

Aromatherapy Versus Oral Ondansetron for Antiemetic Therapy Among Adult Emergency Department Patients: A Randomized Controlled Trial

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Study Objective: We compare aromatherapy with inhaled isopropyl alcohol versus oral ondansetron for treating nausea among emergency department (ED) patients not requiring immediate intravenous access.

Methods: In a randomized, blinded, placebo-controlled trial, we enrolled a convenience sample of adults presenting to an urban tertiary care ED with chief complaints including nausea or vomiting. We randomized subjects to 1 of 3 arms: inhaled isopropyl alcohol and 4 mg oral ondansetron, inhaled isopropyl alcohol and oral placebo, and inhaled saline solution placebo and 4 mg oral ondansetron. The primary outcome was mean nausea reduction measured by a 0- to 100-mm visual analog scale from enrollment to 30 minutes postintervention. Secondary outcomes included receipt of rescue antiemetic medications and adverse events.

Results: We enrolled 122 subjects, of whom 120 (98.3%) completed the study. Of randomized subjects, 40 received inhaled isopropyl alcohol and oral ondansetron, 41 received inhaled isopropyl alcohol and oral placebo, and 41 received inhaled saline solution placebo and oral ondansetron. The mean decrease in nausea visual analog scale score in each arm was 30 mm (95% confidence interval [CI] 22 to 37 mm), 32 mm (95% CI 25 to 39 mm), and 9 mm (95% CI 5 to 14 mm), respectively. The proportions of subjects who received rescue antiemetic therapy in each arm were 27.5% (95% CI 14.6% to 43.9%), 25.0% (95% CI 12.7% to 41.2%), and 45.0% (95% CI 29.3% to 61.5%), respectively. There were no adverse events.

Conclusion: Among ED patients with acute nausea and not requiring immediate intravenous access, aromatherapy with or without oral ondansetron provides greater nausea relief than oral ondansetron alone. [Ann Emerg Med. 2018;■ :1-10.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Multiple trials report that isopropyl alcohol has efficacy in treating postoperative nausea and vomiting.¹ Numerous animal models have demonstrated the safety of isopropyl alcohol.^{2,3} Human studies are without documented adverse events after isopropyl alcohol inhalation.¹ This substance is widely available in most health care settings in the form of pads used in the routine course of delivering care.

Fewer data exist in regard to the therapeutic efficacy of inhaled isopropyl alcohol in the emergency department (ED) setting. A single randomized controlled trial demonstrated superior nausea relief with inhaled isopropyl alcohol versus inhaled saline solution placebo in ED

patients.⁴ That study assessed outcomes during 10 minutes. It remains unclear whether the symptomatic relief from aromatherapy persists beyond 10 minutes. It is also uncertain whether nasally inhaled isopropyl alcohol provides greater nausea relief compared with other common antiemetic therapies used in the ED setting, such as ondansetron.

Importance

In the United States, chief complaints related to nausea or vomiting account for approximately 4.8 million ED visits each year.⁵ Commonly used antiemetics, including ondansetron, promethazine, and metoclopramide, have proven efficacious in the treatment of specific patient

Editor's Capsule Summary*What is already known on this topic*

Inhaled isopropyl alcohol is antiemetic.

What question this study addressed

How does isopropyl alcohol aromatherapy compare with oral ondansetron?

What this study adds to our knowledge

In this 3-arm double-blind trial of 122 nauseated adults not requiring immediate intravenous access, aromatherapy alone provided relief similar to that of aromatherapy plus oral ondansetron, and both of these arms provided greater relief than oral ondansetron alone.

How this is relevant to clinical practice

Aromatherapy was a more potent antiemetic than oral ondansetron in this sample of nauseated emergency department adults without intravenous access.

populations (eg, ondansetron for chemotherapy patients). Although the anecdotal experience of many emergency physicians is that these medications effectively treat nausea, randomized trials of undifferentiated ED patients have not demonstrated superior nausea relief with these agents versus placebo.⁶⁻⁸ Identification of an antiemetic whose therapeutic benefit outperforms these commonly used medications could have a material influence on the routine treatment of this symptom frequently encountered in the ED population.

Goals of This Investigation

The goal of this study was to compare nasally inhaled isopropyl alcohol versus oral ondansetron for treating nausea among ED patients.

MATERIALS AND METHODS**Study Design and Setting**

We conducted a single-center, placebo-controlled, blinded, randomized trial of patients presenting to the ED with chief complaints including nausea or vomiting (eg, abdominal pain and nausea). Subjects underwent randomization to 1 of 3 arms: inhaled isopropyl alcohol and 4 mg oral ondansetron, inhaled isopropyl alcohol and oral placebo, and inhaled saline solution placebo and 4 mg oral ondansetron. We included a dual treatment (nonplacebo) arm, given concerns that our

methods to blind subjects to the inhaled intervention may be ineffective. We did not want subjects to reliably predict the identity of the oral intervention to which they underwent allocation on the basis of the scent of the inhaled medication. We did not include a dual placebo arm, given concerns that this would discourage patient participation and that the outcomes for such an arm would not contribute much new information beyond that of the placebo-only arm in a recent trial of inhaled isopropyl alcohol.⁴

The study setting was an urban tertiary care academic hospital. The annual ED census was approximately 84,000 patients. Our institutional review board approved the protocol.

Selection of Participants

Nursing staff identified a convenience sample of potential study subjects presenting to the ED during periods when study investigators were present for enrollment. Nursing staff notified investigators on the arrival of patients with a chief complaint related to nausea or vomiting at ED triage. Investigators then approached these patients to screen for inclusion and exclusion criteria.

Inclusion criteria included adults (≥ 18 years) presenting to the ED with a chief complaint including nausea or vomiting, with self-reported nausea severity of 3 or greater on a verbal numeric response scale (range 0 to 10).⁴ Exclusion criteria included known allergy to isopropyl alcohol or ondansetron; inability to inhale through the nares (eg, rhinitis); recent intake of medications contraindicating alcohol administration, including cefoperazone, disulfiram, or metronidazole; altered mental status precluding signed informed consent; a known history of QT-segment prolongation; clinical suspicion for serotonin syndrome; or treating provider discretion. Our institutional review board further requested that we exclude patients with suspected or known pregnancy on the basis of a potential association between ondansetron use in pregnancy and fetal cardiac abnormalities.⁹ We further excluded patients who had already undergone intravenous catheter placement or received antiemetic pharmacotherapy in ED triage, to include aromatherapy.

Study investigators obtained written informed consent from all subjects. Consent forms identified sodium chloride, ondansetron, and isopropyl alcohol as the substances under investigation. Forms did not specify study hypotheses or designate substances as either experimental treatments or active comparators. All subjects and treating providers were made aware of their right to withdraw from the study at any time. We documented subject study participation in accordance with the Consolidated Standards of Reporting Trials statement (Figure 1).¹⁰

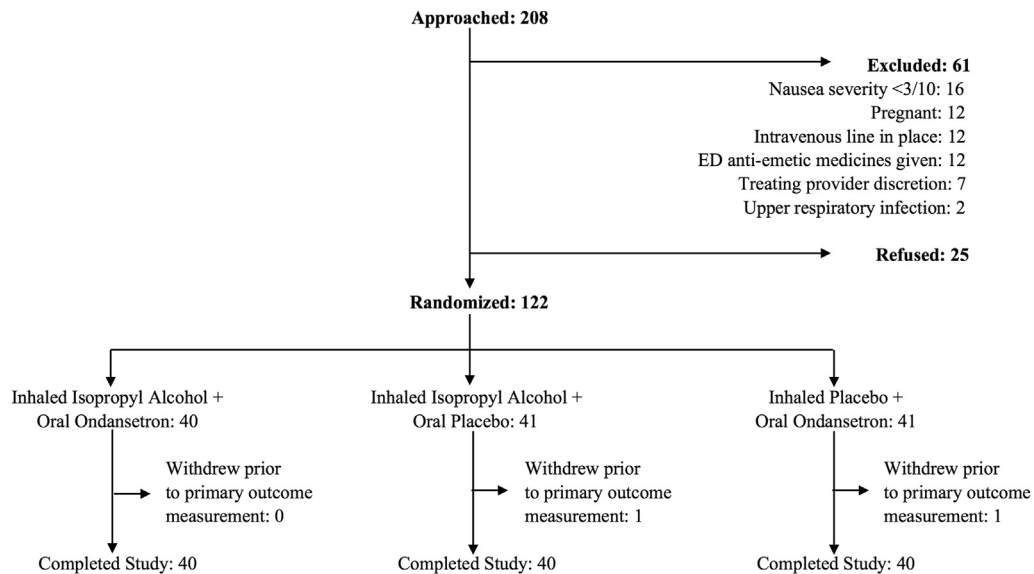


Figure 1. Consolidated Standards of Reporting Trials statement diagram of patient flow.

Interventions

All subjects consumed a solution stored in a 5-mL syringe, which was either ondansetron 4 mg/5 mL (West-Ward Pharmaceutical Corp., Eatontown, NJ) or placebo solution comprising 0.25 mL ORA-Sweet SF (Perrigo, Allegan, MI) mixed in 4.75 mL of sterile water (B. Braun Medical Inc., Bethlehem, PA). Additionally, investigators instructed subjects to inhale from a commercially prepared medical pad saturated with either isopropyl alcohol (Professional Disposables International, Inc., Orangeburg, NY) or normal saline solution (Hygea Holdings Corp., Doral, FL). They specifically advised subjects to take deep nasal inhalations as frequently as required to achieve nausea relief, with the pad held approximately 1 to 2 cm from the nares. Data collection times were 10, 20, 30, and 60 minutes after study medication administration, and then hourly until the subject's provider made a disposition decision. At each data collection period, investigators allowed subjects to take another identical preparation pad for further inhalation.

Our pharmacy blinded the oral medications through production of ondansetron elixir and placebo, which were identical in terms of volume (5 mL) and appearance (clear). Investigators sought to blind the nasally inhaled medications by maintaining the pads in their original commercial packaging, and then obscuring the package labels (commercial packaging was otherwise identical except for the labels) with opaque tape. The tape's adherence to the commercial packaging made it inseparable from the package during opening, thus ensuring blinding both before and after pad use. Subjects opened all medication preparation pads unless unwilling or unable to

do so, in which case investigators opened the pad at arm's length to avoid detecting the pad's scent. Investigators also instructed subjects to avoid behaviors that might indicate pad contents (ie, describing pad scent to either investigators or subsequent providers during the ED visit). We blinded study participants, their providers, and investigators to each subject's respective treatment allocation.

We used a computer-generated randomization sequence to allocate subjects to each of the 3 treatment arms in permuted blocks of 6. After screening, consent, and enrollment, we assigned successive subjects a unique study identification number. Investigators retrieved a study syringe pre-labeled with each subject's study identification number and filled with the oral solution of the subject's allocation arm by a pharmacist not otherwise affiliated with the study. Investigators then retrieved a study packet pre-labeled with each subject's unique identification number and prepackaged with a data collection form, and 10 identical medication preparation pads of the subject's allocation arm for administration. A research assistant not otherwise affiliated with the study prepared all medication pads.

Study participation did not prevent subjects from receiving appropriate routine care as determined by the presenting chief complaint and the treating provider, to include receiving an intravenous catheter after study enrollment. For example, patients with abdominal pain and nausea could receive analgesia according to study protocol. Furthermore, subjects could receive rescue antiemetic therapy at any time, although investigators advised treating providers that subjects received at least one medication known to treat nausea at study start. Investigators prompted

each subject's provider to consider administration of rescue antiemetic therapy of their choice if the subject either vomited or requested additional antiemetic therapy.

Methods of Measurement

Investigators used hard-copy data collection forms to record subjects' baseline characteristics and details in regard to symptoms; specifically, duration (hours) and the presence or absence of any emesis since symptom onset. Subjects annotated baseline nausea and pain scores on the collection forms, using 2 separate 0- to 100-mm visual analog scales (VAS).^{11,12} On these scales, 0 mm represented no nausea or pain, whereas 100 mm represented the worst nausea or pain imaginable.

After collection of baseline data, investigators reassessed each subject's nausea and pain VAS scores at the predefined intervals after study medication administration. They also recorded additional medications administered to each subject (analgesia, rescue antiemetic, etc) and vomiting episodes since the preceding data collection period. We defined discrete vomiting episodes as forceful expulsion of gastric content, with each episode separated by at least 2 minutes, excluding nonproductive retching or drooling.

At the provider's disposition decision, investigators queried subjects about final nausea and pain VAS scores. In addition, we asked subjects to report their satisfaction specifically in regard to the treatment of their nausea by placing a mark on a VAS ranging from 0 mm (completely satisfied) to 100 mm (completely unsatisfied).^{13,14} Investigators recorded the patients' final dispositions and the providers' presumed causes in regard to the most likely underlying reasons for the patients' symptoms. To assess the efficacy of our methods of blinding, subjects, providers, and investigators reported separately whether they believed the inhaled and oral medications administered to each subject represented a "study treatment" or a "placebo." We did not specifically ask participants whether they believed the inhaled medication was isopropyl alcohol or normal saline solution or whether they believed the oral solution was ondansetron or sugar water. Finally, investigators recorded ED length of stay (minutes) for each subject.

Outcome Measures

Our primary outcome was the change in nausea from baseline to 30 minutes postintervention, as delineated on a 0- to 100-mm VAS. Secondary outcomes included change in pain VAS score from baseline to 30 minutes postintervention, nausea scores until ED disposition, pain score at ED disposition, and satisfaction VAS scores. Secondary outcomes also included vomiting during ED stay, receipt of rescue antiemetic medications during ED

stay, admission to the hospital (binary variables), and ED length of stay.

Primary Data Analysis

The analysis of the primary outcome comprised 2 separate comparisons of the nausea VAS score reduction between subjects allocated to 1 of the 2 study arms receiving inhaled isopropyl alcohol versus subjects allocated to the single study arm receiving inhaled normal saline solution placebo. These comparisons, defined a priori, entailed 2-sided testing for superiority. Our sample size estimate assumed $\alpha=.025$, given a Bonferroni correction for 2 separate comparisons, and $\beta=.20$. We powered our study to detect a difference in nausea VAS score reduction of 20 mm, the lower bound of the 95% confidence interval (CI) for minimally clinically significant difference in nausea VAS score reported by Meek et al.¹¹ We anticipated a SD in our primary outcome measure of approximately 29 mm.^{8,15} These inputs yielded a sample size estimate of 40 subjects per arm (120 subjects total). Given concerns for the potential of patients withdrawing before measurement of the primary outcome, we requested approval to recruit up to 60 subjects per arm (180 subjects total).

We double entered all hard-copy data collection forms into a secure Excel database (version 14; Microsoft, Redmond, WA). We then exported all data into SPSS (version 22; IBM, Armonk, NY) for statistical analysis. All analyses were intention to treat. We summarized patient baseline characteristics with descriptive statistics. We compared the primary and all secondary outcomes between the treatment arms through calculation of effect size differences with 95% CIs.

RESULTS

Characteristics of Study Subjects

We screened 208 patients for study inclusion. Of these, 61 subjects did not meet all inclusion and exclusion criteria, and 25 declined to participate. We enrolled and randomized the remaining 122 subjects. Of these subjects, we randomized 40 to receive inhaled isopropyl alcohol and 4 mg oral ondansetron, 41 to receive inhaled isopropyl alcohol and oral placebo, and 41 to receive inhaled saline solution placebo and 4 mg oral ondansetron. Two enrolled subjects withdrew from the study before measurement of the primary outcome, given concerns about inadequate symptom relief if allocated to a study intervention without oral ondansetron. We performed a modified intention-to-treat analysis of the remaining 120 subjects (Figure 1).

Baseline patient characteristics were comparable across the 3 groups, although we observed a trend toward fewer women in the group receiving inhaled isopropyl alcohol

Table 1. Patient baseline characteristics.

Variables	Inhaled Isopropyl Alcohol + Oral Ondansetron (n=40)	Inhaled Isopropyl Alcohol + Oral Placebo (n=40)	Inhaled Placebo + Oral Ondansetron (n=40)
Age, mean (SD), y	30.5 (10.9)	34.2 (15.5)	29.25 (10.6)
Female sex (95% CI), %	50 (33.8–66.2)	35.0 (20.6–51.7)	52.5 (36.1–68.5)
Weight, mean (SD), kg	77.5 (16.9)	78.1 (19.4)	83.7 (18.8)
Symptom duration, median (IQR), h	13.5 (6–48)	24 (8–72)	19 (10–48)
Vomited since symptom onset (95% CI), %	82.5 (67.2–92.7)	73.2 (57.9–84.4)	75.6 (59.7–87.6)
Initial nausea score, mean (SD), VAS	53 (22)	51 (21)	51 (20)
Initial pain score, mean (SD), VAS	37 (31)	39 (28)	44 (29)

IQR, Interquartile range.

and oral placebo (Table 1). According to ED diagnoses, there was a diverse array of presumed causes of nausea and emesis. The most common of these causes included infectious gastroenteritis (55.2%), food poisoning (8.6%), and urinary tract infections, including cystitis and pyelonephritis (5.2%) (Table 2).

Main Results

Initial mean nausea VAS scores were 53 mm in the inhaled isopropyl alcohol and oral ondansetron group, 51 mm in the inhaled isopropyl alcohol and oral placebo group, and 51 mm in the inhaled placebo and oral ondansetron group. In regard to the primary outcome, mean VAS nausea scale reduction at 30 minutes posttreatment in each of these arms was 30 mm (95% CI 22 to 37 mm), 32 mm (95% CI 25 to 39 mm), and 9 mm (95% CI 5 to 14 mm), respectively (Figure 2). The effect size difference in 30-minute VAS nausea reduction among subjects who received inhaled isopropyl alcohol and oral ondansetron versus inhaled placebo and oral ondansetron was 20 mm (95% CI 10 to 30 mm). The effect size difference in 30-minute VAS nausea reduction among subjects who received inhaled isopropyl alcohol and oral placebo versus inhaled placebo and oral ondansetron was 23 mm (95% CI 14 to 31 mm).

Compared with the inhaled placebo group, both inhaled isopropyl alcohol groups generally experienced lower mean nausea VAS scores throughout their ED stay (Figure 3). The groups exposed to isopropyl alcohol also had lower mean nausea VAS scores at the disposition decision and better satisfaction scores (lower scores reflecting more satisfaction). Subjects receiving inhaled isopropyl alcohol and oral placebo had greater pain reduction compared with the inhaled placebo group at 30 minutes. Subjects receiving inhaled isopropyl alcohol and oral ondansetron had lower VAS pain scores compared with the inhaled placebo group at the disposition decision. No subjects received rescue antiemetics before measurement of the primary outcome. There were no differences in the proportions of patients

receiving rescue antiemetics after the primary outcome measurement between the 3 study arms (Table 3).

In regard to the effectiveness of our blinding methodology, the proportions of subjects correctly identifying the inhaled substance to which they underwent allocation as either a study treatment or placebo ranged from 37.5% to 60.0% across the 3 treatment arms. The proportions of subjects correctly identifying the oral substance to which they underwent allocation as study treatment versus placebo ranged from 7.5% to 10.0% (Table 4).

LIMITATIONS

This study had several limitations. First, our study population comprised a relatively healthy subset of patients with nausea and vomiting. We excluded all patients with intravenous catheters in place, removing a significant proportion of patients with nausea and vomiting whose symptoms were likely more severe. We did require that patients express a nausea verbal numeric response scale score greater than or equal to 3 to ensure that subjects had significant symptoms at the time of enrollment. Nevertheless, our results may not be generalizable to more severely nauseated populations.

Table 2. Presumed causes of nausea.*

Diagnostic Category	No. (%)
Infectious gastroenteritis	64 (55.2)
Food poisoning	10 (8.6)
Urinary tract infection	6 (5.2)
Headache	4 (3.4)
Other infective illness	4 (3.4)
Gastroesophageal reflux	4 (3.4)
Constipation	3 (2.6)
Electrolyte abnormalities	3 (2.6)
Appendicitis	2 (1.7)
Gallbladder disease	2 (1.7)
Medication reaction	2 (1.7)
Pelvic inflammatory disease	2 (1.7)
Vertigo	2 (1.7)
Other	8 (6.9)

*Reported for 116 of 122 patients.

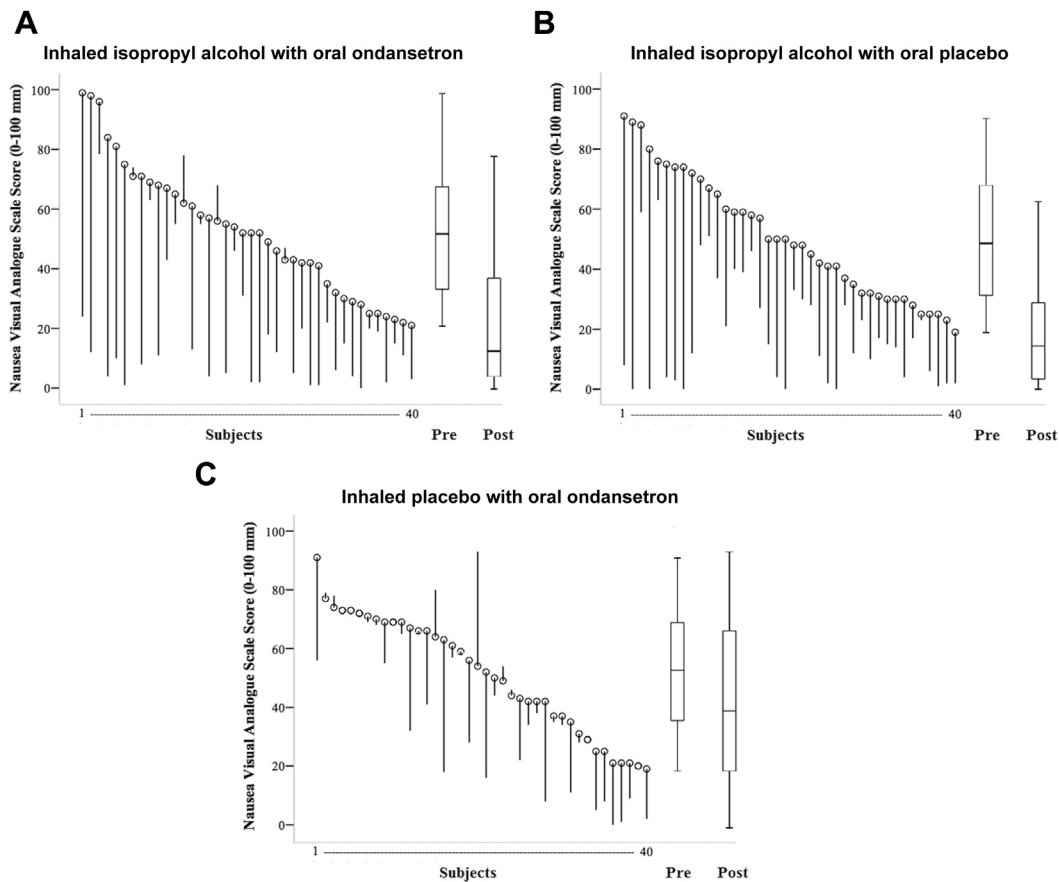


Figure 2. Nausea VAS scores at baseline and 30 minutes postintervention. Each panel represents a separate study arm including subjects allocated to inhaled isopropyl alcohol with oral ondansetron (A), inhaled isopropyl alcohol with oral placebo (B), and inhaled placebo with oral ondansetron (C). The vertical axes represent mean VAS scores (0 to 100 mm). The horizontal axes separate data for individual subjects. Each circle represents the initial VAS score for each patient, and the end of the vertical line represents the VAS at 30 minutes postintervention. The box plots on the figure margins represent summary statistics, with the central lines representing medians, boxes representing interquartile ranges, and outermost plots representing maximum and minimum nausea VAS values for the subjects composing each study arm at baseline and 30 minutes postintervention.

Selection bias was possible, given recruitment of a convenience sample. We attempted to limit selection bias by making study personnel available for patient recruitment during a broad range of times to include nighttime and weekend hours. Furthermore, we emphasized to nursing triage staff to notify study personnel of every patient presenting to the ED with nausea during these periods. Nevertheless, we did not collect data on every patient presenting to our ED with nausea during the study period, making it impossible to quantify the extent to which our efforts controlled for selection bias.

Another limitation relates to the challenges of blinding patients, providers, and investigators to scent. We instituted several measures to ensure effective blinding to include obscuring the pad label, instructing investigators to maintain physical distance (arm's length or more) from opened pads, and instructing patients to not reveal the pad's scent. Also, although we disclosed to patients during

the consent process the substances to which they might undergo allocation, we did not discuss the study hypothesis or otherwise identify which substances we considered to be control versus study treatments. Approximately half of subjects correctly categorized the inhaled substance they received as either study treatment or placebo, suggesting that our blinding efforts did achieve some success.

We used VAS scores to measure nausea and pain reduction and determine overall patient satisfaction. These outcome measures are subjective. Yet we believe these measurements are important patient-centered outcomes with a low likelihood of measurement bias that allow comparisons to other studies that use these same outcome measures.

DISCUSSION

Nausea is a frequent symptom for patients presenting to the ED. Survey data indicate that many patients believe nausea and vomiting cause more suffering than severe pain.¹⁶

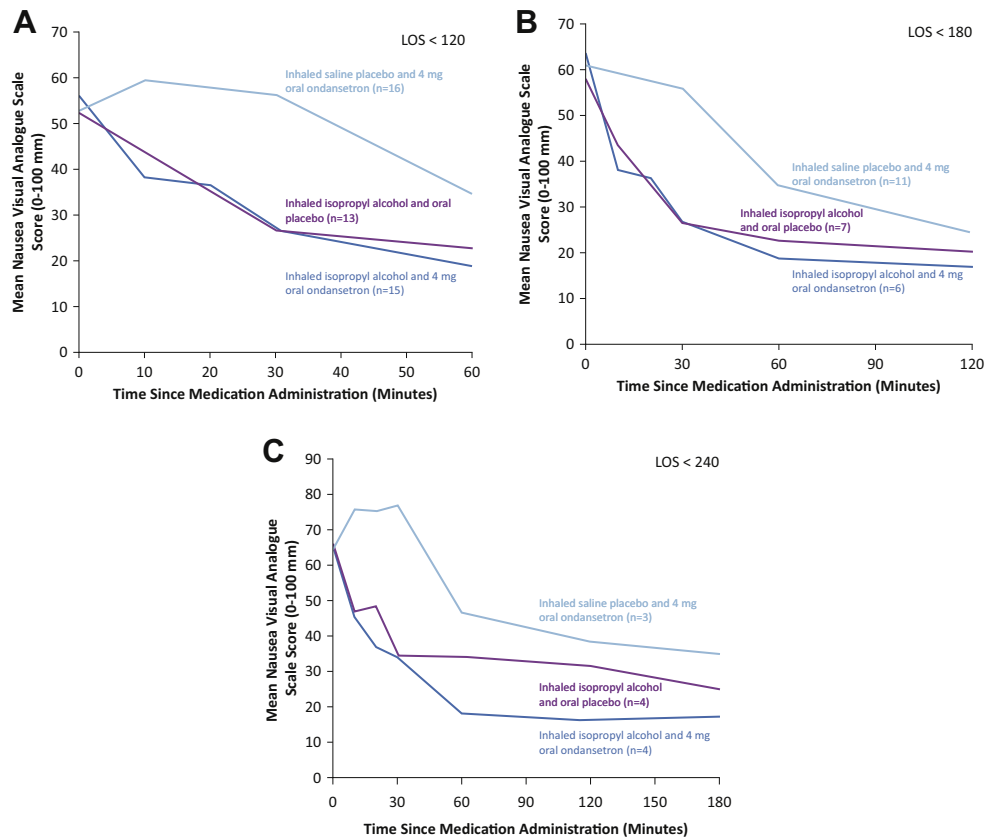


Figure 3. Mean nausea VAS scores from study medication administration until ED disposition decision, stratified by time until ED disposition decision. Each panel presents data for subjects with different times until ED disposition decision, including less than 120 minutes (A), less than 180 minutes (B), and less than 240 minutes (C). The vertical axes represent mean VAS score (0 to 100 mm). The horizontal axes represent time since study treatment administration (minutes). The lines represent mean VAS for the subjects belonging to each study arm at each study interval for subjects allocated to inhaled isopropyl alcohol with oral ondansetron (solid lines), inhaled isopropyl alcohol with oral placebo (bold lines), and inhaled placebo with oral ondansetron (dashed lines). LOS, Length of stay.

Isopropyl alcohol is a simple and inexpensive agent with previously demonstrated efficacy in the treatment of nausea among patients in the postoperative setting.¹ A more recent ED-based study demonstrated superior nausea relief with inhaled isopropyl alcohol versus inhaled placebo.⁴ This trial adds to this literature by demonstrating superior nausea relief among ED patients receiving inhaled isopropyl alcohol with either oral placebo or oral ondansetron compared to inhaled placebo with oral ondansetron.

Our study builds on the previous study showing improved nausea reduction with inhaled isopropyl alcohol versus inhaled placebo⁴ in several important ways. First, our study group that received inhaled placebo and oral ondansetron demonstrated that aromatherapy resulted in superior nausea relief compared with a commonly used antiemetic agent. Second, the present study measured nausea VAS score reduction at 30 minutes after medication administration as the primary outcome versus the 10-minute study period in the previous study. We further

collected nausea measurements through the time of ED disposition decision. Our present study found that subjects who received inhaled isopropyl alcohol had greater nausea relief compared with subjects who received inhaled placebo and oral ondansetron at both 30 minutes and at the time of ED disposition decision. Third, our present study reported additional outcomes of interest to emergency physicians, including receipt of rescue antiemetic therapy and hospital admission, although we did not find that aromatherapy resulted in any benefits as measured by these outcomes.

It is possible that our choice of 30 minutes as the time of primary outcome measurement did not allow adequate time for ondansetron to take full effect. We chose this time to align our study outcome with that used by most other ED studies of nausea therapy.^{6-8,15} We further believed that 30 minutes represents the time after which many emergency physicians would consider an alternative antiemetic medication if the patient continued to have symptoms. That said, we found that the groups exposed to

Table 3. Patient outcomes.

Variables	1. Inhaled Isopropyl Alcohol + Oral Ondansetron (n = 40)	2. Inhaled Isopropyl Alcohol + Oral Placebo (n = 40)	3. Inhaled Placebo + Oral Ondansetron (n = 40)	Pairwise Differences (95% CI)	
				1 vs 2	2 vs 3
VAS nausea score reduction at 30 min, mean (SD)	30 (27)	32 (23)	9 (16)	20 (10 to 30)	23 (14 to 31)
VAS pain score reduction at 30 min, mean (SD)	10 (21)	11 (16)	3 (14)	7 (-1 to 15)	8 (2 to 15)
Final nausea score, mean (SD), VAS*	16 (19)	16 (18)	29 (25)	-13 (-23 to -4)	-13 (-23 to -3)
Final pain score, mean (SD), VAS*	18 (21)	22 (21)	30 (27)	-12 (-23 to -1)	-8 (-19 to 3)
Nausea therapy satisfaction, mean (SD), VAS*†	19 (29)	22 (27)	44 (36)	-25 (-39 to -11)	-22 (-36 to -8)
Vomited during ED stay (95% CI), %	7.5 (1.6–20.4)	0.0 (0–10.4)	7.5 (1.6–20.4)	0.0 (-11.9 to 11.9)	-7.5 (-15.9 to 0.9)
Receipt of rescue antiemetics (95% CI), %	27.5 (14.6–43.9)	25.0 (12.7–41.2)	45.0 (29.3–61.5)	-17.5 (-38.8 to 3.8)	-20.0 (-41.0 to 1.0)
ED length of stay, mean (SD), min	217 (140)	224 (136)	210 (112)	6 (-50 to 63)	14 (-42 to 69)
Admitted (95% CI), %	12.5 (4.2–26.8)	2.5 (0.0–13.2)	0.00 (0–10.4)	12.5 (2.0 to 23.0)	2.5 (-2.5 to 7.5)

*Measured at the time of disposition decision.
†Scale ranges from completely satisfied (0) to completely unsatisfied (100).

isopropyl alcohol generally had lower mean nausea throughout their ED stay and at the time of ED disposition decision, although the differences in nausea scores narrowed as more time elapsed since the study start. This narrowing may reflect the fact that many patients after measurement of the primary outcome received intravenous fluid and additional antiemetic therapy.

These findings are notable, given anesthesia data suggesting that the nausea relief provided by isopropyl alcohol is short lasting.¹⁷⁻¹⁹ Our results do not contradict those of previous studies describing a transient antiemetic effect of isopropyl alcohol because we encouraged patients to continue inhaling from new medications pads at each data collection period if they thought that doing so improved their symptoms. Our protocol did not strictly define dosing frequency or administration of the inhaled medications because our intent was to examine the real-world applicability of this intervention.

Our findings suggest that supplying patients with multiple isopropyl alcohol pads for use at their discretion during the entirety of their visit may result in sustained nausea relief throughout their ED stay. We believe the existing studies of

isopropyl alcohol support an excellent safety profile and that repeated dosing for recurrent symptoms is likely to be safe, with minimal risk of adverse events related to overdose, provided the route of administration is nasal inhalation alone.¹⁻⁴

Aromatherapy may also be particularly useful in triage settings when intravenous access is not immediately necessary. It would also be reasonable to prescribe outpatient aromatherapy treatment with repeated inhalations at approximately 10-minute intervals as needed for nausea relief, although it may be useful to simultaneously prescribe these patients a traditional antiemetic agent for longer-term symptom control.

Emergency physicians commonly use ondansetron to treat ED patients with nausea. This drug has demonstrated efficacy in treating nausea and vomiting among many patients undergoing chemotherapy.²⁰⁻²² Conversely, studies examining ondansetron use among undifferentiated patients in the ED setting have not shown this medication to outperform placebo.⁶⁻⁸ Despite this lack of demonstrated efficacy and known adverse effects such as QT-segment prolongation, many consider ondansetron to

Table 4. Blinding effectiveness.

Survey Responses	Inhaled Isopropyl Alcohol + Oral Ondansetron (n = 40)	Inhaled Isopropyl Alcohol + Oral Placebo (n = 40)	Inhaled Placebo + Oral Ondansetron (n = 40)
Correctly identifies inhaled substance as study treatment versus placebo, No. (%)			
Subject	24 (60.0)	18 (45.0)	15 (37.5)
Provider	13 (32.5)	7 (17.5)	8 (20.0)
Investigator	8 (20.0)	7 (17.5)	7 (17.5)
Correctly identifies oral substance as study treatment versus placebo, No. (%)			
Subject	3 (7.5)	3 (7.5)	4 (10.0)
Provider	9 (22.5)	6 (15.0)	7 (17.5)
Investigator	3 (7.5)	3 (7.5)	5 (12.5)

be the ideal first-line agent for treatment of nausea and vomiting in the ED.²³ Our study provides high-quality evidence indicating that inhaled isopropyl alcohol provides greater nausea relief than this ubiquitous medication.

Anesthesia literature provides precedent for our finding that inhaled isopropyl alcohol has efficacy in treating nausea. The specific results of these studies are variable, with some demonstrating improved nausea relief with this intervention compared with placebo^{19,24,25} and others finding no effect.^{18,26,27} In aggregate, the evidence as summarized by meta-analysis suggests isopropyl alcohol has superior efficacy in treating postoperative nausea compared with placebo.¹

The mechanism of isopropyl alcohol's antiemetic effect remains unclear. This effect may be related to olfactory distraction. Indeed, multiple studies demonstrate equivalent or superior²⁷ nausea reduction with nasally inhaled scented oils compared with nasally inhaled isopropyl alcohol.^{26,27} The trend toward increased pain alleviation among our patients receiving isopropyl alcohol compared with placebo provides some support for this explanation. Another theory relates to the controlled breathing because of the inhalation instructions instead of a pharmacologic effect.²⁶ Further research is necessary to elucidate this agent's mechanism of action.

Comparison of the nausea reduction after inhalation of isopropyl alcohol estimated by this study with that reported by previous anesthesia studies of aromatherapy is difficult, given heterogeneity in outcome measures and statistical methods. In the ED setting, estimates of mean nausea VAS score reduction 30 minutes postintervention range from 16 to 39 mm for placebo (normal saline solution)⁶⁻⁸ and 22 to 34 mm for ondansetron.^{6,8,15} These values are greater than the mean VAS reduction we observed in our study among subjects receiving inhaled placebo and oral ondansetron (9 mm). We suspect the greater nausea reduction achieved in alternative studies relates to the concomitant administration of intravenous fluid and the study medications, which likely contributed significant nausea relief.

This study highlights several areas for future research. First, study of alternative aromatherapies (eg, peppermint oil) in the ED may be high yield because these have demonstrated anti-emetic efficacy in the anesthesia literature.^{27,28} Second, study of inhaled isopropyl alcohol or other aromatherapy interventions in alternative patient populations, such as children and pregnant women, would be useful. Third, comparisons of intravenous fluid administration with aromatherapy would be interesting to clarify which of these interventions yields superior nausea relief. Fourth, although many contemporary medications for nausea are relatively inexpensive, cost-effectiveness analyses might clarify whether routine use of isopropyl

alcohol pads yields any material improvement in the efficiency of ED care delivery to patients with nausea and vomiting.²⁹ Finally, triage protocols enabling aromatherapy before provider evaluation may improve treatment of nausea and patient satisfaction.

This study indicates that nasally inhaled isopropyl alcohol with or without oral ondansetron outperforms inhaled placebo together with oral ondansetron in treating nausea in the undifferentiated ED patient with nausea or vomiting not requiring immediate intravenous access. Emergency providers should consider incorporation of aromatherapy into their clinical practice in patients with nausea and vomiting who do not require urgent intravenous therapy.

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Author contributions: MDA and CJH conceived the study and designed the protocol. MDA, JJO, WTD, DO, EMS, and PCG undertook subject recruitment, data collection, and data management. MDA contributed data analysis and interpretation. All authors substantively contributed to article preparation and revision. MDA takes responsibility for the paper as a whole.

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