The effect of transdermal scopolamine on the incidence and severity of postoperative nausea and vomiting in a group of high-risk patients given prophylactic intravenous ondansetron

LCDR Shari Jones, CRNA, MSN, NC, USN
San Diego, California

LT Robert Strobl, CRNA, MSN, NC, USN
Lemore, California

LCDR Dan Crosby, CRNA, MSN, NC, USN
USS Ronald Reagan, CVN-77

CDR Joseph F. Burkard, CRNA, DNSc, NC, USN
San Diego, California

CDR John Maye, CRNA, PhD, NC, USN
CAPT Joseph E. Pellegrini, CRNA, DNSc, NC, USN
Bethesda, Maryland

Specific risk factors place patients at greater risk for postoperative nausea and vomiting (PONV). Routinely, these patients are treated prophylactically with intravenous (IV) ondansetron or transdermal (TD) scopolamine. No study has examined what effect using a combination of these prophylactic treatments would have on the incidence of PONV in a group of high-risk patients.

A total of 56 patients at high risk for PONV were treated prophylactically with IV ondansetron and randomized to receive a TD scopolamine patch or placebo. Demographics, incidence, and severity of PONV and side effects and antiemetic requirements were measured. Nausea was measured using a 0 to 10 verbal numeric rating scale. Descriptive and inferential statistics were used for analysis.

No difference in demographics or the incidence of side effects was noted between groups. Patients in the scopolamine group had a lower incidence of PONV (P = .043), longer time to first reported nausea (P = .044), longer time to first episode of emesis (P = .031), and decreased supplemental antiemetic requirements (P = .016) compared with the placebo group.

Based on this study, we recommend using a combination of TD scopolamine and IV ondansetron to prevent PONV in patients identified as high risk for PONV.

Key words: **Ondansetron, postoperative nausea and vomiting, prevention, scopolamine.**

Postoperative nausea and vomiting (PONV) is one of the most frequent and distressing complaints reported by patients following surgery.[1,2] Certain risk factors have been identified that place patients at considerable risk for the occurrence of PONV. These risk factors include nonsmoker, female gender, history of PONV, history of motion sickness, and undergoing general anesthesia for longer than 60 minutes. In fact, it has been noted that the incidence of PONV increases exponentially from 16% when 1 risk factor is present to as high as 87% when all 5 risk factors are present.[3-5] Therefore, it has become routine in many clinical anesthesia practices to specifically identify patients with these risk factors so that an aggressive management plan can be implemented to prevent PONV.[6-10] Prevention of PONV often involves the use of antiemetic agents that work specifically on receptors in an area of the brain called the chemoreceptor trigger zone. Studies have shown that stimulation at one or more of the receptors found in this region will stimulate the vomiting reflex; therefore, most pharmacological regimens include medications that block one of these receptor sites.[1,2,10] Of the multitude of antiemetic agents available for use in clinical anesthesia practice, the most common agents used are ondansetron, droperidol, metoclopramide, dexamethasone, and scopolamine. Of these, many clinicians prefer ondansetron to prevent and treat PONV, especially for patients who are highly susceptible to PONV.[7-10]

Ondansetron was the first serotonin receptor antagonist approved for the prevention and treatment of

PONV in oral and intravenous (IV) forms and has been designated as the first-line treatment regimen for nausea and vomiting.[11,12] Studies have shown that a 4-mg dose is very efficacious in the prevention of early PONV but less efficacious in the prevention of PONV beyond an interval of 2 hours following surgery.[12]

Scopolamine, another medication that can be administered prophylactically, offers several advantages over traditional antiemetic agents. These advantages include transdermal (TD) patch application, known efficacy in the treatment and prevention of PONV in patients with a history of motion sickness, and a duration of action of approximately 72 hours. Because of these factors, TD scopolamine seems to be an ideal prophylactic medication for patients at high risk for PONV. However, there are some problems with TD scopolamine. Foremost, TD scopolamine often has to be placed on the patient several hours before surgery to achieve clinical effectiveness, and studies have shown that it often will not prevent the occurrence of PONV in the immediate postoperative period. There also is some evidence to indicate that TD scopolamine may not be efficacious in the prevention of PONV for all types of surgical procedures and may be better suited when used in combination with another antiemetic agent.[13]

Using 2 known antiemetic agents is becoming more common in the clinical setting. This approach, called the *multimodal approach*, has been shown to be highly effective in the treatment and prevention of PONV for a wide variety of surgical procedures.[14-16] Using the multimodal approach to prevent and treat PONV makes sense because by using more than one agent, one can take advantage of the unique pharmacokinetics and dynamics of each agent. More specifically, using agents that work at various areas of the chemoreceptor trigger zone that have different onsets and duration of actions, provides the patient with a greater degree of prophylaxis and treatment. To date, no study has evaluated how effective the prophylactic administration of IV ondansetron and TD scopolamine would be in the prevention of PONV in a group of patients identified as highly susceptible to PONV.

The purpose of this study was to determine if using a combination of TD scopolamine and IV ondansetron would be more efficacious in preventing PONV in a group of patients at high risk for PONV compared with a similar group given IV ondansetron alone.

Methods

After approval by the institutional review board, this randomized, double-blind, placebo-controlled, prospective study was performed in groups of high- risk patients scheduled to receive general anesthesia of longer than 1 hour. Only ASA physical status I and II patients who were 18 years or older and reported at least 3 of the 5 risk factors were considered for inclusion. Determination of risk factors was assessed during the preoperative screening process. Subjects were excluded if they reported a recent upper respiratory tract infection; the recent use of serotonin antagonists, scopolamine, antiemetic drugs, or psychoactive drugs; hypersensitivity to serotonin antagonists or scopolamine; or being pregnant.

After inclusion criteria were met, informed consent was obtained and subjects were randomized into a control (group 1, received a placebo patch) or scopolamine (group 2, received a scopolamine patch) group via a computer-generated randomization process. The placebo patches were supplied by Novartis (Basel, Switzerland) and contained no active ingredients. They were identical in appearance to the TD scopolamine patches that were purchased for this study and were not in the hospital formulary. The scopolamine patches were designed to deliver 1.5 mg of scopolamine in a time-release manner during 72 hours. The pharmacy generated a random number table and placed the patches in dark plastic bags numbered 1 to 60. All of the patches then were maintained in a secure location by the investigators until subjects were consented and enrolled in the study. The patches were numbered individually before being placed on subjects by the investigators. Subjects and investigators were unaware of which patch was being placed until the completion of data collection.

Patients were screened using either of two methods. The first method consisted of distributing a questionnaire to all surgical patients through the individual surgical clinics and the preoperative clinic. Patients who were identified to be at high risk and scheduled for procedures requiring general anesthesia for longer than 60 minutes were contacted for participation. In addition, a second method that involved scanning the next days' surgical schedule for procedures requiring general anesthesia for longer than 60 minutes was used to help identify patients. These patients' preoperative charts were reviewed to determine whether they had any of the other risk factors. Subjects who had 3 or more of the 5 risk factors were contacted by telephone the night before surgery to determine if they would be interested in study participation.

On the day of surgery, after informed consent was obtained, subjects were admitted to the preoperative hold area. All subjects were assigned a subject number and randomized into group 1 or group 2. The pharmacy department kept a log that identified the group for each subject. Neither the investigators nor the subjects were informed of group assignment until the conclusion of data collection.

Before placement of the patch, nausea was measured using an 11-point, 0 to 10 verbal numeric rating scale (VNRS) in which a score of "0" indicated "no nausea" and a score of "10" indicated "the worst nausea imaginable" to determine a baseline. The patch then was placed behind one of the subject's ears. Ideally, this occurred at least 2 hours before induction of general anesthesia; however, due to operating room scheduling, the first contact with the majority of subjects was approximately 40 minutes before induction. An IV infusion of lactated Ringer's was started, and subjects were premedicated with 0 to 5 mg of midazolam and 0 to 150 µg of fentanyl.

Subjects then were transported to the operating room where standard monitors, including a noninvasive blood pressure monitoring device, an electrocardiogram, and a pulse oximeter were placed. General anesthesia was induced per provider preference and maintained with inhalation agent of choice and less than 50% nitrous oxide. At 30 minutes before emergence, each subject received 4 mg of IV ondansetron. Reversal of neuromuscular blockade was left to the discretion of individual providers. After extubation, subjects were transported to the postanesthesia care unit (PACU) with oxygen supplementation.

Following transport to the PACU, nausea was measured using the 0 to 10 VNRS on arrival, every 15 minutes while in the PACU, and again on arrival and discharge in same-day surgery unit or inpatient ward and at a complaint of nausea for 72 hours following surgery. All subjects were asked to keep the patch in place for at least 72 hours following surgery and were given instructions concerning patch care following discharge from the hospital. All subjects were asked to keep a log of the time and severity of nausea (using the 0-10 VNRS) for 72 hours following surgery. They were instructed that they would be receiving a follow-up phone call from one of the investigators 72 hours following surgery to obtain information recorded in their logs. In addition, all subjects were told that they would be asked to rate their overall satisfaction with their quality of nausea relief at the 72-hour follow-up phone interview. Satisfaction was measured using a 5-point Likert scale that used the follow grading criteria: (1) dissatisfied, (2) somewhat dissatisfied, (3) somewhat satisfied, (4) satisfied, and (5) very satisfied.

Inferential and descriptive statistics were used for data analysis. Descriptive statistics were used for demographic variables. Satisfaction scores were analyzed using a Mann-Whitney *U* test. A Pearson correlation was used to predict overall level of satisfaction in subjects who complained of nausea postoperatively, controlling for group assignment. A Student *t* test was used to analyze VNRS scores, postoperative analgesic requirements, and antiemetic requirements between groups. A *P* value of less than .05 was considered significant. Before implementation of the study, a power analysis was performed using an of .05 and a power of 0.8. It was determined that a sample size of 27 per group would produce an estimated 20% difference in PONV scores between the groups. Factoring an attrition rate of 10% (3 subjects per group), the final sample size required was 60 subjects, or 30 subjects per group.

Results

We enrolled 60 subjects in this double-blind, randomized, placebo-controlled study. A total of 4 subjects were disenrolled, 1 for inadvertent removal of the patch, 1 for incomplete data collection, and 2 for intentional removal of patches secondary to headaches (ondansetron only group). This left a total of 56 subjects with data for analysis (28 in each group). No difference was noted in gender, age, weight, height, ethnic background, or number of risk factors present between groups (Table 1). No significant differences in preoperative, intraoperative, or postoperative analgesic or anxiolytic requirements; volatile agent requirements; or need for reversal from neuromuscular blockade were noted between groups.

There was no difference found between the groups in the mean time from patch placement and time to induction or from patch placement and arrival in the PACU (Table 2). No difference in incidence of side effects was noted between groups, but it was noted

Table 1. Variables associated with demographics*

Demographics	Placebo group (n = 28)	Scopolamine group (n = 28)
Gender		
Female	23	24
Male	5	4
Race		
White	17	19
African American	5	2
Hispanic	1	2
Asian	5	5
Height (cm)	165	165
Weight (kg)	74	77
No. of risk factors present		
3	14	12
4	6	8
5	8	7

*** No significant differences were noted in demographic variables or the number of risk factors for postoperative nausea and vomiting between the placebo and scopolamine groups.**

Table 2. Patch placement times*

	Placebo group (n = 28)	Scopolamine group (n = 28)
Time from patch placement to induction of anesthesia (min)	45.6 ± 45	57.8 ± 41.3
Time from patch placement to arrival in the PACU (min)	213.4 ± 121.7	251.3 ± 89.3

* No significant differences were noted between groups in relation to mean ± SD time from patch placement to induction of anesthesia ($P = .263$) or to postanesthesia care unit (PACU) arrival ($P = .204$).

that a higher incidence of side effects occurred in group 1 than in group 2 (Table 3).

When the overall incidence of nausea was analyzed for the first 24 hours following surgery, it was noted that 17 (61%) of subjects in group 2 reported "no nausea" compared with only 7 (25%) of subjects in group 1 ($P = .007$) (Figure 1). Initial PACU antiemetic treatment was required for 8 subjects in group 2 and 19 subjects in group 1 ($P = .007$) (Figure 2). Analysis of the second treatment for complaints of PACU nausea revealed that only 1 subject in group 2 required treatment compared with 8 subjects in group 1 ($P = .025$) (see Figure 2).

The mean ± SD time to first request for nausea treatment was longer in group 2 (361 ± 171 minutes) than for group 1 (259 ± 108 minutes) ($P = .044$). The incidence of emesis also was lower in group 2 (6 episodes) than in group 1 (12 episodes), but the difference did not achieve statistical significance ($P = .152$). However, when the time to first emetic event was analyzed, a significant difference was noted. The mean ± SD time for the initial episode of emesis was 498 ± 102 minutes for group 2 vs 324 ± 129 minutes for the control group ($P = .031$) (Figure 3). In addition, 1 patient in group 2 reported an episode of PONV following discharge from the hospital compared with patients in group 1 ($P = .043$). The use of reversal agent was not correlated with any nausea or emetic event.

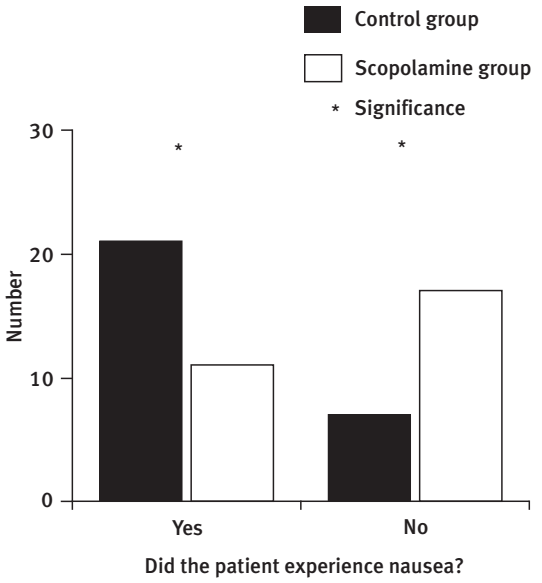
Overall patient satisfaction scores between groups were similar with the median level of satisfaction being 4 in group 1 compared with 5 in group 2. However, when patients who complained of nausea were isolated, the satisfaction scores were significantly lower in group 1 ($P = .006$). There was no statistical significance between the groups when analyzing VNRS scores; however, the scores tended to be lower in group 2 compared with group 1.

Table 3. Side effects experienced by group*

	Placebo group (n = 28)	Scopolamine group (n = 28)
Side effects		
Dry mouth	1	1
Headache	3	2
Other	3	0
Total	7	3

* No significant differences were noted between groups in relation to occurrence of side effects ($P > .05$), although a higher incidence was noted in the placebo group than in the scopolamine group.

Figure 1. Overall incidence of nausea within 24 hours of surgery (PACU, SDSU, ward, home)



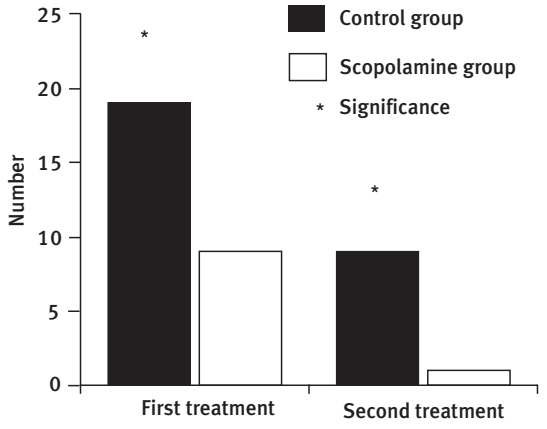
When overall incidence of nausea was analyzed for the first 24 hours following surgery, it was noted that 17 (61%) of subjects in the scopolamine group reported "no nausea" as compared with only 7 (25%) of the subjects in the placebo group ($P = .007$).

PACU indicates postanesthesia care unit; and SDSU, same-day surgery unit.

Discussion

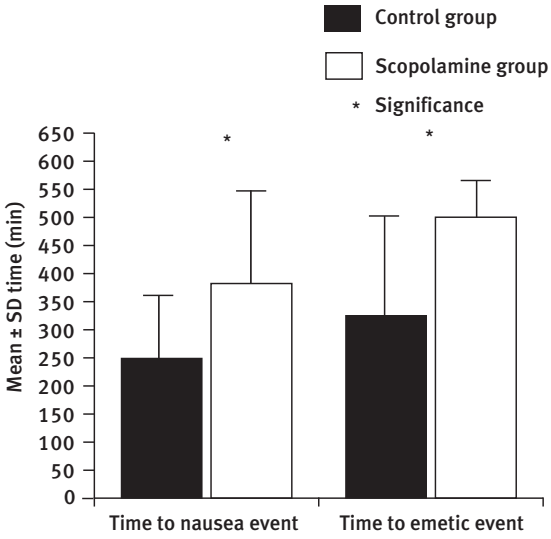
Postoperative nausea and vomiting is multifactorial in etiology and has given rise to investigations proposing prophylactic measures to minimize these symptoms. Factors contributing to PONV can be categorized into 3 groups, including patient-related factors, surgery-related factors, and anesthesia-related factors. In our study, we focused on patient-related factors that placed patients at an increased risk of developing PONV. Koivuranta et al[5] proposed a simple method of classifying patients based on 5 patient-related criteria.

Figure 2. PACU antiemetic treatment requirements



Initial postanesthesia care unit (PACU) antiemetic treatment was required for 8 subjects in the scopolamine group and 19 subjects in the placebo group ($P = .007$). When second treatment for complaints of PACU nausea was analyzed, it was noted that only 1 subject in the scopolamine group required treatment compared with 8 subjects in the placebo group ($P = .025$).

Figure 3. Time from patch placement to nausea event



When the time to first emetic event was analyzed, a significant difference was noted. The mean ± SD time for the initial episode of emesis was 498 ± 102 minutes for the scopolamine group vs 324 ± 129 minutes for the control group ($P = .043$).

Using this simplified method, patients meeting 3 of 5 risk factors would have an incidence of PONV of 54%.[5] We suggest that the incidence of PONV at this percentage would justify prophylactic treatment.

During the past several decades, there have been numerous research studies supporting the effectiveness of reducing PONV with ondansetron as a single agent and in combination with other agents, including metoclopramide, droperidol, and dexamethasone.[7-12,14,17] In a study by Sadhasivam et al,[8] ondansetron used as a single agent decreased PONV from 81% to 33% compared with a placebo.

In our study, the control subjects received ondansetron as a single agent and reported a 75% incidence of PONV. In analysis of risk factors present, it was noted that approximately 50% of the sample in both groups had 4 or 5 of the risk factors present, placing them at a higher risk for PONV. Koivuranta et al[5] reported that the risk of PONV increases exponentially based on the number of risk factors present (67% with 4 risk factors and 87% with 5 risk factors); therefore, it was not surprising that we had a higher incidence of PONV for the entire sample than the projected 54% when only 3 risk factors are present.

What was surprising was that we still had such a high incidence of PONV despite all subjects receiving a prophylactic dose of 4 mg of ondansetron. The high rate could have been attributed to study design (allowing for patients to receive 50% nitrous oxide or not controlling for surgical procedures). Perhaps not isolating the patient populations to a specific surgical procedure or allowing the use of nitrous oxide may have decreased the degree of PONV prophylaxis from the ondansetron. A repeat of this study in which these variables are controlled is needed to determine whether these variables were possible causative factors attributing to the high degree of PONV found in our sample.

There also have been a number of studies supporting that TD scopolamine is safe and effective for the treatment and prevention of PONV.[18-20] When scopolamine was compared with a placebo in women who received epidural morphine after cesarean section, nausea and vomiting was reduced from 50% to 13% during the first 24 hours postoperatively.[18] Bailey et al[21] showed that scopolamine reduced nausea and vomiting from 62% to 37% compared with a placebo after laparoscopic surgery. Our study did not compare scopolamine as a single agent; however, this might be included in future investigations.

Our study combined scopolamine and ondansetron and tested 56 patients who were classified as high risk for PONV. We found that patients who received a combination of TD scopolamine and ondansetron overall did better than those receiving ondansetron alone. Pueyo et al[22] showed that combination therapy reduced PONV from 72% to 8%. We found that the combination of ondansetron and scopolamine reduced PONV from

75% to 39%. The difference could be attributed to the differences in patient population. Our study included men, and we did not control for surgical procedure, whereas Pueyo et al[22] limited their population to women undergoing intra-abdominal surgery.

One of the dangers of prophylactic treatment of PONV is the potential of increased side effects. In a meta-analysis of antiemetic use performed by Domino et al,[7] there were no significant differences for any side effects, but ondansetron had an increased risk for headache compared with droperidol. Our study findings agree with these results. We monitored both groups for side effects normally attributed to scopolamine and ondansetron, including itching, headache, and dry mouth. The most frequently reported side effect was headache, which has been attributed to ondansetron.[7] Two of our patients experienced headaches early in the recovery period and removed their patches before 72 hours.

Ondansetron continues to be a popular choice in the treatment and prevention of PONV. Transdermal scopolamine is becoming a popular choice in the treatment of motion sickness. Our study suggests that the combination of ondansetron and scopolamine produced a better outcome in the prevention and successful treatment of PONV. Future studies using scopolamine along with other antiemetics affecting alternative receptor pathways could prove even more effective in the reduction of PONV.

REFERENCES

1. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment and prevention. *Anesthesiology.* 1992;77:162-184.
2. Kovak AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs.* 2000;59:213-243.
3. Apfel CC, Haubitz GI, Usadel CG, Sefrin P, Rower N. A risk score to predict the probability of postoperative vomiting in adults. *Acta Anaesthesiol Scand.* 1998;42:495-501.
4. Eberhart LHJ. Evaluation of three risk scores to predict postoperative nausea and vomiting. *Acta Anaesthesiol Scand.* 2000;44:480-488.
5. Koivuranta M, Laara E, Snare L, Alahunta S. A survey of postoperative nausea and vomiting. *Anaesthesia.* 1997;52:443-449.
6. Haigh CG, Kaplan LA, Durham JM, Dupeyron JM, Harmer M, Kenny GNC. Nausea and vomiting after gynaecological surgery: a meta-analysis of factors affecting their incidence. *Br J Anaesth.* 1993;71:517-522.
7. Domino K, Anderson E, Polissar N, Posner K. Comparative efficacy and safety of ondansetron, droperidol and metoclopramide for preventing postoperative nausea and vomiting: a meta-analysis. *Anesth Analg.* 1999;88:1370-1379.
8. Sadhasivam S, Saxena A, Kathirvel S, Kannan TR, Trikha A, Mohan V. The safety and efficacy of prophylactic ondansetron in patients undergoing modified radical mastectomy. *Anesth Analg.* 1999;89: 1340-1345.
9. Jokela RM, Kangas-Saarela TA, Valanne JVI, Koivuranta MK, Ranta PO, Alahuhta SM. Postoperative nausea and vomiting after sevoflurane with or without ondansetron compared with propofol in female patients undergoing breast surgery. *Anesth Analg.* 2000; 91:1062-1065.
10. Naguib M, El Bakry AK, Khoshim MHB, et al. Prophylactic antiemetic therapy with ondansetron, tropisetron, granisetron, and metoclopramide in patients undergoing laparoscopic cholecystectomy: a randomized double-blind comparison with placebo. *Can J Anaesthesiol.* 1996;43:3226-3231.
11. Tramer MR, Reynolds DJM, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting. *Anesthesiology.* 1997;87:1277-1289.
12. Leeser J, Lip H. Prevention of postoperative nausea and vomiting using ondansetron, a new, selective, 5-HT_3 receptor antagonist. *Anesth Analg.* 1991;72:751-755.
13. Sohi HS, Heipel J, Inman KJ, Chinnick B, Cunningham DG, Holliday FL. Preoperative transdermal scopolamine does not reduce the level of nausea and frequency of vomiting after laparoscopic cholecystectomy. *Can J Surg.* 1994;37:307-312.
14. Fujii Y, Tooyooka H. Prevention of postoperative nausea and vomiting with the combination of granisetron and droperidol. *Anesth Analg.* 1998;86:613-616.
15. Wrench IJ, Ward JE, Walder AD, Hobbs GJ. The prevention of postoperative nausea and vomiting using a combination of ondansetron and droperidol. *Anaesthesia.* 1996;51:776-778.
16. Fujii Y, Tooyooka H. Granisetron-dexamethasone combination reduces postoperative nausea and vomiting. *Can J Anaesthesiol.* 1995;42:387-390.
17. Reinhart D, Klein KW, Schroff E. Transdermal scopolamine for the reduction of postoperative nausea in outpatient ear surgery: a double-blind, randomized study. *Anesth Analg.* 1994;79:281-284.
18. Clissold SP, Heel RC. Transdermal hyoscine (scopolamine): a preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs.* 1985;29:189-207.
19. Kotuku DM, Rittman RL, Wright WC, Stone JJ, Hampshire AY, Rosenblatt RM. Transdermal scopolamine decreases nausea and vomiting following cesarean section in patients receiving epidural morphine. *Anesthesiology.* 1989;71:675-678.
20. McKenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady H. Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. *Anesth Analg.* 1994;79:961-964.
21. Bailey PL, Streisand JB, Pace NL, et al. Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. *Anesthesiology.* 1990;72:977-980.
22. Pueyo FJ, Carrascosa F, Lopez L, Iribarren MJ, Garcia-Pedrajas F, Saez A. Combination of ondansetron and droperidol in the prophylaxis of postoperative nausea and vomiting. *Anesth Analg.* 1996; 83:117-122.

AUTHORS

LCDR Shari Jones, CRNA, MSN, NC, USN, is a staff nurse anesthetist of the Naval Medical Center San Diego, Calif.

LT Robert Strobl, CRNA, MSN, NC, USN, is a staff nurse anesthetist at Naval Hospital Lemore, Calif.

LCDR Daniel Crosby, CRNA, MSN, NC, USN, is a staff nurse anesthetist stationed on board the USS *Ronald Reagan, CVN-77*.

CDR Joseph F. Burkard, CRNA, DNSc, NC, USN, is a clinical research coordinator for the Navy Nurse Corps Anesthesia Program, San Diego, Calif. Email: JFBurkard@nmcsd.med.navy.mil

CDR John Maye, CRNA, PhD, NC, USN, is the clinical research coordinator for the Naval Postgraduate Dental School, Bethesda, Md.

CAPT Joseph E. Pellegrini, CRNA, DNSc, NC, USN, is the director of clinical research for the Navy Nurse Corps Anesthesia Program, Bethesda, Md.

ACKNOWLEDGMENT

The Chief, Bureau of Medicine and Surgery, Navy Department, Washington, DC, Clinical Investigation Program sponsored this report # S-02-099, as required by NSHSBETHINST 6000.41A.

DISCLAIMER

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