The Dose–Response of Nitrous Oxide in Postoperative Nausea in Patients Undergoing Gynecologic Laparoscopic Surgery: A Preliminary Study

Boris Mraovic, MD*

Tatjana Šimurina, MD, MSc†

Zdenko Sonicki, MD, PhD‡

Neven Skitarelić, MD, PhD§

Tong J. Gan, MD‖

BACKGROUND: Whether nitrous oxide (N_2O) increases the incidence of postoperative nausea and vomiting (PONV) after laparoscopic gynecologic surgery is still controversial, which may be due to the administration of different concentrations of inspired N_2O. We investigated whether N_2O results in a dose–response increase in PONV.

METHODS: Patients undergoing gynecologic laparoscopic surgery were randomized to receive 30% oxygen with air (G0, $n = 46$), 50% N_2O with oxygen (G50, $n = 46$), or 70% N_2O with oxygen (G70, $n = 45$). A standardized general anesthetic was used with no PONV prophylaxis. Known risk factors for PONV were controlled. Metoclopramide was used as a rescue antiemetic. The incidence of nausea, vomiting, use of rescue antiemetic, and pain visual analog scale (VAS) score was measured at 2 and 24 h postoperatively.

RESULTS: Patient demographics were comparable, and there were no differences among groups regarding factors that may influence PONV. The incidence of PONV at 24 h was 33% (15 of 46) in the G0 group, 46% (21 of 46) in the G50 group, and 62% (28 of 45) in the G70 group ($P = 0.018$). Subgroup analysis revealed a difference between G0 versus G70 groups ($P = 0.018$), but no significant difference between G0 versus G50 groups and G50 versus G70 groups. The incidence of nausea showed a similar difference (G0 = 26%, G50 = 35%, and G70 = 56%; $P = 0.012$), but the incidence of vomiting was not different among the groups although there was a trend (G0 = 28%, G50 = 35%, and G70 = 42%; $P = 0.377$). The severity of nausea (measured by VAS 100 mm) was significantly increased with increasing N_2O concentration (G0 = 10.9, G50 = 12.7, and G70 = 20.5; $P = 0.027$). The highest VAS score during 24 h was used for the analysis. There was no difference in the use of a rescue antiemetic among groups. Pain VAS scores and opioids consumption were not different among groups (at 2 and 24 h after surgery).

CONCLUSIONS: N_2O increases the incidence of postoperative nausea after gynecologic laparoscopic surgery. This preliminary finding indicates that N_2O may increase PONV in a dose-dependent fashion. A study with a sample size of >400 patients in each group would be necessary to demonstrate a statistically significant difference among each of these three groups. We do not recommend using a high concentration of N_2O in this clinical setting.

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Postoperative nausea and vomiting (PONV) are common complications after gynecologic laparoscopic surgery. In the absence of prophylactic antiemetics, the incidence of PONV may be as high as 40%–77%.[1–4] The administration of prophylactic antiemetics, either alone or in combination, have been shown to reduce this incidence. However, the routine administration of antiemetics increases costs and side effects.[5,6] Reducing baseline risk has been recommended as an effective strategy for reducing PONV, including using specific anesthetic techniques that minimize the risk of PONV.[7,8]

From the *Department of Anesthesiology, Thomas Jefferson University, Philadelphia, Pennsylvania; †Department of Anesthesiology and ICU, General Hospital Zadar, Zadar, Croatia; ‡Department of Medical Statistics, Epidemiology and Medical Informatics, School of Public Health "Andrija Štampar," Faculty of Medicine, University of Zagreb, Zagreb, Croatia; §ENT Department, General Hospital Zadar, Zadar, Croatia; and ‖Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

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Address correspondence and reprint requests to Boris Mraovic, MD, Assistant Professor of Anesthesiology, Department of Anesthesiology, Thomas Jefferson University, 111 South 11th St. Suite G8490, Philadelphia, PA 19107, USA. Address e-mail to Boris.Mraovic@jefferson.edu.

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Nitrous oxide (N_2O) has analgesic and sedative properties,[9] but may potentially increase the incidence of PONV.[10,11] N_2O might increase the incidence of PONV by several potential mechanisms: (1) increase in middle ear pressure[12,13]; (2) bowel distension, which is controversial.[14–16] A meta-analysis revealed that each additional hour of anesthesia using N_2O doubles the risk of bowel distension (odds ratio, 2.09; 95% CI: 1.27–3.59) compared with anesthesia using air/oxygen[14]; (3) activation of the dopaminergic system in the chemoreceptor trigger zone[17]; and (4) interaction with opioid receptors.[18]

The evidence on PONV after N_2O/volatile anesthetic (enflurane or isoflurane) in gynecologic laparoscopic surgery is controversial. N_2O has been demonstrated to increase the incidence of PONV in some studies,[10,11,19–22] but not in others.[23–26] Most of the studies concerning the influence of N_2O on PONV used 60%–70% inspiratory concentration (FI) of N_2O. It is not clear if limiting N_2O to a lower concentration decreases the risk of PONV. We postulate that the FI of N_2O has a dose–response relationship to the incidence of PONV. Our experimental hypothesis is that the incidence of PONV would increase as the FI N_2O increases from 50% and 70%, when compared with an air/oxygen (FI O_2 30%) control group in gynecologic laparoscopic surgery under general anesthesia.

METHODS

After IRB approval, written informed consent was obtained from 150 ASA physical status I and II patients, between 19 and 75 yr old, undergoing elective laparoscopic gynecological surgery (removal of ovarian tumors and cysts, myomectomy, laparoscopic-assisted vaginal hysterectomy, and infertility surgery). The exclusion criteria were obesity (body mass index >33 kg/m^2), pregnancy, breast-feeding, known hypersensitivity to drugs used in the study protocol, use of antiemetics, psychotropic drugs and steroids within 72 h before surgery. Patients with known comorbidities that could increase the incidence of PONV were also excluded, i.e., diseases which impaired gastric motility (diabetes mellitus, chronic cholecystitis, gastric and intestinal disease, neuromuscular disorders, neuropathies, and liver dysfunction), vestibular disease, history of migraine headache, central nervous system injury, renal impairment, irregular menstrual cycle (duration of <21 or >35 days and/or variations between cycles >4 days), alcoholism, and opioid addiction.

As per standard practice in the hospital, patients received 7.5 mg of midazolam PO 1 h before the surgery with no prophylactic antiemetics. Standard monitoring was applied including electrocardiography, noninvasive arterial blood pressure, pulse oximetry, and capnography.

After induction of anesthesia with thiopental 5 mg/kg and fentanyl 1–2 μg/kg, patients were manually ventilated with oxygen via facemask. Endotracheal intubation was facilitated with vecuronium 0.1 mg/kg IV. Patients were randomized by computer-generated random numbers to receive air and oxygen, FI O_2 30% (group G0), 50% N_2O and oxygen (group G50) or 70% N_2O and oxygen (group G70). Anesthesia was maintained with sevoflurane (end-tidal concentration approximately 1 minimum alveolar concentration) and supplemental bolus doses of fentanyl IV (1 μg/kg) to keep heart rate and arterial blood pressure within 20% of baseline values and additional vecuronium was administered to maintain 1 or 2 twitches on the train-of-four monitor. All patients received 10 mL/kg of crystalloids intraoperatively. Insertion of a nasogastric tube and gastric suction were not used. Neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1 mg IV.

Postoperatively, patients received 1000 mL (5 mL $\cdot$ kg^{-1} $\cdot$ h^{-1}) of crystalloids. The incidence of postoperative nausea, vomiting (POV) and the use of rescue antiemetics were collected at 2 and 24 h after surgery. The severity of postoperative nausea and pain were evaluated using a 100-mm visual analog scale (VAS) during the first 24 h postoperatively (VAS 0 = no pain/nausea, 100 = maximal pain/nausea). A nausea VAS score was measured for each episode, but the highest score during the early and the late period was used for statistical evaluation. Patients who experienced at least one episode of nausea, POV or retching, or any combination of these during 24 h postoperatively were considered to have had PONV. POV was defined as at least one episode of vomiting or retching that occurred within 24 h postoperatively. PONV was defined as early (within the first 2 h) or late (2–24 h postoperatively). Clinical nurses specifically trained for the study collected the data and were blinded to the anesthesia technique used and randomization. Pain VAS score and total amount of opioids were recorded at 2 h and at 24 h postoperatively. Metoclopramide 10 mg IV was used as the rescue antiemetic. This was the standard clinical practice in the hospital. The administration of rescue antiemetic was based on the following criteria: patients who had 2 or more episodes of POV or retching within a period of 30 min, nausea lasting more than 15 min or nausea VAS score 50 mm or more, or when a patient requested treatment. Diclofenac 75 mg IM was given immediately after surgery and, if needed, 12 h later. For severe pain (VAS score >40 mm), meperidine 25 mg up to 100 mg IV was used. All patients remained in the hospital for at least 24 h, as was our standard practice for laparoscopic gynecological surgery.

Calculation of sample size was based on preliminary data collected at General Hospital Zadar, Zadar, Croatia.[27] We determined that 45 patients per group would be sufficient to demonstrate a reduction of

PONV by 20% from G70 to G50 and by 20% from G50 to G0 with a power of 0.8 and $\alpha < 0.05$. The expected incidence of PONV at 24 h for the three groups was G0 = 30%, G50 = 50%, and G70 = 70%. The data were analyzed using the statistical program SAS 8.2. Quantitative values were compared using Kruskal-Wallis test and Mann-Whitney *U*-test with correction for multiple comparisons among groups. Categorical data were analyzed by Pearson χ^2 test or Fisher's exact test with correction for multiple comparisons as appropriate. Data were expressed as number or percentages and mean ± SD. A *P* value of <0.05 was considered statistically significant.

RESULTS

Of 150 patients, 137 completed the study (G0 = 46, G50 = 46, and G70 = 45). Thirteen patients were excluded from the analysis. Four patients were excluded in group G0: one patient was treated with corticosteroids for urticaria at induction of anesthesia, one patient had an anesthesia time <30 min, two patients had a protocol violation. Four patients were excluded in group G50: 1 patient had a conversion to laparotomy, 1 patient's anesthesia time was <30 min, and 2 patients had a protocol violation. Five patients were excluded in group G70: 2 patients' surgery was converted to laparotomy, 1 patient each had severe hypotension after induction, which lasted more than 5 min, acute coronary syndrome postoperatively, and anesthesia time <30 min.

There was no difference among groups regarding age, weight, height, body mass index, ASA physical status, smoking status, history of motion sickness and/or PONV, phase of menstrual cycle, thiopental dose, duration of anesthesia and surgery, and type of surgery (Table 1).

There was an overall difference in the incidence of PONV for 24 h after surgery among the groups ($P = 0.018$) (Table 2). Group G0 was significantly different from group G70 ($P = 0.018$), but no difference was noted between groups G0 and G50 ($P = 0.855$) or G50 and G70 ($P = 0.426$) (Table 2). Although there was a trend towards an increase in the incidence of early PONV (2 h postoperatively) and the late postoperative period (2–24 h) with increasing N_2O concentration, this did not reach statistical significance, $P = 0.071$ and 0.437, respectively (Table 2). The incidence of nausea showed a similar significant difference, with $P = 0.012$, but the incidence of POV was not different among the groups, although there was a trend (Table 2). The severity of nausea was significantly increased with increasing N_2O concentration. There was no difference in the need for rescue antiemetic (Table 2), pain scores or opioids consumption among the groups (at 2 and 24 h after surgery) (Table 3).

DISCUSSION

This study demonstrates that N_2O, when administered with oxygen and sevoflurane, increases the incidence of postoperative nausea. The preliminary findings indicate that N_2O may increase PONV in a dose–response fashion. The FI of 70% N_2O significantly increases the incidence of PONV at 24 h, nausea at 24 h, and nausea VAS scores when compared with no N_2O. In contrast, FI of 50% N_2O did not cause significantly increased PONV, nor nausea at 24 h compared with only oxygen/air.

We chose 50% and 70% N_2O in this study because of their clinical relevance. FI of N_2O lower than 50% is rarely used in anesthesia practice. The FI of 50% N_2O was chosen because it is generally perceived by anesthesiologists that this concentration minimally affects

Table 1. Patient Demographics

	G0 ($n = 46$)	G50 ($n = 46$)	G70 ($n = 45$)
Age (yr)	35.8 ± 10.5	36.7 ± 11.9	37.8 ± 14.1
Weight (kg)	66.2 ± 9.1	68.3 ± 10.5	67.4 ± 10.6
Height (cm)	169.9 ± 6.9	168.9 ± 5.0	167.9 ± 5.7
ASA physical status (I/II)	36/10	35/11	35/10
Smoking *n* (%)	20 (43)	17 (37)	18 (40)
History of motion sickness and/or PONV *n* (%)	16 (35)	23 (50)	16 (36)
Phase of menstrual cycle (*n*)			
Follicular/luteal	28/14	25/14	23/12
Postmenopause	4	7	10
Thiopental (mg)	331 ± 45	341 ± 52	337 ± 53
Duration of anesthesia (min)	72.3 ± 36.1	76.3 ± 36.2	70.4 ± 31.9
Duration of surgery (min)	54.6 ± 33.9	59.8 ± 34.8	53.3 ± 30.8
Type of surgery (*n*)			
Ovarian cystectomy/tumorectomy	29	29	25
Myomectomy	6	7	6
Laparoscopic assisted vaginal hysterectomy	3	2	4
Laparoscopy for infertility	8	8	10

No statistical differences among groups (G0 = air, G50 = 50% nitrous oxide, and G70 = 70% nitrous oxide).

Data presented as mean ± SD or *n* (%).

PONV = postoperative nausea and vomiting.

Table 2. Incidence of PONV, Nausea, Vomiting, and Use of Rescue Antiemetic

	G0-air (n = 46)	G50–50% N_2O (n = 46)	G70–70% N_2O (n = 45)	P
PONV (24 h) (n, %)	15 (33)	21 (46)	28 (62)†	0.018*
PONV (0–2 h) (n, %)	10 (22)	16 (35)	20 (44)	0.071
PONV (2–24 h) (n, %)	9 (20)	11 (24)	14 (31)	0.437
Nausea (24 h) (n, %)	12 (26)	16 (35)	25 (56)†	0.012*
Nausea (0–2 h) (n, %)	9 (20)	12 (26)	19 (42)	0.05
Nausea (2–24 h) (n, %)	6 (13)	8 (17)	9 (20)	0.668
Nausea VAS scores (mm)	10.9 ± 20.5	12.7 ± 19.5	20.5 ± 21.8†	0.027*
Severe nausea	3 (7)	3 (7)	4 (9)	0.882
Vomiting (24 h) (n, %)	13 (28)	16 (35)	19 (42)	0.377
Vomiting (0–2 h) (n, %)	8 (17)	11 (24)	14 (31)	0.31
Vomiting (2–24 h) (n, %)	8 (17)	9 (20)	12 (27)	0.527
Vomiting episodes in patients who vomited	2.6 ± 1.1	2.7 ± 2.3	2.4 ± 1.9	0.463
Severe vomiting	5 (11)	6 (13)	6 (13)	0.926
Metoclopramide (n, %)	7 (15)	10 (22)	10 (22)	0.642

Data presented as mean ± SD.

Severe nausea–visual analog scale >50 mm or duration longer than 15 min.

Severe vomiting–2 or more episodes of vomiting and retching within a period of 30 min or total number of 3 or more emetic episodes during 24 h postoperatively.

PONV = postoperative nausea and/or vomiting.

* Statistically significant difference ($P < 0.05$).

† Statistically significant vs G0 ($P < 0.05$).

Table 3. Pain Visual Analog Scale (VAS) Score and Opioid Consumption

	G0 (n = 46)	G50 (n = 46)	G70 (n = 45)	P
Pain VAS scores (mm)				
Postoperative at				
2 h	21.6 ± 13.0	25.4 ± 12.9	23.9 ± 15.1	0.30
24 h	16.8 ± 8.5	13.8 ± 11.9	12.6 ± 12.3	0.06
Intraoperative fentanyl (μg)	180 ± 70	190 ± 60	180 ± 80	0.22
Postoperative meperidine (mg)	6.5 ± 22.0	7.1 ± 16.4	10.1 ± 19.6	0.27

No statistical differences among groups (G0 = air, G50 = 50% nitrous oxide, and G70 = 70% nitrous oxide).

Data presented as mean ± SD.

the incidence of PONV.[28] However, there are no data to support that assumption. N_2O 70% was selected as it represents the highest concentration of N_2O used in clinical anesthesia practice.

All the reported studies on PONV after N_2O/volatile anesthetic (enflurane or isoflurane) in gynecologic laparoscopic surgery compared a single FI of N_2O, usually in the range of 66%–70%, with control.[20,21,23,24] The results from this study agree with those of Felts et al. who demonstrated that PONV is increased from 9.3% in air/oxygen (FI O_2 33%) to 29.2% with 66% of N_2O in oxygen after enflurane anesthesia for outpatient gynecologic laparoscopy ($P < 0.001$).[21] Contrary to our study, Hovorka et al. did not find significant differences in the incidence of PONV among three groups of patients anesthetized with either isoflurane or enflurane with 70% N_2O in oxygen, and isoflurane without N_2O, after gynecological laparoscopy.[23] This discrepancy could be explained by the different duration of the anesthesia (the mean anesthesia times among groups were 37–40 min in Hovorka et al.'s study and 70–76 min in our study). One of the mechanisms of N_2O-induced nausea and vomiting might be related to middle ear pressure. The longer duration of N_2O exposure, as in our study, likely caused a larger increase in middle ear pressure as the time to reach peak middle ear pressure is about 60 min after the introduction of N_2O and about 30 min to return to baseline after N_2O is discontinued.[12] Also, in Hovorka et al.'s study, smoking status was unknown, which could have biased the results.

Lonie and Harper found a significant increase only in the incidence of POV between study groups (from 17% without N_2O to 49% with N_2O 67% in oxygen after enflurane anesthesia), but not nausea.[20] This could have been due to the more frequent administration of rescue antiemetic in our study. We treated our patients who had severe nausea and patients who vomited (22% of patients in both groups with N_2O and 15% in the group without N_2O). However, only a few patients were treated in Lonie and Harper's study (7.5% patients in the N_2O group and 7.1% in the group without N_2O). Sengupta and Plantevin reported results similar to Lonie and Harper, but their study was under-powered, with a smaller number of patients (64), which resulted in a nonstatistically significant difference between the N_2O group and oxygen group, 33% versus 12.9%, respectively.[24]

Results from the IMPACT study suggest that omitting N_2O in a multimodal PONV prophylaxis strategy

further decreases the incidence of PONV by about 12%, if a volatile anesthetic is used.[29] However, the study did not address the dose–response relationship of N_2O. The preliminary results from our study, which showed that 70% N_2O increases the incidence of nausea concur with the IMPACT study and a meta-analysis.[10,29] Although our initial power analysis was expected to provide adequate power to demonstrate a dose–response, our actual results showed a smaller than expected difference. Assuming that this trend in the incidence of PONV at 24 h were to persist, a study with a sample size of 221 patients in each group would have been necessary to produce a statistically significant difference among each of the three groups with a power of 0.8 and $\alpha < 0.05$. Using the same assumption, it would require 410 patients per group to show a significant difference in the incidence of nausea at 24 h, and 691 patients per group for the incidence of POV at 24 h. The value of this study is that it provides preliminary data that indicate that N_2O may increase PONV in a dose–response fashion. We feel it would be valuable if a large prospective study were performed to confirm if 50% N_2O causes a lower incidence of PONV than 70% N_2O.

There are several limitations to our study. We can be criticized for not administering a prophylactic antiemetic or combination strategy given the high-risk nature of this surgical population for PONV. We, however, wanted to specifically investigate the dose–response effect of N_2O, which may have been masked by the use of prophylactic antiemetics. The difference in N_2O concentrations among the groups also means that the FI O_2 was different in groups G50 and G70. High FI O_2 (0.8) has been shown to reduce the incidence of PONV.[30,31] However, more recent studies have cast doubt on previous findings. Purhonen et al., in ambulatory gynecological laparoscopic patients, showed that supplemental oxygen does not reduce the incidence of PONV.[32] The authors compared FI O_2 30% and FI O_2 80% with additional O_2 in the postanesthesia care unit up to 1 h, but did not find a difference in the PONV incidence after 24 h, 62% versus 55%, respectively. Our study had only a 20% difference in FI O_2 among the groups compared with a 50% difference in Purhonen et al.'s study, and we did not use supplemental O_2 in the postanesthesia care unit. Therefore, the impact of O_2 in our study is likely to be small, if any. Furthermore, a large study involving 560 patients investigating the impact of O_2 on PONV concluded it has no impact on PONV regardless of the site or surgery or the observational period (early or late PONV).[33]

In conclusion, we demonstrated that 70% N_2O increases the incidence of nausea and severity of nausea at 24 h after laparoscopic gynecological surgery in the absence of any prophylactic antiemetic. This preliminary finding indicates that N_2O may increase PONV in a dose-dependent fashion. A study with a sample size of >400 patients in each group would be necessary to produce a statistically significant difference among groups with no N_2O, 50% N_2O, and 70% N_2O. We do not recommend using high concentrations of N_2O in this clinical setting.

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