Timing of ondansetron administration to prevent postoperative nausea and vomiting

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Background: **The original guidelines for using ondansetron recommending its administration prior to induction of anesthesia have been questioned.**

Method: **In an effort to determine the most effective timing of ondansetron administration to prevent postoperative nausea and vomiting (PONV), a prospective, randomized, double-blind study was performed. Patients undergoing ambulatory plastic surgery procedures estimated to last two hours or more and who had at least two risk factors for PONV (female gender, non-smoker, previous history of PONV and postoperative opioids) participated in the study. General anesthesia for all patients followed the same standard institutional protocol and all patients received dexamethasone 4 mg intravenously at the start of surgery. The control group (n = 188) received 4 mg of ondansetron intravenously prior to the induction of anesthesia. The study group (n=184) received 4 mg of ondansetron intravenously 30 minutes prior to completion of the surgery. The incidence of PONV during the early (0-2 hours) and delayed (2-24 hours) postoperative periods was recorded.**

Results: **No significant difference was found between the groups regarding early postoperative nausea or vomiting ($p>0.05$). However, a significant difference ($p<0.05$) was noted in both late postoperative nausea (control: 30% vs. study group: 20%) and late postoperative vomiting (control: 17% vs. study group: 8%).**

Conclusion: **This clinical study indicates that when performing prolonged surgical procedures, late administration of ondansetron (within 30 minutes prior to completing the surgery) is significantly more effective in the prevention of late PONV than when administered prior to the induction of anesthesia.**

Key words: Postoperative nausea and vomiting, Entiemetics, Ondansetron.

Ondansetron, a selective blocking agent of the serotonin 5-HT_3 (5-hydroxytryptamine type 3) receptor type, is a highly effective antiemetic that has been used successfully for both the prophylaxis and treatment of postoperative nausea and vomiting (PONV) in the high-risk outpatient surgical population (1-6). This drug, which was considered to represent the first universally effective antiemetic for postoperative nausea and vomiting (7-8), was later found to have less anti-nausea and more anti-vomiting efficacy (9).

Post-discharge nausea and vomiting is a significant issue for ambulatory patients and the most effective time to provide antiemetic medications is of importance; however, the correct timing for use of ondansetron has not been clearly established.

The manufacturer recommends that ondansetron, when used for prophylaxis against PONV, should be administered before induction of anesthesia (Zofran® package insert; GlaxoSmithKline, Research Triangle Park, NC). This recommendation is based on the hypothesis that blockade of receptors in the chemoreceptor trigger zone before the arrival of emetic stimuli associated with anesthesia and surgery provides greater antiemetic effect. However, Joslyn (5), reported that the rationale behind the administration of ondansetron prior to the induction of anesthesia was that a more accurate assessment of the safety profile of the drug could thus be obtained. "This approach allowed for more accurate recording of adverse events such as complaints of injection site reactions, dizziness or lightheadedness, while also allowing for a more precise assessment of any changes in hemodynamic parameters which may otherwise be masked in a patient receiving the study drug while anesthetized. Because of the relatively short half-life of ondansetron (3.5-4 hours),

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it may be relevant to administer it intra-operatively near the end of the surgical procedure especially those of over 2 hours duration" (5).

The optimal timing of ondansetron administration has been questioned in two clinical studies, one in patients undergoing otolaryngologic surgery and the other in women undergoing outpatient gynecological laparoscopy (10-11). The sample size was small in both studies but results favored late administration of ondansetron.

To evaluate this issue with a larger study population, of similar age and sex and undergoing relatively standardized surgical procedures over two hours, a double-blind randomized study was designed to test the hypothesis that the timing of ondansetron administration is an important factor in determining its efficacy in the prevention of PONV.

Patients and Methods

A prospective, randomized, double-blind study was performed to compare the efficacy of early versus late administration of ondansetron for the prevention of PONV. Patients undergoing ambulatory plastic surgery procedures estimated to last two hours or more and who had at least two of the risk factors for PONV (female gender, non-smoker, previous history of PONV and postoperative opioids) participated in the study. Two facilities contributed patients to the study; an Ambulatory Surgical Center and the University Hospital. Both facilities manage similar populations of ambulatory elective plastic surgery patients and have similar fees for cosmetic procedures not covered by medical insurance. The study design was approved by the institutional review board of the University of Puerto Rico. Patients were informed of the purpose of the study and permission was obtained before surgery. The envelope containing the group to which the case had been assigned was opened just before the induction of general anesthesia for every patient. The anesthesia nurse administered ondansetron according to the instructions in the randomization envelope. The anesthesiologists responsible for intraoperative management were not blinded to the treatment, but they were not involved in the postoperative assessment. However, both the evaluator and the patients were blinded as to the timing of the drug administration. The control group (n=188) received 4 mg of ondansetron intravenously immediately prior to the induction of anesthesia. The study group (n=184) received 4 mg of ondansetron intravenously 30 minutes prior to completion of the surgery. All patients also received a single dose of dexamethasone (4 mg intravenously) at the beginning of surgery. The use of a combination of a 5-HT_3 receptor antagonist with dexamethasone has demonstrated improved efficacy in groups at high risk for PONV (12-17) and, since the selected population had a risk of PONV that exceeded 40% (two or more risk factors) (18), the multiple drug prophylaxis was selected as a more appropriate option than the single drug prophylaxis.

General anesthesia followed a standardized protocol. Sedation was obtained with midazolam (2.5 mg intravenously). During induction of anesthesia the following drugs were given intravenously: pancuronium bromide 0.5 mg, pentobarbital sodium 4-5 mg/kg, and succinylcholine 1.5 mg/kg. The patient was also given 100% oxygen by mask during induction. This was followed by endotracheal intubation. Anesthesia was maintained with isoflurane 1-3% in combination with 60-70% nitrous oxide in oxygen; fentanyl 0.5-1.0 mcg/kg and cisatracurium 0.2 mg/kg were administered as needed. After completion of the procedure, residual neuromuscular blockade was reversed with neostigmine (.05 mg/kg) and atropine (.02mg/kg). All patients were extubated in the operating room. Patients were observed in the recovery room until they were hemodynamically stable, fully conscious and comfortable for an average of two hours. Nalbuphine hydrochloride (Nubain) 10 mg, was administered intravenously at the recovery room, if needed for relief of pain. For the management of postoperative pain at home all patients received tramadol with acetaminophen (Ultracet) tablets, unless the patient had hypersensitivity to the medication or it was contraindicated.

Information collected included age, gender, history of PONV and/or motion sickness, non-smoking status, use of postoperative opioids, and the type and duration of surgery.

A questionnaire was completed for each patient regarding the occurrence of nausea, vomiting, and the need for rescue treatment during the early (0-2 hours) and late (2-24 hours) postoperative periods. The evaluator, who was blinded as to the treatment group, recorded all the recovery variables, including the incidence of PONV and the need for rescue antiemetic medication. The subjective sensation of nausea was determined by the patient, not the evaluator. Data for early PONV was recorded by the evaluator in the recovery room during the average two hour stay following the surgery. Data for late PONV was obtained by the evaluator by telephone on the day following the surgery (24 hours postoperatively). Nausea was defined as the unpleasant sensation associated with awareness of the urge to vomit but without the presence of expulsive muscular movements. Vomiting was defined as the forceful expulsion of gastric contents from the mouth.

The statistical software program Statistical Package for

Social Sciences (version 12.0; SPSS Inc, Chicago, IL) was used to perform the analysis. Comparisons between the two treatment groups for categorical variables were assessed by the chi-square test. Similarly, comparisons among the two groups involving quantitative variables were assessed by the t test. Differences between groups were declared to be statistically significant at $p<0.05$.

Table 2. Control group (ondansetron given prior to induction) and study group (ondansetron given 30 minutes before completing the surgery) were compared using the chi-square test, which was considered significant when p is <0.05.

	Control Group			Study Group			*P*
	Yes	**No**	**Total**	**Yes**	**No**	**Total**	
Early post-op nausea	36 (19%)	152	188	28 (15%)	156	184	p=.315
Early post-op vomiting	17 (9%)	171	188	11 (6%)	173	184	p=.263
Late post-op nausea	57 (30%)	131	188	36 (20%)	148	184	p=.017
Late post-op vomiting	32 (17%)	156	188	15 (8%)	169	184	p=.010

Results

A total of 372 patients (367 females and 5 males) participated in the study and provided all required information by telephone after surgery. The control group had 188 patients and the study group had 184 patients. No significant difference was found between the control group and the study group regarding age (41±11 vs. 38±11), risk factors (3-±1 vs. 3±1), and duration of surgery (2.63±0.83 hours vs. 2.57+0.84 hours). Breast reduction surgery was the most common procedure in both groups (38% vs. 38%). The types of surgery in both groups are noted in Table 1. Postoperative opioids (tramadol with acetaminophen), in tablet form, were prescribed upon discharge for pain relief in 93% of both groups.

Table 1. Type of surgery performed to patients in the control group and the study group.

	Control Group	**Study Group**
Breast reduction	38%	38%
Breast augmentation	7%	6%
Mastopexy	5%	6%
Abdominoplasty	25%	29%
Breast surgery & abdominoplasty	24%	19%
Facelift	0%	1%
Rhinoplasty	0%	1%
Other	1%	0%
Total	**100%**	**100%**

Early postoperative nausea occurred in 19% of the control group and 14% of the study group, while early postoperative vomiting occurred in 9% of the control group and 6% of the study group with no significant difference between the groups ($p>0.05$). However, both late postoperative nausea and late postoperative vomiting reached clinical and statistical significance ($p<0.05$) with late nausea occurring in 30% of the control group and 20% of the study group and late vomiting occurring in 17% of the control group and 8% of the test group. The results are summarized in Table 2.

Among the patients who vomited, the mean frequency of early vomiting (0-2 hours) was 1±1 episode for both groups and of late vomiting (2-24 hours) was 2-±1 episodes for both groups, with no significant differences between control and study groups.

As expected for a group of patients with an average of three risk factors for PONV, the overall incidence of nausea and vomiting was 62% in the control group, but was noted to have a statistically significant decrease to 38% in the study group (Table 3).

Table 3. The overall incidence of PONV is compared between the control and study groups using the chi-square test.

	Control Group			Study Group			*P*
	Yes	**No**	**Total**	**Yes**	**No**	**Total**	
Overall PONV incidence	78(62%)	110	188	47(38%)	137	184	p=.001

Rescue treatment was required in 10% of the control group, but this decreased to 5% in the study group.

Discussion

About 30% of patients who undergo general anesthesia will be affected by PONV (16-17). From a surgical perspective, the potential consequences of postoperative emesis include bleeding and formation of large hematomas, the result of elevation of blood pressure during retching or vomiting (19). Delayed recovery time and unintended admissions for observation and treatment are some of the problems that ambulatory surgery patients face when affected by vomiting. From the patient's perspective, PONV is undoubtedly distressing, interfering with the patient's comfort. The fear of suffering PONV was reported more often by surgical patients than the fear of postoperative pain (20).

The selected group of plastic surgery patients in our study was ideal to test the hypothesis. The patient's are of similar age and sex with similar risk factors for nausea and vomiting. The selected operative procedures are relatively standardized and of longer duration (more than

two hours) so that the results of the investigation might answer the research question. This study would appear to have a more appropriate study population to evaluate the research question than previously conducted studies that address the timing of ondansetron administration.

As revealed in our study, plastic surgery patients very often have a mean of three risk factors for PONV. Using the simplified risk score suggested by Apfel (18), this is interpreted to mean that the risk for PONV is 60% in this particular population if no preventive measures are utilized. The four most important risk factors for PONV are female gender, non-smoking status, history of PONV or motion sickness, and the use of postoperative opioids. Using the simplified risk score it is estimated that if none, one, two, three or four risk factors are present the risk for PONV is approximately 10, 20, 40, 60 and 80 percent, respectively (18).

Many drugs have been used for prophylaxis and treatment of PONV, but the serotonin 5-HT_3 antagonists, such as ondansetron, have been found to be safe and effective. A very large study of 4,123 patients at high risk for PONV found that ondansetron, dexamethasone, and droperidol each reduced the risk of postoperative nausea and vomiting by about 26% (21). All the interventions acted independently of one another and independently of the patients' baseline risk.

Our patient population with a mean of 3±1 risk factors had an overall incidence of PONV of 62% in the control group. On the other hand, in the study group (late administration of ondansetron) the overall incidence of PONV decreased to 38%, which is in agreement with Apfel's report that late administration of ondansetron decreases the risk of PONV by 26% from the patient's baseline risk (21).

The correct timing of ondansetron administration has been an issue in several reports (10-11). The manufacturer recommends that ondansetron, when used for prophylaxis against PONV, should be administered before induction of anesthesia (Zofran® package insert; GlaxoSmithKline, Research Triangle Park, NC). However, given the relatively short elimination half-life of 3.5-4 hours, its antiemetic benefit may thus be lost in long surgical cases (6). Our study found that late postoperative nausea occurred in 30% of the patients who received the ondansetron during induction of anesthesia, but when given 30 minutes before completing the surgery, only 20% of the patients reported nausea. Similarly, the effect of ondansetron on late postoperative vomiting was also significantly reduced from 17% to 8% when ondansetron administration changed from prior to induction to 30 minutes before the end of anesthesia.

Other reports in the literature concerning the timing of ondansetron administration include a comparison in otolaryngologic surgery of ondansetron 4 mg given before induction of anesthesia, ondansetron 4 mg given at the end of the surgery, and a placebo group (10). The sample size was small, 25 patients in each of the three groups. No significant difference was found in the incidence of postoperative nausea or vomiting between the placebo and the ondansetron groups. However, when ondansetron was administered at the end of the operation, it significantly reduced the need for rescue antiemetics in the recovery room (36% versus 64% in the control group). The authors concluded that prophylactic ondansetron appeared to be more effective when administered at the end of the surgery. Another study of similar design in women undergoing outpatient gynecological laparoscopic procedures compared different timings of ondansetron administration for the prevention of PONV (11). The women were randomly assigned to one of four groups: placebo, ondansetron 2 mg at the start and 2 mg at the end of surgery, ondansetron 4 mg before induction, and ondansetron 4 mg after surgery. The sample size was again small, each group composed of 38 to 40 patients, but they found that administration of ondansetron after surgery was better in decreasing late nausea and late incidence of frequent emesis (more than two episodes).

It is generally agreed that prophylaxis of PONV with monotherapy does not work very well (17). Drug combinations are considered to be more useful for balanced antiemesis. A combination of a serotonin 5-HT_3 receptor antagonist with dexamethasone has been reported to be quite effective for patients at high risk for PONV (12-15). It has been shown that dexamethasone is most effective when administered at the time of induction of anesthesia (22) and that its half-life is about 36 hours (23). We thus chose to use dexamethasone for all patients and add ondansetron either prior to induction or within 30 minutes before completing the surgery depending upon the randomization assignment of each patient. We decided that the drug combination would provide better prophylaxis while still permitting us to evaluate the best timing for administration of ondansetron.

In summary, this study of 372 plastic surgery patients at high risk for PONV demonstrated that late administration of ondansetron (within 30 minutes of completing the surgery), compared to pre-anesthetic administration provided significantly better prevention of late postoperative nausea and vomiting.

Conclusion

This study shows that when performing surgery with a duration longer than two hours in an ambulatory setting,

late administration of ondansetron is significantly more effective in the prevention of late PONV than when it is administered prior to the induction of anesthesia.

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