ORIGINAL RESEARCH

THE EFFECT OF NITROUS OXIDE ON POSTOPERATIVE NAUSEA AND VOMITING

Hatice Türe, Arzu Takıl, Zeynep Eti, F. Yılmaz Göğüş
Marmara Üniversitesi, Tıp Fakültesi, Anesteziyoloji ve Reanimasyon A.D., İstanbul, Türkiye

ABSTRACT

Objective: Postoperative nausea and vomiting (PONV) is a common problem and its cause is multifactorial. The relationship between PONV and nitrous oxide is under debate. The aim of this study was to evaluate the relationship between nitrous oxide and PONV in patients undergoing laparoscopic cholecystectomy.
Patients and Methods: Forty premedicated female patients, ASA I or II, age 18-60 years and weigthing between 50-80 kg, were scheduled to undergo elective laparoscopic cholecystectomy. They were randomly assigned to two groups. Anaesthesia was induced in all patients with thiopental sodium, remifentanil and atracurium. Anaesthesia was maintained with sevoflurane, nitrous oxide in oxygen in group I and sevoflurane, air in oxygen in group II. Perioperatively remifentanil was infused in all patients. The patient's PONV and pain scores were assessed 24 hours postoperatively.
Results: In group I, PONV scores were significantly higher at the 1st and 4 th h postoperatively, however, there was no significant difference in group II. There was no significant difference in PONV and pain scores and the percentage of patients needing antiemetics between groups. No correlation was found between PONV and postoperative pain.
Conclusion: Our data demonstrate that nitrous oxide does not increase the incidence or severity of PONV in patients undergoing laparoscopic cholecystectomy.

Keywords: Nitrous oxide, Postoperative, Nausea, Vomiting

NİTRÖZ OKSİDİN POSTOPERATİF BULANTI VE KUSMA ÜZERİNE ETKİSİ

ÖZET

Amaç: Postoperatif bulantı ve kusma (POBK) birçok nedenden kaynaklanan ve sık karşılaşılan bir problemdir. POBK ve nitröz oksit arasındaki ilişi yeterince araştırılmıştır.Bu çalışmada laparoskopik kolesistektomi geçiren hastalarda, nitröz oksitin POBK`ya etkisinin araştırılması amaçlanmıştır.
Yöntem: Premedikasyon yapılmış, ASA I-II, 18-60 yas arasında, 50-80 kg ağırlığında, elektif laparoskopik kolesistektomi operasyonu geçirecek 40 kadın hasta çalışmaya dahil edildi. Hastalar randomize olarak 2 gruba ayrıldı. Tüm hastalara tiyopental sodyum, remifentanil ve atrakuryum ile anestezi indüksiyonu uygulandı. Anestezi idamesinde, grup I`de sevofluran ve nitröz oksit-oksijen karışımı,grup II`de sevofluran ve hava-oksijen karışımı kullanıldı. Tüm hastalara peroperatif remifentanil infüzyonu verildi. Hastaların POBK ve ağrı skorları 24 saat süre ile takip edildi.
Bulgular: POBK skorları, grup I`de 1. ve 4. saatlerde diğer saatlere göre yüksekti, ancak grup II`de saatler arasinda istatistiksel fark saptanmadı. Gruplar arasında, POBK ve ağrı skorları, antiemetik ilaç ihtiyacı olan hasta yüzdesi açısından fark saptanmadı. Hastaların POBK ve ağrı skorları arasında ilişki saptanmadı.
Sonuç: Çalışmamız sonucunda, laparoskopik kolesistektomi operasyonu geçiren hastalarda, peroperatif kullanılan nitröz oksidin, postoperatif bulantı ve kusmanın sıklığı ve şiddetini arttırmadığı sonucuna varılmıştır.

Anahtar Kelimeler: Nitröz oksit, Postoperatif, Bulantı, Kusma

Corresponding author:
Hatice Türe, M.D.
Marmara Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon A.D., Altunizade, İstanbul, Türkiye
e-mail: htcture@yahoo.com

Marmara Medical Journal 2007;20(2);85-91

INTRODUCTION

In the literature, postoperative nausea and vomiting (PONV) has been variously described as the "big little problem," the "final therapeutic challenge" for the anaesthesiologist, and the "big, big problem" of the ambulatory surgery[1,2].

The cause of PONV is multifactorial. Some of the factors are well known, although others remain unknown or poorly understood. Studies have attempted to identify factors associated with PONV and to predict which patients are at the highest risk for this complication[3,4]. These factors may be related to the patient, the surgical procedure, or the choice of anaesthetic[5]. However, one of the factors contributing to PONV is the use of nitrous oxide during anaesthesia[6]. Several studies investigating the cause and effect relationship between PONV and nitrous oxide in adults have produced conflicting results, some claiming that nitrous oxide increases PONV[7,8] while others were unable to confirm these findings[6,9]. In this prospective, randomized, double-blind study, the role of nitrous oxide anaesthesia in increasing PONV was studied in female patients undergoing laparoscopic cholecystectomy.

PATIENTS AND METHODS

After the approval of the Institutional Ethics Committee and the patients' written consent, 40 female patients, ASA physical status I or II, aged 18-60 years and weighing between 50-80 kg, scheduled for elective laparoscopic cholecystectomy were studied. They were randomly assigned to two study groups of 20 patients each. Patients with significant cardiac, respiratory, hepatic, renal or hematologic disorders, contraindications to administration of the study drugs, history of gastrointestinal bleeding, monoamino oxidase inhibitor therapy, alcohol abuse and motion sickness or previous PONV were excluded from the study. Forty-five minutes prior to the induction of anaesthesia, all the patients were premedicated with midazolam 0.07 mg/kg and atropin 0.015 mg/kg IM. Anaesthesia was induced in all patients with thiopental sodium 3-5 mg/kg and remifentanil 1mgr/kg IV. Atracurium 0.5 mg/kg IV was administered to achieve muscle relaxation prior to tracheal intubation. After tracheal intubation a nasogastric tube was inserted and kept in place until just before extubation. Anaesthesia was maintained with 2% sevoflurane, 70% nitrous oxide in oxygen in group I and 2% sevoflurane, 70% air in oxygen in group II. Perioperatively, remifentanil was infused in all patients at a rate of 0.5 mgr/kg/min. The sevoflurane concentration was titrated to maintain mean arterial pressure and heart rate within 20% of baseline values. The lungs were ventilated mechanically to maintain the end tidal carbon dioxide pressure between 35-40 mmHg. Heart rate, non-invasive arterial blood pressure, oxygen saturation and end tidal carbon dioxide pressure were measured and recorded every five minutes during surgery. In both groups, diclofenac sodium 75 mg IM was administered 30 minutes before the end of surgery. Following the last skin suture, 10 ml 0.25% bupivacaine was infiltrated at the incisions and the remifentanil infusion was discountinued.

The patients were then extubated and transported to the postanaesthetic care unit (PACU). Routine PACU management included recording of vital signs. Oxygen (6 lt/min) was administered on admission and discontinued before discharge to the ward. After the patient arrived in the PACU, a blind investigator observed the patient postoperatively. The patient's PONV and pain scores were assessed at 30 minutes, 1^{st} ,2^{nd} ,4^{th} , 6^{th} ,12^{th} , and 24^{th} hour postoperatively. PONV scores ranged from 0 to 3 (0: no nausea and vomiting, 1: mild nausea not vomiting and not requiring treatment, 2: moderate nausea, mild vomiting and requiring treatment, 3: severe vomiting). Metoclopramide 20 mg IV was administered when the PONV score was greater than 1. The incidence of nausea and vomiting separately during the early (0-6 h) and delayed (6-24 h) period and the percentage of patients requiring antiemetic therapy were also recorded Pain intensity was assessed with the

5 point verbal pain scale (0; no pain, 1: mild pain, 2: moderate pain, 3: severe pain, 4: excruciating pain). Meperidine 1 mg/kg IV was administered when the pain score was greater than 1 (until a subsequent pain score was <2).

The χ^2 test with Fisher correction was utilized to analyze differences between groups in demographics and the incidence of PONV. Pain and PONV scores were compared by using repeated measures of ANOVA and the student's t-test. P<0.05 was considered as significant. All data were recorded as mean ± SD.

RESULTS

There was no significant difference between groups in the demographic characteristics of the patients and duration of the operation (Table I). Intraoperatively, the mean amount of remifentanil was similar in the two groups.

There was no significant difference in the incidence of nausea or vomiting between the groups during the 24 h postoperative period (Table II). The incidence of nausea during the early period (0-6 h) was 20% in group I and 15% in group II while it was 20% in group I and 10% in group II during the delayed period (6-24 h) (p>0.05). The incidence of vomiting during the early period was 40% in group I and 25% in group II while it was 5% in group I and group II during the delayed period (p>0.05). 40% of the patients in group I and 55% of group II did not experience PONV symptoms during 24 h postoperatively. In group I, the PONV scores were significantly increased at 1st and 4th h (p<0.05) but there was no significant change in group II (Figure I). However, no difference was found in the PONV scores of patients between groups. Eight patients (40 %) in group I and 5 patients (25 %) in group II required antiemetic therapy once or more time during the 24 h postoperatively (Table II). There was no significant difference in the percentage of patients requiring antiemetic therapy between groups (Table II).

Twenty patients (100 %) in group I and 18 patients (95 %) in group II required additional analgesics postoperatively (Table II). There was no significant difference in postoperative pain scores between groups (Figure 2). No significant correlation was found between PONV and pain.

Table I. Demographic characteristics, duration of surgery and total remifentanil dose (mean± SD).

	N_2O+O_2 (n=20)	**Air+O_2** (n=20)
Age (yr)	39.85± 11.11	48.35± 11.61
Weight (kg)	59.9± 8.08	64.8± 10.35
Duration of surgery (min)	60± 9.2	58± 7.05
Dose of remifentanil (μgr)	1840± 495.8	1891± 510.2
ASA class (I/II)	14/6	11/9

Table II. Incidence and Severity of Postoperative Nausea, Vomiting and Pain (%).

	$N_2O+ O_2$ (n:20)	$Air+O_2$ (n:20)
PONV (n)		
None	8 (40 %)	11(55 %)
Only nausea	12 (60 %)	9 (45 %)
Vomiting	8 (40 %)	5 (25 %)
Antiemetic medication needed (n)		
None	12 (60 %)	15 (75 %)
Once	4 (20 %)	1 (5 %)
More often	4 (20 %)	4 (20 %)
Pain (n)		
None	0	2 (10 %)
Mild	0	0
Moderate	18 (95 %)	17 (85 %)
Severe	8 (40 %)	2 (10 %)
Persistent	2 (10 %)	1 (5%)

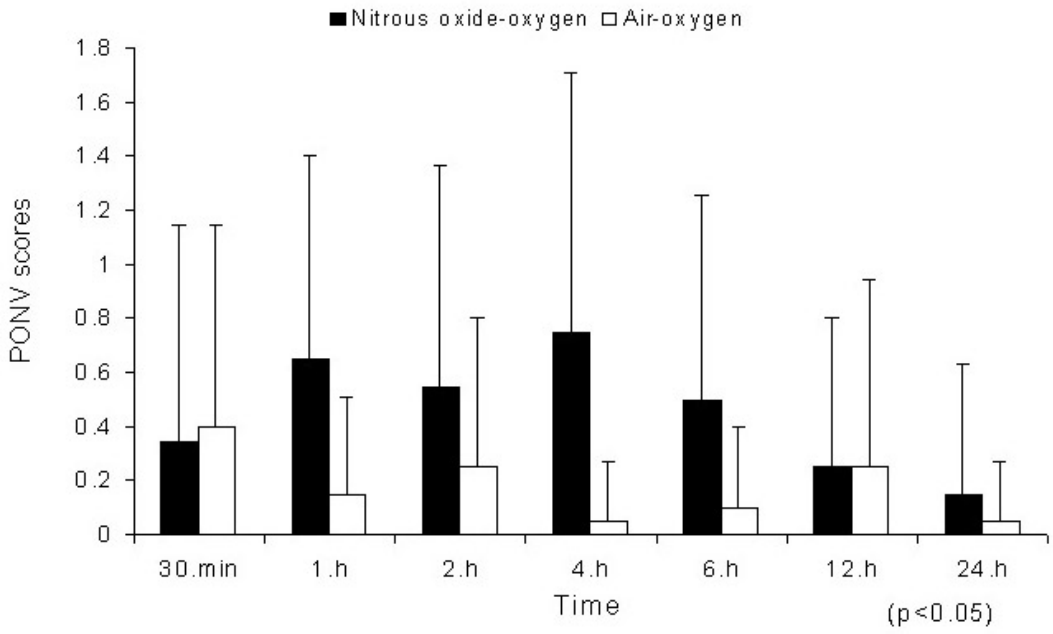

Figure 1. PONV scores of patients within 24 hours (mean ± SD).

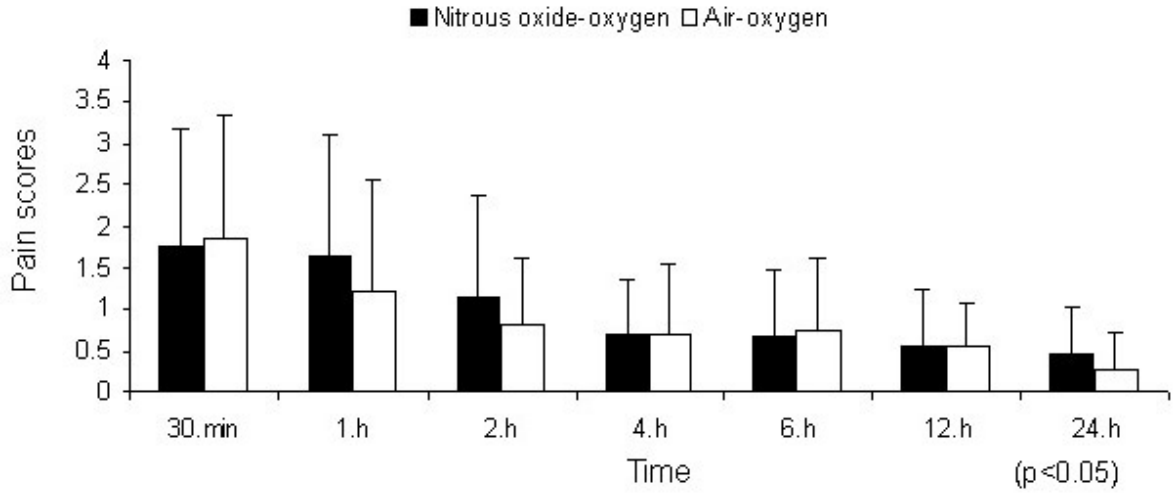

Figure 2. Pain scores of patients within 24 hours (mean ± SD).

DISCUSSION

Postoperative nausea and vomiting have been associated for many years with the use of general anaesthetics for surgical procedures [5,10] The incidence of PONV is approximately 9% to 10% during the stay in the post anaesthesia care unit and increases to 30% during the first 24 hours postoperatively, leading to delayed discharge or, rarely, serious complications[11]. There are hundreds of published randomized controlled trials investigating the efficacy of interventions which are thought to have impact on the incidence of PONV. However there are still many unanswered questions[12]. There have been attempts to identify patient related and non-related risk factors for PONV. Sinclair et al[13] in their prospective study with 17638 outpatients concluded that age,sex,smoking status, previous history of PONV,type and duration of anaesthesia and type of surgery are independent predictors of PONV. Also Apfel et al[14] found that the four main risk factors for PONV were female gender, prior history of PONV and motion sickness, nonsmoking and the use of opioids. Among all these risk factors, there have been several studies evaluating the effect of anaesthetics, in particular nitrous oxide. However the results are conflicting and today there is still no consensus for omitting nitrous oxide during general anaesthesia. Divatia et al[15] performed a meta analyses of published randomized controlled trials studying the effect of nitrous oxide on PONV. Twenty-four studies were found to be eligible for meta analyses. There were only 5 statistically significant "positive" trials showing that omission of nitrous oxide decreased PONV. There were 15 "negative" trials and no effect in 4 trials. However they concluded that omission of nitrous oxide can reduce the risk for PONV by nearly 30%, stressing the need for further studies and randomized controlled trials. The main reason for the conflicting results is the methodological problems in the studies looking at PONV. Kortilla[4] and Watcha[5] stated that it is important to have an appropriate study design whereby all confounding factors are evenly distributed between the study groups and this is achieved by limiting the study to a standardized surgical procedure during a standardized anaesthetic and assigning patients to receive an intervention according to a predetermined randomized double blind method. Also populations studied in the PONV trials should represent a reasonable clinically relevant baseline risk[16]. In our study; we studied a population having relevant risk factors: those who were female, non-smoker,undergoing laparoscopic surgery, and those who were

administered opioids peri and postoperatively. We also standardized the surgical procedure and anaesthetics as all patients received the same anaesthetics (thiopental, remifentanil and sevoflurane) with nitrous oxide being the only variable.

Watcha[5] and Tramer[12] in their reviews of PONV suggested that nausea and vomiting must be considered separate endpoints for more precise results. Also Kortilla[4] stated that the outcome should be included in studies on PONV as the need to give antiemetic and the number of patients needing antiemetics are good endpoints for statistical analyses. In our study; we considered nausea and vomiting and the number of patients needing antiemetics as separate endpoints and found no significant difference in the incidence of nausea or vomiting and the percentage of patients needing antiemetics when nitrous oxide was omitted. According to Watcha[5], separate time-based analyses should be performed for the early (0-6 h) or delayed (6-24 h) postoperative period in the studies. Short term efficacy has an economic impact, mainly in day surgery where patients are meant to be discharged within hours after surgery; while long term efficacy is a better indicator of antiemetic efficacy and patient comfort[16]. We also studied the early and delayed effects of nitrous oxide on PONV and could not find a significant difference.

In the reviews about PONV, it was emphasized that the effect of omitting nitrous oxide was most pronounced for postoperative emesis in adults undergoing procedures known to be associated with a high risk for PONV and have little influence on nausea itself[5,12,15]. In our study, although the patients were female,nonsmoker,administered opiods and underwent laparoscopic surgery,the omission of nitrous oxide did not have a significant influence on either nausea or vomiting. The decrease in PONV when nitrous oxide is avoided may reflect the use of higher inspired oxygen concentration rather than a direct effect of nitrous oxide[17]. We used air instead of nitrous oxide with the same inspired oxygen concentrations in all patients.

Postoperative pain is another predicting factor for PONV[18,19]. Pain significantly prolongs recovery and discharge times and contributes to postoperative nausea and vomiting, often leading to unanticipated admission after ambulatory surgery. Cholecystectomy can cause inflammation or local irritation around the gall bladder bed,liver, diaphragm and/or peritoneum, exacerbating pain[20]. The intensity of pain is most severe during the first 2-3 h after the laparoscopic cholecystectomy[21]. Postoperative pain control for laparoscopic cholecystectomy is attainable using a multimodal pain management strategy. Michaloliakua[20] stated that the concomitant use of local anaesthetics, nonsteroidal antiinflammatory drugs and opioids proved to be highly effective after laparoscopic cholecystectomy. Although our strategy for postoperative pain control included intramuscular diclofenac Na and incisional bupivacaine infiltration, the percentage of patients needing additional opioid analgesics was very high in the two groups (100% in group I and 95% in group II). However, no correlation was found between PONV and pain.

It is commonly observed that the use of opioids during surgery increases the incidence of PONV[3,12,14]. In our study, remifentanil was infused perioperatively. This agent has a pharmocokinetic profile characterized by rapid equilibration with the central compartment, easy titrability and a short termination half-life independent of infusion duration. Our results about the postoperative additional analgesics also imply the need for a longer-acting opioid for postoperative analgesia[22]. Whether there is a synergistic effect between opioids and nitrous oxide in increasing emetic symptoms in the postoperative period is still a conjecture[7]. Our results do not support this idea since we used intraoperative and postoperative opioids (remifentanil and meperidine in all patients but did not find a higher incidence of nausea or vomiting in the nitrous oxide group as in the study by Pandit et al[6].

We concluded that nitrous oxide did not increase the incidence of nausea and

vomiting. In addition, nitrous oxide did not increase the percentage of patients needing antiemetic therapy in female patients undergoing laparoscopic cholecystectomy.

REFERENCES

1. Fisher DM. The "big little problem" of postoperative nausea and vomiting; do we know the answer yet (editorial)? Anesthesiology 1997; 87: 1271-1275.
2. Kapur PA. The big "little problem". Anesth Analg 1991; 73: 243-245.
3. Alexander GD, Skupski JN, Brown EM. The role of nitrous oxide in postoperative nausea and vomiting. Anest Analg 1984; 63: 17S.
4. Korttila K. The study of postoperative nausea and vomiting. Br J Anaesth 1992; 69 (suppl): 20S-23S.
5. Watcha MF. Postoperative nausea and emesis. Anesthesiology Clinics of North America 2002; 20: 471-484.
6. Pandit UA, Malviya S, Lewis IH. Vomiting after outpatient tonsillectomy and adenoidectomy in children: the role of nitrous oxide. Anesth Analg 1995; 80: 230-233.
7. Hopkins PM. Nitrous oxide: a unique drug of continuing importance for anaesthesia. Best Pract Res Clin Anaesthesiol 2005; 19: 381-389.
8. Lonie DS, Harper NJN.Nitrous oxide and vomiting. The effect of nitrous oxide on the incidence of vomiting following gynecological laparoscopy. Anaesthesia 1986; 141: 703-707.
9. Felts JA, Poler M, Spitznagel EL. Nitrous oxide, nausea and vomiting after outpatient gynecologic surgery. J Clin Anesth 1990; 2: 168-171.
10. Andrews PLR. Physiology of nausea and vomiting. Br J Anaesth 1992; 69 (suppl 1): 2S-19S.
11. Junger A, Hartmann B, Benson M, et al. The use of an anaesthesia information management system for prediction of antiemetic rescue treatment at the postanesthesia care unit. Anesth Analg 2001; 92: 1203-1209.
12. Tramer MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues. Acta Anaesthesiol Scand 2001; 45: 4-13.
13. Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? Anesthesiology 1999; 91: 109-118.
14. Apfel CC, Laara E, Koivuranta M,Greim CA, Roewer N. A simplified risk sore for predicting postoperative nausea and vomiting. Anesthesiology 1999; 91: 693-700.
15. Divatia JV, Vaidya JS, Badwe RA,Hawaldar RW. Omission of nitrous oxide during anesthesia reduces the incidence of postoperative nausea and vomiting. A meta-analysis. Anesthesiology 1996; 85: 1055-1062.
16. Tramer MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part II. Recommendations for prevention and treatment,and research agenda. Acta Anaesthesiol Scand 2001; 45: 14-19.
17. Greif R, Laciny S, Rapf B, et al. Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Anesthesiology 1999; 91: 1246-1252.
18. White PF, Shafer A. Nausea and vomiting: Causes and prophylaxis. Semin Anesth 1988; 6: 300-308.
19. Anderson R, Krohg K. Pain as a major cause of postoperative nausea. Can Anaesth Soc J 1976; 23: 366-369.
20. Michaloliakua C, Chung F, Sharma. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. Anesth Analg 1996; 82: 44-51.
21. Narchi P, Lecoq G, Fernandez H, Benhamou D. Intraperitoneal local anesthetics and scapular pain following daycase laparoscopy. Lancet 1991; 338:1569-1570.
22. Beers RA, Calimlim JR, Uddoh E, Esposito BF, Camporesi EM. A comparison of the cost-effectiveness of remifentanil versus fentanil as an adjuvant to general anesthesia for outpatient gynecologic surgery. Anesth Analg 2000; 91: 1420-5.