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The Effect of Nitrous Oxide Anesthesia on Early Postoperative Opioid Consumption and Pain

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Abstract

Background and Objectives—Many patients experience moderate to severe postoperative pain. Nitrous oxide exerts analgesia by inhibition of *N*-Methyl-D-aspartate (NMDA) receptors. Ketamine, another NMDA receptor-antagonist, reduces postoperative opioid consumption and pain. A similar effect of nitrous oxide is plausible, yet understudied. The goal of this study was to determine the effects of nitrous oxide anesthesia on early postsurgical opioid consumption and pain.

Methods—This was a retrospective, secondary analysis of the Vitamins In Nitrous Oxide trial, where 500 patients undergoing general anesthesia for noncardiac surgery received 60% nitrous oxide and 125 received no nitrous oxide (otherwise, inclusion/exclusion criteria were identical). Exclusion criteria for this study were regional anesthesia; not extubated after surgery; transfer to ICU; no available PACU record; postsurgical sedation; or treated with naloxone. Primary outcomes were cumulative opioid consumption measured in morphine equivalents and pain scores during the immediate recovery phase.

Results—Four hundred forty-two patients met inclusion criteria. No difference in intraoperative and postoperative opioid consumption was observed between patients who received nitrous oxide ($n=353$) and patients who did not ($n=89$). The median [interquartile range] postoperative morphine equivalent dose was 6.7 mg [1.7–14.1] for patients who received nitrous oxide and 6.7 mg [2.1–15.4] for patients who did not ($P = 0.73$). The maximum pain score was 6 [4–8] for patients who received nitrous oxide versus 6 [3–8] for patients who received nitrous oxide-free anesthesia ($P = 0.52$). The prevalence of moderate to severe pain was 69% for patients who received nitrous oxide and 68% for patients who did not ($P = 0.90$).

Conclusions—Nitrous oxide anesthesia was not associated with decreased opioid administration, pain, or incidence of moderate to severe pain in the early postoperative phase.

Keywords

Analgesia; Nitrous Oxide; Pain; Postoperative; Anesthesia; General

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Conflicts of Interest

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INTRODUCTION

Moderate to severe postoperative pain occurs in 20% to 80% of patients.^{1,2} Nitrous oxide (N₂O), a widely used anesthetic gas, modulates pain perception and consciousness.^{2–6} The dominant mechanism of its analgesic action is central inhibition of NMDA receptors.^{5–8} Ketamine, another NMDA-receptor antagonist, has been shown to alleviate postoperative pain.^{9,10} Based on a similar mechanism of action, the intraoperative use of N₂O may also exert a similar effect on acute postoperative pain and analgesic drug requirements. However, the effects of N₂O on early postoperative pain are not well understood, and studies have provided inconclusive evidence.^{1–4} While some found a reduced duration of patient-controlled analgesia use² or reduced opioid-induced hyperalgesia,⁴ others found increased early postsurgical pain after N₂O anesthesia.¹ Most recently Chan and others showed a reduction of chronic, but not acute postoperative pain after N₂O anesthesia.³ We recently completed a clinical trial where patients undergoing non-cardiac surgery received N₂O or N₂O-free anesthesia in a nonrandomized fashion [the Vitamins In Nitrous Oxide (VINO) Trial; clinicaltrials.gov, NCT00655980].¹¹ In this post-hoc analysis, we compared early postsurgical opioid consumption and pain in patients who received N₂O during general anesthesia with patients who did not receive N₂O during general anesthesia.

METHODS

The institutional review board (Washington University, St. Louis, Missouri) approved the VINO trial as well as this retrospective analysis, for which patient consent was waived. In the VINO trial,¹¹ 500 patients undergoing noncardiac surgery were randomly allocated to receive either 60% N₂O/40% O₂ plus a vitamin B infusion (n=250) or 60% N₂O/40% O₂ plus placebo infusion (n=250). A nonrandomized reference group of 125 patients without N₂O was concurrently enrolled. For this post-hoc analysis, patients who received N₂O will be compared with patients who did not.

Study population and data collection

To be eligible for enrollment in VINO trial patients had to be 18 years or older, diagnosed with or at risk for coronary artery disease, and scheduled for elective noncardiac surgery under general anesthesia lasting more than 2 hours. They were ineligible for enrollment in VINO if the use of N₂O was contraindicated; pulmonary disease requiring supplemental oxygen existed; they had ASA V physical status; took supplemental vitamin B12 or folic acid; had allergy or hypersensitivity to cobalamins; or had Leber disease or a seizure disorder.

For this study, patients from the VINO trial population were excluded if they had regional anesthesia (peripheral or neuraxial anesthesia) performed; were not extubated at the end of surgery; were transferred to the ICU; had no available postanesthesia care unit (PACU) record; did not receive general anesthesia; had postsurgical sedation; or were treated with naloxone. We decided to further exclude patients who received remifentanyl or sufentanyl as the main intraoperative opioid due to low census. In this study, the two groups that received N₂O during surgery were pooled into one group (group N₂O) and compared to the group of patients who did not receive N₂O (group non-N₂O) during anesthesia. The use of anesthetic drugs other than N₂O was at the discretion of the anesthesia team.

Patient characteristics and related surgical data were available through the VINO trial database. Opioid consumption and pain scores were accessed via electronic anesthesia information system and, for patients that were enrolled before the implementation of the anesthesia information system, manual data extraction via patient charts was performed.

Data were collected for the intraoperative period and the postsurgical recovery period in the PACU. Assessment of all measurements and data was the same for both groups.

Measurements

The primary outcome was the cumulative opioid consumption during the immediate postoperative recovery phase (PACU stay). The PACU stay was the time (in minutes) from patients entering the postoperative care unit immediately after surgery to discharge to the ward. Secondary outcome measures included intraoperative cumulative opioid consumption, pain scores rated by patients on an 11-point (0 = no pain and 10 = worst imaginable pain) Numeric Rating Scale (NRS-11) and prevalence of moderate to severe pain (pain rated as 5–10) in the PACU. For comparison, all opioids were converted to intravenous morphine dose equivalents using an equianalgesic dose ratio table (Table 1) designed for acute care (Available at: <http://www.globalrph.com/opioidconverter2.htm>. Accessed April 24, 2013).¹²

For the intraoperative period, we retrieved types and doses of analgesics and anesthetics, as well as the duration of exposure to volatile anesthetics, recorded in minute-by-minute intervals in electronic, and in 15-minute intervals in paper records. For the postoperative phase, types and doses of analgesic, anxiolytic, neuroleptic and sedative medications were obtained, as well as pain scores in 10-minute intervals and duration of PACU stay. Pain scores and medication was noted by nurses. If patients were asleep no pain score was entered by the nurse, but it was noted that the patient was asleep at that time. No pain scores were imputed and it was rather chosen to report maximum pain scores in PACU to avoid bias by individually differing numbers of available assessments. There was no institutional standard protocol for postoperative pain management. Type and dose of used opioids were influenced by attending preferences and individual patient factors. If patient controlled anesthesia was started in the PACU but the readout was after discharge from the PACU, the dose amount administered during the stay in the PACU was used. To test for effect modification of intra- and postoperative opioid requirements due to preoperative chronic opioid use, a sensitivity analysis was performed that distinguished patients with chronic opioid use from opioid-naïve patients. Patients were defined as routine opioid users when their daily home medication contained opioids.

Statistical Analysis

Statistical analysis was performed using nonparametric tests (Wilcoxon rank sum) for ordinal and skewed continuous data and parametric tests for normally distributed continuous data. Chi-squared test and, if appropriate, Fisher exact test were used for dichotomous variables. IBM SPSS 2 (IBM, Armonk, New York) was used as statistical analysis software. Data are presented as median [25th percentile – 75th percentile] or mean (SD).

Results

We included 442 patients of whom 353 (80%) had received N₂O and 89 (20%) had not received N₂O. A total of 183 patients were excluded (Fig 1). Patient, surgical, and anesthetic characteristics are shown in Table 2. The length of stay in the PACU was 131 minutes [IQR 98–175] for patients who received N₂O and 134 minutes [IQR 103–188] for patients who did not receive N₂O ($P=0.49$).

Opioid consumption

No difference in intraoperative and postoperative opioid consumption was observed between patients who received N₂O and patients who did not. The median intraoperative morphine equivalent dose was 35.0 mg [IQR 25.0–45.0] for patients who received N₂O and 35.0 mg [IQR 27.6–53.2] for patients who did not ($P = 0.09$) (Fig 2). The median postoperative

morphine equivalent dose was 6.7 mg [IQR 1.7–14.1] for patients who received N₂O and 6.7 mg [IQR 2.1–15.4] for patients who did not ($P = 0.73$) (Fig. 3). The analgesic drugs administered during and after surgery are presented in Table 3.

Pain scores

PACU pain scores were available in 404 (91.4%) postoperative records. The maximum pain score was 6 [IQR 4–8] for patients who received N₂O (n=319) and 6 [IQR 3–8] for patients who did not (n=85) ($P=0.52$). Pain score at discharge – noted in 408 (92.3%) records – was 3 [IQR 1–4] for patients who received N₂O (n= 331) and 3 [IQR 0.5–4.5] for patients who did not (n=77) ($P=0.83$).

The prevalence of moderate to severe pain in the PACU was 69% for patients who received N₂O and 68% for patients who did not ($P = 0.90$).

Chronic pain patients

Chronic pain patients defined as patients who routinely used opioid analgesics had an increased opioid consumption during and after surgery compared with opioid naïve individuals. However, no statistically significant differences between group N₂O and group non-N₂O were observed (Table 4).

DISCUSSION

The main finding of this study is that N₂O was not associated with intra- and early postoperative opioid consumption and pain, an observation that was also present among patients taking chronic opioid medication.

Including our results, the totality of evidence suggests that N₂O has a negligible, or even absent, association with intra- and early postoperative pain and opioid consumption. In a recent, well conducted and powered ancillary study of the ENIGMA trial, Chan and others³ also found no evidence that N₂O had an effect on pain during the first 3 days after surgery. However, they observed that the use of N₂O during anesthesia may reduce the risk of chronic postoperative pain by a factor of 2. This result raises the possibility that the use of N₂O may be beneficial for patients at risk of developing chronic postoperative pain, but perhaps not acute pain. Ketamine, on the other hand, alleviates acute and chronic pain despite the fact that N₂O and ketamine have similar blocking action at the NMDA receptor.^{9,10} Two questions must be discussed to understand that alleged disparity. First, what is the role of NMDA receptor antagonism in acute and chronic pain? Second, what might contribute to different effects in acute pain between ketamine and N₂O?

First, NMDA receptor activation is the main trigger for central sensitization and chronic nociception,¹³ but not acute nociception.^{14,15} Subanesthetic doses of NMDA receptor antagonists effectively prevent sensitization of spinal dorsal horn neurons and formation of pathologic, hyperalgesic pain memory, but have a smaller effect on acute pain.^{14,15} Therefore, the central analgesic effect of both N₂O and ketamine can be less evident or even missing during acute nociception but is most pronounced beyond the early postoperative phase, when pathological pain states dominate.^{3,4,14,15} Stubhaug and others¹⁴ showed by studying hyperalgesia, a distinct measure for central sensitization and predictor of chronic pain, that prevention of central sensitization can be prominent, while the effect on acute analgesia may be minimal. Likewise Echevarria and others⁴ recently showed sustained antihyperalgesic properties without affecting pain scores 12 to 18 hours after N₂O exposure. Differences in the pharmacological profile between N₂O and ketamine may explain why N₂O does not seem to reduce postoperative morphine consumption and pain compared to

ketamine.^{5,13} Differences in pharmacokinetics, namely N₂O's shorter half-life and weaker potency compared to ketamine, might be one cause. Differences in pharmacodynamics, in particular a different action on various ion channels and receptor subtypes, such as ketamine's nonselective inhibition of NR_{2A}- and NR_{2B}-NMDA receptors and action on nicotinic, muscarinic, cholinergic, monoaminergic, opioid, or excitatory non-NMDA receptor systems, might be another reason.¹³ Another reason for N₂O's lack of analgesic effect in acute pain might be due to acute tolerance.⁵ In contrast to ketamine the analgesic effect of N₂O diminishes over time during continuous administration; a phenomenon seen already after 40 minutes of inhalation.¹⁶ N₂O's antinociceptive action is partially mediated via activation of central opioidergic neurons in the periaqueductal grey area. Animal studies support the hypothesis that continuous N₂O exposure might trigger release of endogenous opioid peptide so excessively that depletion occurs.⁵ As a consequence, descending antinociceptive pathways might not be activated any longer and analgesic action vanishes. Taking into account that the treatment group of the VINO trial received N₂O for at least 2 hours, acute depletion of central opioid peptides might have occurred and an analgesic effect may have disappeared. Thus, several potential explanations exist, why we did not detect an effect of N₂O on early postoperative pain.

The study has several limitations. First, we only could assess postoperative opioid consumption and pain during the PACU stay but not on the floor, which restricted the interpretation of our results to the immediate postoperative period. Second, due to the retrospective study design, pain scores, part of the secondary outcome measures, were not recorded in all cases. In 8.6 % of patients, PACU pain scores, and, in 7.7 % of patients, discharge pain scores were missing. Their characteristics and perioperative data were similar to the patients included in the analysis of pain scores, and it seems unlikely that a derived information bias would have changed the results substantially. However, opioid consumption, the primary outcome measure, was available for all patients. Third, the parent trial aimed to determine if patients who carry a gene variant in the core enzyme of the folate cycle have a higher risk for postoperative cardiac events after N₂O anesthesia. 500 patients in the trial received N₂O and 125 received N₂O-free anesthesia as part of a nonrandomized reference group. The fact that the allocation to receive N₂O was nonrandomized is a limitation of this study and reduces its validity. While both groups appear very similar and are drawn from the same patient population, we cannot rule out confounding and selection bias. However, the possibility of a selection bias is reduced by the fact that patients of both groups were nearly concurrently enrolled and identical inclusion and exclusion criteria were applied. Fourth, the VINO study targeted older patients with increased cardiac risk. Previous studies showed younger age as an independent risk factor for postsurgical pain^{1,17}; an effect we could not assess in the current study due to the advanced age of our cohort. Lastly, we decided not to perform subgroup analyses based on surgical characteristics, because the sample size of subgroups would have been too small. However, the broad variety of anesthetic regimens and surgical procedures in our study population strengthens the generalizability of our results. In summary, the results of this study suggest that the intraoperative use of N₂O is not associated with decreased opioid consumption and pain in the early postoperative phase.

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Figure 1.
Study flow chart

Figure 2. Opioid consumption during surgery

Opioid consumption during surgery was not significantly different in patients with N₂O (white boxplot) compared with patients without N₂O (shaded boxplot) anesthesia ($P = 0.09$).

Figure 3. Opioid consumption during PACU stay

Opioid consumption during PACU stay was not significantly different in patients with N₂O (white boxplot) compared to patients without N₂O (shaded boxplot) anesthesia ($P=0.73$).

Table 1

Equianalgesic conversion of opioids.

Opioid (mg)	10 mg morphine dose equivalent	Route
Hydrocodone	30	oral
Hydromorphone	1.5	parenteral
Fentanyl	0.1	parenteral
Meperidine	75	parenteral
Methadone	5	parenteral
Morphine	10	parenteral
Oxycodone	20	oral
Tramadol	100	oral

This table shows the equianalgesic doses used to calculate parenteral morphine dose equivalents and the route of application. For example, 1.5 mg of parenteral hydromorphone was converted to 10 mg parenteral morphine. (Available at: <http://www.globalrph.com/opioidconverter2.htm>. Accessed April 24, 2013.)

Table 2**Patient characteristics and perioperative data**

Patient characteristics	N₂O** (n=353)	non-N₂O (n=89)
Age Mean (SD*)	64.4 (10.9)	67.3 (11.0)
Weight (kg) Mean (SD)	89 (21)	88 (23)
Height (cm) Mean (SD)	172 (11)	172 (10)
Male N† (%)	220 (62.3)	54 (60.7)
Caucasian N (%)	269 (76.2)	72 (80.9)
ASA‡ classification N (%)		
II	59 (16.7)	8 (9.0)
III	282 (79.9)	76 (85.4)
IV	12 (3.4)	5 (5.6)
Alcohol abuse N (%)	31 (8.8)	8 (9.0)
Drug abuse N (%)	21 (5.9)	2 (2.2)
Chronic use of analgesic medication N (%)	150 (42.6)	48 (53.9)
Opioid N (%)	103 (29.2)	35 (39.3)
Non-opioid N (%)	110 (31.2)	32 (36.0)
Chronic use of antidepressive, anticonvulsant or anxiolytic medication N (%)	131 (37.8)	39 (44.8)
Diabetes N (%)	130 (37)	26 (29.2)
Insulin dependent	58 (16.4)	13 (14.6)
Malignancy N (%)	106 (30)	32 (36)
Perioperative data		
Surgical Service N (%)		
Vascular	135 (38.2)	40 (44.9)
Orthopedic	88 (24.9)	12 (13.5)
Gynecology	35 (9.9)	6 (6.7)
Ear, Nose and Throat	29 (8.2)	13 (14.6)
Urologic	37 (10.5)	7 (7.9)
Neurosurgery	16 (4.5)	10 (11.2)
Other	13 (3.7)	1 (1.1)
Surgical time (minutes) Median [IQR§]	163 [117–230]	173 [126–243]
Anesthesia time (minutes) Median [IQR]	205 [150–265]	216 [167–289]
Local anesthetic infiltration by surgeon N (%)	95 (26.9)	33 (37.5)
Anesthetic drugs		
Desflurane N (%)	247 (70)	68 (76)
Endtidal MAC¶ adjusted for age Median [IQR]	0.55 [0.46–0.65]	0.86 [0.78–0.93]
Sevoflurane N (%)	136 (39)	40 (44.9)
Endtidal MAC adjusted for age Median [IQR]	0.67 [0.49–0.81]	0.90 [0.65–1.02]
Isoflurane N (%)	15 (4.2)	3 (3.4)
Lidocaine (intravenous) N (%)	300 (85)	81 (91)
mg Median [IQR]	100 [60–100]	80 [60–100]

Patient characteristics	N ₂ O ^{**} (n=353)	non-N ₂ O (n=89)
Propofol N (%)	327 (92.6)	85 (95.5)
mg Median [IQR]	150 [120–200]	150 [120–200]
Midazolam N (%)	291 (82.4)	67 (75.3)
mg Median [IQR]	2 [2–3]	2 [2–3]
Etomidate N (%)	24 (6.8)	5 (5.6)
mg Median [IQR]	20 [18–25.5]	20 [14–30]
Dexmedetomidine N (%)	3 (0.8)	3 (3.4)
Droperidol N (%)	7 (2)	1 (1.1)
Thiopental N (%)	5 (1.4)	0 (0)
Recent general anesthesia (<30 days) N (%)	16 (4.5)	5 (5.6)
With nitrous oxide	2 (0.6)	1 (1.1)

This table shows characteristics and perioperative data of patients undergoing N₂O or N₂O-free anesthesia for non-cardiac surgery. Values are mean (SD), median [IQR], or number (proportion).

* SD; Standard Deviation

[†] N; count

[‡] ASA; American Society of Anesthesiologists

[§] IQR; interquartile range

[¶] MAC; minimal alveolar concentration

** N₂O; nitrous oxide

Table 3

Intra- and postoperative analgesic drug usage

Analgesic drug	N ₂ O [†] (n=353)	non-N ₂ O (n=89)
<i>During surgery</i>		
Opioids N* (%)		
Hydrocodone	1 (0.3)	0
Hydromorphone	103 (29.2)	32 (36.0)
Fentanyl	335 (94.9)	88 (98.9)
Meperidine	9 (2.5)	0
Methadone	11 (3.1)	3 (3.4)
Morphine	82 (23.2)	6 (6.7)
Oxycodone	0	0
Tramadol	1 (0.3)	1 (1.1)
Non-opioids N (%)		
Ketamine	4 (1.1)	1 (1.1)
NSAIDs (acetaminophen, ketorolac)	25 (7.1)	14 (15.7)
Gabapentin	0	0
<i>After surgery</i>		
Opioids N (%)		
Hydrocodone	9 (2.5)	0
Hydromorphone	202 (57.2)	65 (73.0)
Fentanyl	43 (12.2)	14 (15.7)
Meperidine	14 (4.0)	1 (1.1)
Methadone	1 (0.3)	0
Morphine	81 (22.9)	7 (7.9)
Oxycodone	14 (4.0)	0
Tramadol	0	0
Non-opioids N (%)		
Ketamine	0	0
NSAIDs (acetaminophen, ketorolac)	37 (10.5)	9 (10.1)
Gabapentin	1 (0.3)	0

This table shows the analgesic drugs usage during and after noncardiac surgery in patients undergoing N₂O or N₂O-free anesthesia. Values are number (proportion).

* N; count

[†] N₂O; nitrous oxide

Table 4

Outcomes for opioid-naïve patients and patients with chronic opioids use

	Routine intake of opioid medication (n=138)		Naïve to opioids (n=304)	
Morphine equivalent dose during surgery (mg)	38.3 [26.7–53.7]		32.3 [25.0–43.3]	
Morphine equivalent dose after surgery (mg)	10 [3.3–18.3]		6.7 [0.0–13.3]	
Maximum pain score	8 [5–9]		5.5 [3–8]	
Pain score at discharge	3 [2–5]		3 [1–4]	
			0.02 <i>P</i> -value	

	N ₂ O* (n=103) (74.6%)		non-N ₂ O (n=35) (25.4%)		N ₂ O (n=250) (82.2%)		non-N ₂ O (n=54) (17.8%)	
Morphine equivalent dose during surgery (mg)	38.3 [25.0–50.0]		38.3 [30.3–73.3]		31.7 [25.0–41.9]		35 [25.3–48.3]	
Morphine equivalent dose after surgery (mg)	10 [3.3–18.3]		11.5 [3.3–19.8]		6.7 [0.0–13.3]		5.8 [1.5–10.4]	
Maximum pain score	8 [5–9]		7 [4.5–8]		6 [3–8]		5 [3–7]	
Pain score at discharge	3 [2–5]		3.5 [0–5]		3 [1–4]		3 [1–4]	
					0.50 <i>P</i> -value		0.89 <i>P</i> -value	

This table presents an analysis with special emphasis on patients who had routine intake of opioid analgesic medication and patients who were opioid naïve. Morphine equivalent doses during surgery and in the recovery area, maximum pain score during the early postoperative phase and pain score at discharge from the recovery area were compared using Wilcoxon-rank sum test. *P*-values were significant for differences between patients who had routine intake of opioid analgesic medication and patients who were opioid naïve. No difference was seen within these groups for patients with nitrous oxide and without. Data are presented as median [25th percentile – 75th percentile].

* N₂O = nitrous oxide