IS NITROUS OXIDE NECESSARY FOR GENERAL ANAESTHESIA?

Syed Mushtaq Gilani, Khalid Sofi*

Ayub Medical College, Abbottabad Pakistan, *King Fahad National Guard Hospital, Riyadh, Saudi Arabia

Background Nitrous oxide (N_2O) has been used for about 150 years in clinical anaesthesia. Several recent reviews of the effect of nitrous oxide have concluded that there are certain contraindications to the use of this gas for general anaesthesia and its ecological effects, ozone depleting potential, immune depression and the proven factor of PONV have questioned the routine use of nitrous oxide in patients undergoing surgical procedures in general anaesthesia. **Methods:** This study comprised of 200 adult patients undergoing general anaesthesia with 40% O_2 and Sevoflurane with and without N_2O. All patients had standard anaesthetic care and monitoring with BIS monitoring in 120 patients. The effect of avoiding N_2O was observed on anaesthetic perioperative management and haemodynamics, PONV and pain in PACU. **Results:** Demographic and perioperative characteristics were similar to both groups. Nitrous oxide free group needed only 0.233% (mean) more Sevoflurane. There was a marked reduction in incidence of PONV (11% to5 %) in N_2O free group. Duration of surgery (97.72±52.393 in N_2O group, 103.75±48.671 in N_2O free group) and induction dose of propofol (155.30 ±38.572 in N_2O group and 158.50± 36.164 in N_2O free group) did not differ significantly in the two groups. **Conclusion:** The omitting of N_2O from anaesthetic regimen has a substantial impact on patient comfort after surgery by reducing incidence of PONV and it does not have any justifiable indication of its use in General anaesthesia.

Keywords Nitrous Oxide, PONV

INTRODUCTION

Nitrous Oxide has been used since the very first day of clinical general anaesthesia despite the adverse effects that may result directly from nitrous oxide or from the restriction of inspired oxygen concentration, the use of nitrous oxide in patients undergoing surgery remains near routine in different anaesthetic techniques worldwide.

Thus for many years a mixture of oxygen and nitrous oxide has been used as the carrier gas to deliver inhalational agents with no thought given to its true value or disadvantages. The common opinion that nitrous oxide is a near inert (anaesthetic) gas which can be used without problem is no longer sustainable in the light of current knowledge.[1–4] Generally accepted contraindications to the use of nitrous oxide include ileus, occlusion of Eustachian tube,[5] bowel distension[6] head injury, raised intracranial tension[7] patients with compromised coronary perfusion,[8] patients with chronic Vitamin B deficiency,[4,10] folate deficiency[11] and congenital neutropenia. Due to its proven harmful effect on DNA synthesis nitrous oxide may be considered to be contraindicated in pregnant women in first two trimesters, during IVF and in immunodeficiency. Nitrous oxide is responsible for the development of diffusion hypoxia in the emergence phase and its use leads to increased cuff pressure, necessitating frequent cuff–pressure adjustments.[12] Finally nitrous oxide is proven factor for PONV.[13–15]

Nitrous oxide is also not inert in respect to ecology as it is known to have ozone depleting potential and greenhouse warming potential.[16] Though medical use of nitrous oxide contributes only 0.35 to 2% to total amount of nitrous oxide released[17] by avoiding N_2O we can make a small but important impact on climate change during our average working day.

The low toxicity of modern anaesthetic agents and accumulating evidence about the adverse effects of nitrous oxide provide compelling reasons to question the continued routine use of nitrous oxide in anaesthesia for patients undergoing major surgery and there is a strong acceptance to the complete cessation of routine use of nitrous oxide.[18,19] A questionnaire survey in UK[20] has shown that 49% of consultant anaesthetists had reduced their use of nitrous oxide to eliminate the exposure to a hazardous substance where practicable.

The present study is undertaken to evaluate the effect of nitrous oxide- free general anaesthesia on the undesirable clinical outcomes in PACU like PONV, shivering, fever, incisional pain, respiratory complication and PACU overstay.

MATERIAL AND METHODS

This study comprised of 200 in-patients and day care patients of both sex above age of 18 years (Table-1) undergoing various elective and emergency surgical procedures under general anaesthesia (Table-2). Patients undergoing cardiac surgery or thoracic surgery were excluded. Patients were randomly assigned to receive either nitrous oxide free or nitrous oxide based general anaesthesia.

All the cases were seen by anaesthesiologist in the pre-anaesthesia round or in pre-anaesthesia clinic. Preoperative demographic characteristics and

details of patient medical and surgical history were recorded. All the cases had Intravenous line inserted in the holding area or had it from the ward and anaesthesia induced by Intravenous anaesthetic, Propofol. General anaesthesia was maintained by 40 % oxygen (FiO_2 0.4) with Air or nitrous oxide and volatile anaesthetic Sevoflurane (MAC 1.2–1.3) through oral endotracheal tube or laryngeal mask depending on the study group and type of surgery. All patients received standard anaesthetic care and monitoring. Inspired, expired FiO_2, end tidal CO_2, inspired and expired anaesthetic concentration and MAC were monitored in all cases. Tidal volume and respiratory rate was adjusted to maintain Pet_{CO2} at approximately 30–35 mmHg. Choice of anaesthetic drugs, narcotic analgesic, muscle relaxants, anti emetic and intravenous fluids was at the discretion of the attending anaesthesiologist. Anaesthetic depth was adjusted according to clinical judgement and in 120 cases on Bispectral Index monitoring. Authors avoided any intraoperative hypothermia (<35.5 ºC) by monitoring the body temperature and using warming machines during surgery. The patients with high risk of PONV were given prophylactic anti-emetic during anaesthesia. The risk of PONV was based on a recently validated criteria[21] which resulted in a score of 0 (low risk) to 4 (high risk).

All the patients were shifted to post-anaesthesia care unit after surgery and PACU nursing staff were advised to record the time of fitness for discharge, which was defined as a modified Aldrete Score (1995) of 9 or greater. The pain or emesis if any was controlled.

RESULTS

Demographic, medical and perioperative characteristics at baseline were similar to both groups (Table 1). There were statistically significant differences in anaesthetic drug administration as a result of addition of nitrous oxide to the inspired gas mixture. The values of intraoperative and postoperative heart rate and blood pressure did not differ between the groups. There was a marked reduction in the incidence of nausea and vomiting after surgery in nitrous oxide free groups. It was reduced from 11% in nitrous oxide group to 5% in nitrous oxide free group. Average intraoperative temperatures did not differ among anaesthetic groups at any time. None of our patients had any shivering in PACU. The duration of anaesthesia did not differ between anaesthetic groups (Table-2). The time from end of anaesthesia to extubation did not differ between anaesthetic groups nor did the duration of stay in recovery room. All the patients were transferred from PACU within two hours after end of anaesthesia.

Table-1: Patient Demographic Characteristics

	N_2O	No N_2O
No of Patients	100	100
Age mean (years)		
Male	31.8±13.65	33.46±14.71
Female	35.58±14.11	39.28±13.51
Sex		
Female (%)	58	60
ASA I (%)	60	58
Body Weight (Kg)	74.5±17.7	73.2±14.5
Baseline SBP (mmHg)	115±24	117±22
Pre-existing conditions		
Asthma	7	8
Coronary artery disease	6	7
Diabetes	10	10
Hypertension	6	8
Obesity	5	4
Hypothyroidism	4	4
Renal disease	2	1
Type of Surgery		
Abdominal	48	49
Gynaecology	11	10
Orthopaedic	26	25
ENT	8	10
Maxillofacial	7	6

Table 2: Variables associated with Anaesthesia

	N_2O	No N_2O	*p*-Value
Propofol (mg) mean	155.30±38.572	158.50±36.164	0.546
Fentanyl (mcg)	100	100	
Rocuronium(mg/Kg)	0.64±0.3	0.85±0.35	
Maintenance end tidal Sevo%	1.436± 0.4036	1.669 ±0.5445	0.001
BIS monitoring (% of patients)	50	70	
Lowest intraop temp (ºC)	34.9+0.8	35+0.8	
Mean duration of anaesthesia (min)	97.72± 52.393	103.7±48.671	0.400

Table 3: Haemodynamics during Recovery

	First hour		Second hour	
	N_2O	No N_2O	N_2O	No N_2O
Systolic BP (mmHg)	122±26	123±27	127±21	129±22
Heart Rate (beats/min)	90±16	87±15	82±15	81±15

Table 4: Pain and Orientation in PACU

Pain Score	15 min		30 min		60 min	
	N_2O	No N_2O	N_2O	Non N_2O	N_2O	Non N_2O
0	20	27	8	10	2	3
1	43	42	34	40	22	34
2	20	23	26	31	33	34
3	10	7	23	16	37	20
4	7	1	9	3	6	9

DISCUSSION

The history of nitrous oxide is more than 200 years old and its clinical use as anaesthetic is more than 150 years old. However it is not the ideal anaesthetic. It can not be used effectively without decreasing the concentration of oxygen that may be delivered. Although widely used for many decades, there are certain clinical situations where nitrous oxide should be avoided. Due to the increase of cerebral blood flow

the use of nitrous oxide is a contraindication in all cases with raised intracranial pressure.[22] In patients with significant vitamin B_{12} deficiency even a short exposure of only 1–3 hours may lead to severe neurological impairments and shall be avoided in such cases especially in children.[23] Several recent reviews of the effects of nitrous oxide have come up with the conclusions regarding the appropriate role of this drug in modern practice and there is currently a large clinical trial in adults looking at the clinical outcomes with the use of nitrous oxide in general anaesthesia[24] which has questioned the routine use of nitrous oxide in patients undergoing surgical procedures in general anaesthesia. This prompted the authors to undertake this study to find an answer to this question and to see if the continued traditional use of nitrous oxide as a carrier gas in general anaesthesia could be avoided in our hospital where the new anaesthesia machines allow the combination of oxygen and air as carrier gas and there are new inhalational agents (e.g., Sevoflurane, Desflurane) as controllable as nitrous oxide and new I/V agents.

The authors in this study used the mixture of oxygen with medical air as a substitute for nitrous oxide. There are no contraindications for a mixture of nitrogen with oxygen; it can be used in every patient, in every surgical procedure and under every condition. The anaesthetist can freely choose the oxygen concentration and adapt it to the needs of an individual patient or the respective surgical procedure. In the present study the authors used 40% oxygen in air/N_2O for all the cases as carrier gas during the surgical procedure and monitored the inspired oxygen concentration and pulse oximetry. Aggarwal *et al*[25] have proved that in young healthy patients undergoing general anaesthesia ventilation with nitrogen/ oxygen mixture (FiO_2 0.4) improved pulmonary gas exchange if compared with the use of nitrous oxide/oxygen or pure oxygen.

In our study though there was a marked reduction in the incidence of nausea and vomiting after surgery in nitrous oxide free groups it was reduced from 11% in nitrous oxide group to 5% in nitrous oxide free group. Postoperative nausea and vomiting is rated by patients as one of the most undesirable postoperative complications.[26] The use of nitrous oxide may have increased the incidence of vomiting and sore throat in some of his patients as reported by Eger *et al*.[27] Kamakura *et al*[28] have shown that postoperative inflammatory reaction in lung may increase when Sevoflurane and N_2O are used during general anaesthesia. The simple intervention of omitting nitrous oxide from the anaesthetic regimen should therefore have a substantial impact on patient comfort after surgery.

The loss of analgesic and hypnotic effect exerted by 60% nitrous oxide in clinical practice proved to be remarkably less than generally assumed. This missing effect of nitrous oxide can be replaced by an increase of not more than 0.2–0.25 times the minimal alveolar concentration (MAC) of respective anaesthetic agent and only small supplemental doses of opioids.[27] This fact was observed in the present study and is in line with the findings of Eger *et al*[27] When renouncing the use of nitrous oxide a possible increase in the rate of intraoperative awareness may be a matter of concern as per the meta-analysis[27] and its experience would be a real nightmare for any patient (Rowan[29]). In balanced or inhalation anaesthesia the volatile anaesthetic safeguards intraoperative awareness as the expiratory concentration exceeds the MAC awake. In the present author's clinical experience not a single case of intraoprative awareness was reported as we used an extended MAC of 1.2–1.3 of anaesthetic agents in our study contrary to the recommendations (0.8–1) of Eger *et al*[39] and corresponding to the ETAG-guided (Endtidal Anaesthesia Gas) anaesthesia at a target MAC of 0.7–1.3 in the study of Avidan *et al.*[30] The maintenance of BIS value below 50 gave us the freedom to manipulate the expired concentration of the volatile anaesthetic. In a recent study the BIS-guided anaesthesia at a target range of 40–60 has been shown to avoid any awareness during general anaesthesia.[30] In the present study the absence of any cardiovascular suppression resulting from higher concentration of volatile agents was observed and the credit goes to the precisely controllable injector system of the volatile anaesthetics in our anaesthesia machines.

Though there are no economic constraints in our hospital but the better patient care and high quality performance with cost effectiveness and minimum work place contamination is a priority. Significant cost savings will result from consistent omission of nitrous oxide as the entire technical infrastructure for supplying and logistics for delivering this gas becomes dispensable. The availability of precisely controllable new volatile anaesthetics and opiods, the cost of long list of side effects of nitrous oxide with its minimal hypnotic sparing effect, lack of any justified indication for its use and its deleterious effect on ecology are the conditions favouring the omission of nitrous oxide in general anaesthesia.

ACKNOWLEDGEMENT

The authors are highly grateful indebted to the Chairman of Anaesthesia department Dr. M. El-Gemmal for his constant guidance, encouragement and support during the study. We are highly thankful to all

our colleagues and supportive staff in the department for their kind cooperation.

REFERENCES

1. James MFM. Nitrous oxide: still useful in the year 2000? Curr Opin Anaesthesiol 1999;12:461–6.
2. Brodsky JB and Cohen EN. Adverse effects of nitrous oxide. Med Toxicol 1986;1:362–74.
3. Myles PS, Leslie K, Silbert B, Paech M, Peyton P: a review of the risks and benefits of nitrous oxide in current anaesthetic practice. Anaesth Intensive Care 2004;32:165–62.
4. Krajewski W, Kucharska M, Pilacik B, Fobker M, Stetkiewicz J, Nofer JR and Wronska-Nofer T. Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide. Br J Anaesth 2007;99:812–8
5. Majstorovic BM, Radulovic RB, Dukic VB, Kastratovic DA, Popovic NP, Gajic MM. Effects of nitrous oxide on middle year pressure. Med Pregl.2007;60:473–8.
6. Akca O, Lenhardt R, Fleischmann E, Treschan T, Greif R, Fleischhackl R, Kimberger O, Kurz A Sessler DI. Nitrous oxide increases the incidence of bowel distension in patients undergoing elective colon resection. Acta Anaesthesiol Scand 2004;48:894–8.
7. Kaisti KK, Langsjo JW, Aalto S, Oikonen V, Sipila H, Teras M, Hinkka S,Metsahonkala L,Scheinin H: Effects of Sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 2003;99:603–13.
8. Hohner P and Reiz S. Nitrous oxide and the cardiovascular system. Acta Anaesthesiol Scand 1994;38:763–6.
9. Sesso RMCC, Iunes Y and Melo ACP. Myelonueropathy following nitrous oxide anaesthesia in a patient with macrocytic anaemia. Neuroradiology 1999;41:588–90.
10. Nunn JF. Clinical aspects of interaction between nitrous oxide and vitamin B_{12}. Br J Anaesth 1987;59:3–13.
11. Deleu D, Louon A, Sivagnanam S, Sundaram K, Okereke P, Gravell D, *et al*. Long-term effects of nitrous oxide anaesthesia on laboratory and clinical parameters in elderly Omani parents: a randomized double-blind study. J Clin pharm Ther. 2000;25:271–7.
12. Felten ML, Schmautz E, Delaporte-Cerceau S, Orliaguet GA, Carli PA.. Endotracheal tube cuff pressure is unpredictable in children. Anesth Analg 2003;97:1612–6.
13. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, vedder I, *et al*. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med. 2004;350:2441–51.
14. Nader ND, Simpson G, Reedy RL. Middle ear pressure changes after nitrous oxide anaesthesia and its effect on postoperative nausea and vomiting. Laryngoscope 2004;114:883–6.
15. Mraovic B, Simurina T, Sonichi Z, Skitarelic N, Gan TJ. The dose response of nitrous oxide in postoperative nausea in patients undergoing gynaecologic laporoscopic surgey –A preliminary study. Anesth Analg 2008;107:818–23.
16. Logan M and Farmer JG. Anaesthesia and ozone layer. Br J Anaesth 1998;53:645–6.
17. Ratcliff A Burns A, Gwinnutt CL. The contribution of medical nitrous oxide to the greenhouse effect. Health Trends 1991;23:119–20.
18. McGain F. Why anaesthetists should no longer use nitrous oxide. Anaesth Intensive Care. 2007;35:808–9.
19. Hopf, HW. Is it time to retire high concentration nitrous oxide? Anesthesiology 2007;107:200–1.
20. Henderson KA, Raj N, Hall JE. The use of nitrous oxide in anesthetic practice; a questionnaire survey. Anaesthesia 2002;57:1155–8.
21. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting. Anesthesiology 1999;91:693–700.
22. Iacopino DG, Conti A, Battaglia C, Siliotti C, Lucanto T, Santamaria LB, *et al*. Transcranial Doppler ultrasound study of the effects of nitrous oxide on cerebral autoregulation during neurosurgical anaesthesia: a randomized controlled trial. J Neurosurg 2003;99(1):58–64.
21. Baum VC. When nitrous oxide is no laughing matter; nitrous oxide and pediatric anesthesia. Pediatric Anesthesia 2007;17:824–30.
22. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe, E: Avoidance of nitrous oxide for patients undergoing major surgery A randomized controlled trial. Anesthesiology 2007;107:221–31.
23. Aggarwal A, Singh PK, Dhiraj S, Pandey CM, Singh U. Oxygen in Air (FiO2) improves gas exchange in young healthy patients during general anaesthesia. Can J Anaesth 2002;49:1040–43.
24. Macario A, Weinger M, Kim A. Which clinical anaesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg 1999;89:652–8.
25. Eger EI, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK and Donagan JH. Clinical pharmacology of nitrous oxide; an argument for its continued use. Anesth Analg 1990;71:575–85.
26. Kamakura S, Kikuchi T, Yamaguchi K, Kugimiya T, Inada E. Exposure to nitrous oxide may increase airway inflammation during sevoflurane anaesthesia. Masui 2008;57:1200–6 [Japanese]
27. Rowan KJ. Awareness under TIVA; a doctor's personal experience. Anaesth Intensive Care 2002;30:505–6.
28. Avidan MS, Zhang L, Burnside BA, Finkel KJ, Searleman AC, Selvidge JA, *et al*. Anaesthesia awareness and the bispectral index. N Engl J Med 2008;358:1097–108.

Address for Correspondence:

Dr. Syed Mushtaq Gilani, Associate Professor Anaesthesia, Ayub Medical College, Abbottabad, Pakistan.
Present Address: King Fahad National Guard Hospital, Riyadh, Saudi Arabia.
Email: gilani.m@gmail.com