

The Efficacy of Postoperative Ondansetron (Zofran[®]) Orally Disintegrating Tablets for Preventing Nausea and Vomiting After Acoustic Neuroma Surgery

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Postoperative nausea and vomiting is a frequent complication of craniotomy. We evaluated the ability of intraoperative IV ondansetron followed by postoperative ondansetron in an orally disintegrating tablet formulation to reduce the frequency and severity of postoperative nausea and vomiting in a prospective, randomized, placebo-controlled double-blind trial of 60 patients undergoing acoustic neuroma resection. Each patient received intraoperative ondansetron (4 mg IV) or placebo 30 min before case end. Postoperatively, patients received ondansetron in an orally disintegrating tablet formulation (8 mg BID) or placebo twice a day for up to 72 h. Metoclopramide was available as rescue therapy for both groups. Severity of nausea (as measured on a 10-cm visual scale), number of emetic episodes, and

requirement for rescue therapy were recorded. In the immediate postoperative period, nausea severity was less in patients treated with ondansetron than placebo (3.3 ± 4.1 versus 7.3 ± 4.2 ; $P < 0.001$) and fewer patients experienced vomiting (3 of 28 versus 11 of 32; $\chi^2 P < 0.01$). More patients required some form of rescue treatment in the placebo group on the first postoperative day (26 of 32 versus 16 of 28; $\chi^2 P < 0.01$). We conclude that after acoustic neuroma surgery IV ondansetron treatment prevents immediate postoperative nausea and vomiting. Postoperative treatment with ondansetron in an orally disintegrating tablet formulation was associated with less frequent rescue therapy as compared with placebo on the first postoperative day.

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Postoperative nausea and vomiting (PONV) is a common complication after craniotomy. Postcraniotomy nausea occurs in approximately half of all patients, with 39 percent of patients experiencing one or more episodes of emesis (1). Of all craniotomy patients, those undergoing resection of an acoustic neuroma would seem to experience PONV most frequently, possibly because of tumor and/or surgical involvement of the vestibular nerve.

Fabling et al. (2) evaluated the efficacy of preemptive ondansetron in adult patients undergoing infratentorial craniotomy. They observed that treatment with ondansetron before emergence from anesthesia prevented early PONV but did not have an effect on delayed PONV (after 12 h). In the current study

we evaluate the therapeutic efficacy of intraoperative ondansetron combined with postoperative, preemptive treatment with an orally disintegrating tablet (ODT) formulation of ondansetron (Zofran[®] ODT, GlaxoSmithKline, Research Triangle Park, NC; henceforth ondansetron ODT) in the prevention of delayed PONV after infratentorial craniotomy in patients with a diagnosis of acoustic neuroma. Ondansetron ODT was used because it was previously demonstrated to be well tolerated by patients and to have similar efficacy as oral ondansetron for cyclophosphamide-induced emesis in cancer patients (3). Ondansetron ODT has also been demonstrated to significantly reduce the incidence of postdischarge nausea and vomiting in ASA physical status I-II patients undergoing outpatient gynecological laparoscopy (4). This formulation may be particularly helpful in patients who have difficulty swallowing postoperatively because of trauma to lower cranial nerves during surgery.

This study was designed to test the hypothesis that ondansetron (IV followed by ODT) would reduce both the frequency and severity of PONV in a population of adult patients undergoing craniotomy for acoustic neuroma resection.

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Table 1. Standardized Anesthetic for Acoustic Neuroma Resection

Event	Drug	Standardized dose
Induction	Midazolam	1-4 mg IV
	Sodium Thiopental	3-5 mg/kg IV
	Fentanyl	7-10 μ g/kg IV
	Rocuronium	0.6-1.2 mg/kg IV
Placement of Mayfield Head Holder	Sodium Thiopental	Up to 3 mg/kg IV
	Lidocaine	Up to 1 mg/kg IV
Maintenance	Fentanyl	1-2 μ g/kg/h IV infusion
	Rocuronium or Pancuronium	Titrated to maintain 2-3 twitches for train-of-four monitoring
	Isoflurane	0.4%-1.5% end-tidal in oxygen
Closure	Fentanyl	Discontinued
	Isoflurane	Reduced/discontinued
Randomization (blinded) (30 min before extubation)	Study medication	As provided by pharmacy, IV bolus injection
Tracheal extubation	Glycopyrrolate	10 μ g/kg (maximum 1 mg)
	Neostigmine	70 μ g/kg (maximum 5 mg)
	100% oxygen	

Methods

After obtaining IRB approval, we conducted a randomized, prospective, placebo-controlled, double-blind trial in ASA I-III patients 18-80 yr of age undergoing acoustic neuroma resection at The Johns Hopkins Hospital. After obtaining informed consent, 60 patients were divided into 2 groups (ondansetron IV plus ondansetron ODT, $n = 28$; placebo IV plus placebo ODT, $n = 32$). Exclusion criteria included any patients experiencing emesis in the 24 h preceding surgery, taking antiemetic medications during the immediate preoperative period, or with a history of intolerance to serotonin receptor antagonists. Patients requiring postoperative mechanical ventilation were also not included because they would not be able to express their degree of PONV and would likely require additional sedation.

All ASA I-III patients between the ages of 18 and 80 yr scheduled for acoustic neuroma resection at our institution between October 2000 and December 2002 were approached for informed consent during the initial anesthesia evaluation on the day of surgery. The patient's age, gender, ASA classification, medical history, and current state of health were recorded with emphasis on the presence of systemic disease, recent emesis and/or use of antiemetic medications, and drug sensitivities. The first day of the last menstrual cycle was recorded for female subjects. Tumor size was recorded from either preoperative or postoperative sources (e.g., pathology reports, imaging studies). All study participants received routine perioperative monitoring for acoustic neuroma resection, including continuous electrocardiogram, pulse oximetry, temperature, noninvasive blood pressure, intraarterial blood pressure via radial or femoral arterial line, somatosensory evoked potentials, brainstem auditory evoked potentials

(BAERs), and electromyography of the facial nerve. A standardized isoflurane/opioid anesthetic was provided (Table 1), representing routine anesthetic management for this procedure in our institution. All patients in the study received both intraoperative (standard dose of 8 mg, IV at the time of incision) and postoperative dexamethasone (as requested by the surgeon). At the completion of surgery the subject's trachea was extubated if deemed appropriate by the attending anesthesiologist. Patients requiring continued mechanical ventilation for any reason were excluded from further participation to avoid the confounding effects of the endotracheal tube on the gag response and because of the possibility of limited patient communication.

At the time of randomization the research pharmacist was provided with the patient's gender and whether a change in eighth cranial nerve function (as determined by BAERs at completion of tumor resection) was detected, as both of these factors appeared to independently alter the incidence of PONV in our preliminary observations. Postoperatively, patients received antiemetic medication on a regularly scheduled basis, either orally disintegrating ondansetron (ondansetron ODT 8 mg BID) or placebo for up to 72 h. The first dose of ondansetron or placebo was administered between 4 h and 8 h after tracheal extubation. Metoclopramide (10 mg IV prn every 8 h) was provided as rescue therapy to any patient as needed for PONV events.

For each patient, the number of emetic episodes and requirement for rescue antiemetic treatment was determined from nursing notes and medication administration records. Severity of nausea was recorded using a 10-cm visual analog scale (VAS) twice daily during an interview with the patient. "No nausea" was considered a VAS score of 0, whereas the occurrence of any emesis during the preceding 12-h period was considered a VAS score of 10. Patient satisfaction

with control of PONV, as well as the presence of any side effects potentially related to antiemetic therapy, was also recorded using a VAS and by discussion with the physician and nursing staff. Decision to withdraw from the study could be made by an individual patient or primary care team at any time during the postoperative period. All patients stayed in the study long enough to obtain data on the day of surgery.

The study safety committee reviewed the accumulated data after enrollment of 30 patients to determine appropriateness of continuing the study to the planned completion of 60 patients. The safety committee was instructed to stop the study if there appeared to be an overwhelming benefit of drug treatment or if drug treatment was found to have unexpected toxic effects. The investigators were unaware of the findings of the safety committee but were advised to complete the planned study of 60 patients.

Values are expressed as mean \pm SEM. Comparisons between groups for parametric data were accomplished with Student's *t*-test. Expected frequencies for patients receiving ondansetron were compared with the observed frequencies in patients treated with placebo using χ^2 tests. *P* values of less than or equal to 0.05 were considered statistically significant.

Results

A total of 133 patients with a preoperative diagnosis of acoustic neuroma presented to our operating rooms during the period of patient recruitment. Sixty patients participated in the study. Other patients either refused to participate in the study ($n = 20$), presented to the operating room on a day no investigator was available to obtain informed consent ($n = 7$), had medical conditions that were in our exclusion criteria ($n = 28$, of which 10 were excluded because they were not tracheally extubated at the end of the case) or presented at a time when the IRB approval had expired and was being re-reviewed ($n = 18$). Of the 60 patients who entered the study, there were no differences between groups in demographic data (Table 2). The most common presenting complaint in patients in both groups was hearing loss, followed by tinnitus and vertigo.

In the immediate postoperative period, the VAS score for nausea was lower ($P < 0.001$) in patients treated with intraoperative IV ondansetron (3.3 ± 4.1) as compared with patients treated with intraoperative IV placebo (7.3 ± 4.2). In the placebo group, 11 of 32 patients experienced immediate postoperative vomiting. However, only 3 of 28 patients in the ondansetron group experienced immediate postoperative vomiting ($\chi^2 P < 0.01$). In the placebo group, 11 of 32 patients asked to be removed from the study before completing the 3 days of evaluation (6 on the morning of

Table 2. Demographic Data for Patients Treated with Placebo (IV Placebo and Placebo ODT) or Ondansetron (IV Ondansetron and Ondansetron ODT)

	Placebo	Ondansetron
Age (yr)	50 \pm 12	51 \pm 10
Female/male	21/11	17/11
Time in OR (h)	7.6 \pm 1.5	8.2 \pm 1.9
BAER lost during surgery (number of pts)	20 of 32	12 of 27
Tumor size (cm)	2.1 \pm 0.8	1.8 \pm 0.9

There were no differences between groups for any of the demographic variables.

OR = operating room; BAER = brainstem auditory responses; pts = patients; ODT = orally disintegrating tablet.

postoperative day 1). In the ondansetron group, 7 of 28 patients asked to be removed from the study before completing the 3 days of evaluation (none on the morning of postoperative day 1 but 6 on the afternoon of postoperative day 1). Female gender was associated with worse intensity of immediate postoperative nausea (higher VAS) in patients treated with intraoperative placebo ($P < 0.001$) but not in patients treated with intraoperative IV ondansetron. Loss of vestibular nerve function did not predict severity of immediate postoperative nausea in patients treated with placebo or ondansetron.

After 24 h of recovery, emesis was rare and not different between groups (1 patient in the ondansetron group; 2 patients in the placebo group). However, more patients still required some form of rescue treatment in the placebo group (26 of 32 in the placebo group; 16 of 28 in the ondansetron group; $\chi^2 P < 0.01$) on the first postoperative day. On the second postoperative day, rescue treatment was required in 5 of 21 remaining patients in the placebo group and in 2 of 22 remaining ondansetron-treated patients.

We did not observe any complications associated with IV or ondansetron ODT treatment. Two patients withdrew from the study because they did not like the taste of the ondansetron ODT. A third patient developed a transient superficial mucosal ulcer under her tongue but completed the study.

Discussion

The main finding of the study is that IV ondansetron treatment, administered 30 minutes before the end of surgery, prevents immediate PONV in patients undergoing acoustic neuroma resection. Postoperative ondansetron ODT treatment in patients treated with intraoperative IV dexamethasone plus ondansetron was associated with less frequent rescue therapy on the first postoperative day as compared with patients receiving IV intraoperative placebo plus dexamethasone and postoperative placebo-ODT. In most patients,

PONV after resection of acoustic neuroma is self-limiting and does not benefit from preventive treatment with ondansetron after the second postoperative day.

Before initiating the current study, therapy for PONV in our hospital involved the use of intraoperative dexamethasone prophylaxis and postoperative metoclopramide or prochlorperazine as needed in response to emesis or patient complaint of nausea (i.e., rescue therapy). Serotonin type 3 (5-hydroxytryptamine; 5-HT₃) receptor antagonists such as ondansetron (Zofran[®]) have proven effective in reducing early PONV in patients undergoing middle ear surgery (5,6). An initial study of ondansetron in pediatric craniotomy patients failed to reach statistical significance (7) when evaluating total number of emetic events, but this early study was not designed to reveal differences between ondansetron and placebo groups in either severity of nausea or in requirement for rescue therapy.

In a retrospective analysis the frequency of PONV was increased after infratentorial as compared with supratentorial craniotomy (1). However, this was not substantiated in a prospective analysis that compared postoperative pain and nausea in patients having either craniotomy or spine surgery (8). In a retrospective analysis initial PONV (first four postoperative hours) was more frequent in patients undergoing craniotomy under general anesthesia as compared with patients who have craniotomy in the awake state (9). The increased frequency of PONV in patients after acoustic neuroma surgery probably relates to disruption of the vestibular system during surgery (10). Although movement often provokes PONV after acoustic neuroma surgery, lack of movement may delay recovery and prevent adaptation to vestibular disruption. Our study suggests that aggressive use of antiemetic strategies, including ondansetron ODT, may allow patients the opportunity to participate in vestibular adaptation exercises earlier.

In a prospective, double-blind, placebo-controlled study, ondansetron 4 mg IV administered within 1 hour after the end of surgery was found to decrease the incidence of both nausea and vomiting for the first 24 postoperative hours. However, Fabling et al. (2) demonstrated that 8 mg IV ondansetron at skin closure did not decrease the incidence of PONV at any of their individual measurement points but was associated with a decrease in the overall likelihood of developing PONV within the first 12 postoperative hours. The authors of this study suggested further evaluation of scheduled antiemetic therapy during the first 48 hours after infratentorial surgery. We believe that our study addresses this suggestion.

All patients in this study were treated with dexamethasone before surgical incision at the request of

the faculty surgeon with the intent to decrease post-surgical brain edema. Dexamethasone also has antiemetic properties. In particular, dexamethasone was demonstrated to be effective for prophylaxis of PONV after tympanomastoid surgery (11). Some authors (12) have demonstrated similar efficacy for dexamethasone in comparison to ondansetron, but this has not been evaluated specifically in neurosurgical patients. Many authors believe that overall superior antiemetic therapy is achieved by combining dexamethasone with a 5-HT₃ receptor antagonist (13). Although the mechanism by which dexamethasone decreases the incidence of PONV is unknown, it is likely that it affects multiple important pathways (13). In the current study it was not possible to determine if the effects of ondansetron ODT would have been similar in the absence of concurrent dexamethasone treatment.

Although ondansetron ODT was effective in decreasing the intensity and frequency of PONV in this patient population, many patients in this group also benefited from multimodal antiemetic therapy. We believe that this study supports the conclusion that when one drug has efficacy in preventing or treating PONV it should be continued, using a dosing strategy that is consistent with its pharmacodynamic and pharmacokinetic properties. However, when a single drug does not demonstrate adequate efficacy, combination therapy should be initiated (14,15). Repeat treatment with a drug (single modality therapy) that shows no efficacy after the first dose is not likely to be effective after the second dose (16). In our control group multimodal therapy was achieved with the combination of dexamethasone and metoclopramide. Prophylactic metoclopramide has been demonstrated in one study to be more effective than ondansetron in preventing PONV in neurosurgical patients (17). Our data demonstrate that ondansetron plus dexamethasone prevents PONV better than dexamethasone alone. Although ondansetron ODT decreased the need for rescue treatment with metoclopramide, once metoclopramide was administered nausea intensity and frequency of emesis were similar between groups.

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