body weight were excluded from the study. All patients received 1 to 2 mg midazolam as premedication. Patients were randomly assigned to one of four groups using computer-generated random numbers concealed in envelopes. Patients in group O received 4 mg ondansetron in 10 ml 0.9% saline, and groups PI, PIP, and PP received 10 ml 0.9% saline before induction of anesthesia. Group O received 2 to 3 mg/kg fentanyl and 3 to 5 mg/kg thiopental intravenously, followed by 0.5% to 1.5% isoflurane and 66% nitrous oxide in oxygen. Group PI received 2 to 3 mg/kg fentanyl and 2 mg/kg propofol intravenously, followed by 0.5% to 1.5% isoflurane and 66% nitrous oxide in oxygen. Group PIP received 2 to 3 mg/kg fentanyl and 2 mg/kg propofol given intravenously, followed by 0.5% to 1.5% isoflurane and 66% nitrous oxide in oxygen. Thirty minutes before expected skin closure, isoflurane was discontinued and 50 to 150 µg·kg⁻¹·min⁻¹ propofol was given intravenously to maintain anesthesia. Group PP received 2 to 3 mg/kg fentanyl and 2 mg/kg propofol intravenously, followed by 50 to 150 µg·kg⁻¹·min⁻¹ propofol intravenously and 66% nitrous oxide in oxygen. All patients received intravenous vecuronium to facilitate tracheal intubation and subsequent neuromuscular blockade during surgery. Fentanyl to a maximum intravenous dose of 5 µg·kg⁻¹·h⁻¹ was used during the procedure. At the end of surgery, 40 µg/kg neostigmine and 8 µg/kg glycopyrrolate were used to antagonize neuromuscular blockade. Postoperative pain relief was provided by morphine (1 mg/ml) through the patient-controlled analgesia machine (LifeCare PCA, Abbott Laboratory, Chicago, IL) with standard settings (20 µg/kg demand dose, 8 min lock-out intervals with maximum dose of 30 mg in 4 h). The incidence of nausea, retching, or vomiting and patient requests for rescue antiemetics (12.5 mg promethazine) were recorded at 0.5, 1, 6, 12, 18, and 24 h by an independent observer blinded to the patients' treatment groups. Observer assessment of sedation scores (based on Wilson and colleagues28; table 1) and patient assessment of pain scores (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; 4 = worst pain), incidence of pruritus and other adverse events, blood pressure, and heart and respiratory rates were also recorded at the same time periods.

Sample size was estimated based on a two-tailed test of the difference between proportions in independent groups at alpha = 0.05.19 Considering PONV as the primary outcome, with a baseline (control) incidence of about 65%, a sample size of 22 patients per group was found to provide 80% power to detect a difference of 50%; that is, a reduction from 65% to 35% incidence. Based on the literature, a difference at least this large was expected between the control group (PI) and the treatment groups. Therefore, if either the propofol treatment group or the ondansetron group showed a greater reduction than placebo, the study would have at least 80% power to detect this difference. Categorical data were analyzed using the chi-squared test, and continuous data were analyzed by one-way analysis of variance. Post hoc analysis (Bonferroni adjustment) was performed to detect intergroup differences. A probability value less than 0.05 was declared statistically significant.

Results

Eighty-nine patients participated in the study. Groups O, PI, PIP, and PP contained 21, 22, 25, and 21 patients, respectively. There were no significant differences among the groups with respect to age, weight, duration of anesthesia, previous history of PONV or motion sickness, and use of intraoperative fentanyl and postoperative morphine (table 2). No patient had a nasogastric tube inserted during the study period.

The combined overall incidence of PONV was 57%. The incidence of nausea in groups O and PP was less than in groups PI and PIP. This difference was statistically significant at 0.5, 1, and 6 h (P < 0.05). The incidence of postoperative vomiting and the use of rescue antiemetics within 24 h were significantly less in group PP compared with the other three groups (P < 0.05).

Table 1. Sedation Scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Completely awake</td>
</tr>
<tr>
<td>1</td>
<td>Awake but drowsy</td>
</tr>
<tr>
<td>2</td>
<td>Asleep but responds to verbal commands</td>
</tr>
<tr>
<td>3</td>
<td>Asleep but responds to physical stimulus</td>
</tr>
<tr>
<td>4</td>
<td>Unarousable</td>
</tr>
</tbody>
</table>

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Table 2. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 21)</th>
<th>Group B (n = 22)</th>
<th>Group C (n = 25)</th>
<th>Group D (n = 21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45 ± 3</td>
<td>46 ± 12.5</td>
<td>46 ± 12.6</td>
<td>48 ± 14.2</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 ± 16</td>
<td>72 ± 19</td>
<td>69 ± 17</td>
<td>70 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of anesthesia (h)</td>
<td>2.6 ± 1.2</td>
<td>3.1 ± 1.5</td>
<td>2.8 ± 1.5</td>
<td>2.4 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>History of PONV/motion sickness (n)</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative fentanyl (µg)</td>
<td>305 ± 150</td>
<td>312 ± 200</td>
<td>332 ± 218</td>
<td>310 ± 239</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative (24 h) morphine (mg)</td>
<td>10 ± 12</td>
<td>7 ± 6</td>
<td>10 ± 8</td>
<td>7 ± 8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
NS = not statistically significant.

Table 3 summarizes the incidence of nausea, vomiting, and use of rescue antiemetics among the groups.

Group PP patients consistently had lower sedation scores compared with the other groups (fig. 1). These differences reached statistical significance for group PP versus group O at 30 min and for group PP versus group PIP 1 h after the operation (P < 0.05 after Bonferroni adjustment for post hoc comparison). There were no differences among the groups in pain scores, blood pressure, heart and respiratory rates, and incidence of pruritus.

Discussion

Major breast surgery is associated with a high incidence of PONV. A previous study found the incidence of nausea or vomiting to be as high as 60% and that most of these symptoms occur after patients leave the postoperative care unit. The combined overall incidence of PONV in this study was 57% and was as high as 68% in patients receiving propofol as an induction agent only followed by maintenance of anesthesia with isoflurane and nitrous oxide in oxygen. Recent reviews on PONV have not included major breast surgery as a high-risk procedure, probably because similar studies in this patient category have been lacking. However, there are many common denominators that may account for the very high incidence. Women have approximately two to three times the incidence of PONV compared with men, and the severity of vomiting is also greater in women. This may be due in part due to the difference between men and women in levels of sex hormones.

Ondansetron is an effective antiemetic against PONV and has minimal side effects compared with other routinely used antiemetics. In particular, when com-

Table 3. Cumulative Incidence of Postoperative Nausea, Vomiting and 24-Hour Request for Rescue Antiemetic

<table>
<thead>
<tr>
<th></th>
<th>Group O (n = 21 (%)</th>
<th>Group PIP (n = 22 (%)</th>
<th>Group PIP (n = 25 (%)</th>
<th>Group PIP (n = 21 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0.5</td>
<td>3 (14)</td>
<td>10 (45)</td>
<td>9 (36)</td>
<td>1 (5)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4 (19)</td>
<td>11 (50)</td>
<td>9 (36)</td>
<td>2 (10)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5 (24)</td>
<td>13 (59)</td>
<td>11 (44)</td>
<td>4 (19)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>9 (43)</td>
<td>13 (59)</td>
<td>12 (48)</td>
<td>6 (29)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>13 (62)</td>
<td>14 (64)</td>
<td>14 (56)</td>
<td>9 (43)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>13 (62)</td>
<td>15 (68)</td>
<td>14 (56)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.5</td>
<td>1 (5)</td>
<td>3 (14)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2 (10)</td>
<td>3 (23)</td>
<td>3 (12)</td>
<td>1 (5)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4 (19)</td>
<td>10 (45)</td>
<td>8 (32)</td>
<td>2 (10)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>8 (38)</td>
<td>13 (59)</td>
<td>10 (40)</td>
<td>2 (10)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>8 (38)</td>
<td>14 (64)</td>
<td>12 (48)</td>
<td>4 (19)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>10 (48)</td>
<td>14 (64)</td>
<td>15 (32)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Request for rescue antiemetic</td>
<td>24</td>
<td>13 (62)</td>
<td>15 (68)</td>
<td>15 (60)</td>
<td>6 (29)</td>
</tr>
</tbody>
</table>

NS = not statistically significant.
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Fig. 1. Sedation scores versus time (mean ± SD). Group PP had lower sedation scores compared with groups O, PI, and PIP at 30 and 60 min (P < 0.05, analysis of variance).

pared with droperidol, it is associated with less postoperative drowsiness, restlessness, anxiety, or dizziness.29 Although some data suggest that ondansetron is superior to droperidol in the outpatient population,10 the two drugs appear to have similar efficacy in inpatient populations.13-15 A multiple-center study of prophylactic intravenous ondansetron found that 4 mg is equally effective to prevent PONV as 8 mg; the researchers recommend the use of 4 mg as the standard dose for this purpose.12

Propofol was recently found to possess direct anesthetic properties,25 and this effect is not due to the intralipid emulsion in the formulation of propofol.26 Propofol-based anesthetics have been associated with a lower incidence of PONV compared with enflurane,27 isoflurane,28 or desflurane anesthesia.29,30 These studies found a low incidence of PONV only when propofol was used throughout the procedure. The protective effect of propofol against PONV seemed to disappear when it was used as an induction agent only. We found that when propofol was used as an induction agent and anesthesia was maintained with isoflurane, nitrous oxide, and oxygen (group PI), it was not protective against PONV. On the other hand, propofol used only as an induction agent has been associated with a lower incidence of PONV in relatively short surgical procedures (less than 30 min).31,32 Thus it is possible that a therapeutic range of plasma concentrations of propofol may be related to PONV protection.

We included group PIP (propofol as an induction agent and anesthesia maintained with isoflurane, nitrous oxide, and oxygen, followed by propofol substituted for isoflurane 30 min before the expected end of surgery) because we believed that propofol used in this regimen might be associated with more rapid recovery and provide protection against PONV. Our study, however, demonstrated that this technique, which is popular in clinical practice, did not confer any advantage with respect to PONV or more rapid recovery as judged by sedation scores. In contrast, the group receiving propofol for maintenance of anesthesia did.

The plasma concentration of propofol effective against nausea and vomiting was 200 ng/ml in one patient.33 This was much less than that needed for sedation (1,500 to 2,000 ng/ml) and maintenance of general anesthesia (3,000 to 10,000 ng/ml). Borger and associates34 found an 85% to 90% success rate when 17 µg·kg⁻¹·min⁻¹ propofol (1 mg·kg⁻¹·h⁻¹) was used to control chemotherapy-induced nausea and vomiting in a group of patients who did not respond to treatment with ondansetron and steroids during their previous chemotherapy cycle. We simulated their dosing regimen and showed that plasma concentrations of propofol lie between 300 and 500 ng/ml for the 24-h period. The simulation was based on the pharmacokinetic parameters for propofol reported by Gepts and colleagues.35 In addition, the plasma concentrations of propofol associated with at least a 50% reduction of postoperative nausea is 405 ± 59 ng/ml (mean ± SEM) with 95% confidence intervals of 280 to 530 ng/ml.§ Using the data on propofol dosing regimens in patients in groups PI, PIP, and PP, we similarly simulated the plasma concentration of propofol in each of these patients for 6 h after the induction of anesthesia. The results of the simulated data (fig. 2) showed that patients in group PP had higher plasma concentrations of propofol compared with those in groups PI and PIP (P < 0.01; analysis of variance) at all times during the 6-h recovery period. The simulated median plasma propofol concentration 1 h after termination of infusion was 424 ng/ml for group PP, 128 ng/ml for group PIP, and 41 ng/ml for group PI. This pharmacokinetic simulation may explain the difference in incidence of PONV among the three groups. Furthermore, the “sandwich technique” may have been protective against PONV for the

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Fig. 2. Simulated plasma propofol concentrations for groups PI, PIP, and PP 6 h after completion of surgery. Bold lines indicate the median concentrations for each group.

first hour (36% vs. 50% for postoperative nausea and 12% vs. 23% for postoperative vomiting for group PIP vs. control, respectively) or after surgery of shorter duration, when the induction dose would contribute to the maintenance of therapeutic concentrations of propofol to prevent nausea and vomiting for a longer period.

In this study, the antiemetic effects of propofol and ondansetron persisted through 6 h. Paxton and coworkers\(^{14}\) found that the lower visual analogue score for postoperative nausea associated with ondansetron when compared with other antiemetics disappeared after 4 h. Ondansetron has a relatively short half-life of 2.8 ± 0.6 h after a single 8-mg intravenous dose.\(^{38}\) Most of a parent drug is metabolized by hydroxylation and excreted in the urine. Although the metabolites have some 5HT3-antagonist activity, they do not contribute significantly to the therapeutic effect. However, the efficacy of ondansetron\(^{39}\) and droperidol\(^{40}\) have been shown to exceed their elimination half-lives. This suggests that redistribution and termination half-life alone may not have a direct relation with clinical efficacy. Factors such as diffusibility and retention of drug within the site of action may be important. Unfortunately there are no data on the influence of these factors.

The mechanism of action of propofol as an antiemetic is not known. It has been postulated that propofol may act via an antidopaminergic pathway.\(^{42}\) However, two recent studies have not been able to substantiate this claim. Appadu and colleagues\(^{43}\) showed that propofol did not interact strongly with D\(_2\) dopamine receptors. Hwarfner and associates\(^{44}\) on the other hand, investigated subhypnotic doses of propofol infusion in healthy volunteers after they were given apomorphine (acting on dopamine D\(_1\) receptors in the chemoreceptor trigger zone) to induce vomiting. They concluded that propofol given in a non-sedative dose has no effect on apomorphine-induced vomiting. However, the total amount of apomorphine given to induce vomiting was significantly larger during propofol sedation than during saline infusion. They also did not measure blood concentrations of propofol. Several mechanisms may be possible for propofol's antiemetic action. Propofol may have a direct depressant effect on the emetic center in the brainstem, the vagal nuclei, and other centers in the area postrema and vomiting. Propofol also has been shown to decrease the release of excitatory amino acids such as glutamate and aspartate, which may be related to its antiemetic activity.\(^{35}\) Recently researchers showed that prolonged infusions of propofol (20 to 25 mg·kg\(^{-1}\)·h\(^{-1}\) for 6 h) cause decreased concentrations of serotonin in the area postrema,\(^{46}\) and this may be mediated through gamma-aminobutyric acid, receptor mechanisms.\(^{7}\)

One of the advantages of ondansetron compared with phenothiazines such as droperidol, prochlorperazine, or promethazine is that it lacks the sedative effect commonly seen with the latter agent.\(^{26}\) In our study, we noted a significantly lower sedation score in the early recovery phase (up to 1 h) when propofol was the induction and the maintenance agent compared with the other groups. The patients who received ondansetron (group O) had very similar sedation scores compared with those in the placebo group (PI), indicating the lack of sedative effects of ondansetron. The absence of side effects is a particularly desirable characteristic of any drug considered for antiemesis against PONV. Propofol, used for induction and maintenance, was effective in preventing PONV, was associated with early postoperative patient recovery, and did not cause other side effects.

Propofol (when used to induce and maintain anesthesia) and ondansetron are equally effective for prophylaxis against postoperative nausea in the first 6 h. Propofol used in this manner was more effective than ondansetron in decreasing the incidence of vomiting and...
The use of rescue antiemetics and sedation in the early recovery period. Propofol used only as an induction agent (group PI) or for induction and at the end of surgery (group PIP) were not as protective against PONV.

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References

47. Gelb AW, Dib A, Ceccetto DF: Effects of propofol on neuronal activity in the area postrema of the rat [Abstract]. Anesthesiology 1995; 83:A752

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