Patient-controlled Antiemesis

A Randomized, Double-Blind Comparison of Two Doses of Propofol versus Placebo


Background: The role of propofol for the management of postoperative nausea and vomiting (PONV) is not well established. This study determines the efficacy of small doses of propofol administered by patient-controlled device for the treatment of PONV.

Methods: Patients presenting for ambulatory surgery received a standardized general anesthetic. Those who experienced significant nausea or emesis within 1 h of arrival in the recovery room were randomized to receive repeated doses of propofol 20 mg (P 20), propofol 40 mg (P 40), or intralipid (placebo) on demand. Study medications (in equal volumes) were administered with a patient-controlled delivery device for 2 h. A look-out interval of 5 min between doses was used. The following parameters were assessed: nausea, vomiting, rescue antiemetic use, recovery profile, study drug administration history, and satisfaction with treatment.

Results: Sixty-nine patients participated in the study. Patient demographics were similar. The average nausea score for a patient in the P 20 and P 40 groups was 25% and 29% less, respectively, compared with placebo during the study period (P < 0.05). This difference was apparent 15 min after initiation of therapy. More placebo patients vomited (P 20, 12%; P 40, 25%; placebo, 56%; P = 0.003) and needed rescue antiemetics (P 20, 17%; P 40, 23%; placebo, 70%; P = 0.001) compared with treatment groups. Sedation scores were similar between groups. Propofol-treated patients had shorter stays in the post-anesthesia care unit (PACU; P 20, 131 ± 55 min [mean ± SD]; P 40, 141 ± 34 min; placebo, 191 ± 92 min; P = 0.005) and higher satisfaction with their control of PONV than placebo (P < 0.01).

Conclusions: Propofol is effective in managing PONV with shorter PACU stay and great degree of patient satisfaction. There were two episodes of oversedation in the P 40 group. Hence, propofol at a demand dose of 20 mg seems more appropriate. (Key words: Antiemetic; nausea; vomiting.)

POSTOPERATIVE nausea and vomiting (PONV) are unpleasant experiences, and intractable PONV is the most frequent anesthetic-related cause for unexpected hospital admission of surgical outpatients. The use of propofol as a maintenance anesthetic agent intraoperatively is associated with a reduced incidence of PONV. However, the use of subhypnotic doses of propofol as a direct postoperative antiemetic has produced mixed results. Borgeat et al. demonstrated that small doses of propofol (10 mg) were efficacious in managing PONV. On the other hand, Zestos et al. found 0.2 mg/kg doses of propofol were no different in efficacy than placebo.

The use of subhypnotic doses of propofol infusion for the prevention of PONV has not been proven conclusively. Although Ewalenko et al. demonstrated the efficacy of propofol when administered as a postoperative infusion, other investigators have not been able to produce similar results. We therefore investigate the efficacy of patient-controlled (on demand) propofol for the management of PONV.

Methods

After Institutional Review Board approval and written informed patient consent, American Society of Anesthesiologists (ASA) physical status I and II adult patients having day surgery with high emetogenic potential under general anesthesia were approached to participate in
the study. A patient-controlled analgesia machine (Lifecare™ PCA, Abbott Laboratory, Chicago, IL) was used to deliver the study solution. All patients were instructed on the use of the machine preoperatively. Patients received a standardized general anesthetic that consisted of premedication with midazolam, 1-2 mg, induction with fentanyl, 2-5 μg/kg, thiopental, 3-5 mg/kg, and anesthesia was maintained with fentanyl < 4 μg·kg⁻¹·h⁻¹, isoflurane, 0.5-1.5%, N₂O 66% in O₂. Tracheal intubation and subsequent neuromuscular blockade were achieved with rocuronium or vecuronium. At the end of surgery, neuromuscular blockade was antagonized by glycopyrrolate and neostigmine.

Patients who experienced significant nausea (nausea score ≥ 5 of 10, on an 11-point nausea verbal rating score [VRS], where 0 represents no nausea and 10 indicates worst possible nausea) or emesis and who requested an antiemetic within 1 h of entry to the recovery room were enrolled into the study. They were randomized to receive, in a double-blind fashion, propofol, 20 mg (P-20), propofol, 40 mg (P-40), or intralipid (placebo). The study drugs were prepared by the pharmacy in a 50-ml glass syringe with equal volume (4 ml) for each demand. A lockout interval of 5 min with no maximum dose limit was prescribed. The volume of study solution was made up to 4 ml in the P-20 group with 2 ml of intralipid. Rescue antiemetic (ondansetron, 4 mg) was administered on patient’s request or when patient had two or more episodes of emesis in 30 min. The administration of propofol was discontinued 2 h after commencement of the study. The following parameters were assessed before initiating treatment and at 15, 30, 60, 90, and 120 min thereafter: nausea verbal rating scores (0-10), episodes of vomiting or retching, rescue antiemetic use, sedation (table 1), respiratory rate, and hemodynamics. Satisfaction with treatment (satisfied, neither satisfied nor dissatisfied, dissatisfied) and patient’s study drug use pattern (delivered and undelivered demands) were collected at the end of the 2-h study period. The time to readiness for PACU discharge was noted (discharge criteria in table 2). There was no minimal stay in the PACU. A questionnaire on the incidence of post-discharge nausea, vomiting, and satisfaction with treatment were obtained at 24 h. Data on propofol use were downloaded, and the concentrations at the point when patients self-administered a dose were simulated using a previously published propofol pharmacokinetic data set.⁹

Sample size was estimated based on a two-tailed test of the difference between proportions in independent groups at α = 0.05.¹⁰ As there were no previous data on the efficacy of propofol for the management of PONV using this regimen, we based our power calculation on the incidence of nausea in patients having high-risk surgery.¹¹ Considering nausea as the primary outcome, with a baseline (control) incidence of 60%, a sample size of 20 patients per group was found to provide 80% power to detect a difference of 30%. Mantel-Haenszel test, generalized estimating equations, and logistic regression model were used to analyze the data. A P value < 0.05 was considered significant.

Results

Two hundred patients consented to participate in the study. Sixty-nine patients met entry criteria and participated in the study. There were 24, 22, and 23 patients in the P-20, P-40, and the placebo groups, respectively. There were no significant differences among the groups with respect to age, weight, type of surgery, duration of anesthesia, previous history of PONV or motion sickness, and use of intraoperative and postoperative fentanyl (table 3).

All three groups demonstrated decreasing VRS for nausea over time (fig. 1). Patients in the P-20 group had a 25% less likelihood of being nauseous, and patients in the P-40 group had a 29% less likelihood of being nauseous compared with the placebo group during the study period (P-20 vs. placebo, P = 0.03; P-40 vs. placebo, P = 0.006). The difference in nausea scores between treatment groups and placebo was apparent 15 min after initiation of therapy, and this difference was seen throughout the study period. The complete response rate (no nausea, vomiting, or rescue antiemetic use) during the 2-h study period was significantly higher in the propofol-treated groups than placebo (P-20, 19/24 [79%]; P-40, 16/22 [73%]; placebo, 5/25 [22%]; P = 0.01). There were significantly more patients in the pla-
Table 2. Patients' Response, Time to Readiness for Discharge and Satisfaction with Postoperative Nausea and Vomiting Control in Post Anesthetic Care Unit and at 24 h

<table>
<thead>
<tr>
<th></th>
<th>Propofol 20 mg (n = 24)</th>
<th>Propofol 40 mg (n = 22)</th>
<th>Placebo (n = 23)</th>
<th>Propofol 20 mg (n = 24)</th>
<th>Propofol 40 mg (n = 22)</th>
<th>Placebo (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response*</td>
<td>19 (79)</td>
<td>16 (73)</td>
<td>5 (22)§</td>
<td>12 (50)</td>
<td>12 (55)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (12)</td>
<td>5 (23)</td>
<td>13 (56)†</td>
<td>8 (33)</td>
<td>8 (36)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>Rescue anemic</td>
<td>4 (17)</td>
<td>5 (23)</td>
<td>16 (70)**</td>
<td>22 (92)</td>
<td>16 (76)</td>
<td>12 (52)</td>
</tr>
<tr>
<td>PACU discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>readiness† (min)</td>
<td>131 ± 35</td>
<td>141 ± 34</td>
<td>191 ± 92†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient satisfaction‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfied</td>
<td>23 (96)</td>
<td>21 (95)</td>
<td>10 (43)</td>
<td>22 (92)</td>
<td>16 (76)</td>
<td>12 (52)</td>
</tr>
<tr>
<td>Neither satisfied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nor dissatisfied</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>3 (13)</td>
<td>2 (8)</td>
<td>2 (10)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>0</td>
<td>0</td>
<td>10 (44)</td>
<td>0</td>
<td>3 (14)</td>
<td>7 (31)</td>
</tr>
</tbody>
</table>

Values are numbers (percentages) or mean ± SD.

* Complete response rate at 24 h was no nausea and vomiting.
† PACU discharge criteria: hemodynamically stable; blood pressure and heart rate within 20% of preoperative values; protective reflex present; patient fully conscious and able to protect own airway; operative pain controlled; verbal rating score for pain ≤3 of 10; absence of severe nausea (verbal rating score for nausea ≥5 of 10) or active vomiting; skin warm and dry; absence of bladder distention; oral temperature ≥35°C.
‡ P < 0.05, placebo versus P-20 and P-40 groups at 2 and 24 h.
§ P = 0.01, **P = 0.003, †P = 0.001, ††P = 0.005, placebo versus P-20 and P-40 groups.

cobo group who experienced vomiting (P-20, 3/21 [12%]; P-40, 5/22 [23%]; placebo, 13/23 [56%]; P = 0.003) and the use of rescue anemic (P-20, 4/24 [17%]; P-40, 5/22 [23%]; and placebo, 16/23 [70%]; P = 0.001) compared with the propofol-treated groups (table 2).

The time (mean ± SD) to PACU discharge was significantly shorter in the propofol-treated groups compared with the placebo groups (P-20, 131 ± 35 min; P-40, 141 ± 34 min; placebo, 191 ± 92 min; P = 0.005). Two patients in the placebo group were admitted because of persistent and uncontrolled nausea and vomiting. There was no difference in sedation scores between the groups (fig. 2). Two patients in the P-40 group experienced oversedation (one patient had a sedation score of 3 [asleep but responds to loud verbal command], and another had a brief episode of apnea with a sedation score of 1 [does not respond to shaking]). However, they returned to normal by the next assessment time point. No difference in pain scores, blood pressure, heart rate, respiratory rate, and blood oxygen saturation were detected between the groups.

Table 3. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Propofol 20 mg (n = 24)</th>
<th>Propofol 40 mg (n = 22)</th>
<th>Placebo (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>3:21</td>
<td>5:17</td>
<td>2:21</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>40 ± 13</td>
<td>40 ± 13</td>
<td>43 ± 11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.2 ± 17.5</td>
<td>78.8 ± 24.4</td>
<td>81.6 ± 20.1</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>7</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Breast</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>ENT</td>
<td>5</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>General</td>
<td>5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Surgical duration (h)</td>
<td>2.3 ± 1.4</td>
<td>2.2 ± 1.4</td>
<td>2.2 ± 1.5</td>
</tr>
<tr>
<td>Intraoperative fentanyl use (µg)</td>
<td>429 ± 275</td>
<td>440 ± 379</td>
<td>380 ± 250</td>
</tr>
<tr>
<td>Postoperative fentanyl use (µg)</td>
<td>17 ± 34</td>
<td>23 ± 41</td>
<td>29 ± 48</td>
</tr>
<tr>
<td>Prehistoric history of PONV/motion sickness</td>
<td>8/7</td>
<td>10/9</td>
<td>7/7</td>
</tr>
</tbody>
</table>

Values are numbers or mean ± SD.

ENT = ear-nose-throat; PONV = postoperative nausea and vomiting.

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More patients in the propofol-treated groups were satisfied with their control of PONV compared with the placebo group during their recovery room stay and at 24 h after discharge, \( P < 0.05 \), chi-square test (table 2). Ninety-six percent and 95% of the patients in the P-20 and P-40 groups, respectively, were satisfied with the treatment compared with 43% in the placebo groups, \( P < 0.05 \). Similar trends were observed at 24 h (table 2).

Total propofol dose and patients’ delivered and undelivered demands for propofol are presented in table 4. There was a statistically significant difference in the undelivered demands between the propofol treatment groups compared with placebo group. Figure 3 represents the raw data of the simulated minimum effective plasma propofol concentrations (MEC) for the two propofol treatment groups. The median (25–75th percentile) of the simulated MEC of propofol for the P-20 and P-40 groups was 174 ng/ml (170–297) and 296 ng/ml (240–437), respectively.

**Discussion**

This study demonstrated that subhypnotic doses of propofol are more efficacious than placebo for the man-

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**Fig. 1. Nausea scores versus time (mean ± SD).**

**Fig. 2. Sedation scores versus time (mean ± SD).**
Table 4. The Total Dose of Propofol Administered, the Number of Successful Deliveries, and Undelivered Patient Demands

<table>
<thead>
<tr>
<th></th>
<th>Propofol 20 mg (n = 22)</th>
<th>Propofol 40 mg (n = 22)</th>
<th>Placebo (n = 23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total propofol (mg)</td>
<td>100 ± 60</td>
<td>200 ± 80</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Successful deliveries</td>
<td>5 ± 3</td>
<td>5 ± 2</td>
<td>8 ± 3</td>
<td>0.0003</td>
</tr>
<tr>
<td>Undelivered demands</td>
<td>3 ± 4</td>
<td>2 ± 4</td>
<td>68 ± 136</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

agement of PONV and they are associated with an earlier readiness for PACU discharge and more frequent patient satisfaction. A patient-controlled device may be used to deliver propofol in small boluses (20 mg) for this purpose.

Intraoperative use of propofol for maintenance of anesthesia is associated with a lower incidence of PONV compared with patients anesthetized with inhalational agents. More recently, propofol in subhypnotic doses has been used with success for the management of chemotherapy-induced emesis and PONV. The antiemetic action of propofol is not a result of the intralipid emulsion in the formulation. However, the efficacy of subhypnotic doses of propofol as a direct antiemetic has not been proven conclusively. Zestos et al. found that propofol, 0.2 mg/kg, was no more effective than placebo when administered for the management for PONV.

The use of subhypnotic doses of propofol administered as an infusion for the prevention of PONV has produced mixed results. Although a number of studies have demonstrated efficacy when propofol was used as a low-dose infusion (1–2 mg · kg⁻¹ · h⁻¹), others have failed to show such results using similar infusion regimen. Propofol infused at a rate of 1 mg · kg⁻¹ · h⁻¹ for 20 h postoperatively has been shown to be effective in the prevention of PONV. However, other investigators have used similar propofol infusion regimen but were unable to demonstrate superiority of propofol over placebo.

The dosing regimen used in this study was based on our previous work wherein we defined the plasma concentrations of propofol for a 50% reduction in nausea scores to be 343 ng/ml. Pharmacokinetic simulation suggested a bolus dose of 20–40 mg every 10 min would be required to achieve and maintain this concentration range. This study confirms that doses able to provide such concentration range are more effective than placebo in controlling PONV.

The concept of patient-controlled analgesia in the postoperative settings has been widely accepted and resulted in better pain relief and a great degree of patient satisfaction. This study is the first reported wherein propofol is used as antiemetic delivered by a patient-controlled device. We use a patient-controlled delivery device as it is a convenient way of drug delivery, without involving the nurses in the recovery room who may have 3 or 4 patients to attend to at anytime. In addition, the pharmacokinetics of propofol make it an ideal drug for patient-controlled delivery. This study demonstrated that patient-controlled antiemetic drug delivery is a feasible technique. However, future studies are needed to com-

Fig. 3. Simulated minimum plasma propofol concentrations in the propofol, 20 mg, and propofol, 40 mg, groups.

x = Propofol 20 mg group  o = Propofol 40 mg group
PATIENT-CONTROLLED ANTIEMESIS WITH PROPOFOL

pare the cost-to-benefit ratio of this with other methods of deliveries, such as small-dose continuous infusion or nurse-administered propofol, and other antiemetics.

The results from this study seem to suggest that rapid, successful control of PONV may have resulted in shorter PACU stay and improved patient satisfaction. Although placebo effect cannot be ruled out completely, we believe its effect is small. The placebo group had poor control with symptoms of nausea and vomiting, and more patients rated poor satisfaction with the treatment. The commonly held notion that nausea and vomiting in the immediate postoperative period are usually brief and get better without treatment is also untrue. Patients in the placebo group were more likely to have persistent nausea and vomiting.

Based on the patient's dose and time of propofol administration, we simulated the minimum effective propofol concentrations, i.e., the concentrations just before each dose. This yielded a median simulated minimum effective plasma propofol concentrations of 174 ng/ml (interquartile range, 170–297 ng/ml) and 296 ng/ml (interquartile range, 240–437 ng/ml) for the P-20 and P-40 groups, respectively. As these are the simulated minimum effective concentrations, they are expectedly lower than the 345 ng/ml reported for the median plasma propofol concentrations associated with successful control of nausea. The simulated narrow interquartile range of propofol concentrations indicates that interpatient variability of the minimum effective antiemetic concentration of propofol is small and well below that needed for sedation (900–1,300 ng/ml) and maintenance of general anesthesia (3,000–10,000 ng/ml).

A previous study compared the use of intraoperative propofol with ondansetron administered at the beginning of an isoflurane-maintained anesthetic. The group that had propofol at induction as well as maintenance had significantly greater efficacy compared with the ondansetron group. The incidence of emesis and rescue antiemetic use was lower in the propofol group. However, the group wherein propofol was administered at induction and toward the end of surgery (sandwich technique) was not protective against PONV. Simulations of plasma propofol concentrations suggested that this group had subtherapeutic levels. Hence, it appears that propofol has a concentration–response relationship for the prevention of PONV.

It was interesting to note that patients in the P-20 group had a lower risk of subsequent emesis and likelihood of using a rescue antiemetic compared with the P-40 group. It appeared that propofol used as an antiemetic may have a ceiling effect above 20 mg per dose. We do not have specific explanation for this phenomenon. It may be that patients in the P-40 group were more sedated and less clear headed, which could leave patients more susceptible to emesis. Two patients in the P-40 group experienced oversedation (OAA/S scores of 3 and 1, respectively). However, their peripheral oxygen saturations were above 96%. One of these patients had surgery lasting 3.5 h and received 980 μg fentanyl intraoperatively. Hence, it is important to realize that high doses of propofol combined with another sedative can result in unwanted side effects.

Patients' delivered and undelivered demand data and their satisfaction with treatment provide the most compelling evidence that propofol possesses antiemetic properties. Patients in the placebo group did not receive relief of their symptoms and hence continued to demand study medication during the lock-out interval. These patients had higher incidence of vomiting, use of rescue antiemetic, and also rated this modality of treatment poorly.

In this study, we have demonstrated that propofol is effective for the management of PONV and is associated with a shorter PACU stay and a high degree of patient satisfaction. The delivery of propofol by a patient-controlled device is a feasible technique. As there was no difference between the P-20 and P-40 groups in efficacy and the potential of side effects with the high dose group, a 20-mg demand dose is recommended. Further studies are needed to compare the cost effectiveness of propofol patient-controlled antiemesis to other antiemetics and the advantages of this drug delivery system over more conventional methods.

References


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20. Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. ANESTHESIOLOGY 1997; 87:779-84.