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RESEARCH

A prospective, randomised, controlled clinical trial to evaluate the effect of nitrous oxide on propofol requirement in elective craniotomy in which entropy was used to measure depth of anaesthesia

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Background: Propofol is known to have a favourable effect on cerebral haemodynamics. The role of nitrous oxide (N_2O) in neurosurgical anaesthesia is still being debated. The primary aim of this study was to assess the dose-sparing effect of N_2O on propofol infusion maintenance dosing.
Method: Fifty American Society of Anesthesiology (ASA) grade I and II adults scheduled for elective craniotomies for supratentorial tumours were enrolled in the study. The patients received a standard anaesthetic comprising a fentanyl 2 µg/kg bolus prior to propofol induction. Anaesthesia was maintained with an infusion of fentanyl (2 µg/kg/hour), atracurium and propofol. The patients were randomised into two groups. Group A received 67% N_2O. Group B did not receive N_2O concomitantly with the propofol infusion. Entropy was used to guide the titration of the propofol infusion in both groups.
Results: The propofol maintenance dose requirements were 47% lower in Group A (54.30 ± 11.47 µg/kg/minute) vs. Group B (102.30 ± 14.00 µg/kg/minute), ($p < 0.001$).
Conclusion: The use of supplemental N_2O significantly decreased propofol infusion rate requirements, compared with the propofol infusion alone, in ASA I and II patients undergoing elective supratentorial tumour excision.

Keywords: anaesthesia depth, entropy, intracranial surgery, nitrous oxide, propofol

Introduction

The maintenance of a strict cerebral physiological balance and early recovery for neurological assessment is required for neurosurgical anaesthesia. Propofol is a standard induction, as well as a maintenance agent, owing to its favourable effects on neurophysiology. It causes a dose-dependent decrease in intracranial pressure (ICP), while maintaining cerebral perfusion at a modest dose, and also decreases the cerebral metabolic rate without any disturbance in cerebral vascular reactivity to carbon dioxide and autoregulation.[1,2] Furthermore, propofol total intravenous anaesthesia results in a clinically relevant reduction in postoperative nausea and vomiting (PONV). However, the potentially higher cost is a concern.[3]

Nitrous oxide (N_2O) is used widely in neuroanaesthetic practice as it produces amnesia, analgesia and haemodynamic stability. It also enables rapid recovery. It has been shown in clinical trials to reduce the dose requirement of other anaesthetic agents.[4,5] N_2O reduces the cost of intravenous anaesthesia.[6] We hypothesised that the drug-sparing effect of N_2O should reflect on the maintenance dose requirement of propofol. Still, certain controversies surround the role of N_2O in neuroanaesthesia owing to its unfavourable effects on neurophysiology, and other side-effects, such as tension pneumoencephalus, nausea and vomiting, a neurological deficit in vitamin B_{12}-deficient patients and increased wound infections.[7–9] A randomised study was conducted to determine the dose requirement of propofol when used with and without N_2O in patients undergoing an elective craniotomy, in which entropy was used to measure depth of anaesthesia.[10,11] The surgical conditions were also observed, and the haemodynamic profile and recovery characteristics compared, with and without N_2O, in the two groups. The primary aim of our study was to evaluate the effect of N_2O on propofol dose requirement. The secondary aim was to evaluate the safety profile of N_2O in neuroanaesthesia.

Method

After obtaining approval from the hospital ethics committee and receiving the informed consent of the patients, 50 American Society of Anesthesiologists (ASA) physical status grade I/II patients, of either gender, aged 18–60 years, and scheduled for elective craniotomies for supratentorial tumours, were included in the study. Patients who were pregnant, drowsy, likely to require postoperative mechanical ventilation, who had evidence of major cardiopulmonary, hepatic or renal disease, and those with a known allergy to the study drugs, were excluded from the study.

Patients were kept fasting for six hours and premedicated with oral alprazolam 0.5 mg at bedtime, and two hours before surgery.

Monitoring included:

- Noninvasive blood pressure.
- An electrocardiogram.
- Heart rate.
- Pulse oximetry.
- Response entropy (RE).
- State entropy (SE) [with M-Entropy S/5TM Module® (GE Healthcare)] using a sensor attached to the forehead of the patient.
- Capnography [end-tidal carbon dioxide ($EtCO_2$)].

- Invasive arterial blood pressure.
- Nasopharyngeal temperature.
- Urine output.
- A 16-G long line in the cephalic vein to monitor central venous pressure (CVP).
- Expiratory N_2O concentration.
- Oxygen concentration by oxygen analyser.

The patients were randomised into two groups using a random digit table. Group A (the N_2O group) received a N_2O, oxygen and propofol infusion, and Group B (the propofol group) received an air, oxygen and propofol infusion. A similar type and size of supratentorial tumour resection, mostly meningiomas or gliomas, were operated on in both the groups. Baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR), SE and RE were recorded. The patient's lungs were preoxygenated for three minutes. Fentanyl 2 µg/kg intravenously was administered, followed by propofol 2 mg/kg and atracurium 0.5 mg/kg, to facilitate tracheal intubation with a flexometallic tube. The propofol infusion was started at a rate of 50 µg/kg/minute simultaneously with induction, keeping the entropy value ≤ 40 until tracheal intubation, and between 40 and 60 intraoperatively. During induction and maintenance, the lungs were ventilated using 67% N_2O in oxygen in group A, and 33% oxygen in air in group B, maintaining a fraction of inspired oxygen of 33%. Fentanyl (2 µg/kg/hour) and atracurium (10 µg/kg/minute) infusions were started.

The intraoperative entropy score was maintained between 40 and 60, CVP between 5 cmH_2O and 8 cmH_2O, $EtCO_2$ between 28 mmHg and 32 mmHg, and nasopharyngeal temperature between 36 °C and 37 °C. Normal saline was used as an intravenous fluid to maintain the CVP. Mannitol (1 g/kg) was administered over 20 minutes, starting at the time of skin incision in all patients. Brain condition was assessed by the operating surgeon (who was unaware of the group allocation of the patient) after opening the cranial cavity as tense (swollen and bulging), reasonable (minimal swelling and acceptable) or ideal (no swelling and excellent). Hypotension, a fall in MBP to less than 20% of baseline or MBP ≤ 65 mmHg, was treated with ephedrine 6 mg intravenously after excluding hypovolaemia. Bradycardia (HR ≤ 45/minutes) was treated with glycopyrrolate 0.2 mg intravenously. Episodes of hypertension or tachycardia (a rise of ≥ 20% from baseline) were treated by increasing the propofol infusion rate. Atracurium and fentanyl infusions were discontinued after dura closure. Propofol and N_2O/air were stopped after the removal of the head clamps. Residual neuromuscular blockade was antagonised with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg, both intravenously.

The trachea was extubated following the return of adequate spontaneous respiration, protective reflexes and an entropy score > 70. Heart rate, MBP, SBP and DBP, entropy values (RE and SE), $EtCO_2$, and inspiratory and expiratory N_2O concentrations were recorded at baseline, post induction, post intubation and every five minutes thereafter intraoperatively.

Time to eye opening after the cessation of propofol was noted. Recovery characteristics were recorded as a modified Aldrete score at 10 minutes and 30 minutes postoperatively.

Patients were transferred to the neurointensive care unit (NICU), when the modified Aldrete score was ≥ 8. Adverse effects, such as nausea and vomiting, or episodes of haemodynamic instability, were recorded for six hours in the NICU. Patients were questioned 24 hours after surgery about what they remembered last, and if they had any memories of the surgery.

The sample size was calculated using data from a previous study.[12] A sample size of 50 patients was required to achieve a 33% reduction in effective concentration 50 (EC50) of propofol with 67% N_2O, with a power of 80% and α of 0.05. Statistical analysis was performed using Windows® SPSS® version 12.0. The data are presented as continuous variables in terms of mean and standard deviation (MBP, DBP, SBP and propofol infusion rate and time to eye opening), and as categorical variables in terms of percentage (sex and ASA grade). Student's *t*-test was used for the continuous data after normal distribution of the continuous variables validated by the Kolmogorov-Smirnov one-sample test, and for catagorical data chi squre test and Fischer's exact test were used. A *p*-value of ≤ 0.050 was taken to be the level of statistical significance.

Results

The two groups were comparable in terms of age, weight, sex distribution, ASA grade and duration of anaesthesia ($p > 0.050$) (Table 1).

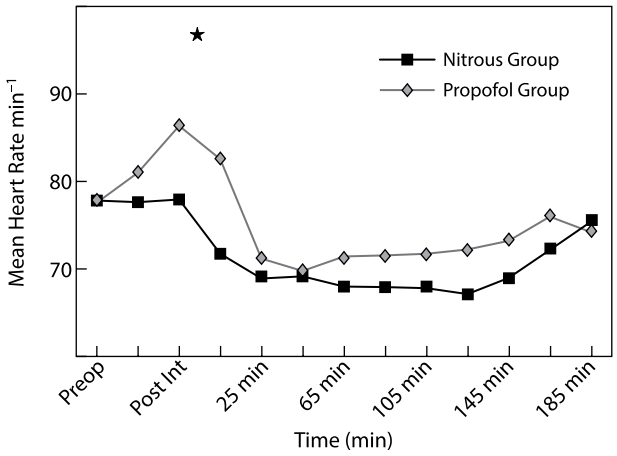
The mean dose requirement of propofol during maintenance was significantly higher (47%) in the propofol group (102.30 ± 14.00 µg/kg/minute) compared with the N_2O group (54.30 ± 11.47 µg/kg/minute) (Table 1).

The intergroup comparison of mean HR at different time intervals is shown in Figure 1. The baseline mean HR was comparable between the two groups (p 0.967). The mean HR was significantly lower in group A (the N_2O group) compared to that in group B (the propofol group) after five minutes of intubation (71.76 ± 13.91 µg/kg/minute vs. 82.56 ± 14.08 µg/kg/minute, respectively) (p 0.009). Thereafter, the HR was comparable in both the groups (p-value ≥ 0.050).

Table 1: Demographic data, duration of anaesthesia and propofol dose requirement

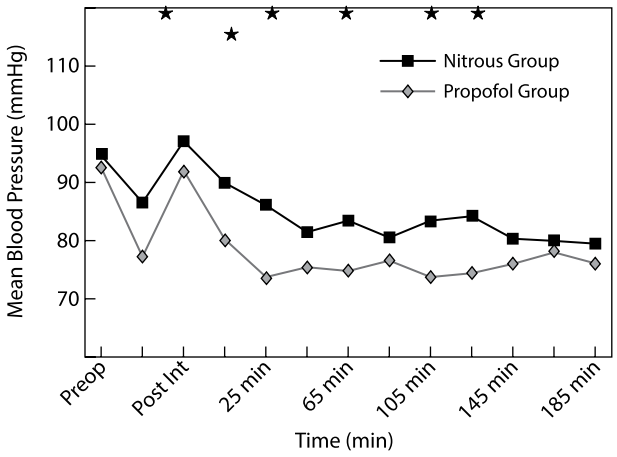
Demographic data	Group A (N_2O group)	Group B (propofol group)	*p*-value
Age (years)	48.00 ± 13.30	46.20 ± 10.70	0.609
Weight (kg)	63.40 ± 10.60	60.20 ± 7.20	0.268
Sex (male and female) (*n*, %)	16 (64):9 (3 6)	14 (56):11 (44)	0.564
ASA grade (I and II) (*n*, %)	12 (48):13 (52)	10 (40):15 (60)	0.569
Duration of anaesthesia (minutes)	161.60 ± 31.10	157.60 ± 31.00	0.651
Propofol dose (µg/kg/minute)	54.30 ± 11.47	102.30 ± 14.00	< 0.001

Note: ASA: American Society of Anesthesiologists, N_2O: nitrous oxide.



Star denotes significance; $p < 0.05$

Figure 1: Heart rate trend in the study.



Note: MBP: mean blood pressure. Star denotes significance; $p < 0.05$

Figure 2: Mean blood pressure trend in the study.

at several time points, for which an increase in the propofol infusion rate was required (Figure 2).

The recovery characteristics are shown in Table 2. The mean time to eye opening was significantly longer in group B (8.54 ± 8.15 minutes) than in Group A (2.51 ± 1.03 minutes) ($p <$ 0.001). The Aldrete score was significantly lower in group B than in group A at 10 minutes (p 0.001) and at 30 minutes (p 0.039).

There were no intraoperative or postoperative complications, i.e. pneumoencephalus, PONV, respiratory depression or the need for postoperative ventilatory support, in either group. None of the patients in either group reported being aware of intraoperative events when questioned 24 hours postoperatively.

Discussion

The results of our study indicate that when N_2O was used with the propofol infusion for the maintenance of anaesthesia, the propofol dose requirement was significantly less compared to the propofol infusion alone requirement in patients undergoing supratentorial surgery. We found in our study that the maintenance dose of propofol was 54.30 ± 11.47 µg/kg/minute, and 102.30 ± 14.00 µg/kg/minute, with and without N_2O, respectively. Thus, the propofol requirement was considerably lower when used together with N_2O. Davidson et al.[12] reported that the addition of 67% N_2O reduced the EC50 of propofol by 33%. Similarly, Dube et al.[13] also found that the maintenance dose of propofol, with and without N_2O, was 71.26 ± 11.78 µg/kg/minute and 90.82 ± 19.13 µg/kg/minute, respectively. Hemelrijck et al.[14] reported that the electroencephalography (EEG)-titrated propofol requirement was significantly less when used with N_2O, when compared with the use of propofol alone (123 ± 5.27 µg/kg/minute vs.150 ± 2.77 µg/kg/minute, or 7.4 ± 1.9 mg/kg/hour vs. 9.0 ± 1.0 mg/kg/hour). Singh et al.[15] also reported that there was an increased consumption of opioids and muscle relaxants in the N_2O-free group of patients undergoing supratentorial tumour surgery. This emphasises the analgesic potency of N_2O. Ng and Hwang[5] found that the co-

Table 2: Recovery characteristics of the study participants*,**

Time (minutes)	Group A (N_2O group)	Group B (propofol group)	*p*-value
Time to eye opening (minutes)	2.51 ± 1.03	8.54 ± 8.15	< 0.001
Aldrete score at 10 minutes	9.24 ± 0.77	7.88 ± 1.61	0.001
Aldrete score at 30 minutes	10.00 ± 0.00	9.84 ± 0.37	0.039

Note: N_2O: nitrous oxide.
*: Values are expressed as mean ± standard deviation.
**: A difference was not found in the intraoperative condition of the brain in both groups (p 0.600) (Table 3).

Table 3: Intraoperative brain status of the study participants

Brain status	Group A (N_20 group)*	Group B (propofol group)	*p*-value
Tense (swollen and bulging)	1 (4)	0 (0)	0.600
Reasonable (minimal swelling and acceptable)	23 (92)	24 (96)	
Ideal (no swelling and excellent)	1 (4)	1 (4)	

Note: N_20: nitrous oxide.
*:Values are expressed as number (per cent).

The baseline MBP was comparable in the two groups (p 0.573). A statistically significant lower MBP was observed in group A at post induction, and at five minutes post intubation, compared with that in group B. A higher MBP was observed in group B (the propofol group) compared with that in group A (the N_2O group), administration of N_2O during the induction of anaesthesia reduced the induction dose requirement of propofol.

A propofol requirement of 100-200 µg/kg/minute, together with N_2O and an opioid analgesic in orthopaedic surgery,[16] Caesarean section and other surgery, has been demonstrated in previous

studies.[17] The propofol dose requirement in patients undergoing intracranial surgery in our study was substantially lower, possibly because of the entropy-guided titration of the propofol dose, although the difference in the nature of the surgery could have affected the dose. Vakkuri et al.[18] also reported that entropy monitoring assisted the titration of propofol and decreased the consumption of propofol, with early recovery in the entropy group.

We found that hypertensive episodes were more frequent in the propofol group. Dube et al.[13] also observed that HR and MBP were lower in the N_2O-propofol group, and attributed it to additive analgesic effect of N_2O. N_2O can produce direct myocardial depression.[19] However, this is compensated by the simultaneous sympathetic activation of the brain nuclei which control β-adrenergic activity.[20] In addition, N_2O can also inhibit the uptake of noradrenaline by the lungs, which results in α-adrenergic stimulation.[19] Some cardiovascular depression is the net result. In contrast, Carlier et al.[21] found that the inhalation of 70% N_2O in oxygen did not alter the haemodynamic variables during propofol induction. This could be because their patients received 500 ml of intravenous hydroxyethyl starch prior to induction. Our patients received intravenous fentanyl prior to induction, which could have blocked the centrally mediated β-adrenergic stimulation of N_2O.[20] The haemodynamic and recovery profile, with and without N_2O, in patients receiving EEG-titrated propofol infusion during neuroanaesthesia, was compared in the study by Hemelrijck et al.[14] They found that the use of N_2O with propofol produced more hypotension during induction ($p < 0.050$). However, improved haemodynamic stability was observed during the maintenance period compared to that achieved in the propofol-only group. Singh et al.[15] reported a wide fluctuation in HR and BP, and a higher incidence of intraoperative hypertension and tachycardia, in the isoflurane, compared to the N_2O-isoflurane, group, undergoing supratentorial craniotomies. Inada et al.[22] studied the effect of N_2O on haemodynamic responses caused by noxious stimulation during propofol anaesthesia, and observed that N_2O significantly attenuated the tetanic stimulation-induced rise in blood pressure.

It is widely appreciated that N_2O decreases the incidence of awareness,[23] although this observation has been questioned by certain investigators.[24] Entropy has now been established as a useful monitor with which to assess the depth of anaesthesia in patients undergoing supratentorial neurosurgical procedures.[26] We maintained the entropy value between 40 to 60 during the maintenance phase, as recommended by Vakkuri et al.[17] Anderson and Jakobsson found that loss of consciousness with N_2O was not associated with a change in the entropy index.[25] In contrast, Hans reported that the addition of N_2O during balanced anaesthesia provoked a decrease in the RE and SE of EEG.[26] Dube et al.[13] also observed a significantly higher bispectral index value in the propofol group than that in the N_2O group.

Mean time to eye opening, after discontinuing propofol infusion, was significantly shorter in the N_2O group 2.51 ± 1.03 minutes vs. 8.54 ± 8.15 minutes in the propofol group. Singh et al.[15] reported smoother recovery and early tracheal extubation in the N_2O-based group when compared with what was achieved with isoflurane-only anesthesia. Similarly, Hemelrijck et al.[14] found that time to awakening was shorter when a EEG-titrated propofol infusion was used together with N_2O (24 ± 13 minutes, compared to 34 ± 18 minutes in the propofol-only group).

The Aldrete score at 10 minutes of cessation of the propofol infusion revealed that recovery was significantly faster in the N_2O group compared to that in the propofol group. This is probably because of the significantly higher dose of propofol required by patients in the propofol group. The Aldrete score at 30 minutes was statistically significantly different between the two groups, although the difference was not clinically significant.

The surgical conditions assessed by the surgeon were comparable in the two groups. Hemelrijck et al.[14] also reported that the surgical conditions (brain relaxation) were similar in the two groups.

PONV is unacceptable following neurosurgical procedures. N_2O has been implicated in causing PONV. [27,28] However, none of the patients in our study experienced nausea or vomiting. This could be owing to the antiemetic action of propofol. Although N_2O has been implicated in complications, such as raised ICP and pneumoencephalus,[29,30] these were not observed in our study. Singh et al.[15] also found that using N_2O in patients undergoing supratentorial craniotomies did not prolong the duration of intensive care unit or hospital stay.

The unfavourable effects of N_2O on neurophysiology, such as an increase in the cerebral metabolic rate, cerebral blood flow and ICP, have caused its role in neuroanaesthesia to be debated.[7,9] To an extent, these effects of N_2O are masked by the concomitant use of propofol.[31] The impact of these unfavourable effects of N_2O were not found in our study on awake (albeit with a small rise in ICP) patients. Since patients with significantly raised ICP, or who were drowsy, were not included in our study, the results cannot be extrapolated to such patients.

Conclusion

We conclude that the use of supplemental N_2O significantly decreased the propofol infusion rate requirement, compared with a propofol infusion alone, in ASA I and II awake patients undergoing supratentorial craniotomies.

References

1. Matta BF, Lam AM, Strebel S, et al. Cerebral pressure autoregulation and carbon dioxide reactivity during propofol-induced EEG suppression. Br J Anaesth. 1995;74:159–63.
2. Karsli C, Luginbuehl I, Farrar M, et al. Cerebrovascular carbon dioxide reactivity in children anaesthetized with propofol. Pediatr Anesth. 2003;13:26–31.
3. Visser K, Hassink EA, Bonsel GJ, et al. Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane–nitrous oxide. Anesthesiology. 2001;95:616–26.
4. Ng JM, Hwang NC. Inhaling nitrous oxide reduces the induction dose requirements of propofol. Anesth Analg. 2000;90:1213–6.
5. Tsutsui H, Kodaka M. Effect of nitrous oxide on propofol requirement during target controlled infusion for oocyte retrieval. Int J Obstet Anesth. 2003;16:13–6.
6. Heath KJ, Sadler P, Winn JH, et al. Nitrous oxide reduces the cost of IV anaesthesia. Anesthesiology. 1996;13:369–72.
7. Hancock SM, Nathanson MH. Nitrous oxide or remifentanil for the at risk brain. Anaesthesia. 2004;59:313–5.
8. Satapathy GC, Dash HH. Tension pneumocephalus after neurosurgery in the supine position. Br J Anaesth. 2000;84:115–7.
9. Culley DJ, Crosby G. Nitrous oxide in neuroanesthesia. Anesthesiology. 2008;108:553–4.
10. Oja HV, Maja V, Sarkela M et al.. Discription of Entropy algorithm as applied in Datex–ohmeda S/5 Entropy module. Acta Anaesthesiol Scand. 2004;48:154–61.
11. Stanski DR. Monitoring depth of anaesthesia. In: Miller RD, editor Anaesthesia. New York, NY: Churchill Livingstone; 1990. p. 1019–1023.

12. Davidson JAH, Macleod AD, Howie JC, et al. Effective concentration 50 for propofol with and without 67% nitrous oxide. Acta Anesthesiol Scand. 1993;37:458–64.
13. Dube SK, Dube RK, Mishra LD. Propofol requirement during propofol and butorphanol anesthesia with and without nitrous oxide in short duration intracranial surgeries: a Bispectral Index Guided Study. J Anesth Clin Res. 2012;3:1–4.
14. Hemelrijck JV, Tempelhoff R, White PF, et al. EEG-Assisted Titration of Propofol Infusion During Neuroanesthesia. J Neurosurg Anesthesiol. 1992;4:11–20.
15. Singh GP, Prabhakar H, Bithal PK, et al. A comparative evaluation of nitrous oxide-isoflurane vs isoflurane anesthesia in patients undergoing craniotomy for supratentorial tumors: a preliminary study. Neurol Ind. 2011;59:18–24.
16. Rosenberg MK, Brown M, Bridge P. Cost comparison: a desflurane versus a propofol based general anaesthetic technique. Anesth Analg. 1994;79:852–5.
17. Stanski D, Shafer S. Quantifying anesthetic drug interaction. Anesthesiology. 1995;83:1–5.
18. Vakkuri A, Hankala A, Sandin R. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol –nitrous oxide alfentanil anesthesia. Anesthesiology. 2005;103:1–8.
19. Kawanura R, Stanley TH, English JB, et al. Cardiovascular responses to nitrous oxide exposure for two hours in man. Anesth Analg. 1980;59:93–9.
20. Fukunaga AF, Epstein RM. Sympathetic excitation during nitrous oxide – halothane anaesthesia in cat. Anesthesiology. 1973;39:23–36.
21. Carlier S, Aken HV, Vandermeersch E, et al. Does nitrous oxide affect the hemodynamic effects of anesthesia induction with propofol? Anesth Analg. 1989;68:728–33.
22. Inada T, Shingu K, Nakao S, et al. Effects of nitrous oxide on haemodynamic and electroencephalographic responses induced by tetanic electrical stimulation during propofol anaesthesia. Anaesthesia. 1999;54:423–6.
23. Tramer M, Moore A, McQuay H. Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. Br J Anaesth. 1996;76:186–93.
24. Ghoneim MM, Block RI, Haffarnan M, et al. Awareness during anesthesia: risk factors, causes and sequelae: a review of reported cases in the literature. Anesth Analg. 2009;108:527–35.
25. Anderson RE, Jakobsson JG. Entropy of EEG during anaesthetic induction: a comparative study with propofol or nitrous oxide as sole agent. Br J Anaesth. 2004;92:167–70.
26. Hans P. Effect of nitrous oxide on spectral entropy of EEG during surgery under balanced anesthesia with sufentanil and sevoflurane. Acta Anaesthesiol Belg. 2005;56:37–43.
27. Gan T. Risk factors for postoperative nausea and vomiting. Anesth Analg. 2006;102:1884–98.
28. Lonie DS. Nitrous oxide anaesthesia and vomiting. Anaesthesia. 1986;41:703–7.
29. Matta BF, Lam AM. Nitrous oxide increases cerebral blood flow velocity during pharmacologically induced eeg silence in humans. J Neurosurg Anesthesiol. 1995;7:89–93.
30. Lunsford LD, Maroon JC, Sheptak PE, et al. Subdural tension pneumocephalos. J Neurosurg. 1979;50:525–7.
31. Kaisti KK, Långsjö JW, Aalto S, et al. Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiol. 2003;99:603–13.

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