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Role of Nitrous Oxide and Other Factors in Postoperative Nausea and Vomiting: A Randomized and Blinded Prospective Study

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Postoperative nausea and vomiting have been reported to be associated with the use of nitrous oxide. To further investigate this possibility, 780 patients undergoing anesthesia and surgery were randomly divided into four groups: group I: enflurane/nitrous oxide/oxygen; group II: enflurane/air/oxygen; group III: isoflurane/nitrous oxide/oxygen; and group IV: isoflurane/air/oxygen. The frequency of postoperative nausea and vomiting was ascertained in the recovery room and at 24-h follow-up by blinded observers. Other data collected included gender, age, body mass index, previous history of postoperative nausea and vomiting, and postoperative narcotic use. The authors found no association between the use of nitrous oxide and subsequent development of postoperative nausea and vomiting. Use of the 95% confidence interval allowed the authors to project a maximum potential increase in the frequency of postoperative nausea and vomiting associated with nitrous oxide to be 5.4% with enflurane and 9.7% with isoflurane in the immediate postoperative period. Female gender, younger age, and a previous history of postoperative nausea and vomiting, but not body mass index, were found to be associated with postoperative nausea and vomiting ($P < 0.05$). It is concluded that there is no association between the use of nitrous oxide and the development of postoperative nausea and vomiting. (Key words: Anesthetics: gases—nitrous oxide. Complications: vomiting. Gastrointestinal tract: nausea; vomiting.)

THE FIRST ISSUE of a journal devoted entirely to anesthesiology discussed prophylaxis of postoperative nausea and vomiting (PNV).[1] Despite this early recognition, PNV persists as a clinical problem, and is often the complication most feared by patients undergoing anesthesia and surgery. Numerous studies have implicated factors associated with PNV, including anesthetic techniques,[2] anesthetic agents,[3-5] narcotics,[6-9] age,[10,11] gender,[12,13] weight,[11,14] type of surgical procedures,[15-17] and pain.[18,19] Recently, the use of nitrous oxide (N_2O) has been postulated to increase the frequency of PNV.[20,21] To determine the frequency of PNV associated with and without the use of N_2O, we prospectively studied, in a randomized and blinded design, 780 patients undergoing surgical procedures who received N_2O/oxygen (O_2) or air/O_2 in addition to a standard enflurane or isoflurane anesthetic.

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Methods

Approval for the study was granted by the Institutional Review Board. Informed consent was obtained from 780 ASA I or II patients. Patients were eligible for inclusion in the study if they fulfilled the following criteria: 1) free of nausea and vomiting preoperatively, 2) did not have known middle ear disease, 3) undergoing procedures that were not otologic, neurologic, intraabdominal, or ophthalmologic, 4) suitable for anesthesia with either enflurane or isoflurane with or without N_2O at an FI_{O_2} of 0.4, and 5) not using medication known to have an antiemetic effect. Surgical procedures known to be associated with PNV[15-17] were not included in the study, so that PNV could be related to the anesthetic, and not surgical factors such as bowel manipulation. Because prolonged fasting has been associated with nausea in healthy volunteers,[22] all patients were fed nothing by mouth for only 8–12 h preoperatively. Collected preoperative data included age, gender, weight, height, and history of nausea or vomiting after previous, if any, anesthesia and surgery.

A standard anesthetic technique was used. Patients were premedicated with diazepam 0.1 mg/kg orally 1 h prior to surgery. Following preoxygenation and a defasciculation dose of curare 3 mg iv, anesthesia was induced with thiopental 5–7 mg/kg iv. Endotracheal intubation was facilitated with succinylcholine 1.5 mg/kg iv. Positive pressure ventilation by mask was avoided to prevent gastric distension. After trachael intubation, anesthesia was maintained with one of the following techniques assigned on a random basis: group I: enflurane/N_2O/O_2 (N = 198 patients); group II: enflurane/air/O_2 (N = 196 patients); group III: isoflurane/N_2O/O_2 (N = 188 patients); and group IV: isoflurane/air/O_2 (N = 198 patients).

In all groups, the FI_{O_2} was 0.4. Inspired concentrations of the volatile anesthetic were adjusted as clinically indicated to maintain a stable level of anesthesia and hemodynamics. Because pain itself may cause nausea and vomiting in the immediate postoperative period,[18,19] all patients were given morphine sulfate 0.1 mg/kg iv 1 h prior to the anticipated end of the surgical procedure to provide

analgesia upon awakening. This was the only narcotic given intraoperatively.

If muscle relaxation was needed, short-acting, nondepolarizing relaxants (atracurium or vecuronium) were used. In no case was it necessary to reverse muscle relaxants, thus avoiding the effect on bowel of anticholinergic and anticholinesterase medications.

In the post-anesthesia recovery room (PAR), patients were questioned every 30 min for the presence or absence of nausea by observers blinded to the anesthetic used. The frequency of retching or vomiting was recorded every 30 min. Before leaving the PAR, the durations of anesthesia and PAR stay were noted.

Patients were seen postoperatively by observers blinded to the anesthetic group. Postoperative visits were possible within 24 h of surgery for 718 of the 780 patients. Sixty-two patients were not seen because of early discharge from the hospital. In the 718 patients seen postoperatively, the presence or absence of PNV following PAR discharge was ascertained. In addition, the use of postoperative analgesics was noted. These analgesics were either meperidine 0.7–1.0 mg/kg iM, morphine sulfate 0.07–0.1 mg/kg im, or non-narcotic oral analgesics (aspirin or acetaminophen). The choice of postoperative analgesics was at the discretion of each surgical service. The number of doses depended upon patient request.

Statistical Analysis

The presence of either nausea and/or vomiting was considered an emetic symptom, and the presence of either symptom was included as an endpoint for analysis. Two-tailed, two-sample Chi-square tests were used to test for significant differences in the proportion with PNV between the four anesthetic groups at two distinct times: 1) during the PAR stay, and 2) during the 24 postoperative hours (including PAR). The 95% confidence interval, using the normal approximation for differences between proportions in each pair of groups, was also calculated. The study was designed to have a statistical power of ≥ 0.90 in detecting a two-sided difference in the proportion with PNV of ≥ 0.16 between pairs of groups with the conventional α-level of 0.05.

In addition, patients who left the PAR without emetic symptoms were studied for PNV in relation to postoperative analgesic use. Two-tailed, two-sample Chi-square analyses were used to compare the three postoperative analgesic groups. In all analyses, $P < 0.05$ was chosen to reflect statistical significance.

A secondary analysis was carried out in an attempt to identify any variables associated with PNV. The logistic model with backward elimination of non-significant variables was used. Many variables were considered.

The body mass index $\left(\text{BMI} = \frac{\text{kg}}{\text{m}^2}\right)$ was used as an index of obesity. It is a widely used method to evaluate obesity.[23] The effects of gender, age, history of previous PNV (if any), and BMI on PNV were evaluated using logistic regression models at two timepoints: 1) during the PAR stay (all patients, N = 780), and 2) during the 24-h postoperative period (all patients who did not receive postoperative narcotics, N = 496). In these statistical models, patients who received narcotics following PAR discharge but before the 24-h postoperative visit were excluded because of the marked effect meperidine and morphine sulfate had on the frequency of PNV. Variables were considered both singly and in combination. Models using only the main effects and models using all the interaction terms were evaluated. All patients undergoing anesthesia and surgery for the first time would not have a history of PNV; therefore, models were run with and without this variable. In addition, separately for men and women, obesity, reflected by the mean BMI, was compared in those with *versus* without PNV using a two-tailed *t*-test on the means. $P < 0.05$ was considered significant.

Results

The characteristics of the randomly assigned anesthetic groups are shown in table 1. There were no significant differences in the frequency of emetic symptoms between the anesthetic groups or any pair of groups, either in the PAR or within 24 postoperative hours, including PAR (table 2). The differences in frequency of PNV between anesthetic groups in both the PAR and PAR plus 24-h visit periods were calculated, and corresponding 95% confidence intervals constructed (table 3). The study had a statistical power of ≥ 0.90 in detecting a two-sided difference in the proportion with PNV of ≥ 0.11 between pairs of groups in the PAR with the conventional α level of 0.05. There was a statistical power of ≥ 0.90 in detecting a two-sided difference in the proportion with PNV of ≥ 0.16 between pairs of groups within 24 h of surgery (including PAR) with an α level of 0.05.

Although all patients were randomly assigned into anesthetic groups, there were significantly more patients undergoing urologic procedures assigned to group I (enflurane/N_2O/O_2) than the other three groups. Also, there were more patients undergoing head and neck surgery with isoflurane/air/O_2 anesthesia (group IV) than underwent similar surgery under enflurane/N_2O/O_2 anesthesia (group I).

The incidence of emetic symptoms, both in the PAR and at 24 h follow-up, was the same in all patients undergoing urologic procedures, regardless of the anesthetic group to which the patient was assigned ($P > 0.05$). There was no difference in the incidence of emetic symptoms in patients undergoing head and neck surgery, regardless of anesthetic group ($P > 0.05$).

There were 638 patients who left the PAR without

TABLE 1. Characteristics of the Study Population

	Group I: Enflurane/N_2O/O_2	Group II: Enflurane/Air/O_2	Group III: Isoflurane/N_2O/O_2	Group IV: Isoflurane/Air/O_2	Total
Variable	N = 198	N = 196	N = 188	N = 198	N = 780
Female (%)	55.2	59.9	57.5	60.3	58.2
Male (%)	44.8	40.1	42.5	40.7	41.8
Procedure					
Head and neck (%)	12.9	19.3	20.2	23.2	18.8
Extremities (%)	3.5	2.0	5.3	4.6	3.8
Chest wall (%)	16.9	22.8	19.7	17.5	19.3
Urologic (%)	49.3	33.5	36.2	34.5	38.5
Gyn (%)	7.5	6.6	5.3	7.2	6.7
Other (%)	10.0	15.8	13.3	12.9	12.9
Nausea and/or vomiting with previous general anesthesia %	N = 170 24.7	N = 169 30.2	N = 155 19.4	N = 155 29.2	648 25.9
Age (years)					
$\bar{x} \pm SD$	53.6 ± 16.2	52.1 ± 16.7	52.8 ± 17.5	52.1 ± 16.4	52.7 ± 16.7
Range	18–87	18–87	18–89	18–89	18–89
Body mass index (kg/m^2)					
$\bar{x} \pm SD$	26.3 ± 5.6	26.4 ± 5.6	26.2 ± 5.4	26.1 ± 5.1	26.2 ± 5.4
Range	16.6 ± 68.1	17.6 ± 61.2	15.6 ± 55.5	7.9 ± 52.9	7.9 ± 68.1
PAR stay (min)					
Median	65	65	70	65	65
Range	30–217	30–255	15–185	30–165	15–255
Length of anesthesia (min)					
Median	70.5	75.0	80.0	75.0	75.0
Range	20–550	30–300	20–400	10–440	10–550

emetic symptoms who had 24-h postoperative follow-up. These patients were categorized into one of three postoperative analgesic groups (non-narcotic oral analgesics, morphine, or meperidine) and were comparable in regard to gender, age, BMI, anesthetic, type of surgical procedure, anesthetic time, and PAR time. However, the number of narcotic injections depended upon patient request. We cannot state that all patients received equipotent amounts of narcotics. Morphine and meperidine were more likely to be associated with PNV than were oral non-narcotic analgesics, $P = 0.011$ (fig. 1). When meperidine was compared to morphine, meperidine was more likely to be associated with PNV than was morphine, $P = 0.028$.

The roles of gender, age, a history of PNV, and BMI in the development of PNV are summarized in tables 4 and 5. For patients in the PAR, age and a previous history of PNV were associated with PNV when considered both as single variables or in combination (table 4). Young patients tended to have more PNV, as did patients with a previous history of PNV (table 6). In patients followed for 24 h postoperatively (including the PAR stay, but excluding those who received narcotics postoperatively), age, a history of previous PNV, and gender were associated with PNV when considered as single variables (table 5). When considered in combination with the other variables, only gender and age were significantly associated with PNV. As was true for patients during the PAR stay, young

TABLE 2. Nausea and/or Vomiting Outcomes

	Group I: Enflurane/N_2O/O_2	Group II: Enflurane/Air/O_2	Group III: Isoflurane/N_2O/O_2	Group IV: Isoflurane/Air/O_2
PAR (N = 780)	(N = 198)	(N = 196)	(N = 188)	(N = 198)
Any nausea (%)	9.4	10.7	11.7	8.2
Any vomiting (%)	6.6	5.6	8.0	4.6
Any nausea and/or vomiting (%)	10.1	10.7	12.2	8.6
Within 24 postoperative hours (including PAR) (N = 718)	(N = 178)	(N = 181)	(N = 173)	(N = 186)
Any nausea (%)	36.0	34.2	36.4	31.7
Any vomiting (%)	28.7	26.0	24.3	21.0
Any nausea and/or vomiting (%)	37.6	37.0	37.6	33.3

TABLE 3. Comparison of Frequency of Nausea and/or Vomiting Between Anesthetic Groups and the Calculated 95% Confidence Limits

	Actual Differences (%)	95% Confidence Interval for Difference (%)
PAR		
Group I (enflurane/N_2O/O_2) *vs.* group II (enflurane/air/O_2)	−0.61	−6.6 to +5.4
Group III (isoflurane/N_2O/O_2) *vs.* group IV (isoflurane/air/O_2)	3.6	−2.4 to +9.7
Groups I & II *vs.* groups III & IV (enflurane *vs.* isoflurane)	0.05	−4.2 to +4.3
Groups I & III *vs.* groups II & IV (N_2O *vs.* air)	1.5	−2.7 to +5.7
Within 24 postoperative hours (including PAR)		
Group I (enflurane/N_2O/O_2) *vs.* group II (enflurane/air/O_2)	0.6	−9.4 to +10.6
Group III (isoflurane/N_2O/O_2) *vs.* group IV (isoflurane/air/O_2)	4.3	−5.7 to +14.1
Group I & II *vs.* groups III & V (enflurane *vs.* isoflurane)	2.0	−5.1 to +9.0
Groups I & III *vs.* groups II & IV (N_2O *vs.* air)	2.5	−4.6 to +9.4

TABLE 4. Logistic Regression Results

Factor	PAR Symptoms					
	Univariate		Multivariate			
	(N = 780)		(N = 647)		(N = 780)	
	2†	*P*‡	2	P	2	P
Gender	2.6	NS	1.1	NS	2.4	NS
Age	11.5	<0.001	7.3	.007	11.7	<.001
Hx nausea & vomiting*	17.0	<0.001	12.2	<.001	Variable excluded	
Body mass index	0.0	NS	0.2	NS	0.7	NS

* N = 647 with information.
† Chi-square value from logistic regression.
‡ Two-tailed *P* value from logistic regression testing null hypothesis that the regression coefficient was zero.

patients and those with a previous history of PNV tended to have more PNV (table 6). In addition, the female patients in this group had more PNV than males. None of the interaction terms were significant in the models based on main effects and interaction terms. In addition, there was no difference in the mean BMI between females (or males) who had PNV compared to those who did not have PNV.

Discussion

We were unable to show any difference in the frequency of PNV between the four anesthetic groups in the PAR or at the 24-h postoperative visit. Specifically, we were unable to demonstrate any increase in PNV associated with the use of nitrous oxide. Our results are in marked contrast to other studies that imply nitrous oxide to be associated with a 2–3.5-fold increase in the frequency of PNV. Alexander *et al.*[20] have demonstrated a twofold increase in the frequency of postoperative emetic symptoms in patients receiving O_2/N_2O and fentanyl (62%) compared to patients receiving O_2/isoflurane and fentanyl (30%). Buffington[21] reported a 3.5-fold increase in the frequency of vomiting in patients who received O_2/N_2O/isoflurane compared to patients who received O_2/isoflurane.

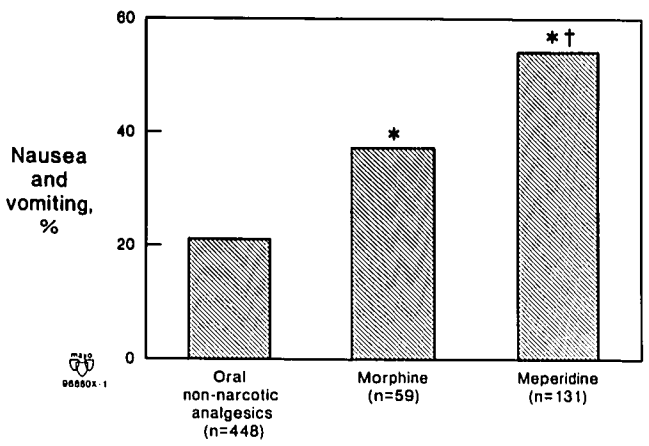

FIG. 1. The frequency of PNV associated with common analgesics during the period from PAR discharge to the 24-h postoperative visit in 638 patients who left the PAR without PNV. **P* = 0.011 compared to oral non-narcotic analgesics. †*P* = 0.028 compared to morphine.

Within the confines of 95% confidence intervals, we have calculated the maximum potential increase in the frequency of PNV associated with the addition of N_2O to enflurane to be 5.4% in PAR and 10.6% at 24 postoperative hours. Similarly, the potential increase in the frequency of PNV associated with the addition of N_2O to isoflurane anesthesia is 9.7% in the PAR and 14.1% at 24-h follow-up. While we cannot with certainty rule out the possibility that N_2O may contribute to PNV, we conclude that the effect, if any, is substantially less than has been suggested by other authors.[20,21]

Previously proposed mechanisms for the association of N_2O with PNV include increased sympathetic activity, changes in middle ear pressure, and gastrointestinal distension caused by N_2O. Eger[24] has suggested that increased sympathetic activity associated with N_2O might be the cause of increased PNV after N_2O administration. This possibility is supported by work reported by Hornbein *et al.*[25] documenting the development of emetic symptoms in all volunteers recovering from hyperbaric N_2O anesthesia (1.5 atm), during which all exhibited signs of sympathetic stimulation. Changes in middle ear pressure have been reported to range from +400 mm H_2O (3.92 kPa) during N_2O administration to −500 mm H_2O (−4.9 kPa) after N_2O was discontinued.[26] This negative pressure during recovery could irritate the vestibular system (and cause nausea and vomiting) by placing traction

on the round window membrane. Gastrointestinal distension by N_2O can produce nausea and vomiting in two ways: 1) gas forced into the GI tract by ventilation with a mask, and 2) increased volume of existing gas by N_2O transfer. Eger and Saidman[27] have established that bowel volume may increase by as much as 200% during anesthesia with 75% N_2O. These mechanisms may play a role in the development of PNV in individual patients. Nevertheless, we were unable to find any association between PNV and the use of N_2O in our study population. The conflict between our study and the other studies[20,25] may be explained, in part, on the basis that our patients were older.

We have attempted to standardize our anesthetic techniques and select only those procedures not previously associated with an increased incidence of PNV. Bonica *et al.*[16] noted a 70% frequency of PNV in patients undergoing gastrointestinal procedures compared to 15% in patients undergoing abdominal wall procedures. A high frequency of PNV has been reported following otologic and opthalmic procedures.[11,17] However, the site of surgery as a factor in the incidence of PNV is controversial, with some investigators reporting the site of surgery to be unimportant.[6,12] For these reasons, we limited our study to patients undergoing other procedures in an effort to minimize the surgical procedure as a factor in the development of PNV.

TABLE 5. Logistic Regression Results

Factor	Within 24 Postoperative Hours					
	Univariate		Multivariate			
	(N = 496)		(N = 414)		(N = 496)	
	2†	P‡	2	P	2	P
Gender	13.1	<0.001	12.3	<0.001	12.2	<.001
Age	8.1	0.002	8.7	.002	6.7	.004
Hx nausea & vomiting*	5.1	0.02	1.4	NS	Variable excluded	
Body mass index	0.0	NS	1.1	NS	1.2	NS

* N = 414 with information.
† Chi-square test from logistic regression.
‡ Two-tailed *P* value from logistic regression testing null hypothesis that the regression coefficient was zero.

As reported by others,[2,22] gender, age, and a history of prior PNV were important determinants of predicting PNV in our patients. In addition, obesity has been associated with PNV.[8,11,15] We were unable to demonstrate obesity to be a significant factor in the development of PNV. This difference may be due to our deliberate avoidance of ventilating any patient with a mask prior to endotracheal intubation. Because obese patients may be difficult to ventilate by mask, ventilation by mask in these patients may predispose to anesthesia gases inflating the stomach, possibly leading to an increased risk of PNV.

We were particularly interested by our findings of an

TABLE 6. Nausea and/or Vomiting by Age Groups, Body Mass Indices, and History of PNV with Prior Surgery

	Nausea and/or Vomiting in PAR (N = 780)				Nausea and/or Vomiting in PAR or at 24-H Follow-up (N = 496) Excluding Those Who Received Meperidine or Morphine for Postoperative Pain Relief			
	Females		Males		Females		Males	
	N	Percent With Symptoms	N	Percent With Symptoms	N	Percent With Symptoms	N	Percent With Symptoms
Overall	454	11.9	326	8.3	295	32.9	201	17.9
Age (yr)								
10–19	14	21.4	6	16.7	12	33.3	3	33.3
20–29	32	15.6	33	15.2	22	45.5	18	22.2
30–39	68	17.7	44	13.6	38	34.2	24	33.3
40–49	79	12.7	40	5.0	47	40.4	25	20.0
50–59	88	12.5	61	6.6	59	35.6	38	13.2
60–69	103	7.8	81	7.4	67	28.4	50	14.0
70–79	55	7.3	53	5.7	39	23.1	36	16.7
80–89	15	6.7	8	0.0	11	18.2	7	0.0
Body mass index								
<20.0	49	8.2	5	0.0	35	28.6	3	0.0
20–22.9	104	15.4	64	12.5	67	29.9	41	29.3
23–25.9	101	8.9	93	6.5	63	34.9	52	25.0
26–28.9	86	9.3	92	10.9	58	31.0	58	8.6
29–31.9	48	14.6	53	3.8	33	27.3	35	11.4
32+	66	15.2	19	5.3	39	46.2	12	16.7
History of nausea and/or vomiting with prior surgery								
No previous general anesthesia	76	6.6	57	8.8	51	27.5	31	25.8
No	254	9.1	227	6.6	169	32.5	147	15.0
Yes	124	21.0	42	16.7	75	37.3	23	26.1

increased frequency of PNV in patients between the time of PAR discharge and the 24-h postoperative visit. Depending upon the specific postoperative analgesic used, there was a two- to fivefold increase in PNV during that period compared to during the PAR stay. Many factors, including pain, analgesic use, mental stress and anxiety, and even delay of eating, may play a role in this increase. It is possible that the increase in PNV after leaving the PAR may have been related to the morphine that our patients received intraoperatively. Comroe and Dripps[28] noted a close relationship between morphine use and PNV after movement, and observed that this effect could last for hours. Patients' movement appears to play a major role. Numerous patients felt fine upon PAR discharge, but developed PNV during transport to their rooms. Reports that evaluate emetic symptoms only in the PAR probably underestimate the true frequency of PNV.

Our data suggest that morphine is associated with less PNV than meperidine when used for postoperative pain control. No attempt was made to control the total amount of narcotic any patient received, and not all patients received equipotent amounts of narcotics. Previous reports are contradictory concerning the emetic potential of meperidine and morphine. Didier *et al.*[7] reported meperidine to cause more PNV than morphine. In contrast, Dundee *et al.*[9] and Burtles and Peckett[6] have shown morphine to cause more PNV than meperidine. It is difficult to compare results from these reports because of variations in premedication, anesthetic management, and antiemetic use. More study is needed to define the role of postoperative narcotics in the development of PNV.

In summary, we have been unable to demonstrate in our study population an association between the use of nitrous oxide with either enflurane or isoflurane and the development of PNV. If such an association exists, the maximum potential increase in frequency of PNV in the immediate postoperative period associated with the addition of nitrous oxide to enflurane or isoflurane is less than 9.7%, based on a 95% confidence interval for the difference between groups. There was a suggestion that the choice of postoperative narcotic might play an important role in the development of PNV. However, all patients did not receive equipotent doses during the first 24 postoperative hours, and we cannot arrive at any firm conclusions regarding this issue. Gender, age, and history of prior PNV, but not obesity, were associated with PNV.

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