

THE EFFECTIVENESS OF INHALATION ISOPROPYL ALCOHOL VS GRANISETRON FOR THE PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING

MAJ Lara Teran, CRNA, MSN, ANC, USA
LTC John K. Hawkins, CRNA, PhD, ANC, USA
Ft Bragg, North Carolina

We evaluated preemptive treatment for postoperative nausea and vomiting (PONV) with intravenous (IV) granisetron, 0.1 mg, intraoperatively as compared with the use of 70% inhalation isopropyl alcohol and a control group for the prevention of PONV.

We randomly assigned 57 women, 18 to 50 years old, undergoing laparoscopic procedures to 1 of 3 groups: (1) inhalation of 70% isopropyl alcohol, (2) 0.1 mg granisetron IV, and (3) no prophylactic treatment control. Participants were asked to rate their nausea and vomiting preoperatively, on arrival to postanesthesia care unit (PACU), at discharge from PACU, 6 hours after extubation, and 24 hours after extubation and any occurrence of nausea and vomiting

using the numeric rating scale (NRS), 0 to 10.

Group 1 experienced more PONV episodes than groups 2 and 3 during the 6- to 24-hour postsurgical timeframe (P = .02). There were no significant differences among the 3 groups in demographics, first episode of PONV, total number of episodes in 24 hours, NRS rating at rescue, and anesthetic duration. PONV and menstrual cycle phase had no positive correlation (P > .05). History of smoking, PONV, and motion sickness had no significant difference against any measure of PONV (P > .05).

Key words: Granisetron, postoperative nausea and vomiting, inhalation isopropyl alcohol.

Postoperative nausea and vomiting (PONV) has been reported to affect between 20% and 30% of people who receive general anesthesia.¹ It is an adverse event that has a negative impact on patient satisfaction.

Research has shown that many risk factors contribute to the incidence of PONV. Gender appears to be the biggest predictor of PONV, with females at higher risk. When all types of surgery are examined, the average occurrence of PONV for women and men is 30%. The female population can average an occurrence rate up to 45% after gynecological surgery alone.² Other risk factors include age, smoking status, menstruation, anesthetics used, opioids, and surgery duration and type.³ Patients younger than 20 years have an increased incidence compared with older adult patients.⁴ A cigarette smoker's risk is decreased by 34% compared with the risk for nonsmokers due to induced hydrocarbons in the liver.⁵ Women who are menstruating at the time of surgery have a 4-fold increase in the likelihood of vomiting compared with nonmenstruating women.⁶

Many anesthetic agents can stimulate nausea and vomiting. Historically, nitrous oxide use in conjunction with volatile anesthetics has been implicated. However, recent studies have revealed that the causative agents are volatile anesthetics and not nec-

essarily nitrous oxide.² The effect of nitrous oxide in provoking PONV appears to be overestimated. Some literature suggests that nitrous oxide is not one of the main causative agents of PONV.² There are several other agents used during anesthesia that are thought to cause PONV such as opioids, etomidate, ketamine, and reversal agents such as neostigmine. An additional correlation in developing nausea is the type of surgical procedure, with orthopedic, laparoscopic, and gynecologic procedures having the highest frequency. Patients undergoing ear, nose, and throat surgery, dental surgery, or plastic surgery are also at high risk. Furthermore, there is a direct correlation with surgical time; for every 30-minute increase in surgery time, the propensity for nausea increases by 59%.⁵

There are 3 major pathophysiologic pathways for triggering PONV: the chemoreceptor trigger zone (CTZ), vestibulocochlear pathway, and gastrointestinal pathway. A combination of these pathways can cause nausea to further progress to vomiting.⁷ The mechanism for PONV is complex due to a wide range of stimuli that contribute to the emetic response. Most anesthetic agents stimulate the vomiting center by traveling through the CTZ. Moreover, pain and other sensory inputs directly stimulate the vestibular apparatus.⁸ High-dose opioids increase the incidence of PONV by direct effect on CTZ in the area postrema.

Alfentanil, sufentanil, fentanyl, and morphine have been shown to have near equal stimulation of the CTZ and vomiting centers in the brain. However, morphine at doses of 5 mg/kg completely blocks emesis.² Etoomidate and ketamine, by direct action on the CTZ, have a higher incidence of PONV when compared with thiopental or propofol. Propofol, in addition to being a sedative-hypnotic, has also been shown to have antiemetic qualities.⁶ Another mechanism by which PONV develops is through the reversal of nondepolarizing neuromuscular blockade by anticholinesterases. The anticholinesterase, neostigmine, causes an increase in the amount of available acetylcholine within the gut and emetic centers of the brain causing nausea. Therefore, doses of neostigmine greater than 2.5 mg predispose the patient to nausea.⁹

Many medications and modalities have been implemented to treat and prevent PONV, and the medications have different mechanisms of action. A medication efficacious for one patient may not be for another, depending on the predisposing and causative factors. Medications commonly used to treat PONV include droperidol (Inapsine), dexamethasone (Decadron), promethazine (Phenergan), ondansetron (Zofran), and granisetron (Kytril). Several homeopathic treatments, such as the inhalation of 70% isopropyl alcohol, ingestion of ginger, inhalation of peppermint oil, and acupuncture, have been studied for the prevention or treatment of PONV. Some of these treatments have been used for centuries (acupuncture and ginger), and more recent discoveries such as the inhalation of isopropyl alcohol have shown promise.¹⁰⁻¹²

Serotonin receptor antagonists such as ondansetron (Zofran) and granisetron (Kytril) have been shown to be effective at treating and preventing PONV.⁸ These medications inhibit the serotonin (5HT₃) receptor in the gastrointestinal tract and in the CTZ.⁹ The review of literature revealed many studies on granisetron comparing varying doses and dosing times.¹³⁻¹⁶ The most commonly studied dose of granisetron for treating symptoms of PONV is 40 µg/kg by the intravenous (IV) route.¹³ However, the lowest effective dose of granisetron for treating symptoms was reported by Wilson et al¹⁴ as 1 mg. In contrast, a study by D'Angelo et al¹⁵ concluded that 0.1 mg given as prophylaxis before emergence from anesthesia was effective in preventing PONV.

Studies involving the inhalation of 70% isopropyl alcohol have shown promising results.^{12,17} The mechanism of alcohol in preventing PONV is not understood, but it appears to interfere with or influence neurotransmitters at the CTZ.¹² Merritt et al¹⁷ suggested

that inhalation of 70% isopropyl alcohol was effective for rescue treatment of PONV. Furthermore, Winston et al¹² compared the inhalation of 70% isopropyl alcohol with use of ondansetron for the treatment of postoperative nausea and found that the inhalation of 70% isopropyl alcohol had a significantly faster onset of action compared with ondansetron. However, the isopropyl alcohol group reported more episodes of nausea at home during the 24 hours after discharge than did the ondansetron group.¹²

The aim of this study was to focus on quality preemptive treatments to reduce the risk of PONV in women undergoing laparoscopic surgical procedures under general anesthesia. The goal was to compare the effectiveness of granisetron, 0.1 mg, IV intraoperatively with the use of inhalation of 70% isopropyl alcohol as a prophylactic treatment for PONV and with a control group. At present, no studies have been found comparing granisetron, 0.1 mg, IV with inhalation of 70% isopropyl alcohol in preventing PONV or the preemptive use of inhalation of 70% isopropyl alcohol to prevent the incidence of PONV.

Methods

A randomized, prospective experimental design was used for this study. The protocol was approved by the Institutional Review Board/Human Use Committee at Womack Army Medical Center, Ft Bragg, North Carolina, and the University of Texas Health Science Center, Houston. The sample consisted of 57 women, ASA physical status category 1 or 2, between 18 and 50 years of age scheduled for an elective laparoscopic surgical procedure. Exclusion criteria consisted of the following: (1) nausea within 24 hours before surgery that required an antiemetic; (2) allergy to isopropyl alcohol, 5-HT₃ antagonists, opioids, or promethazine; (3) laparoscopic procedure that progressed to an open procedure; (4) neuraxial blockade; (5) decreased ability to breathe through the nose; (6) history of alcoholism or disulfiram use; (7) pregnancy; (8) natural or surgical menopause; and (9) emergency procedures. Participants were randomly assigned using a table of random numbers to 1 of 3 groups: (1) prophylactic inhalation of 70% isopropyl alcohol, (2) prophylactic 0.1 mg of IV granisetron, and (3) no prophylactic treatment (control group).

Preoperatively, demographic data were obtained consisting of age, last menstrual period date, height, weight, procedure type, and physical status category. History of smoking, motion sickness, and PONV was also recorded. Participants were asked to rate any preoperative nausea and vomiting using the numeric rat-

ing scale (NRS) with 0 as no nausea or vomiting and 10 as the worst nausea or vomiting ever experienced. Participants were also instructed that the numeric rating scale would be used in the postanesthesia care unit (PACU) and at home to rate nausea and vomiting for the first 24 hours postoperatively.

Once participants agreed to be in the study, IV access was obtained and midazolam was given for anxiolysis. All participants received a general anesthetic with endotracheal intubation. The induction sequence consisted of fentanyl titrated to desired effect; propofol, with lidocaine or following a lidocaine bolus; and a muscle relaxant of the provider's choice to facilitate intubation. Anesthesia was maintained with sevoflurane, fentanyl, and muscle relaxant if indicated. Fractions of inspired oxygen or combination of air-oxygen and end-tidal sevoflurane flow rates were at the discretion of the anesthesia provider. Nitrous oxide was prohibited. Neostigmine and glycopyrrolate were used as needed for reversal of non-depolarizing neuromuscular blocking agents. Doses for all medications were recorded for data analysis. All participants received an oral gastric tube after intubation to evacuate stomach contents.

After extubation and the ability to follow commands was established, participants assigned to group 1 were instructed to take 3 deep breaths of a 70% isopropyl alcohol swab. Group 2 participants received 0.1 mg of granisetron IV approximately 15 to 30 minutes before emergence and extubation. Group 3 received neither treatment.

After extubation, participants were transferred to the PACU for recovery. On arrival, nausea was assessed using the NRS by PACU nursing staff and assessed again at discharge from the PACU. Participants who complained of nausea during the PACU stay were asked to rate the level of nausea on the NRS and then were treated if needed by PACU nursing staff. *Nausea* was defined as the feeling of wanting to expel stomach contents and *vomiting* as expelling stomach contents or dry heaving. Each complaint of nausea or vomiting must have been separated by at least 1 minute to be considered a different event. The PACU nurses recorded type, time, and dose of opioids administered in the PACU to help us determine a cause-and-effect relationship with complaints of nausea and/or vomiting. If at any time participants required or requested treatment of nausea or vomiting, promethazine, 12.5 mg, was given intravenously. The dose of promethazine was repeated 1 time for total dose of 25 mg, if needed. Orders for pain management were at the discretion of the anesthesia

provider. Anesthesia providers and PACU nurses were briefed numerous times on the structure of the study, requirements, and data collection tools. The PACU nurses were blinded to subject treatment group.

Preoperatively, participants were instructed on the use of a take-home data collection tool. Participants were asked to indicate nausea on the NRS at the 6- and 24-hour marks postoperatively and any time in between 6 and 24 hours on the take-home tool. The appropriate times were written on the take-home tool as a reminder for participants. Investigators also asked participants to record the name and dose of pain medication prescribed by the surgeon, the name and dose of nausea treatment if used, and the time of first oral intake after leaving the hospital. Investigators called the subjects 24 hours after surgery to retrieve the recorded information.

Results

Based on G-power analysis, 111 subjects were required for a power of 0.8 and an effect size of 0.3. A *P* value of .05 or less was considered statistically significant. The total number of participants enrolled was 57 (group 1, 22; group 2, 16; and group 3, 19). Statistical analysis was accomplished using a 1-way analysis of variance and Pearson *r* correlation.

There were no significant differences among the 3 groups regarding age, height, weight, duration of anesthesia, neostigmine dose, history of smoking, PONV or motion sickness, menstrual cycle phase, or surgical procedure (Table 1). Types of procedures performed included laparoscopic cholecystectomy, laparoscopic bilateral tubal ligation, diagnostic laparoscopy, and 1 laparoscopic Nissen.

Of the 57 study participants, 47 complained of PONV at least once during the 0- to 24-hour timeframe (group 1, 20; group 2, 13; group 3, 14). Rescue treatment with promethazine was required by 13 subjects in group 1, 10 subjects in group 2, and all 14 in group 3. There were no significant differences among the 3 groups with regard to minutes to first episode of PONV, NRS at rescue treatment, number of episodes of PONV from 0 to 6 hours postoperatively, and total number of PONV episodes in 24 hours. However, there was a significant difference ($F = 4.28, P = .02$) such that group 1 experienced more PONV episodes than group 2 or group 3 during the 6- to 24-hour postsurgical timeframe (Table 2).

We did not find a correlation between patients with a history of motion sickness, PONV, menstrual cycle phase, cigarette smoking, or administration of an anticholinesterase ($P > .05$; data not shown).

Table 1. Demographic and variable data of postoperative nausea and vomiting patients

Demographic data				
Ordinal data analyzed by MANOVA				
Variable	Group	Mean	SE	P
Age	Granisetron	31.18	1.83	.83
	Alcohol	32.18	1.56	
	Control	32.10	1.68	
Height	Granisetron	2.67	0.06	.06
	Alcohol	2.69	0.05	
	Control	2.68	0.06	
Weight	Granisetron	68.93	3.46	.64
	Alcohol	71.90	2.95	
	Control	71.26	3.17	
Duration of anesthesia	Granisetron	82.25	7.80	.44
	Alcohol	71.86	6.65	
	Control	61.78	7.15	
Neostigmine dose	Granisetron	2.46	0.42	.32
	Alcohol	2.02	0.36	
	Control	1.55	0.39	
Categorical data analyzed by χ^2				
Variable				P
Laparoscopic procedure				.23
History of smoking				.38
History of PONV				.27
History of motion sickness				.16
Menstrual cycle phase				.17

There were no significant differences among the 3 groups age, height, weight, duration of anesthesia, neostigmine dose, surgical procedure, history of smoking, postoperative nausea and vomiting (PONV) or motion sickness, or menstrual cycle phase.

Discussion

PONV is a frequent, unpleasant event encountered after surgery for many patients. The incidence of PONV is higher in nonsmoking females with a history of PONV or motion sickness.⁵ The avoidance of this unpleasant event is a greater concern for patients than the avoidance of postoperative pain.³ This study was designed to analyze the incidence of PONV in a fertile female patient population undergoing laparoscopic surgical procedures. The goal was to compare the effectiveness of granisetron, 0.1 mg, IV intraoperatively with the inhalation of 70% isopropyl alcohol as a prophylactic treatment for PONV vs a control group. The attention of this research was on quality preemptive treatments to reduce the risk of PONV in women undergoing laparoscopic surgical procedures under general anesthesia.

The findings from this study suggested that the inhalation of 70% isopropyl alcohol immediately after

extubation was associated with increased episodes of PONV 6 to 24 hours postoperatively ($F = 4.28, P = .02$) compared with no treatment (control) or the IV administration of granisetron, 0.1 mg, 15 to 30 minutes before emergence or extubation. This finding is consistent with the findings of Winston et al,¹² which suggested that inhalation of isopropyl alcohol as a treatment for PONV was associated with increased episodes of nausea at home by participants after discharge compared with use of granisetron. We speculate that this finding may be due to the long duration of action of IV granisetron compared with inhalation of 70% isopropyl alcohol. Whereas granisetron has been reported to inhibit the serotonin receptors for up to 24 hours,¹⁸ exposure to isopropyl alcohol has been reported to have a half-life in women of 22.8 minutes.¹⁹ However, this does not explain why women who inhaled isopropyl alcohol had a higher incidence of PONV 6 to 24 hours postoperatively compared with the control group.

Table 2. Postoperative nausea and vomiting episodes and numeric rating scale

Measure	Group	Mean	SD	F score	P
Minutes to first PONV	Granisetron	92.69	105.73	2.10	.13
	Alcohol	119.38	114.38		
	Control	55.89	57.95		
NRS at rescue	Granisetron	3.88	3.76	2.78	.07
	Alcohol	3.73	3.53		
	Control	6.32	4.18		
No. of episodes of PONV 0-6	Granisetron	1.25	1.18	0.36	.70
	Alcohol	1.41	1.10		
	Control	1.63	1.67		
No. of episodes PONV 6-24 h	Granisetron	.25	.58	4.28*	.02*
	Alcohol	.82	.80		
	Control	.32	.58		
No. of episodes PONV 0-24 h	Granisetron	1.50	1.32	0.81	.45
	Alcohol	2.14	1.32		
	Control	1.95	1.89		

There were no significant differences among the 3 groups with regard to minutes to first episode of postoperative nausea and vomiting (PONV), numeric rating scale (NRS) score at rescue treatment, number of episodes of PONV from 0-6 hours postoperatively, and total number of PONV episodes in 24 hours. However, there was a significant difference such that the group inhaling 70% isopropyl alcohol experienced more PONV episodes than the control or granisetron group during the 6-24 hour postsurgical timeframe.

* Significant difference.

Although our study suggested that there were no significant differences in efficacy among the PONV treatments, suggesting that granisetron may be no more beneficial than no treatment, we speculate that this finding may be a result of inadequate participant recruitment. Our power analysis suggested that 111 participants were required to find a significant difference among the groups using a power of 0.8 and an effect size of 0.3. However, we were only able to recruit 57 participants. Clearly, insufficient recruitment of participants may produce results that are less accurate representations of the larger population and lead to type 1 errors. However a second explanation may be that granisetron, at the dose administered in our study, may not effectively prevent PONV.

Low-dose granisetron, such as the 0.1-mg dose administered in our study, has been suggested to be an effective treatment for PONV. For example, D'Angelo et al,¹⁵ compared the IV administration of 0.1, 0.2, and 0.3 mg of granisetron with placebo in 121 women undergoing abdominal hysterectomy under general anesthesia and found that granisetron was effective in preventing PONV at all 3 doses. Furthermore, 0.1 mg of granisetron was as effective as the other 2 doses with a 95% confidence interval.¹⁵

On the other hand, Mikawa et al¹⁶ randomly assigned 200 women undergoing gynecologic surgery

to receive 2, 5, 10, or 20 µg/kg of IV granisetron or placebo at the time of induction. Participants given doses of 5, 10, or 20 µg/kg experienced fewer emetic episodes than those who were given placebo or 2 µg/kg of granisetron. Moreover, the groups treated with 5 µg/kg or more of granisetron had more PONV-free events 24 hours after surgery compared with the placebo and granisetron 2 µg/kg groups and required less rescue medication compared with patients in the placebo group. From these findings, the authors suggested that the optimal dose of granisetron for PONV prophylaxis was 5 µg/kg.¹⁶

Wilson et al¹⁴ also reported that 0.1 mg of granisetron was not any more efficacious than placebo in preventing PONV. In this study, doses of 0.1, 1, and 3 mg of granisetron given 5 minutes before induction were compared with placebo for the prevention of PONV in 527 women undergoing vaginal hysterectomy or open abdominal surgery. The findings from this study suggested that the administration of 1 and 3 mg of granisetron may be effective in preventing PONV compared with placebo, but not a 0.1-mg dose.¹⁴

Finally, findings from our study suggested that there was no positive correlation between menstrual cycle phase or use of anticholinesterase agents and PONV, nor was there a negative correlation between cigarette smoking and PONV as the literature sug-

gests.^{5,9,20} We attribute this finding to the small sample of this study.

We did not find 70% isopropyl alcohol efficacious as a preoperative antiemetic, nor was 0.1 mg of granisetron more effective than no treatment. Our recommendations for future studies are 2-fold: (1) repeat this study with an adequate sample size as required by power analysis, and (2) continue research into the efficacy of low-dose granisetron for preemptive PONV treatment.

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AUTHORS

MAJ Lara Teran, CRNA, MSN, ANC, USA, is a nurse anesthetist at 28th Combat Support Hospital, Ft Bragg, North Carolina.

LTC John K. Hawkins, CRNA, PhD, ANC, USA, is a nurse anesthetist at Walter Reed Army Medical Center, Washington, DC.

ACKNOWLEDGMENT

Manuscript content has been reviewed in accordance with DA and OTSG OPSEC policies requiring public affairs review of documents and publication/public disclosure. The manuscript complies with DA/OTSG policies. AR 360-1(Public Affairs) and DOD Dir 5230.0 (Clearance of DOD Information for Public Release).

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