Patients identified as high risk for postoperative nausea and vomiting (PONV) are often treated prophylactically with intravenous (IV) ondansetron and an additional agent. Limited options exist for a second agent with no adverse effects. The purpose of this investigation was to determine if combining the prophylactic inhalation of isopropyl alcohol (IPA) vapors, an agent with no adverse effects, with IV ondansetron would be more effective than IV ondansetron alone in the prevention of PONV in high-risk patients.

A total of 76 patients at high risk for PONV were randomized into control (n = 38) and experimental (n = 38) groups. All patients received IV ondansetron before emergence from general anesthesia. In addition, the experimental group inhaled IPA vapors before induction. Severity of PONV was measured using a 0 to 10 verbal numeric rating scale. Other measured variables included time to onset and incidence of PONV, 24-hour composite nausea score, and satisfaction with nausea control.

No significant differences in demographics, surgical or anesthesia time, number of risk factors, severity or incidence of PONV, or satisfaction scores were noted. Prophylactic inhalation of IPA vapors in combination with IV ondansetron was no more efficacious than IV ondansetron alone in the prevention of PONV in a high-risk population.

Keywords: Aromatherapy, isopropyl alcohol, ondansetron, postoperative nausea and vomiting.

Postoperative nausea and vomiting (PONV) is one of the most common problems following general anesthesia resulting in postsurgical complications, delayed discharge, and psychological and physiological distress for the patient.1-4 Predictive risk factors have been identified that allow anesthesia providers to recognize patients who are more likely to experience PONV. These factors include female gender, nonsmoker, general anesthesia, history of PONV, motion sickness, laparoscopic surgery, and gynecological surgery.5-8 The risk of PONV associated with the presence of 1 factor is 17% and increases dramatically to 87% if 5 or more are present.6 Many anesthesia providers routinely screen patients for these risk factors and implement a treatment plan to reduce the incidence and severity of PONV.

The most common method used to prevent or reduce the severity of PONV is to administer an intravenous (IV) antiemetic agent that blocks emetogenic neurotransmitters at the level of the chemoreceptor trigger zone (CTZ) in the area postrema near the floor of the fourth ventricle within the brain. Specific emetogenic neurotransmitters include serotonin (5-HT3), dopamine, histamine, and acetylcholine.4,9 Although many medications are effective in relieving PONV, the agent most commonly used because of its low adverse effect profile is ondansetron, a 5-HT3 antagonist.10-12 A 4-mg IV dose of ondansetron administered 15 to 30 minutes before the end of surgery decreases the incidence of PONV by 50% in low-risk patients and approximately 25% in high-risk patients.10,13 However, because of the reduced efficacy of ondansetron in high-risk patients, most will require an additional antiemetic that antagonizes a different emetogenic neurotransmitter to obtain adequate prophylaxis or to treat breakthrough PONV.14,15

Using a combination of antiemetic agents is termed multimodal antiemetic therapy. Although more effective, multimodal antiemetic therapy may increase the incidence of adverse effects such as prolonged emergence from general anesthesia, delayed hospital discharge, and decreased patient satisfaction.11,15-17 Many anesthesia providers elect to administer a single agent with a low adverse effect profile like ondansetron and reserve the use of an additional agent for the treatment of breakthrough
PONV. However, current pharmacologic alternatives for an additional antiemetic agent such as anticholinergics, antihistamines, phenothiazines, butyrophenones, and benzamides are not without potential adverse effects and/or contraindications. Therefore, anesthesia providers continue to search for alternative antiemetic agents with few to no adverse effects that can be used in combination with ondansetron to treat severe PONV.

Recent investigations suggest that the aromatic inhalation of 70% isopropyl alcohol (IPA) may be an ideal multimodal antiemetic agent because it has no adverse effects when used in isolation or in combination with other antiemetic medications. In addition, IPA inhalation significantly reduces the incidence and severity of PONV among patients classified as high risk and low risk and is easily administered in various perioperative settings. For example, Winston et al and Cotton et al each determined that IPA vapors inhaled via a folded alcohol pad achieved a significantly faster 50% reduction in postoperative verbal numeric rating scale scores (VNRS) for nausea compared with IV ondansetron when administered in the postanesthesia care unit (Winston: 6 min vs 27 min, \(P = .022\); Cotton: 15 min vs 34 min, \(P = .001\)). Also, Wang et al administered IPA vapors to children who experienced nausea in the postoperative period and found a significant reduction in nausea scores compared with saline. Despite its proven antiemetic qualities, the mechanism of action for inhaled IPA vapors within the CTZ remains unclear because it has not been studied. Winston and colleagues suggested that IPA may interact with multiple receptors within the CTZ and therefore, may be useful in a multimodal approach to treat PONV.

Numerous studies have evaluated the effectiveness of IPA to treat acute nausea and vomiting in the postoperative period but only 1 published investigation examined IPA as a prophylactic agent administered before the onset of nausea. Teran and Hawkins randomly assigned 57 women who underwent an elective laparoscopic surgical procedure into 3 groups: (1) prophylactic inhalation of 70% IPA vapors following extubation, (2) prophylactic IV granisetron, 0.1 mg, 15 to 30 minutes before extubation, and (3) no prophylactic treatment (control group). They found no statistical difference among the groups in time to initial onset of nausea and number of emetic events; however, the time to initial onset of PONV as measured from inhalation of IPA vapors was 120 minutes, suggesting approximately a 2-hour period of prophylaxis. However, there were limitations to this study. The authors did not reach their required sample size of 111 patients and their patients received IPA after exposure to emetogenic volatile anesthetics. Therefore, the purpose of the present study was to determine if combining the prophylactic inhalation of IPA vapors with IV ondansetron is more effective than IV ondansetron alone in the prevention of PONV in high-risk patients.

**Materials and Methods**

An institutional review board approved this prospective, randomized study. A convenience sample of patients classified as ASA physical status 1 to 3, possessing 3 or more individual risk factors for PONV were approached for possible inclusion. For the purposes of this study, the investigators considered any patient possessing 3 or more risk factors to be classified as high risk for PONV. Assessed risk factors included female gender, nonsmoker, history of PONV or motion sickness, general anesthesia and laparoscopic and gynecological surgical procedures.

Following written informed consent in the preoperative holding area after inclusion criteria were met, investigators collected demographic data including age, height, weight, gender, race, surgical procedure, and date of last menstrual period if applicable. All patients received instructions on treatments, study requirements, and the home data collection tool. In addition, the investigators instructed each patient on the use of the 0 to 10 VNRS. A baseline 0 to 10 VNRS was obtained, in which a score of 0 indicated “no nausea” and a score of 10 indicated the “worst imaginable nausea.” An emetic event was defined as any episode of postoperative nausea. Nausea was defined as a feeling of sickness with an inclination to vomit. Before transport to the operating room, preoperative midazolam (up to 5 mg) and/or fentanyl (up to 250 µg) for anxiolysis were administered at the discretion of the anesthesia provider.

On arrival to the operating room, the anesthesia provider applied standard monitoring devices including noninvasive blood pressure, electrocardiogram, pulse oximetry, and capnometry. Investigators used a computer-generated random numbers process to previously assign all patients to either the control group or experimental group. Those assigned to the experimental group inhaled IPA vapors from a commercially available 70% IPA pad (Webcol, Kendall Healthcare, Mansfield, Massachusetts) immediately before preoxygenation. The anesthesia provider removed the IPA pad from the package and held it approximately 0.5 inches from the nares and instructed the patient to take 3 deep nasal inhalations of the IPA vapors. Induction of general anesthesia was performed using 1.5 to 2 mg/kg of propofol, 0.5 to 1 mg/kg of lidocaine, up to 250 µg of fentanyl, and a neuromuscular blocking agent of the anesthesia provider’s choice. Maintenance of anesthesia was performed using sevoflurane, desflurane, or isoflurane with oxygen-enriched air. Nitrous oxide was not used as part of the anesthetic of any patients. Intraoperative analgesics were administered at the anesthesia provider’s discretion, and all perioperative opioids were converted to morphine equivalents for data analysis. A 4-mg IV dose of ondansetron was administered 15 to 30 minutes before emergence in both groups. All preoperative and intraoperative medications and doses were recorded.
A nausea VNRS score was obtained for all patients on arrival to the postanesthesia care unit (PACU) and again on arrival to the same-day surgical unit (SDSU). VNRS scores were also obtained at the onset of any episode of nausea. Subsequent VNRS scores were obtained at 15 and 30 minutes following PONV treatment, which included 12.5 mg to 25 mg of IV promethazine every 15 minutes up to a maximum dose of 50 mg, or 10 mg of IV metoclopramide, every 5 minutes up to 20 mg. All treatments and subsequent VNRS scores were recorded. Additional data collected included total PACU and SDSU times, incidence of pain, 0 to 10 VNRS pain score, type of analgesic, and dose administered. Upon meeting PACU and SDSU discharge criteria, staff recorded a final nausea VNRS score. SDSU nurses provided homebound patients with a home data collection tool and completion instructions.

Patients recorded home arrival time, nausea VNRS score on arrival to home, and any nausea or emetic events with accompanying VNRS scores and treatments. Patients also recorded their composite 24-hour nausea VNRS score and rated their satisfaction with nausea control using the following Likert scale: 1, totally dissatisfied; 2, dissatisfied; 3, somewhat satisfied; 4, satisfied; and 5, totally satisfied with nausea control. Investigators collected all home data approximately 24 hours following discharge via a telephone interview.

A power analysis was conducted based on a previous study and unpublished data from the authors that indicated the mean (SD) time to first nausea event would be 59.5 (60.2) minutes in the ondansetron group compared with 119.38 (114.38) minutes in the IPA/ondansetron group. Using an α of .05 and a β of .20 (80% power) we determined that approximately 35 patients per group would be required to achieve significance. Factoring in a 15% attrition rate the sample size was increased to 80 patients (40/group).

Statistical analysis was performed using SPSS software version 15.0. (SPSS Inc, Chicago, Illinois). Data analysis was accomplished using descriptive and inferential statistics. Data were analyzed using a Student’s t test for parametric data and a Mann-Whitney U test for nonparametric data. Incidental data were analyzed using a χ2 test and correlational statistics. A P value of .05 or less was considered significant.

### Results
A total of 80 patients were enrolled, but 4 patients were excluded from data analysis because of protocol violations (n = 3) and loss to follow-up (n = 1) leaving 76 patients (38 in each group) included in the final analysis.

There were no significant differences between the groups regarding demographic variables, anesthesia times, surgical times, risk factors for PONV, type of surgery, or type of volatile anesthetic (Tables 1 and 2). The majority of surgical procedures were gynecological (n = 63), thus,
there were significantly more women (n = 73) than men (n = 3) overall; however, patient gender and surgical procedure type were evenly dispersed and no significant difference was found between the groups. Lastly, there were no differences in the amount of opioid administration during the perioperative period between groups (See Table 2).

The overall incidence of postoperative nausea was similar between groups, with 47% in the IPA/ondansetron group compared with 32% in the ondansetron group (Table 3). The location of the patients during the initial onset of nausea was similar between groups, and there was no difference in the time to first nausea event when measured from induction of general anesthesia (See Table 3). Although no significant difference in the nausea VNRS score was noted between groups, the mean VNRS score on initial nausea event was lower for the IPA/ondansetron group in each setting (Figure). The duration of PACU and SDSU stays was similar between groups. There was no difference in the mean 24-hour composite nausea VNRS score between groups (See Table 3). Satisfaction with nausea control was similar between groups (See Table 3). Approximately 95% of patients in both groups reported a score of either 4 (satisfied) or 5 (very satisfied) with the level of nausea control for the respective treatment regimens.

Discussion
The prophylactic inhalation of IPA vapors did not enhance the antiemetic effect of ondansetron administered to patients classified as high risk for PONV. The authors found no significant difference between groups with respect to incidence and severity of PONV, time to initial nausea event, 24-hour composite nausea score, and patient satisfaction with nausea control. One potential reason for IPA failing to reduce PONV in this study was the possible short duration of action of 70% IPA vapors. Wang et al22 described a limited duration of IPA when used in the acute treatment of postoperative nausea in children. Although IPA quickly relieved the symptoms of PONV, subsequent redosing was required due to an estimated duration of 20 to 60 minutes.22 However, a more recent investigation by Teran and Hawkins24 found prophylactic IPA to have a duration of approximately 2 hours. This 2-hour interval was measured from IPA inhalation, which was performed on arrival to the PACU, to the first emetic event. The mean length of anesthesia time in this investigation, which was measured from induction to emergence, was around 50 minutes. Therefore, the proposed hypothesis was that prophylactic IPA administered with ondansetron for surgical procedures lasting less than an hour would show an enhanced antiemetic effect in the immediate postoperative period compared with ondansetron alone. However, this was not observed. The authors propose that the IPA vapors administered before induction had a limited duration of action, which did not exceed the

Table 3. Nausea Events Data, VNRS scores, and Satisfaction Scores
Abbreviations: PACU indicates postanesthesia care unit; SDSU, same-day surgical unit; VNRS, verbal numeric rating scale; IPA, isopropyl alcohol; OND, ondansetron.

<table>
<thead>
<tr>
<th>IPA/OND (n = 38)</th>
<th>OND (n = 38)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea events, no. (%)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACU 7 (39)</td>
<td>3 (25)</td>
<td>.175</td>
</tr>
<tr>
<td>SDSU 6 (33)</td>
<td>3 (25)</td>
<td>.287</td>
</tr>
<tr>
<td>Home 5 (28)</td>
<td>6 (50)</td>
<td>.744</td>
</tr>
<tr>
<td>Time to first nausea mean (SD), minb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACU 155 (82)</td>
<td>263 (198)</td>
<td>.098</td>
</tr>
<tr>
<td>SDSU 169 (59)</td>
<td>153 (68)</td>
<td>.731</td>
</tr>
<tr>
<td>Home 253 (21)</td>
<td>403 (189)</td>
<td>.114</td>
</tr>
<tr>
<td>24-hour Composite nausea VNRS score, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACU 0.5 (1)</td>
<td>0.6 (1.4)</td>
<td>.582</td>
</tr>
<tr>
<td>SDSU 169 (59)</td>
<td>153 (68)</td>
<td>.731</td>
</tr>
<tr>
<td>Home 253 (21)</td>
<td>403 (189)</td>
<td>.114</td>
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<tr>
<td>Satisfaction score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Somewhat satisfied</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4 Satisfied</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>5 Very satisfied</td>
<td>31</td>
<td>31</td>
</tr>
</tbody>
</table>

Figure. Mean Verbal Numeric Rating Score on Initial Onset of Postoperative Nausea and Vomiting Per Setting
Abbreviations: PACU indicates postanesthesia care unit; SDSU, same-day surgical unit; VNRS, verbal numeric rating scale (0, no nausea to 10, worst imaginable nausea) with standard deviation; IPA, isopropyl alcohol.
length of general anesthesia and resulted in no differences observed between the groups.

In addition to a reduced duration of action, IPA may not be a multimodal complement to ondansetron. It is not known which receptor(s) within the CTZ are affected by IPA vapors. Conceivably, IPA may block the same receptors as ondansetron. Kovac et al\textsuperscript{14} demonstrated that a rescue dose of ondansetron following a 4-mg prophylactic dose of ondansetron offered no additional antiemetic effect. Kovac further suggested that the 5-HT\textsubscript{3} receptors were already occupied by the initial dose of ondansetron, thus preventing any enhanced antiemetic effect from subsequent doses. Similarly, if IPA vapors exert their action on the 5-HT\textsubscript{3} receptor, it is possible that a similar maximum antiemetic effect occurred with the combination of IPA and ondansetron.

The incidence of PONV among patients with 3, 4, and 5 risk factors is estimated at 54\%, 74\%, and 87\% respectively.\textsuperscript{6} The overall mean number of risk factors among the current study patient population was 4; therefore, the anticipated nausea rate was expected to be about 74\%. The overall rate of nausea was found to be approximately 39\%. This decline correlates with a previous study that demonstrated a 25\% reduction of nausea in high-risk patients who received prophylactic ondansetron.\textsuperscript{13} In addition to each patient receiving prophylactic ondansetron in the present study, several additional factors may have led to a reduced nausea rate. The use of a propofol induction for short cases, limited exposure to volatile anesthetics and opioids, omission of nitrous oxide, and inclusion of procedures that resulted in limited stimulation of peripheral emetogenic receptors may have contributed to a reduced incidence of nausea in the present study patient population.\textsuperscript{6,8,25-27}

There were some limitations to this study. The patient and anesthesia provider were not blind to the administration of IPA vapors. The PACU and SDSU staffs performing data collection, however, were blind to the treatment regimen. We were unable to blind the study because of the requirement of the provider to open the alcohol preparation pad packaging before administration and the distinct isopropyl alcohol odor exposed to the patient via inhalation. An additional limitation was our inclusion criteria of scheduled surgical procedures less than 60 minutes long. This limited patient selection and resulted in a greater inclusion of women undergoing gynecological procedures, thus reducing the application of the results to a more diverse surgical population. Despite these limitations, there was no significant difference found between groups.

Prophylactic inhalation of IPA vapors in combination with IV ondansetron was not more efficacious than ondansetron alone in the prevention of PONV in a high-risk population. The authors recommend that a future investigation evaluating prophylactic IPA administration not be limited to high-risk patients but also include or be limited to a low-risk population to allow researchers to evaluate 3 groups: an IPA group, an ondansetron group, and a control group that received no treatment. This proposed study design may result in a more accurate comparison of prophylactic IPA vapors alone vs prophylactic ondansetron in the prevention of PONV.

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