Midazolam: An Effective Antiemetic After Cardiac Surgery—
A Clinical Trial

Orathy Patangi Sanjay, MD, and Deepak Ivan Tauro, MBBS
Department of Anesthesiology, St. John’s Medical College Hospital, Bangalore, Karnataka, India

Cardiac surgery has been associated with a significant incidence of postoperative nausea and vomiting (PONV). To assess the antiemetic property of midazolam, we undertook this double-blinded, randomized trial in 200 patients undergoing cardiac surgery involving cardiopulmonary bypass, and we compared its efficacy with that of ondansetron in preventing PONV. Assessments on the occurrence of PONV were made at regular intervals for the first 24 h after tracheal extubation, along with sedation and pain scoring. We report a 6% incidence of nausea and no incidence of vomiting in the midazolam group, compared with a 21% incidence of PONV in the ondansetron group (P < 0.001). All 21 patients (18 women and 3 men) in the ondansetron group and none of the 6 patients (all women) in the midazolam group required a rescue antiemetic drug (P < 0.001). The sedation scores and postoperative pain scores were comparable in both groups. We conclude that midazolam, instituted as a continuous infusion in a dose of 0.02 mg · kg⁻¹ · h⁻¹, is a more effective antiemetic than ondansetron in a dose of 0.1 mg/kg IV every 6 h for the prevention of PONV after cardiac surgery.

After median sternotomy and total body heparinization, CPB was established with a single right atrial cannula and an ascending aortic cannula. Standard bypass techniques were used with an Edward Vital™membrane oxygenator on a bypass machine (Pemco Inc.). During bypass, the hematocrit was maintained between 20% and 25%, pump flow between 2.2 and 2.5 L·min⁻¹·m⁻², and mean arterial blood pressures between 50 and 60 mm Hg. St. Thomas solution was used as the cardioplegic solution. Cold blood cardioplegia (10°C) was used in all cases. The first dose of cardioplegia was instituted in an antegrade fashion via the aortic root, and subsequent doses of cardioplegia were instituted in a retrograde fashion through the coronary sinus. CPB was conducted under mild hypothermic conditions (30°C–32°C). On CPB, anesthesia was maintained with a continuous infusion of fentanyl 2 μg·kg⁻¹·h⁻¹ along with isoflurane in a concentration of 0.4%–0.8%. After successfully weaning off CPB, the action of heparin was reversed by a calculated dose of protamine sulfate. After skin closure, the patients were shifted to the postoperative critical care unit (CCU) for elective ventilation. All patients received fentanyl 1 μg·kg⁻¹·h⁻¹ as an infusion in the CCU for pain relief. If inadequate, diclofenac sodium in a dose of 75 mg was instituted IV as a rescue medication. No patient was given oral medication or oral feeds in the immediate postoperative period (6 h postextubation).

The patients were divided into two groups based on a computer-generated randomization table. With the exception of the principal investigator, the co-investigator (who assessed the incidence of PONV and the sedation and pain scores) and the nursing staff were blinded to the drug being instituted. The principal investigator loaded the drug and the placebo to be instituted for all cases. According to the study protocol, all patients of Group A were to receive an infusion of midazolam, and Group B patients were to receive a slow IV bolus of ondansetron. To achieve adequacy of blinding, all patients in Group A received 2 mL of IV normal saline as placebo every 6 h, and the patients in Group B received an infusion of normal saline from the time of successfully weaning off CPB until the first 24 h after surgery.

In all patients in Group A, midazolam was instituted as a continuous infusion of 0.02 mg·kg⁻¹·h⁻¹ from the time of successfully weaning off CPB until 24 h after surgery after a 1-mg IV bolus. The infusion rate of midazolam was formulated on the basis of an earlier report (6). All patients in Group B received ondansetron 0.1 mg/kg IV at the time of initiation of CPB, and a second similar dose was instituted after successfully weaning off CPB. From this period of time onward, all patients in this group received ondansetron 0.1 mg/kg IV every 6 h for the first 24 h after surgery. All patients in both groups received ranitidine 1 mg/kg IV every 8 h from the time of weaning off CPB until their stay in the CCU. All patients in both groups received supplemental oxygen 5 L/min by face mask after tracheal extubation until their stay in the CCU.

Assessment for PONV was started at extubation and was performed hourly for the first 4 h and thereafter every 4 h until the first 24 h. Assessment of the severity of nausea was scored as none (0), mild (1), moderate (2), and severe (3) depending on the patient's description of the severity of the symptom. Episodes of vomiting or retching were recorded as vomiting. Patients were offered metoclopramide 10 mg slow IV as a rescue antiemetic when their score was 2 or more.

Sedation and pain scores were assessed along with PONV. Sedation scores were assessed on the basis of an earlier study conducted by Ramsay et al. (7). Six levels of sedation were formulated: 3 with the patient awake and 3 with the patient asleep. Awake levels were as follows: 1, patient anxious and agitated or restless or both; 2, patient cooperative, oriented, and tranquil; and 3, patient responds to commands only. Asleep levels were dependent on the patient’s response to a light glabellar tap: 4, a brisk response; 5, a sluggish response; and 6, no response. Pain scores were assessed on the basis of a visual analog scale: 0 mm indicated no pain, and 100 mm indicated the worst possible pain. Patients were offered diclofenac sodium 75 mg slow IV as rescue pain medication when their score was 30 mm or more.

Sample size calculation was based on the following: we aimed at detecting a reduction in the incidence of PONV from 40% to 20%. On the basis of an α of 0.05 and β of 0.2, 81 patients were estimated to be needed in each group. To compensate for patients not completing the study, we randomized 100 patients to each group. Statistical analysis of data was performed with a Fisher’s exact test and the χ² test. A Mann-Whitney U-test was applied where appropriate.

Results

There were no significant differences between groups (Table 1). The mean duration for the patients to reach the CCU after CPB was terminated was 92 ± 11 min. The mean duration of elective ventilation in Group A (midazolam group) was 5 ± 0.3 h and was 5 ± 0.2 h in Group B (ondansetron group), and the mean duration of stay in the CCU in Group A was 26 ± 3 h, versus 25 ± 4 h in Group B; this was not significant (P > 0.05). The mean duration from the induction of anesthesia to the commencement of assessment of PONV was 782 ± 47 min.

Group A recorded a 6% incidence of nausea and no incidence of vomiting, whereas Group B had a 21%
incidence of PONV ($P < 0.001$; Mann-Whitney U-test; statistically significant). The incidence of nausea between groups was statistically significant ($\chi^2 = 9.62; P < 0.005$). A Fisher’s exact test was performed to compare the incidence of vomiting between groups, and it revealed a $P$ value of $<0.001$ (statistically significant). The 95% confidence interval for the incidence of PONV in Group A was 6% ± 4.7%, whereas it was 21% ± 7.9% for Group B.

Eighteen female patients and three male patients in Group B complained of nausea and vomited. Of the 21 patients, 11 patients (3 men and 8 women) complained of a moderate degree of nausea and vomited in the first hour after extubation. Of the remaining 10 female patients, 4 complained of severe nausea and vomited in the third hour after extubation, and 6 female patients complained of moderate nausea and vomited in the fifth hour after extubation. All patients in Group B who complained of nausea and vomited required rescue medication and responded satisfactorily to it. None of the 21 patients who had PONV in Group B required more than 1 dose of rescue medication. The six patients in Group A who complained of a mild degree of nausea in the second hour after extubation were female, and none required the use of a rescue antiemetic (Table 2). A Fisher’s exact test was performed for the requirement of rescue medication between groups and was statistically significant ($P < 0.001$). When data were examined to investigate the influence of sex on PONV, it became apparent that women were more likely to experience PONV ($P < 0.001$; Table 2). The influence of sex on nausea was computed by using a $\chi^2$ test that revealed a $\chi^2$ of 41.89 and a $P$ value of $<0.001$ (statistically significant). The influence of sex on vomiting was computed by using Fisher’s exact test, which revealed a $P$ value $<0.001$ (statistically significant). These observations may be related to the relatively smaller number of women in the sample, which reduced the power of measurement.

The sedation scores showed that 98% of the patients in Group B and 96% of patients in Group A showed a sedation level between 2 and 4 ($P > 0.05$). One patient in Group B had a sedation score of 1, and the other patient had a sedation score of 5. The remaining four patients in Group A had a sedation score of 5. Pain scores revealed that 8% (three men and five women) and 7% (three men and four women) of the patients in Groups A and B, respectively, required rescue pain medication because their visual analog scale scores were $>30$. There was no statistically significant difference in the postoperative pain scores or in the requirement for rescue pain medication between groups.

No patient in either study group had any drug-related complications or developed any electrocardiographic abnormality. None of the patients developed a low cardiac output or a myocardial infarction on termination of CPB or during the stay in the CCU. None of the patients had the need for a reexploration surgery.

### Discussion

Until recently, it was standard practice to sedate patients after cardiac surgery and to ventilate the lungs for 12 to 16 hours (2). PONV was not perceived as a particular problem with this regimen, and it is possible that a lengthy period of sedation and artificial ventilation reduced the incidence of postoperative emesis. Since fast-tracking postcardiac surgical patients has set in, clinicians have become increasingly aware of the problem of PONV (8).

This is the first clinical trial testing the efficacy of midazolam in comparison to ondansetron as an antiemetic after cardiac surgery in patients who were at a low risk for PONV. Our study has shown that with a small dose of midazolam after cardiac surgery, the
incidence of nausea was 6%, and there was no vomiting. This was in contrast to the 21% incidence of PONV in the ondansetron group.

In our trial, we report a significant ($P < 0.001$) use of rescue antiemetics (21%) in the ondansetron group compared with the midazolam group. This is in contrast to the study by Woodward et al. (9), who reported a 43.4% use of rescue antiemetics in their ondansetron group. There are no published reports on the requirement for rescue antiemetics in patients who have received IV midazolam in the management of PONV. Some authors have argued that the prophylactic administration of antiemetics is unjustified (10), but in view of the frequent incidence of PONV and its potential deleterious effects after cardiac surgery, the prophylactic use of antiemetics has become a part of our standard practice.

The use of benzodiazepines in the management of PONV has been reported in the literature, both for prophylaxis and for treatment (11). In the pediatric population, several studies have demonstrated a significant reduction in postoperative vomiting after tonsillectomy and strabismus surgery when midazolam or lorazepam was used for prophylaxis (12–14). More recently, patients with PONV refractory to other antiemetics have responded satisfactorily to a small-dose infusion of midazolam compared with placebo (15). Midazolam is an effective antiemetic in patients having chemotherapy (16). The suggested mechanism of action of midazolam as an antiemetic is by decreasing dopamine input at the chemoreceptor trigger zone in addition to decreasing anxiety (17,18). It may also decrease adenosine reuptake (19). This leads to an adenosine-mediated reduction in the synthesis, release, and postsynaptic action of dopamine at the chemoreceptor trigger zone (17). Midazolam may also decrease dopaminergic neuronal activity and 5-hydroxytryptamine (5-HT) release by binding to the $\gamma$-aminobutyric benzodiazepine complex (20). Apart from the IV administration of midazolam, it has also been administered sublingually, intranasally, and IM to alleviate PONV and has been found to be relatively successful (6).

The site of action of ondansetron in the prevention of postoperative emesis is varied (21). The area postrema and parts of the nucleus tractus solitarius and adjacent sites in the brain are associated with nausea and vomiting and contain large numbers of 5-HT$_3$ receptors (22). Ondansetron acts on these sites to reduce emesis (21). There is also a peripheral action in the gastrointestinal tract at efferent vagal fibers that are known to possess 5-HT$_3$ receptors (21). Ondansetron has been deemed effective in the prevention and management of PONV without causing any sedation, extrapyramidal reactions, or adverse cardiovascular effects (23). Ondansetron has been used in a myriad of doses both orally and parenterally and has been found to be a good drug for the prevention of PONV (24–27).

The sedation scores recorded in our trial have clearly demonstrated that the patients in both study groups had similar scores and lay to rest the speculation that the patients in the midazolam group were failing to report nausea because they were more sedated than the patients who received ondansetron. Moreover, midazolam has been stated to be a sedative in a larger dose range than that used in our trial (28). We also observed that midazolam as a continuous infusion did not prolong the duration of intubation, increase the degree of sedation, increase the postoperative stay in the CCU, or alter the postoperative pain scores. Keeping in mind the similarity in postoperative stay in the CCU, the need to pursue such regimens in all patients is debatable. Interestingly, a cost analysis of administering these two antiemetic regimens showed that midazolam was less expensive than ondansetron.

Lerman (29) has suggested that PONV is approximately two to three times more frequent in women than in men. In our study, PONV was predominant in women. In common with most other studies on PONV, we found that PONV was associated significantly with the female sex (2,30). In our study we found a sixfold increase in the incidence of PONV in women as compared with men; this could be attributed to the unequal sex distribution. All the women who participated in this trial were postmenopausal and were not receiving any hormone-replacement therapy. This overwhelming incidence of PONV in women suggests that women should be a target population to receive antiemetics after coronary artery bypass grafting.

However, there are a few limitations in our trial. First, plasma levels of midazolam and ondansetron were not measured. Interestingly, all the incidents of PONV that occurred in the ondansetron group were in the first few hours after extubation and did not occur later during the recovery period. This observation could suggest that a single dose of ondansetron 0.1 mg/kg after CPB was insufficient to establish an effective ondansetron plasma level to prevent emesis in the early postextubation phase. Second, fentanyl was used for pain relief in the postoperative period. Fentanyl’s being an opioid could per se cause PONV, and it was used in both study groups. Third, only patients who were at a low risk for PONV were included in the trial. The decision to exclude patients who were at a high risk for PONV was based on the lack of any prior clinical trials suggesting the efficacy of midazolam as an antiemetic. Another clinical trial is already in progress at our institute to assess the antiemetic properties of midazolam in patients at high risk for PONV. Fourth, whether the doses of the two study drugs are really equipotent is debatable. We further
suggest that varying doses of midazolam should be compared with a placebo to evaluate its antiemetic properties.

In summary, we suggest that midazolam instituted as a continuous infusion in a dose of 0.02 mg · kg⁻¹ · h⁻¹ is a more effective and superior antiemetic as compared with ondansetron in a dose of 0.1 mg/kg IV every 6 h for the prevention of PONV after cardiac surgery.

References