

# A COMPARATIVE ANALYSIS OF ISOPROPYL ALCOHOL AND ONDANSETRON IN THE TREATMENT OF POSTOPERATIVE NAUSEA AND VOMITING FROM THE HOSPITAL SETTING TO THE HOME

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*We compared the efficacy of inhaled isopropyl alcohol (IPA) with ondansetron for the control of postoperative nausea and vomiting (PONV) during a 24-hour period in 100 ASA class I-III women undergoing laparoscopic surgery. Nausea was measured postoperatively using a 0 to 10 verbal numeric rating scale (VNRS). The control group received ondansetron, 4 mg intravenously, and the experimental group inhaled IPA vapors. Breakthrough PONV was treated with 25-mg promethazine suppositories.*

*Demographic and anesthesia characteristics were similar between groups. There was a significant difference between groups in mean  $\pm$  SD time to alleviation of PONV symptoms: for a 50% reduction in VNRS scores, 15.00  $\pm$*

*10.6 vs 33.88  $\pm$  23.2 minutes was required in the experimental vs the control group (P = .001). A total of 21 subjects (10 control; 11 experimental) reported PONV symptoms following discharge to home. The IPA treatment was successful in alleviating PONV symptoms in the home in 91% of the experimental group.*

*We determined that using IPA after discharge from the postanesthesia care unit is a valuable method to control PONV in the hospital and at home. The results of this study suggest that IPA is much faster than ondansetron for 50% relief of nausea.*

**Key words:** Aromatherapy, isopropyl alcohol, ondansetron, postoperative nausea and vomiting.

Postoperative nausea and vomiting (PONV) are among the most common and distressing symptoms that occur following surgery. Often, a patient will report that the psychological and physical distress experienced secondary to PONV were the worst part of the entire surgical experience.<sup>1,2</sup> Several individual patient and surgical factors have been identified that predispose a patient to PONV. The individual patient factors include age, gender, weight, amount of stomach contents, motion sickness, a history of nonsmoking, prior PONV, and presence of inner ear pathology.<sup>1,2</sup> Surgical factors include the length of surgery (>60 minutes), type of surgery performed (gynecologic and laparoscopic), type of anesthesia administered (general vs regional), degree of hypotension experienced, opioid requirements during and following the procedure, and the amount of postoperative pain.<sup>1,2</sup> Based on these findings, anesthesia practitioners have customized anesthetic management plans that include controlling for some of the factors and administering

prophylactic antiemetic agents to patients who are at high risk for PONV. Despite these anesthetic treatment plans, the overall incidence can remain as high as 50% in certain patient populations.<sup>1,2</sup>

In addition to the problem of the patient's psychological and physical discomfort that can result from PONV, other complications may occur secondary to PONV. These include aspiration of stomach contents, dehydration, electrolyte disturbances, and interruption of the surgical incision. In addition, PONV can have a major impact on healthcare delivery—it has been noted that patients who experience PONV tend to require longer hospitalization and have a delayed return to the workforce, so PONV acts as a conduit for driving up the cost of healthcare.<sup>2,3</sup>

The exact mechanism of PONV is poorly understood. It is hypothesized that the nausea response is coordinated via a central vomiting center (VC) in the medulla called the chemoreceptor trigger zone (CTZ). When stimulated by noxious substances, receptors relay the information to the vomiting center, which

then acts on the efferent pathways, initiating vomiting. The CTZ is located in the highly vascularized area on the brain surface that is lacking a real blood-brain barrier; therefore, it can react to neurotransmitters involved in eliciting an emetic response. These neurotransmitters include serotonin (5-HT<sub>3</sub>), dopamine, histamine (H<sub>1</sub>), and acetylcholine. It has been shown that blockade of one or more of these neurotransmitters at the level of CTZ decrease the incidence of PONV. Specific pharmacological agents have been developed that successfully block the transmission of these neurotransmitters at the level of the CTZ; however, there is no single agent identified that will block all pathways.<sup>4</sup> To offset this, many practitioners use a combination of neurotransmitter antagonists to block more than one pathway, an approach shown to be more successful than use of separate agents. However, using a monomodal or multimodal pharmacological approach to treat PONV can result in profound sedation and hypotension, resulting in increased morbidity. Therefore, alternative methods to treat PONV that have little to no impact on patient sensorium or vital signs need to be found.

Most health professionals would agree that the best PONV treatment should be cost-effective, self-administered, and cause few to no side effects. One such treatment modality that seems to have all of these characteristics is inhaled isopropyl alcohol (IPA). Several studies have reported the clinical efficacy of inhaled IPA in the treatment of PONV. Most notable are the studies by Wang et al,<sup>5</sup> who found that the inhalation of IPA in children was effective in achieving transient relief of motion related nausea, and Winston et al,<sup>6</sup> who found that inhaled IPA was as effective in the treatment of PONV as ondansetron but also worked considerably faster in alleviating PONV symptoms. However, limitations noted in both studies were that IPA was only clinically effective for a short time and that subsequent treatments were often required to adequately treat PONV. In addition, these studies were designed to analyze IPA efficacy in a very limited setting (during transport and in the postanesthesia care unit [PACU]), and it was unclear whether IPA would be effective beyond these limited uses. Therefore, the purposes of this study were to validate the results reported by Winston et al<sup>6</sup> and to determine whether IPA was just as effective through a patient's entire hospitalization and in the home setting.

## Methods

Once institutional review board approval was obtained, a prospective, randomized study was conducted with 100 women, ASA physical status I, II, or

III, ages 18 to 65 years who were scheduled for laparoscopic same-day surgery. Patients were excluded from the study if they had recent upper respiratory tract infections, inability or impaired ability to breathe through the nose, or history of hypersensitivity to IPA, 5-HT<sub>3</sub> antagonists, promethazine, or any other anesthesia protocol medication. Patients also were excluded if they reported using an antiemetic within 24 hours of surgery; were pregnant or currently breast-feeding; had a history of inner ear pathology, motion sickness, or migraine headaches; or were taking disulfiram, cefoperazone, or metronidazole. Once it was determined that a patient was eligible for inclusion and agreed to participate in the study, the patient was randomly assigned to the control group or the experimental group by using a computer-generated random numbers program.

Following informed written consent, a baseline 0 to 10 verbal numeric rating scale (VNRS) score, in which "0" indicated "no nausea" and "10" indicated the "worst imaginable nausea," was obtained and recorded. Demographic information also was obtained, including age, height, weight, race, and type of surgery. All subjects were prepared for surgery using standard operating procedures that included intravenous (IV) cannulation, prehydration with crystalloid solution, and anxiolysis with midazolam up to 5 mg IV at the discretion of the provider.

Subjects were then transported to the operative suite where standard monitors were placed, including a noninvasive blood pressure device, an electrocardiogram monitor, and pulse-oximetry and capnography devices. All subjects were then administered 100% oxygen via face mask for 5 minutes before induction of anesthesia. Administration of IV lidocaine up to 1 mg/kg; propofol, 1.5 to 2.0 mg/kg; fentanyl up to 5 µg/kg; and a nondepolarizing or depolarizing muscle relaxant of choice were used to induce anesthesia. Following induction, the trachea was intubated and an orogastric tube placed to decompress the stomach. The orogastric tube was removed immediately before extubation of the trachea.

Maintenance of anesthesia was accomplished using desflurane, isoflurane, or sevoflurane in combination with a 50% nitrous oxide-oxygen mixture or a 50% oxygen-air mixture. In addition, all subjects were given up to 5 µg/kg of fentanyl IV to maintain analgesia. Approximately 15 to 30 minutes before the end of the surgical procedure, all subjects were given 30 mg of IV ketorolac. If required, neuromuscular blockade was reversed using neostigmine, 0.05 mg/kg IV, and glycopyrrolate, 0.01 mg/kg IV. All subjects were transferred to the PACU after extubation. All preoperative

and intraoperative medications that were administered were noted and recorded on a data collection sheet.

While in the PACU, the nursing staff was instructed to treat any incidence of shivering with 12.5 mg of meperidine and complaints of pain with 1 to 3 mg of IV morphine sulfate (up to a maximum of 0.15 mg/kg). The PACU personnel were instructed to note time, dose, and effectiveness of all analgesics on the data collection sheet.

In addition to the baseline measurement of the VNRS score for nausea, an additional VNRS score was obtained for all subjects on emergence from anesthesia and at any time they complained of nausea. If a subject complained of nausea, VNRS scores were obtained on initial complaint, every 5 minutes following treatment for 30 minutes, and every 15 minutes thereafter until discharge from the PACU. All treatments and VNRS scores were recorded on the data collection sheet. Successful treatment with ondansetron or IPA was defined as a 50% reduction in the VNRS score.

For subjects assigned to the ondansetron (control) group, nausea was treated with ondansetron, 4 mg IV, every 15 minutes, up to an 8-mg maximum total dose. The PACU personnel were instructed to record the time, dose, and the VNRS scores on the data collection sheet. For subjects assigned to the IPA (experimental) group, nausea was treated by having the PACU nursing personnel hold a folded alcohol pad approximately ½ inch from the opening of the patients' nares and instructing the patient to take 3 deep breaths of the vapors in and out through the nose. The IPA treatments were ordered to be administered on an as needed basis, every 5 minutes, up to a total of 3 administrations. All PACU personnel and subjects were instructed as to the specific use of the IPA and the parameters of the study before the initiation of the study.

Following discharge from the PACU, all subjects were transported to the same-day surgery unit (SDSU). The SDSU nursing personnel were instructed about the specific parameters of the study and protocols before initiation of the study. For complaints of nausea, SDSU personnel were instructed to use the same treatment regimen as that used in the PACU, including the administration of ondansetron, IPA, and recording of VNRS scores for nausea. In case nausea persisted in the ondansetron group following a total IV dose of 8 mg of ondansetron (cumulative amount between PACU and SDSU), nursing personnel were instructed to administer a 25-mg promethazine suppository. If nausea was refractory to treatment in the IPA group, all nursing personnel were instructed to treat nausea with ondansetron, 4 mg IV, every 15 minutes, up to a total dose of 8 mg. All complaints of nau-

sea and treatment regimens used were recorded on a data collection sheet.

Following discharge from the SDSU, all subjects were discharged to home with a data collection tool on which they were asked to record nausea and vomiting events, what treatment was used, and clinical effectiveness of the treatment. Subjects were asked to record this data for a period of 24 hours.

Before discharge from the hospital, all subjects were given two 25-mg promethazine suppositories and instructed on self-administration. All subjects were given written and verbal instructions concerning treatment of PONV at home. Subjects randomized to the ondansetron group were asked to treat episodes of nausea and/or vomiting at home by self-administration of one 25-mg promethazine suppository every 6 hours as needed. Subjects randomized to the IPA group were asked to take 3 deep inhalations from an IPA pad every 15 minutes as needed to a maximum of 3 inhalational treatments. If the IPA was not working to the subject's satisfaction, or if 3 treatment regimens had been performed, IPA subjects were asked to self-administer a 25-mg promethazine suppository every 6 hours as needed, not to exceed 2 administrations. In addition, all subjects were asked to note the time of administration and the time they "felt relief" following administration. Before discharge from the hospital, all subjects in both groups were given instruction concerning the use and administration of promethazine suppositories.

All home data collection information was obtained and recorded by 2 investigators (J.W.C and L.R.R.) approximately 24 hours following discharge via a postoperative telephone interview. In addition, all subjects were asked to rate their anesthesia experience using a 4-point ordinal scale in which a score of 1 indicated a "poor" experience, 2 indicated a "fair" experience, 3 indicated a "good" experience, and 4 indicated an "excellent" experience.

Before initiation of the study, a power analysis was performed based on previous studies that indicated that at 5 minutes following treatment, VNRS scores would decrease from a mean of 5.0 at baseline to a mean  $\pm$  SD of  $4.5 \pm 2.7$  in the ondansetron group and  $2.1 \pm 2.5$  in the IPA group. This indicated a sample size of only 15 subjects per group would be required to show significance when an  $\alpha$  of .05 and a  $\beta$  of .20 were used. However, it was assumed that only approximately 30% of the population as a whole would have complaints of PONV; therefore, the sample size was adjusted; 50 subjects per group would be required to show significance. All data were analyzed for entry errors, missing data, and consistency before statistical

analysis. Statistical analysis was performed using SPSS statistical software (version 11.0, SPSS, Chicago, Ill). The VNRS scores were analyzed with the Student *t* test; demographic data and frequency data were analyzed using a  $\chi^2$  test. Satisfaction scores were analyzed using a Mann-Whitney *U* test. A *P* value of less than .05 was considered significant.

## Results

Of the 100 subjects enrolled, 28 were disenrolled due to failure to adhere to protocol. Protocol violations included 12 subjects in the ondansetron group who were given IPA treatments in SDSU, 6 subjects given other antiemetic agents in the PACU before IPA treatments, and the remaining subjects losing their IPA or promethazine following discharge to home. This left a total of 72 subjects for study (34 control and 38 experimental). Of the 72 subjects, 68 underwent laparoscopic gynecologic procedures, and 4 had other general surgery laparoscopic procedures. Demographic characteristics with regard to age, weight, height, anesthesia times, and PACU and SDSU times were similar between groups (Table). When the intraoperative and postoperative analgesics given, the concentrations of volatile agents administered, and IV medications used were analyzed separately, no significant differences were noted between groups. (*P* > .05).

Nausea events reported in the PACU included 5 subjects (15%) in the control group and 8 subjects (21%) in the experimental group who required treatment. No subject in either group had an emetic event in the PACU or SDSU. Nausea events reported in the SDSU included 15 subjects (44%) in the control group and 21 subjects (55%) in the experimental group who required treatment. We noted significant differences between groups when times to a 50% reduction in VNRS scores were analyzed for the first and second treatments. For the first treatment of PONV symptoms, subjects in the control group required a mean  $\pm$  SD of 33.88  $\pm$  23.2 minutes to achieve a 50% VNRS score reduction compared with 15.00  $\pm$  10.6 minutes for the experimental group (*P* = .011). Similar results also were noted for second treatments: the control group required a mean  $\pm$  SD of 26.25  $\pm$  7.5 minutes to achieve relief as opposed to 15.00  $\pm$  5.25 minutes for the experimental group (*P* = .013) (Figure 1). Only 1 subject (IPA group) reported 3 separate PONV events; therefore, no analysis was performed on time to alleviation for the third nausea event.

When the incidence of subjects requiring rescue treatment in the SDSU was analyzed, it was noted that 13 (38%) of the control group required rescue treatment, whereas only 10 (26%) of the experimental group

**Table. Demographic data and times for anesthesia, postanesthesia care unit (PACU), and same-day surgery unit (SDSU).\***

	Isopropyl alcohol (n = 38)	Ondansetron (n = 34)	<i>P</i>
Age (y)	30.47 $\pm$ 5.7	31.15 $\pm$ 5.0	.32
Height (in)	68.74 $\pm$ 2.4	64.82 $\pm$ 2.5	.266
Weight (kg)	78.87 $\pm$ 17.3	73.29 $\pm$ 12.6	.245
Anesthesia time (min)	95 $\pm$ 39.0	95.24 $\pm$ 36.9	.895
PACU time (min)	63.23 $\pm$ 30.2	62.62 $\pm$ 29.7	.959
SDSU time (min)	191.81 $\pm$ 103.4	197.71 $\pm$ 124.5	.073

\* Data are given as mean  $\pm$  SD.

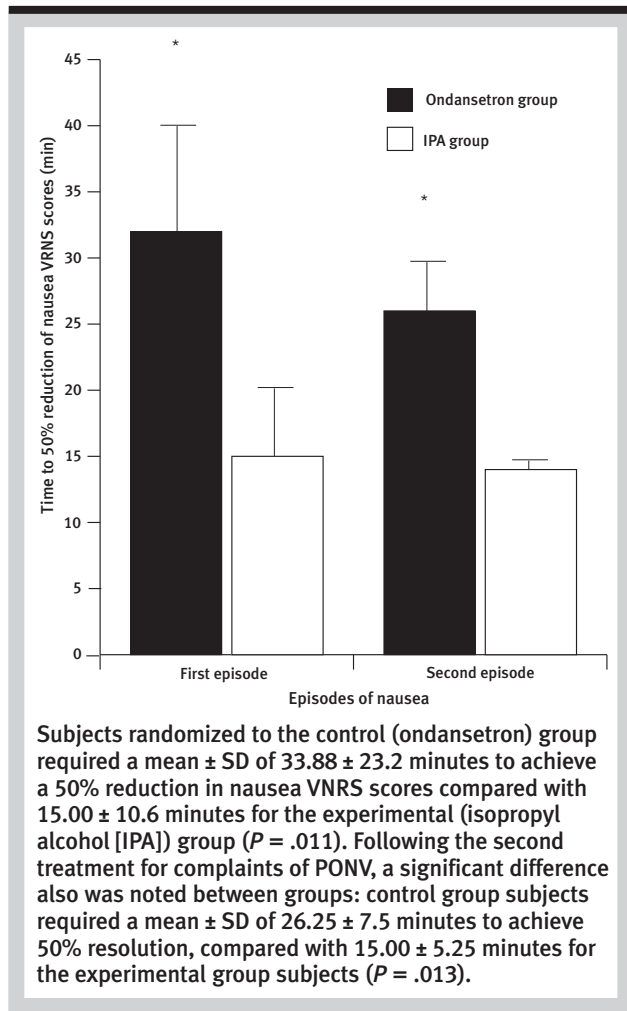
required rescue treatment (*P* = .319). A total of 21 subjects reported nausea events at home (10 control; 11 experimental); however, 5 subjects in the control group reported using promethazine for rescue treatment compared with only 1 subject in the experimental group (*P* = .064) (Figure 2). All remaining subjects in the IPA group reported that their PONV at home was adequately treated by self-administration of IPA.

No significant difference was noted when satisfaction scores for anesthesia experience were analyzed: both groups reported scores of 3 (good) or 4 (excellent) when quantifying their overall anesthesia experience (*P* > .05).

## Discussion

Women undergoing laparoscopic surgeries seem to be at a higher risk for PONV than other populations and, thus, were selected as our target population.<sup>2,6,7</sup> Ondansetron was chosen as our control agent for comparison with IPA because of its proven efficacy in treating PONV and low incidence of side effects.<sup>6-10</sup> Several investigations have reported that the inhalation of IPA is efficacious for the treatment of PONV and has minimal to no associative side effects.<sup>6,11,12</sup> Of these studies, the study that used a method similar to ours was performed by Winston et al.<sup>6</sup> As with our present study, Winston et al.<sup>6</sup> chose to have the patient inhale the vapors produced from a folded alcohol pad at the first complaint of nausea and then they recorded the time to achieve a 50% reduction in the VNRS score for nausea. The study by Winston et al.<sup>6</sup> reported that a 50% reduction in PONV was achieved in approximately 10 minutes in the IPA group, whereas it took a mean average of 30 minutes in the ondansetron group. This finding by itself was impor-

**Figure 1. Time to 50% reduction in 0-10 verbal numeric rating scale (VNRS) nausea scores**

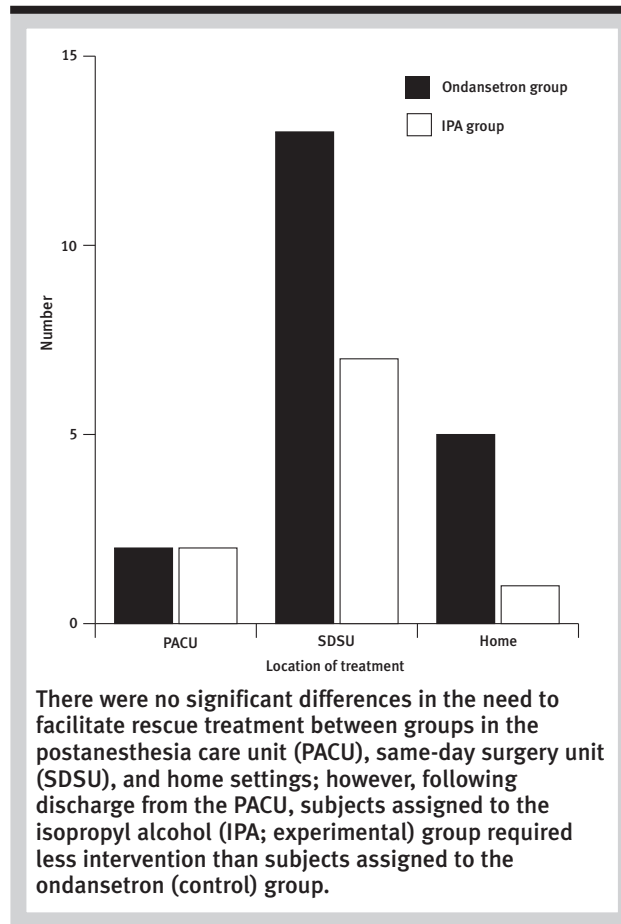


\* Significance  $P < .05$

tant but needed further validation with follow-up studies. We found similar results to the 50% reduction, although it took a mean of about 15 minutes in the IPA group and about 34 minutes in the ondansetron group. Although these times are different, they validate the findings from the first study, which concluded that IPA worked significantly faster and was as effective as ondansetron in reducing PONV symptoms in women undergoing a laparoscopic surgical procedure.

Many practitioners prophylactically treat patients for PONV with the medication ondansetron. Ondansetron costs approximately \$20 per 4-mg dose and, therefore, can be a significant factor in the cost of care. Because the incidence of PONV is reported to be 40% to 50%, some practitioners advocate a “wait and see” philosophy regarding the routine prophylactic

**Figure 2. Number of patients requiring rescue treatment**



treatment of PONV.<sup>13</sup> We argue that administration of a prophylactic dose of an antiemetic agent should not be routine and that it would be more cost-effective and expose the patient to less medication if PONV was only treated when symptoms were present. Some investigators report that none of the current regimens used to prevent PONV with antiemetic agents are sufficient in preventing PONV and are only effective if given for treatment.<sup>14</sup> Therefore, because our study showed that IPA is highly effective in the treatment of PONV and costs only pennies per application, it would be more cost-effective and perhaps safer to treat patients who experience PONV with IPA rather than the antiemetic agents commonly used in clinical practice. However, we realize that given the limited scope of the patient population used in our study, further studies need to be performed to validate such a bold supposition. One of the most attractive aspects of treating PONV with IPA is that all patients could be sent home with alcohol pads that they could self-administer for an episode in transit or while at home.

Implementing the use of IPA for the treatment of PONV for self-administration at home is also reassuring to practitioners and patients because no adverse effects have been associated with the brief inhalation of IPA vapors.

The primary limitations of our study were related to the methods and design. It would be nearly impossible to blind this type of study. Second, data collection among 3 units, providers, and the patients themselves proved challenging. Many practitioners in the PACU and SDSU treated patients with IPA despite patient assignment to the ondansetron group. When these PACU and SDSU nursing personnel were asked about reasons for this breach of protocol, they reported that at the bedside, they administered the IPA because of its convenience and its already proven efficacy that had been noted when other patients were treated with IPA for episodic PONV. Despite breaches in protocol, a total of 72 subjects were included in analysis, and we thought that this number would prove sufficient to determine whether there was difference in the clinical efficacy of each treatment regimen.

A possible future study would be to determine the efficacy of IPA as the principal treatment of PONV in the PACU, SDSU, and home settings in a group of patients given a prophylactic dose of antiemetic agent intraoperatively because the prophylactic administration of antiemetics is common in many anesthesia practices. Another avenue of future study could be the efficacy of IPA administration in a wider variety of patients who have undergone surgical procedures. We chose to limit our patient population to women having any type of same-day laparoscopic procedure in an effort to validate the results of the study by Winston et al<sup>6</sup> and because this target population is particularly susceptible to PONV. Finally, another area of future study may be to investigate whether administration of IPA prophylactically would have any effect on the occurrence of PONV in the postanesthesia settings outlined in this study.

Isopropyl alcohol could become an invaluable tool for anesthesia providers, postanesthesia nursing personnel, and patients for treatment of this often distressing, uncomfortable, and all-too-common aspect of undergoing a surgical procedure.

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