

COMPARISON OF INHALED ISOPROPYL ALCOHOL AND INTRAVENOUS ONDANSETRON FOR TREATMENT OF POSTOPERATIVE NAUSEA

LT Anthony W. Winston, CRNA, MS, NC, USN
Bethesda, Maryland

LT Robert S. Rinehart, CRNA, MS, NC, USN
Portsmouth, Virginia

LT George P. Riley, CRNA, MSN, NC, USN
Bethesda, Maryland

CAPT Charles A. Vacchiano, CRNA, PhD, NC, USN
Pensacola, Florida

CDR Joseph E. Pellegrini, CRNA, DNSc, NC, USN
Bethesda, Maryland

Postoperative nausea, a common complication in patients receiving general anesthesia, was studied in this randomized investigation to compare the efficacy of 70% inhaled isopropyl alcohol and intravenous ondansetron.

For the study, 100 healthy women, ASA physical status I or II, scheduled for outpatient gynecologic laparoscopic procedures randomly received 4 mg of intravenous ondansetron or isopropyl alcohol for the treatment of postoperative nausea. Nausea was measured on arrival to the postanesthesia care unit, at first complaint of nausea, every 5 minutes after initiation of therapy until nausea resolution, and every 15 minutes thereafter using a 0 to 10 verbal numerical rating scale.

At 5, 10, and 15 minutes, the median verbal numerical

rating scores between the ondansetron and alcohol groups were 6.00 and 3.00, 5.00 and 3.00, and 5.00 and 2.00, respectively (P = .002, .015, and .036, respectively). No statistically significant differences were found at any other time interval. Mean times from initiation of therapy to a 50% reduction in nausea between the ondansetron and alcohol groups were 6.3 minutes and 27.7 minutes, respectively (P = 0 .022).

Based on this study, it seems postoperative nausea can be resolved quicker using 70% inhaled isopropyl alcohol compared with intravenous ondansetron in women undergoing outpatient gynecologic laparoscopic procedures.

Key words: Antiemetics, inhaled isopropyl alcohol, ondansetron, postoperative nausea.

Postoperative nausea and vomiting (PONV) is a pervasive problem in patients who undergo general anesthesia. Its quick resolution is important for optimizing the safety and comfort of patients and for increasing their overall satisfaction with the anesthesia and surgical experience.

The etiology of PONV is complex and dependent on many factors, such as the operative site, age, and sex of the patient. The incidence of PONV has been estimated to be 70% following intra-abdominal surgery, 58% following major gynecological surgery, and 40% to 77% following laparoscopic surgery. Children are twice as likely as adults and women are 2 to 4 times as likely as men to experience PONV.¹

To gain a full understanding of the impact of PONV, the direct and indirect costs to the institution and patient should be examined. From the institution's perspective, direct costs are seen in stocking

additional supplies and antiemetics to treat PONV and in additional nursing care hours due to extended postanesthesia care unit (PACU) stays of the patients. Patients with PONV spend an additional 47 to 61 minutes in the PACU.² Indirect costs for the institution are those associated with patient hospitalization and PACU stays. In a typical same day surgery (SDS) center, it was calculated that for every 5 patients who experience PONV, an additional 2 patients could not be scheduled for surgery due to lack of space for recovery of these patients. The annual cost of PONV in that typical SDS center was reported to be between \$250,000 and \$1,500,000.³ The direct costs to the patient are those associated with their treatment and hospitalization, while the indirect costs are those involved with returning them back to their previous functioning level.

There are several mechanisms that can lead to PONV, although the exact pathophysiology is unclear.

The vomiting reflex is composed of peripheral mechanisms in the gastrointestinal tract and central mechanisms in the chemoreceptor trigger zone (CTZ) in the area postrema of the brain. Four neurotransmitters are involved in the activation of the vomiting reflex: histamine, dopamine, serotonin, and acetylcholine. Release of these neurotransmitters stimulates receptors in the CTZ, which in turn stimulate the emetic center to produce nausea and vomiting.⁴ The specific serotonin receptor involved is the 5-HT₃ (hydroxytryptamine) subtype. Surgical manipulation of the gut can cause the release of serotonin, leading to emesis during the postoperative period.⁵ Inhaled anesthetic agents modulate the conductivity of ions through the 5-HT₃ receptor, which suggests a possible mechanism for the nausea and vomiting these agents are known to produce.⁶

Many effective treatments are used to control PONV. Commonly used treatment regimens include a dopamine receptor agonist, such as droperidol or metoclopramide, or a 5-HT₃ (serotonin) receptor antagonist.⁷ Droperidol is a butyrophenone possessing both tranquilizer and antiemetic effects. Control of nausea is accomplished by producing an antagonism at the dopamine D₂ receptor site.⁸ However, droperidol is associated with some clinically significant side effects, most notably extrapyramidal symptoms and sedation.^{9,10}

Ondansetron, a carbazole, produces antiemetic and antinauseant effects via competitive and selective antagonism of the serotonin receptor sites in the vagal afferent nerves in the gastrointestinal tract and blockade of 5-HT₃ binding sites in the CTZ and the nucleus tractus solitarius of the brainstem.¹¹ Because of its selectivity to the 5-HT₃ receptor sites, ondansetron is not associated with the side effects typically found with antagonism of the dopamine receptor. The side effects that most commonly are associated with ondansetron include headache, dizziness, drowsiness, and sedation. For many practitioners, ondansetron's demonstrated efficacy and its low incidence of side effects have made it the "gold standard" antiemetic treatment.¹² However, despite the efficacy of ondansetron, some studies report that 45% of women undergoing outpatient laparoscopic procedures who received ondansetron prophylactically reported ongoing nausea during the postoperative period.¹³

For reasons not clearly understood, the inhalation of isopropyl alcohol (IPA) vapors seems to be effective for treating PONV. In a published abstract, the authors reported that 80% of the subjects treated for PONV with inhaled IPA had an almost complete resolution of symptoms compared with placebo.¹⁴ In a published letter, the

authors reported that 84% of the subjects treated with IPA for transport-related PONV experienced relief of their symptoms.¹⁵ The only formal study published reported that 65% of the children treated with inhaled IPA for PONV had a significant reduction in the severity of nausea or vomiting compared with placebo ($P = .03$).¹⁶ However, this relief was transient. It is hypothesized that the IPA may influence the neurotransmitters that activate the CTZ. To our knowledge, there are no published studies that have compared inhaled 70% IPA with intravenous (IV) ondansetron for treatment of postoperative nausea (PON).

The primary goal of this study was to compare the efficacy of inhaled 70% IPA and IV ondansetron for the treatment and control of PON in groups of women undergoing outpatient gynecological laparoscopic procedures.

Materials and methods

This was an investigational, randomized study. After institutional review board approval, written, informed consent was obtained from 100 women, ASA physical status I or II, older than 18 years scheduled to undergo diagnostic laparoscopy, operative laparoscopy, or laparoscopic bilateral tubal occlusion. Subjects were excluded if they reported sensitivity to IPA or ondansetron, had an impaired ability to breathe through the nose, were pregnant or using the medication disulfiram, reported preexisting nausea, or reported any antiemetic use within 24 hours before surgery. In addition, patients who reported a history of significant PONV, defined as nausea or vomiting resistant to antiemetic therapy, or had a history of alcoholism were excluded from the study. Informed consent was obtained on the day of surgery in the preoperative holding area. Subjects were randomly assigned to receive inhaled 70% IPA (experimental group) or IV ondansetron (control group) for the treatment of PON.

A preoperative assessment for level of nausea was conducted using a 0 to 10 verbal numeric rating scale (NRS) for all subjects in the preoperative holding area to obtain a baseline score. Subjects were asked to rate their nausea on a 0- to 10-point scale with a score of 0 indicating no nausea and 10 indicating the worst nausea imaginable. Subjects then were instructed that this scale would be used to rate the level of nausea during the postoperative period.

Upon arrival in the operating room, routine monitoring devices were placed on all subjects, and baseline vital signs were recorded. General anesthesia was induced with propofol, 2 mg/kg IV, and fentanyl, 2.0 to 3.0 µg/kg IV. Tracheal intubation was facilitated

using rocuronium, 0.3 to 0.6 mg/kg IV. An oral gastric tube was inserted to facilitate evacuation of stomach contents and increase vision in the surgical field. Anesthesia was maintained with isoflurane, 0.5% to 1.0%, in combination with nitrous oxide, 50%, and oxygen, 50%. Fentanyl was administered on an as-needed basis up to a total of 5 µg/kg. Approximately 15 minutes before emergence, all subjects were given 30 mg of ketorolac IV, and the oral gastric tube was removed. Neuromuscular blockade was antagonized using neostigmine, 0.05 mg/kg IV, and glycopyrrolate, 0.01 mg/kg IV, when necessary. All subjects then were extubated and transported to the PACU.

Assessment of nausea (using the 0-10 verbal NRS scale) was performed on all subjects in the PACU when they were awake, on first request for treatment of PON, at 5-minute intervals until nausea resolved, and every 15 minutes thereafter until discharge from the PACU. At the first request for treatment, subjects assigned to the control group received ondansetron, 4 mg IV, to be repeated 1 time in 15 minutes if needed. Those assigned to the experimental group received 70% IPA to inhale, to be repeated 1 time in 15 minutes if needed. Administration of IPA was accomplished using a standard, medium, 2-ply 70% isopropyl alcohol "prep pad" (The Kendall Company, Mansfield, Mass). The package was opened and the pad removed immediately before use. The pad was folded in half and placed under the subject's nose. The subjects were instructed to take 3 consecutive deep breaths through the nose to inhale the vapors, and the pad was then discarded. For subjects receiving supplemental oxygen, it was removed during administration of the IPA. Rescue treatment was provided at the subject's request or if nausea failed to resolve after 2 treatments. Rescue treatment for failed IPA was provided with 4 mg of IV ondansetron every 15 minutes for 2 doses. Rescue treatment for failed IV ondansetron was at the discretion of the anesthesia provider.

Before transport to the PACU from the operative suite, postoperative orders, which identified them as participants in the study, were written for all subjects. These orders identified the treatment protocols to be followed by PACU nursing personnel based on the group assignments (IPA or ondansetron). The preprinted order forms allowed opioids for postoperative pain to be prescribed at the discretion of the individual anesthesia provider in each study case. However, 2 antiemetic regimens (standardized based on the study protocols) were printed on each form, allowing the providers to check only 1 of 2 blanks indicating which regimen was to be followed in case of PONV based on each subject's original group

assignment. All nursing personnel in the PACU were instructed about the parameters of the study and became familiar with data collection tools before initiation of the study.

For the purposes of this study, an *emetic event* was considered vomiting or retching. Episodes must have been separated by at least 1 minute to constitute separate events. *Nausea* was defined as a subjective unpleasant sensation associated with the awareness of the urge to vomit. Demographic data (age, height, weight, sex, and ASA physical status) were obtained during the preanesthesia interview and recorded. Additional data obtained included anesthesia time (arrival time in operating room until arrival time in PACU), surgery time (surgical incision until skin closure), PACU time (arrival until "fit for discharge" from PACU), and SDS time (arrival until discharge from SDS). Frequency data obtained in both the PACU and the SDS included episodes of nausea, episodes of emesis, and number of times opioids were administered. The type of opioid, quantity administered at each request, and total amount administered were recorded. All study subjects were sent home with a simple data collection form to use for tracking nausea and emetic events, subsequent treatment, and overall satisfaction with anesthesia care. Twenty-four hours after discharge, a follow-up telephone call was made to retrieve these data.

A power analysis was performed before initiation of the study and showed that a sample size of 50 subjects per group would be sufficient to provide 80% power to detect a difference between the groups. This was based on the assumption that a mean verbal NRS score in both groups would be 6 at complaint of postoperative nausea and a reduction of this score by 3 (to 3) would denote clinical effectiveness of each treatment using a 2-tailed test at a 5% significance level. All data were analyzed for entry errors, missing data, and consistency before statistical analysis. Statistical analysis was performed using an SPSS statistical package (version 8.0, SPSS, Chicago, Ill). Verbal NRS scores were analyzed with a Mann-Whitney *U* test; demographic data and frequency data were analyzed using a χ^2 test. A *P* value of less than .05 was considered significant. Verbal NRS scores were expressed as median \pm SD. All other data were expressed as mean \pm SD.

Results

For the study, 100 women were enrolled and equally randomized to the experimental IPA group or the control ondansetron group. When surgical procedures were analyzed, it was noted that 40 women underwent laparoscopic bilateral tubal ligation, 41 under-

Table 1. Group comparison of means

	Ondansetron group	IPA group	P value
Intraoperative fentanyl (μg)	183.8 \pm 68.2	195.1 \pm 54.8	.364
Anesthesia time (min)	80.6 \pm 29.3	74.6 \pm 31.4	.326
Surgery time (min)	41.3 \pm 19.0	40.7 \pm 25.8	.895
PACU time (min)	60.3 \pm 24.8	58.4 \pm 26.5	.498
Total postoperative opioid use (morphine equivalent)	5.07 \pm 2.0	4.79 \pm 1.45	.826

IPA = inhaled isopropyl alcohol
 PACU = postanesthesia care unit

went diagnostic laparoscopy, and 19 underwent operative laparoscopy. An equal distribution of surgical procedures was noted between groups. Demographic characteristics with regard to age, weight, height, and ASA physical status were similar between groups. Anesthesia times, surgical times, PACU times, intraoperative fentanyl use, and total postoperative opioid use also were similar between groups (Table 1). The use of neuromuscular blockade reversal agents also was similar between groups.

Of the 100 subjects, 41 experienced PON (29 in the experimental [IPA] group and 12 in the control [ondansetron] group). There were no statistically significant differences in median verbal NRS scores for PON at any time interval measured except at the 5-, 10-, and 15-minute marks. Median verbal NRS scores were 6.00 and 3.00 ($P = .002$), 5.00 and 3.00 ($P = .015$), and 5.00 and 2.00 ($P = .036$) in the ondansetron and IPA groups, respectively (Table 2).

When the mean time from initiation of therapy to 50% relief of PON was analyzed, a mean time of 6.3 minutes was required in the IPA group compared with a mean time of 27.7 minutes in the ondansetron group (maximum of 2 doses for each group). This was statistically significant ($P = .022$; Figure). Despite the difference in time to relief of symptoms noted between the groups, this did not have an impact on the mean stay times in the PACU and SDS units between groups (58.4 minutes for the IPA group compared with 60.3 minutes for the ondansetron group in the PACU; 139.2 minutes for the IPA group compared with 124.12 minutes in the ondansetron group in the SDS).

A total of 8 subjects in the IPA group did not experience relief after 3 treatments with IPA, and they subsequently received ondansetron. Two subjects in the ondansetron group did not experience relief after 2 treatments with IV ondansetron and received metoclopramide or promethazine at the discretion of the anesthesia provider.

Table 2. Median verbal numeric rating scale scores

Relative time	Ondansetron group	IPA group	P value
First complaint	8.00	8.00	.854
5 min	6.00	3.00	.002
10 min	5.00	3.00	.015
15 min	5.00	2.00	.036
30 min	0.00	1.50	.469
45 min	0.00	0.00	.522
60 min	0.00	0.00	.871

IPA = inhaled isopropyl alcohol

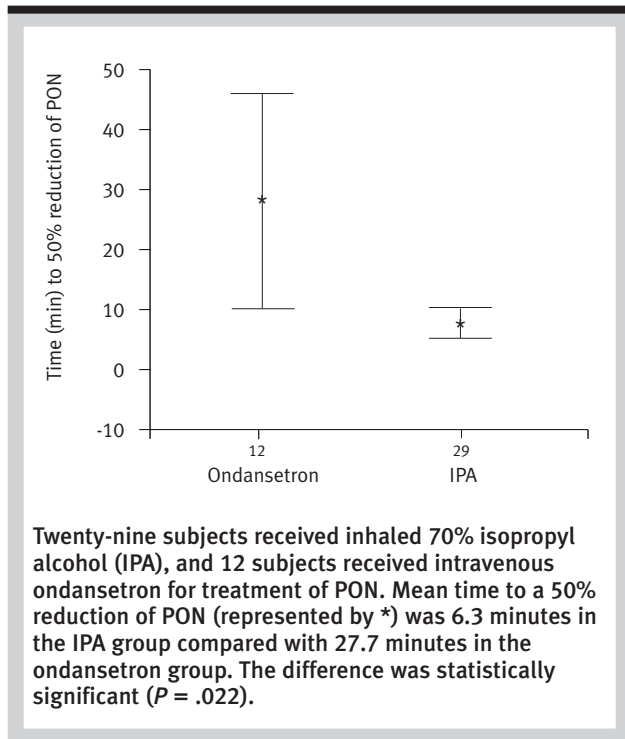
While there were no differences noted in the NRS scores in either group before discharge from the hospital, except at the 5-, 10-, and 15-minute marks, the IPA group reported more episodes of nausea at home during the first 24 hours after discharge than did the ondansetron group. The reported mean incidence of nausea events at home was 0.92 in the IPA group compared with 0.40 in the ondansetron group ($P = .035$). It is possible that subjects who received ondansetron achieved a longer lasting antiemetic effect with their therapy.

Discussion

PONV has been associated with recovery from general anesthesia for many years. The general trend is toward a decrease in its incidence; however, it still occurs with unacceptable frequency. PONV not only is distressing to the patient, but it also can influence the duration of recovery from anesthesia and the time needed for patients to return to their normal functional level.

This study showed that PON can be resolved quicker using 70% inhaled IPA compared with IV

Figure. Time from initiation of antiemetic therapy to a 50% reduction of postoperative nausea (PON) for 41 subjects undergoing laparoscopic tubal occlusion, diagnostic laparoscopy, or operative laparoscopy



ondansetron in groups of women undergoing outpatient laparoscopic procedures—a mean time of 6.3 minutes compared with a mean time of 27.7 minutes for the ondansetron to achieve a 50% reduction in nausea. These data should prove useful to anesthesia providers since PONV is a pervasive problem following anesthesia. It should be noted that this study was conducted on a small portion of the population who undergoes surgery.

One unusual finding in this study was the disproportionate number of subjects in the IPA group who reported nausea, 60% compared with 24% in the ondansetron group, despite the use of block randomization. A possible explanation for this is respondent bias. We chose to administer the IPA by having the subject inhale the IPA from a folded alcohol pad because it offered a simple, readily available method. However, we realized that this did not allow us to blind the study intervention. In fact, a pilot study that investigated the effectiveness of inhaled IPA vs a placebo attempted to keep PACU personnel unaware of the intervention used. That study required that recovery room nurses apply bandages saturated with IPA to their own upper lips before administering treatment to study subjects to mask the investigators' sense of smell, thus preventing them from detecting

the IPA odors.¹⁴ This method of blinding, while effective in that pilot study, was deemed inappropriate for the present study in which a direct comparison of clinical effectiveness was performed between IV ondansetron and inhaled IPA.

Other benefits may be derived from the use of inhaled 70% IPA due to its ease of administration and portability, allowing it to be used easily during patient transport or self-administered after patient discharge. These observations represent opportunities for further research. In addition, cost savings may be realized by using the 70% IPA pads. At our institution, a single 70% IPA pad costs \$0.01 compared with \$17.00 for one 4-mg IV dose of ondansetron. These costs represent the acquisition cost for our institution rather than the charges to the patient.

REFERENCES

- Kenny G. Risk factors for postoperative nausea and vomiting. *Anaesthesia*. 1994;49:6-10.
- Metter S, Kitz D, Young M, Baldeck A, Apfelbaum J, Lecky J. Nausea and vomiting after outpatient laparoscopy: incidence, impact, on recovery room stay and cost [abstract]. *Anesth Analg*. 1987;66(suppl):S116.
- Sanches L, Hirsch J. Identification of cost consequences as the critical step in a cost-of-illness study: post-operative nausea and vomiting in an ambulatory surgery center example. *J Res Pharm Economics*. 1992;4:41-54.
- Watcha M, White P. Postoperative nausea and vomiting: its etiology, treatment, and prevention. *Anesthesiology*. 1992;77:162-184.
- Naylor R, Inall F. The physiology and pharmacology of postoperative nausea and vomiting. *Anaesthesia*. 1994;49(suppl):2-5.
- Machu T, Harris R. Alcohols and anesthetics enhance the function of 5-hydroxytryptamine₃ receptors expressed in *Xenopus laevis* oocytes. *J Pharmacol Exp Ther*. 1994;271:898-905.
- Fujii Y, Saitoh Y, Tanaka H, Tayooka H. Ramosetron for preventing postoperative nausea and vomiting in women undergoing gynecological surgery. *Anesth Analg*. 2002;90:472-475.
- Tang J, Watcha M, White P. A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecological procedures. *Anesth Analg*. 1996;83:304-313.
- Follet C, Farinotti R, Palmer J. Physiology of chemotherapy-induced emesis and antiemetic therapy. *Drugs*. 1997;53:206-234.
- Sung Y. Risks and benefits of drugs used in management of postoperative nausea and vomiting. *Drug Saf*. 1996;14:181-197.
- Markham A, Sorkin E. Ondansetron: an update of its therapeutic use in chemotherapy-induced and postoperative nausea and vomiting. *Drugs*. 1993;45:931-952.
- Splinter W, Rhine E. Prophylaxis for vomiting by children after tonsillectomy: ondansetron compared with perphenazine. *Br J Anaesth*. 1998;80:155-158.
- Ahmed AB, Hobbs GJ, Curran JP. Randomized placebo-controlled trial of combination antiemetic prophylaxis for day-case gynaecological laparoscopic surgery. *Br J Anaesth*. 2000;85:678-682.
- Langevin P, Brown M. A simple, innocuous, and inexpensive treatment for postoperative nausea and vomiting [abstract]. *Anesth Analg*. 1997;84(suppl):S15.
- Smiler BG, Srock M. Isopropyl alcohol for transport-related nausea [letter]. *Anesth Analg*. 1998;87:1214.
- Wang S, Hofstadter M, Zain A. An alternative method to alleviate

postoperative nausea and vomiting in children. *J Clin Anesth.* 1999;11:231-234.

AUTHORS

LT Anthony W. Winston, CRNA, MS, NC, USN, is currently a staff nurse anesthetist at the National Naval Medical Center, Bethesda, Md. He is the principal author of this study. This study was conducted while he was a nurse anesthesia student as part of the Master of Science degree requirements for the nurse anesthesia program at Georgetown University.

LT Robert S. Rinehart, CRNA, MS, NC, USN, is currently a staff nurse anesthetist at the Naval Medical Center, Portsmouth, Va. He was an associate investigator and classmate of LT Winston at Georgetown University.

LT George P. Riley, CRNA, MSN, NC, USN, is currently a staff nurse anesthetist at the National Naval Medical Center, Bethesda, Md.

CAPT Charles A. Vacchiano, CRNA, PhD, NC, USN, is currently on staff at the Naval Aerospace Medical Research Laboratory, Pensacola, Fla.

CDR Joseph E. Pellegrini, CRNA, DNSc, NC, USN, is director of Research, Navy Nurse Corps Anesthesia Program, Bethesda, Md.

ACKNOWLEDGMENTS

We thank the following individuals for their contributions to this research: LT Mark Allen, RN, BSN, NC, USN; LT David Melvin, RN, BSN, NC, USN; CWO4 William Hohman, RN, NC, USN; and Christine Bundy, RN, BSN, CPAN, for assistance in data collection. We also thank the Anesthesia Department, Postanesthesia Care Unit, and Ambulatory Procedures Department at Naval Medical Center Portsmouth, Va, for assistance in data collection.

DISCLAIMER

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.