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Nitrous oxide does not produce a clinically important sparing effect during closed-loop delivered propofol–remifentanil anaesthesia guided by the bispectral index: a randomized multicentre study†‡

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Editor's key points

- The hypothesis that N_2O administration decreases the amount of propofol and remifentanil required to maintain a specific bispectral index (BIS) was tested.
- N_2O did not reduce propofol and remifentanil requirements in men during BIS-guided anaesthesia.
- N_2O has a non-clinically significant sparing effect on propofol and remifentanil in women.

Background. Nitrous oxide (N_2O) offers both hypnotic and analgesic characteristics. We therefore tested the hypothesis that N_2O administration decreases the amount of propofol and remifentanil given by a closed-loop automated controller to maintain a similar bispectral index (BIS).

Methods. In a randomized multicentre double-blind study, patients undergoing elective surgery were randomly assigned to breathe 60% inspired N_2O (N_2O group) or 40% oxygen (AIR group). Anaesthesia depth was evaluated by the proportion of time where BIS was within the range of 40–60 (BIS_{40-60}). The primary outcomes were propofol and remifentanil consumption, with reductions of 20% in either being considered clinically important.

Results. A total of 302 patients were randomized to the N_2O group and 299 to the AIR group. At similar BIS_{40-60} [79 (67–86)% *vs* 76 (65–85)%], N_2O slightly decreased propofol consumption [4.5 (3.7–5.5) *vs* 4.8 (4.0–5.9) mg kg^{-1} h^{-1}, $P=0.032$], but not remifentanil consumption [0.17 (0.12–0.23) *vs* 0.18 (0.14–0.24) μg kg^{-1} min^{-1}]. For the subgroups of men, at similar BIS_{40-60} [80 (72–88)% *vs* 80 (70–87)%], propofol [4.2 (3.4–5.3) *vs* 4.4 (3.6–5.4) mg kg^{-1} h^{-1}] and remifentanil [0.19 (0.13–0.25) *vs* 0.18 (0.15–0.23) μg kg^{-1} min^{-1}] consumptions were similar in the N_2O *vs* AIR group, respectively. For the subgroups of women, at similar BIS_{40-60} [76 (64–84)% *vs* 72 (62–82)%], propofol [4.7 (4.0–5.8) *vs* 5.3 (4.5–6.6) mg kg^{-1} h^{-1}, $P=0.004$] and remifentanil [0.18 (0.13–0.25) *vs* 0.20 (0.15–0.27) μg kg^{-1} min^{-1}, $P=0.029$] consumptions decreased with the co-administration of N_2O.

Conclusions. With automated drug administration titrated to comparable BIS, N_2O only slightly reduced propofol consumption and did not reduce remifentanil consumption. There was a minor gender dependence, but not by a clinically important amount.

Clinical trial registration. This study was registered at ClinicalTrials.gov, number NCT00547209.

Keywords: bispectral index monitor; closed-loop; nitrous oxide; propofol; remifentanil

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Nitrous oxide (N_2O) is a reliable short-acting, well-tolerated, and inexpensive anaesthetic gas. N_2O is not potent enough to be used as a sole agent, but is commonly used as an adjunct to balance volatile or i.v. general anaesthesia; it has a hypnotic action mediated by the *N*-methyl-D-aspartate subtype of glutamate receptors. Moreover, N_2O has an analgesic effect because it acts as a supraspinal opioid agonist in the periaqueductal grey matter and activates noradrenergic neurones in the locus coeruleus which project to α_1 and α_2 adrenoreceptors within the dorsal horn of the spinal cord.[1]

The most obvious advantage of adding N_2O to an anaesthetic regimen is a reduction in hypnotic and opioid consumption. For example, the use of N_2O reduced propofol induction dose by 44%,[2] reduced the propofol concentration required to avoid a response to a surgical stimuli by 30%,[3] and reduced propofol consumption during general anaesthesia maintenance by 15–25%.[4 5] Other studies report that adding N_2O produces a clinical benefit similar to a remifentanil infusion of 0.085 $\mu g\ kg^{-1}\ min^{-1}$ during desflurane anaesthesia guided by the BIS[6] or 0.17 $\mu g\ kg^{-1}\ min^{-1}$ during isoflurane inhalation.[7] A limitation of these studies is that propofol administration was adjusted manually by unblinded investigators in accordance with haemodynamic and clinical criteria.[3–7]

An alternative to haemodynamic and clinical criteria for drug administration during general anaesthesia is titration to electrocortical activity measured by the bispectral index (BIS) monitor (Covidien, Dublin, Ireland).[8] There are reports showing that, in the absence of noxious stimuli, BIS is not affected by N_2O inhalation in volunteers[9] or patients.[10–13] Moreover, several studies showed a poor relationship between clinical sedation scales and the BIS during sedation of volunteers[14] and adult[15 16] or paediatric[17] patients. However, N_2O as an anaesthetic adjuvant modifies electrocortical activation during surgery[18] and the response to noxious stimuli such as laryngoscopy during volatile anaesthesia.[19] Furthermore, electrocortical activity is a function of anaesthetic depth during surgery[20] and in response to noxious stimuli.[19 21 22] There is only slight evidence that N_2O does not affect BIS values during maintenance of general anaesthesia. Studies related to the influence of N_2O on BIS values were performed on volunteers[9] during induction[10] and the number of patients studied during surgery was limited.[11–13] The extent to which N_2O spares i.v. anaesthetics or modifies BIS values during maintenance of general anaesthesia thus remains unclear.

We have developed a closed-loop controller allowing automated titration of propofol and remifentanil solely guided by the BIS. An automated controller of drug delivery is an unbiased assessment of anaesthetic requirements when an adjunct is used.[23] We used this objective system in a randomized controlled multicentre trial to determine the sparing effect of 60% N_2O on propofol or remifentanil consumption during maintenance of general anaesthesia. Specifically, we tested the primary hypothesis that N_2O administration decreases the amount of propofol and remifentanil given by our closed-loop controller to maintain a similar BIS index. Our secondary hypothesis, added at the request of the German Ethics Committee, was that there is an interaction between gender and the drug-sparing effect of N_2O.

Methods

Study population

Our prospective multicentre randomized double-blind clinical trial was approved by the Ethics Committees of the participating French (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Hôpital A. Paré, Boulogne Billancourt, France), Belgian (Comité d'Ethique hospitalo-facultaire Erasme-ULB, Brussels, Belgium), and German universities (Ethikkommission der Charité-Universitätsmedizin, Berlin, Germany). It was also approved by the French national regulatory office (Agence Française de Sécurité Sanitaire des Produits de Santé). This study was registered at ClinicalTrials.gov, number NCT00547209.

Written informed consent was obtained during the preoperative visit performed by the investigators. Patients undergoing elective surgery (vascular, general, orthopaedic, gynaecological, urological, otolaryngological) requiring general anaesthesia without combined regional/general anaesthesia expected to last more than 60 min and requiring tracheal intubation were enrolled at 10 university, general, or private hospitals: Hôpital Foch (Suresnes), Centre Hospitalier Victor Dupouy (Argenteuil), Centre Hospitalo-Universitaire of Besançon and Tours, Clinique Saint Augustin (Bordeaux), La Baie des Citrons (Nouméa) New Caledonia, ULB-Erasme (Brussels) Belgium, and Charité-Universitaetsmedizin Berlin (Berlin) Germany. Patients were aged 18–80 yr and ASA physical status I–IV. Exclusion criteria included cranial procedures, psychiatric illness, supraspinal neurological disorders, and patients equipped with a pacemaker. Moreover, patients undergoing thoracic or cardiac surgery were excluded due to possible occurrence of hypoxaemia or gas embolism, respectively.

Procedures

All patients received a propofol and remifentanil infusion controlled by our automated closed-loop system during induction and maintenance of general anaesthesia.[8] All investigators received a full day of training in the use of the automated controller at the Hôpital Foch, Suresnes, France.

On arrival in the theatre, a dedicated i.v. cannula was inserted, routine monitoring commenced including temperature. Neuromuscular function at the adductor pollicis was monitored after loss of consciousness. A BIS electrode (Zipprep, Covidien) was positioned on the patient's forehead and connected to either an A-2000 XP (version 3.11) BIS monitor or a BIS M-Module (GE-Healthcare S/5™, Helsinki, Finland).

The controller[8] was implemented using Infusion Toolbox 95® version 4.11 software[24] which served as a platform: (i) to calculate effect-site concentrations of propofol and remifentanil using the pharmacokinetic population of Schnider and colleagues[25] and Minto and colleagues[26] for propofol and remifentanil, respectively; (ii) to display these calculated effect-site concentration estimates in real time; (iii) to provide a user

interface that permits entry of patient characteristic data (sex, age, weight, and height) and modification of upper and lower limits of drug concentrations; (iv) to control the propofol and remifentanil infusion pumps (Asena GH®, Alaris Medical, Hampshire, UK); and (v) recording BIS, calculated effect-site concentrations, and haemodynamic data when an AS/5™ monitor was used. In both groups, the investigator chose the initial propofol effect-site target concentration according to his/her clinical judgement and the controller fixed the first remifentanil effect-site target concentration. In both groups, patients received total i.v. anaesthesia in target-controlled infusion mode using the automated controller of propofol and remifentanil. Patients received a neuromuscular blocking agent to facilitate tracheal intubation.

The controller has a cascade structure including a dual proportional-integral-derivative algorithm and a target-controlled infusion system for the administration of i.v. anaesthetics. The controller uses the parameters from the BIS monitor if the signal quality index is more than 50%. The controller measures the electromyographic activity, the percentage of burst suppression ratio (SR), and calculates the BIS_{error} or the difference between the set point of 50 and the actual measured BIS value. If the BIS_{error} is different from 0, the controller determines a new propofol, remifentanil, or both concentrations. The controller increases or decreases the drug concentration according to the BIS_{error} sign. The error size determines which drug will be modified: if the BIS_{error} is small, only the remifentanil is changed; if the BIS_{error} is higher than a threshold, the two drug concentrations are changed. The minimal interval between two consecutive controls is set equal to the time to peak effect of each drug; this time interval is shorter for remifentanil[26] than for propofol,[25] thus remifentanil modifications are made more frequently. The feed-forward term gives the rate of change in the error and amplifies every 5 s the correction of the drugs when a measured BIS value is >60. The interaction rule between propofol and remifentanil is as follows: if the controller successively increases the remifentanil concentration more than three times, then the propofol concentration is increased. A detailed description of the controller has been provided in a previous controlled study.[8] In the current study, the controller was identical for the thresholds, rules, propofol gain constants, and lower and upper limits of propofol (1.3 and 5 $\mu g\ ml^{-1}$) or remifentanil (3 and 12 $ng\ ml^{-1}$) of the previous controller. Only the values of gain constants for the remifentanil were decreased by 15%. Throughout the procedure, the investigator could adjust the lower or the upper limits of propofol remifentanil when the BIS decreased to and remained under 40.

Patients were allocated into two groups in a 1:1 ratio: the AIR group in which the lungs were mechanically ventilated with 40% inspired oxygen fraction after tracheal intubation or the N_2O group in which the lungs were mechanically ventilated using a mixture of 40% inspired oxygen fraction and 60% of inspired N_2O after tracheal intubation. Treatments were segregated into blocks of 10 at each participating centre, and randomization was determined using an online random number generator just before anaesthesia induction. Other than administration of the study drugs, patient management was based on current standards of care. No specific recommendations were given for the treatment of haemodynamic

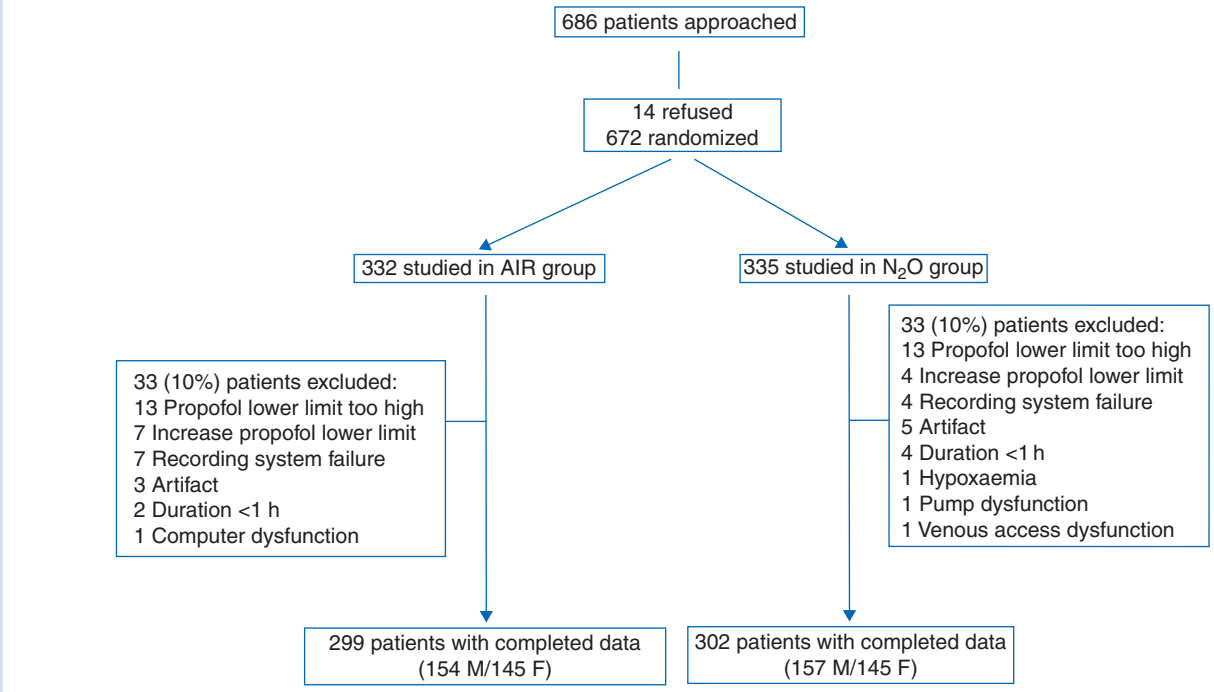

Fig 1 Trial profile. M, male; F, female. N_2O, patients were ventilated with 60% of nitrous oxide; AIR, patients were ventilated with 40% of oxygen.

abnormalities and for the use of a neuromuscular blocking agent. Approximately 45 min before the presumed end of surgery, i.v. analgesics were given to provide postoperative pain relief. Morphine, proparacetamol, nefopam, or non-steroidal anti-inflammatory drugs were given at the discretion of the physician. In both groups, propofol and remifentanil were stopped simultaneously upon completion of surgery and all patients were ventilated with 100% oxygen before tracheal extubation.

The primary outcomes were propofol or remifentanil consumption during maintenance of general anaesthesia. Consumption was defined by drug requirement between the start of mechanical ventilation and the end of drug infusion. Secondary outcomes included the percentage of data points with adequate anaesthesia, defined as BIS between 40 and 60 (BIS_{40-60}), deep anaesthesia ($BIS_{<40}$), and light anaesthesia ($BIS_{>60}$). Excessive anaesthesia was defined as the occurrence of SR with SR >10% lasting at least 1 min.[27] The number of somatic events (i.e. movement, grimacing) was recorded. Recall of intraoperative events was determined by a standardized interview performed in the post-anaesthesia care unit and on the second or third postoperative day.[28] An analysis related to the gender was performed upon request by the German ethical committee.

Statistical analyses

In a previous study during maintenance of general anaesthesia, propofol and remifentanil consumption were 4.7 (1.6) mg kg^{-1} h^{-1} and 0.22 (0.07) μg kg^{-1} min^{-1} using the dual-loop controller.[8] We anticipated that N_2O administration would reduce propofol or remifentanil consumption by at least 20% and thus estimated that a total of 144 patients per group would provide a 95% power for a two-sided α-error of 1%. To provide adequate power for the gender interaction analysis, we planned to recruit 680 patients under the assumption that some would be excluded for various reasons.

Categorical variables, expressed as numbers and frequencies, were compared using Fisher's exact test as appropriate. Continuous variables were described as the median and interquartile range (IQR) and compared using the Mann–Whitney *U*-test. The statistical analysis was performed in the overall

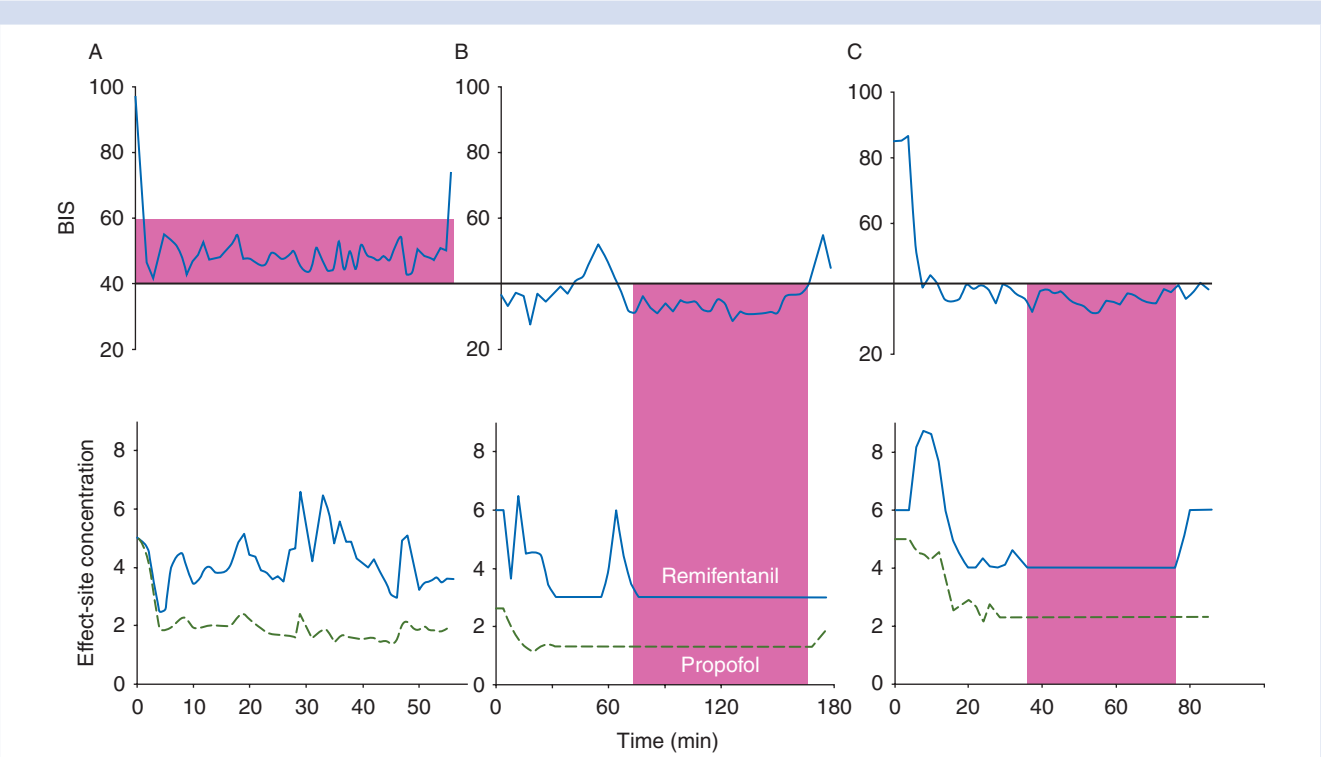

Fig 2 Examples for the interpretation of automated control of propofol and remifentanil guided by the BIS. (A) Ninety-four per cent of anaesthesia maintenance the BIS was adequate or in the range 40 and 60 (BIS_{40-60}) or pink area in the upper figure. The propofol and remifentanil lower limits were never reached. We can conclude that propofol and remifentanil titrations were performed correctly. (B) The BIS_{40-60} =26%, the pink area represents a period of too deep anaesthesia, the lower limits of propofol (1.3 μg ml^{-1}) and remifentanil (3 ng ml^{-1}) were reached and the controller could not decrease the concentrations. This case was excluded from the analysis. (C) The BIS_{40-60} =37%, the pink area represents a period of too deep anaesthesia, the lower propofol and remifentanil limits were increased (2 μg ml^{-1} and 4 ng ml^{-1}, respectively) by the investigator and the controller could not decrease the concentrations. This case was excluded from the analysis. Upper figure: BIS value. Lower figure: effect-site concentration=calculated effect-site concentration of propofol (μg ml^{-1}), or remifentanil (ng ml^{-1}); green dashed line, propofol and blue thick line, remifentanil.

population and by gender after an analysis of variance test to determine the interaction between propofol or remifentanil and gender. Probability values of <0.05 using two-tailed tests were considered statistically significant. Data analysis was performed using IBM-SPSS® version 20 (IBM-SPSS Science, Inc., Chicago, IL, USA).

Results

Among 686 patients who were approached, 672 were recruited between January 2008 and June 2009. Usable data were obtained from 299 patients in the AIR group and 302 patients in the N_2O group (Fig. 1). Different examples for the interpretation of automated control are presented in Figure 2. Baseline characteristics were similar as a function of N_2O administration and gender (Table 1). One-third of subjects took at least one cardiovascular medication before operation. The median BIS values from induction to propofol and remifentanil discontinuation are presented in Figure 3. During induction, propofol requirements were similar with N_2O [1.1 (0.7–1.4) mg kg^{-1}] and AIR [1.0 (0.7–1.4) mg kg^{-1}, $P=0.51$]; remifentanil requirements were also similar with N_2O [1.8 (1.4–2.8) μg kg^{-1}] and AIR [1.8 (1.4–2.9) μg kg^{-1}, $P=0.48$].

The lower limit of propofol was decreased more frequently in the N_2O group than in the AIR group (51% *vs* 34% of patients, $P<0.0001$). The lower limit of remifentanil was decreased in similar occurrence between the two groups (22% *vs* 17% of patients, $P=0.18$ N_2O *vs* AIR respectively). N_2O administration significantly decreased propofol requirement by 6%, although hypnotic effect as determined by the percentage of BIS_{40-60} or procedure duration was similar (Fig. 4, Table 2).

The subgroups of women, N_2O_{women} ($n=145$) and Air_{women} ($n=145$), were well balanced with respect to demography, morphometrics, and surgical procedure (Table 1). There was a significant interaction between gender and anaesthetic: N_2O decreased propofol requirements by 11% ($P=0.004$) and remifentanil requirements by 14% ($P=0.029$) in women, but had almost no effect in men (Table 3, Fig. 4). Women, but not men, were more likely to experience light anaesthesia ($BIS_{>60}$) during AIR than nitrous oxide administration (Table 2). However, in the subgroup of men, N_2O decreased the occurrence of movements and hypertensive episodes with antihypertensive therapy (Table 2). No cases of awareness with recall were reported.

Table 1 Characteristics of patients at entry. Data presented as medians (IQR), or number (%). N_2O, patients were ventilated with 60% of nitrous oxide; AIR, patients were ventilated with 40% of oxygen. Preoperative cardiovascular treatment including β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or diuretics

	N_2O	Air
Number of patients	302	299
Male	157	154
Female	145	145
Age (yr)	58 (46–67)	58 (44–71)
Male	60 (53–68)	61 (50–71)
Female	54 (44–65)	55 (41–69)
Height (cm)	170 (161–175)	170 (161–175)
Male	174 (170–180)	174 (170–178)
Female	163 (159–168)	162 (157–167)
Weight (kg)	72 (63–80)	73 (62–84)
Male	77 (69–83)	79 (71–88)
Female	66 (59–79)	65 (57–77)
ASA physical status III and IV	46 (15)	58 (19)
Male	29 (18)	39 (25)
Female	17 (12)	19 (13)
Cardiovascular treatment	87 (29)	101 (34)
Male	49 (31)	63 (41)
Female	38 (26)	38 (26)
Major surgery	115 (39)	128 (44)
Male	79 (51)	80 (53)
Female	36 (25)	48 (34)

Discussion

Automated administration of anaesthetic drugs is objective and, therefore, an appropriate method for evaluating the contribution of anaesthetic adjuvants since clinician bias is eliminated. This approach has consequently been used, for example, to determine the sparing effect of N_2O on the rocuronium requirement[23] and the sparing effect of remifentanil on propofol.[29] The closed-loop approach that we used thus compares favourably with previous studies in which the sparing effects of N_2O were evaluated by unblinded protocol and depth of hypnosis or analgesia were evaluated by haemodynamic criteria.[3–7] Haemodynamic responses, in particular, are poor indicators of hypnotic depth and influenced by painful stimulation, to say nothing of chronic hypertension and various treatments, blood loss, fluid administration, vasopressor use, heart failure, arrhythmia, and manipulation of great vessels. Our primary result is that in our study population, which was roughly balanced among men and women, N_2O reduced propofol consumption by only 6%. While statistically significant, this small reduction is not clinically important.

Gender differences have been reported for various aspects of anaesthesia care, including postoperative nausea and vomiting[30] or postoperative pain intensity.[31] Women require more propofol than men during maintenance of general anaesthesia[32] and wake up faster.[33–35] Curiously, gender differences have yet to be reported for N_2O, although they may explain apparent discrepancies in reported electrophysiological effects of N_2O. For example, N_2O alone increased the β and θ or excitatory electrocortical activity in a volunteer study in which the sex ratio was well balanced.[9] In contrast, N_2O increased δ activity or central inhibitory action in a surgical patient study in which 14 of 15 patients were female.[18] Our results show that the effect of nitrous oxide on anaesthetic requirement differed as a function of gender, with nearly all the observed sparing being in women. Furthermore, N_2O decreased light anaesthesia or $BIS_{>60}$ only in women. The interaction between N_2O and drug sparing by gender was

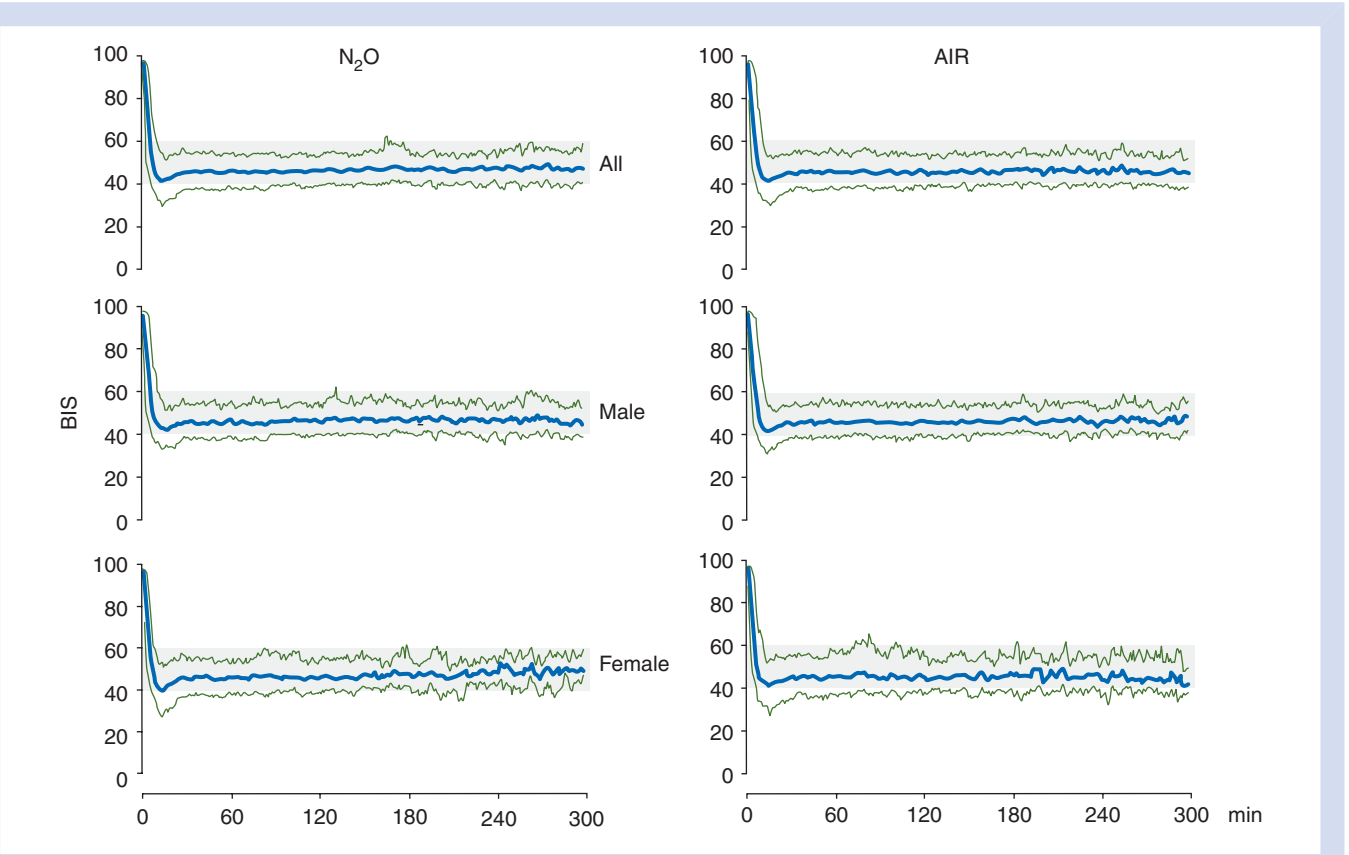

Fig 3 BIS values from induction to the discontinuation of propofol and remifentanil for all, male and female patients. Data are given as median values (blue thick line) with 10th and 90th percentiles (green fine line) with a moving average filter of 1 min duration for graphical representation. N_2O, patients were ventilated with 60% of nitrous oxide; AIR, patients were ventilated with 40% of oxygen.

statistically significant (Table 3); however, the effect is probably not clinically relevant even in women. For example, the propofol-sparing effect of 60% inspired N_2O is only 39 mg h^{-1} and the remifentanil-sparing effect is only 78 μg h^{-1} in a woman weighing 65 kg. A study including stratification by gender is probably necessary to give a definitive conclusion of this difference. However, to detect a difference of 12% propofol consumption with a two-sided α-error of 5% and a power of 80%, the minimum effect size of interest is 112 patients. In the current study, we included more than 145 patients per group (Table 1), thus power was adequate, and the decrease in propofol consumption simply too small to be clinically important.

Intraoperative movement is common (i.e. 60%) during alfentanil and propofol anaesthesia, and the incidence is halved by N_2O administration.[36] Intraoperative movement possibly results more from inadequate analgesia than inadequate hypnosis. N_2O is analgesic; but at least in animals, its analgesic action is to some degree dissociated from immobility.[37] We found that N_2O administration reduced movement and hypertension only in men and this spinal action may be clinically useful (Table 2). Finally, our study reported a supraspinal activity of N_2O in women reflected by the decrease in drug requirements given by the controller, and a spinal activity of N_2O in men suggested by the decreased incidence of hypertension and movements without the decrease in drug requirement related to the absence of cortical activity changes.

Patients included in the current study underwent a variety of surgical procedures, in different centres, with different surgeons, which might have led to different noxious stimuli levels. Unfortunately, we did not record, during the different surgical procedures, the periods with or without noxious stimulation for all patients. Moreover, we lack specific and robust monitors for the quantification of noxious stimuli intensity. The sparing effect of N_2O on anaesthetic requirements is related to the intensity of noxious stimuli[19 22] and mediated by an anti-nociceptive action such as provided by lidocaine.[38] Probably, N_2O is more effective for open rather than laparoscopic procedures, but the difference needs to be clinically relevant during propofol–remifentanil anaesthesia.[39] Indeed, to obtain a desired BIS value, there are several combinations of propofol–remifentanil ratios. But, in both groups, we used the same controller, with the same reproducible titration method for propofol and remifentanil and the results were related to gain constants of the controller. Certainly, the results would be different with another controller gain constant, with a single closed loop of propofol with a continuous and fixed infusion at different targets of remifentanil, or with a continuous fixed infusion of propofol at different targets associated with a single remifentanil closed-loop controller guided by BIS.

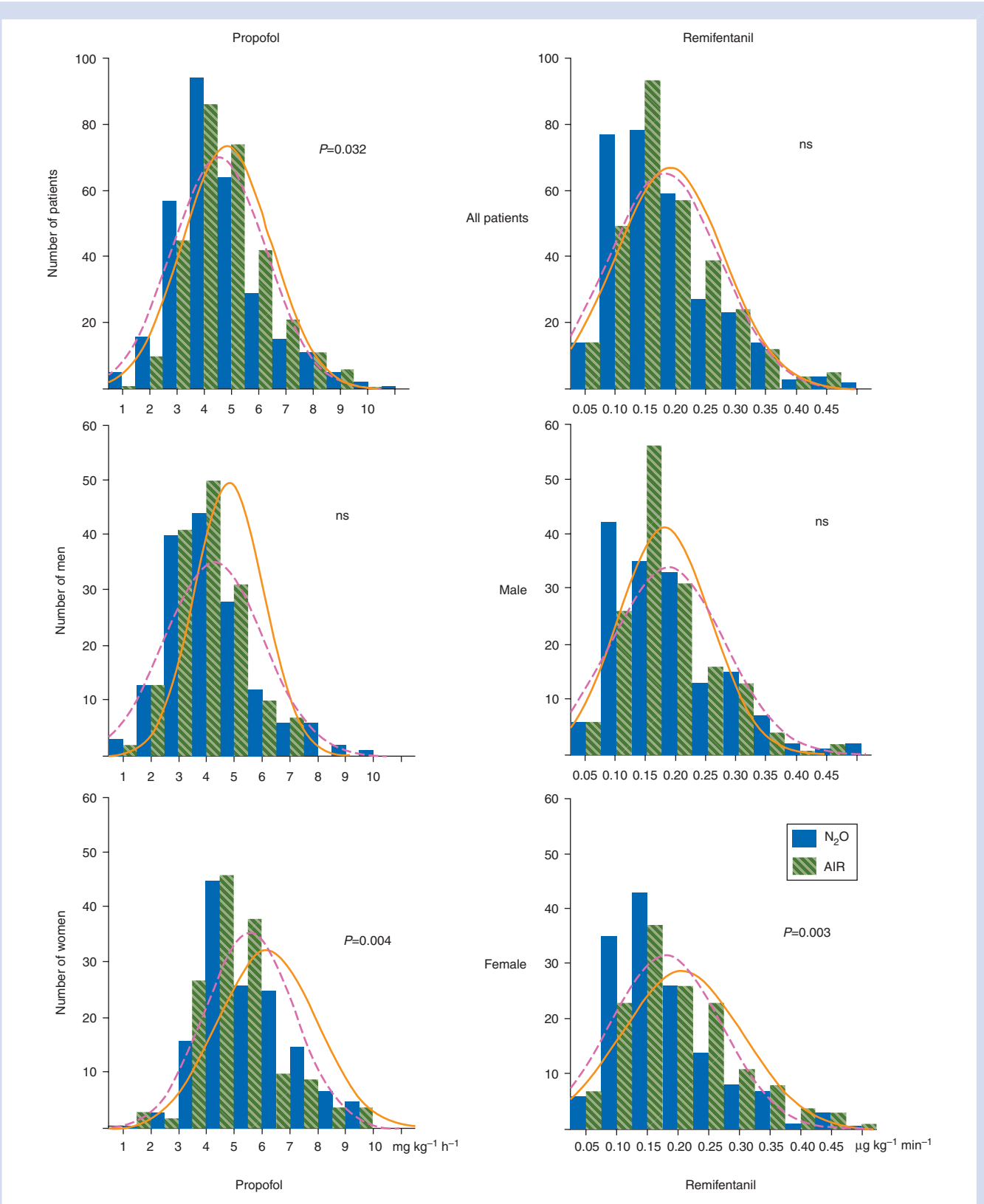

Fig 4 Histogram of propofol and remifentanil consumption. Distribution of propofol (left figures) and remifentanil (right figures) consumptions in all patients and by gender; *P*-values were reported for each figure. N_2O, patients were ventilated with 60% of nitrous oxide; AIR, patients were ventilated with 40% of oxygen. Blue filled histograms represent the N_2O group and green striped histograms represent the AIR group. Normal distribution curve for the N_2O (pink dashed line) and AIR (orange solid line) groups.

Table 2 Comparison of anaesthetic procedures during the maintenance phase. Data presented as medians (IQR), or number (%). N_2O, patients were ventilated with 60% of nitrous oxide; AIR, patients were ventilated with 40% of oxygen. Duration, duration of anaesthesia; SR, suppression ratio; occurrence of SR was defined as SR value >10% lasting more than 1 min. BIS, bispectral index. BIS_{40-60}, percentage of time in which the BIS value was between 40 and 60 during the maintenance. $BIS_{<40}$, percentage of time in which the BIS value was below a value of 40. $BIS_{>60}$, percentage of time in which the BIS value was greater than a value of 60

	N_2O	Air	*P*-value
Number of patients	302	299	
Male	157	154	
Female	145	145	
Duration (min)	129 (83–187)	125 (84–200)	0.83
Male	143 (95–222)	139 (91–225)	0.70
Female	107 (80–148)	109 (70–165)	0.37
BIS_{40-60} (%)	79 (67–86)	76 (65–85)	0.30
Male	80 (72–88)	80 (70–87)	0.85
Female	76 (64–84)	72 (62–82)	0.20
$BIS_{<40}$ (%)	15 (9–23)	16 (10–24)	0.71
Male	15 (9–23)	16 (10–24)	0.98
Female	21 (13–31)	23 (14–32)	0.58
$BIS_{>60}$ (%)	3 (1–5)	4 (2–6)	0.001
Male	2 (1–5)	3 (2–5)	0.69
Female	3 (1–5)	4 (2–7)	0.005
Occurrence of SR	59 (20)	54 (18)	0.75
Male	37 (24)	32 (21)	0.69
Female	22 (15)	22 (15)	1
Propofol (mg kg^{-1} h^{-1})	4.5 (3.7–5.5)	4.8 (4.0–5.9)	0.032
Male	4.2 (3.4–5.3)	4.4 (3.6–5.4)	0.92
Female	4.7 (4.0–5.8)	5.3 (4.5–6.6)	0.004
Remifentanil (μg kg^{-1} min^{-1})	0.17 (0.12–0.23)	0.18 (0.14–0.24)	0.21
Male	0.19 (0.13–0.25)	0.18 (0.15–0.23)	0.58
Female	0.18 (0.13–0.25)	0.20 (0.15–0.27)	0.029
Movement	18 (6)	40 (13)	0.004
Male	6 (4)	21 (14)	0.005
Female	12 (8)	19 (13)	0.26
Anti-hypertensive therapy	21 (7)	46 (15)	0.005
Male	13 (8)	28 (18)	0.012
Female	8 (6)	18 (12)	0.063
Neuromuscular blockers	129 (43)	147 (49)	0.34
Male	73 (46)	85 (55)	0.43
Female	56 (39)	62 (43)	0.66
Ephedrine bolus	109 (36)	96 (32)	0.51
Male	58 (37)	47 (31)	0.43
Female	51 (35)	49 (34)	0.91

Table 3 Interaction of gender with propofol and remifentanil consumption. Two-factors analysis of variance with interaction. One fixed factor was the treatment (group) and one random factor gender. DF, degree of freedom

	Source	DF	*F*-ratio	*P*-value
Propofol	Group	1	1.13	0.48
	Gender	1	56.3	<0.0002
Remifentanil	Group	1	1.11	0.48
	Gender	1	37.5	<0.0001

However, the sparing effect of N_2O would probably be <20% and not clinically relevant. Another limitation of our approach is that N_2O causes a degree of sympathetic activation which activates electroencephalographic signals after noxious stimuli.[21] A consequence is that N_2O decreases BIS less than would be expected based on its MAC.[9] A closed-loop system controlled to another anaesthetic measure of anaesthesia depth might well have identified a greater drug-sparing effect of N_2O. The difficulty, of course, is that there are few well-validated measures of hypnotic effect that do not depend on the electroencephalogram. We only evaluated the sparing

effect on propofol and remifentanil consumption and not postoperative morphine requirements. Specific studies are necessary to determine if N_2O can prevent hyperalgesia related to remifentanil titrate by the BIS.[40]

In summary, N_2O did not reduce propofol and remifentanil requirements in men during BIS-guided anaesthesia. In contrast, N_2O significantly spares propofol and remifentanil in women—although the magnitude of the reduction is unlikely to prove clinically important. Adding nitrous oxide to BIS-guided closed-loop i.v. anaesthesia thus appears to provide little benefit.

Authors' contributions

N.L.: study design, conduct of the study, data analysis, and manuscript preparation. M.L.G.: conduct of the study, data analysis, and manuscript preparation. N.B.: conduct of the study. A.G.: conduct of the study. T.H.: conduct of the study. D.S.: conduct of the study. G.K.: conduct of the study. A.L.: conduct of the study. J.J.B.: conduct of the study. A.C.: conduct of the study. J.B.: conduct of the study. B.R.: conduct of the study and manuscript preparation. S.T.: conduct of the study. T.C.: study design, conduct of the study, and data analysis. D.I.S.: manuscript preparation. M.F.: study design and manuscript preparation.

Declaration of interest

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