Original Article

Intraoperative nitrous oxide inhalation to prevent chronic postsurgical pain in video-assisted thoracoscopic surgery: a prospective observational cohort study

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Background: Chronic postsurgical pain (CPSP) is a significant detriment to postsurgical recovery. Previous studies have shown that nitrous oxide (N_2O) may produce long-term analgesia and may benefit the prevention of CPSP in Chinese patients. We tested the hypothesis that N_2O is a protective factor against chronic pain after video-assisted thoracoscopic surgery (VATS).

Methods: Two groups of patients with and without N_2O inhalation during VATS in Peking Union Medical College Hospital were recruited. Perioperative information was documented, and postsurgical pain was followed up by telephone. The primary outcome was the presence of CPSP at 6 months postoperatively. Odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using a multivariate logistic regression model adjusted for relevant confounding factors.

Results: A total of 833 patients were eligible, among whom 33.6% were male and 66.4% were female, with an average age of 56.3±11.1 years. A total of 387 (46.5%) patients reported incision-related pain at 6 months after surgery, and 160 (40.0%) out of 400 patients with N_2O inhalation during surgery and 227 (52.4%) out of 433 patients without N_2O inhalation during surgery developed CPSP. After adjusting for confounding factors, N_2O inhalation during surgery was associated with lower odds of CPSP (OR =0.654; 95% CI: 0.480–0.890; P=0.007).

Conclusions: N_2O inhalation during surgery was associated with lower odds of CPSP in VATS patients, and N_2O may benefit the prevention of chronic pain after thoracoscopic surgery.

Keywords: Nitrous oxide (N_2O); chronic postsurgical pain (CPSP); video-assisted thoracoscopic surgery (VATS)

Submitted Apr 05, 2024. Accepted for publication Jun 28, 2024. Published online Aug 21, 2024.
doi: 10.21037/jtd-24-556
View this article at: https://dx.doi.org/10.21037/jtd-24-556

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Introduction

Chronic postsurgical pain (CPSP) is a significant clinical problem that negatively affects recovery and quality of life after surgery. CPSP is defined as chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, i.e., at least 3 months after the surgery (1). Due to the location of the incision and the necessity of an indwelling thoracic tube, thoracic surgery is considered to be one of the most painful operations (2), with an overall chronic pain incidence of up to 65% (3). The incidence of chronic pain in the third and sixth months after thoracic lobectomy is 57% and 47%, respectively (4,5). Within 3–6 months after thoracic surgery, the proportion of patients using opioids is as high as 31% (6). Therefore, the prevention of CPSP in thoracic surgery is receiving increasing attention.

The mechanism of CPSP may be related to local trauma, inflammatory reactions and neuropathic pain (7) and involves multiple peripheral and central signalling and modulatory pathways regulated by genes, epigenetics, and psychosocial, perioperative, and gene-environmental interactions (8,9). Some animal and clinical trials have shown that nitrous oxide (N_2O) may produce long-term analgesic effect, and genetic susceptibility may further enhance this effect of N_2O administration (10-12). Evidence has shown that N_2O is a protective factor against chronic postoperative pain in Asian populations with variants in the methylenetetrahydrofolate reductase gene in nonthoracic surgery (13). However, it remains unclear whether this effect also exists in thoracic surgery.

The primary objective of this study was to test the hypothesis that N_2O inhalation during anaesthesia is associated with a lower incidence of chronic pain 6 months after video-assisted thoracoscopic surgery (VATS) in a Chinese population. The impact of N_2O inhalation on postsurgical pain at 3 months and neuropathic pain were also discussed. Our study also provides prospective epidemiological data on CPSP related to thoracic surgery in the Chinese population, as such data are relatively inadequate. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-556/rc) (14).

Highlight box

Key findings

- Nitrous oxide (N_2O) may be a protective factor for chronic postsurgical pain (CPSP) after video-assisted thoracoscopic surgery (VATS).

What is known and what is new?

- Previous studies have shown that N_2O may produce long-term analgesia and may benefit the prevention of CPSP in Asian patients.
- N_2O inhalation during surgery was associated with lower odds of CPSP in VATS patients.

What is the implication, and what should change now?

- To prevent the occurrence of CPSP, perioperative analgesia could be improved by administrating N_2O and applying multimodal analgesia with the combination of different anaesthesia methods.

Methods

Study design

This prospective cohort study was approved by the Ethical Committee of Peking Union Medical College Hospital (Ethical Committee No. JS-2409), Beijing, China (Chairperson Prof. Zhaohui Zhu) on June 23, 2020. The Ethical Committee waived the need for written informed consent due to the observational nature of our study, and verbal consent was attained through verbal questionnaire. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study design, outcome variables, and analysis plan were selected prior to surgery.

Study population

Participants aged 18 years and older who underwent elective VATS at Peking Union Medical College Hospital (PUMCH) were eligible. The medical center stopped supplying N_2O on February 18, 2021. Thus, two groups of participants were recruited by time sequence, with the N_2O group consecutively recruited from November 1, 2020, to January 31, 2021, and the control group consecutively recruited from March 1, 2021, to May 31, 2021.

Exclusion criteria included pre-operative chronic pain and opioid usage ≥3 months, contraindications to the use of N_2O, sensory dysfunction, delayed incision healing, uniportal surgery or the absence of a drainage tube. Patients

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who received a second operation within 6 months and those who refused or were unable to receive our telephone follow-up were also excluded.

Exposure, confounders and endpoints

The primary exposure factor in our study was N_2O inhalation (50–65%) during general anaesthesia, while patients with no N_2O inhalation during anaesthesia represented the control group.

Factors that may have causal relationships with CPSP were regarded as potential confounders in our analysis. Based on clinical experiences and previous studies, we adjusted for the confounding effects of age, sex, body mass index (BMI), American Society of Anaesthesiologists (ASA) score, history of smoking and allergy, blood types, presence of comorbidities, status of employment and marriage, incision length, surgery duration, perioperative chemotherapy, surgery type (wedge resection or lobectomy), intraoperative blood loss, intercostal nerve block, duration of chest tube drainage, malignancy of tumours, length of stay, intraoperative use of nonsteroidal anti-inflammatory drugs (NSAIDs), acute pain on postoperative day 1 (POD 1) and at discharge, patient-controlled analgesia (PCA), pre- and postoperative white blood cell (WBC) counts, preoperative haemoglobin (Hb) level and usage of opioids after discharge. Dosage range of intraoperative fentanyl was 4–6 mcg/kg and remifentanil application were 0.05–0.1 mcg/kg/h (15). Postoperative multi-model analgesia was applied according to patients' requirement, either PCA or single intravenous usage of 5 mg oxycodone.

A verbal questionnaire as well as a standard operating procedure was written a priori and followed by specialized personnel who completed the telephone follow-up 6 months after surgery. Verbal consent was attained at the beginning of the telephone interview. During the interview, patients were asked if they currently felt pain around or related to the incision site. If the pain had developed since the operation and no other causes existed, the presence of CPSP was recorded. The pain intensity was measured by the numeric rating scales (NRS), and characteristics of neuropathic pain was defined by a score of ≥2 on the neuropathic pain screening scale (ID-PAIN). Opioid consumption was recorded if patients claimed to take opioids after discharge.

The primary endpoint in our study was CPSP as judged by the patient's complaint of incision-related pain at the 6-month telephone follow-up. Secondary endpoints included chronic pain 3 months after surgery and the presence of neuropathic CPSP at 3 or 6 months.

Statistical analysis

On our pre-experimental basis, 33% of patients reported CPSP at 6 months after surgery, and the enrolment of ≥649 patients attained 90% power to detect a relative risk reduction of 30% with a type I error of 0.05.

The basic characteristics of patients with and without N_2O inhalation were tabulated and compared using Student's *t*-test and the Mann-Whitney *U*-test for continuous variables and using the χ^2 test for categorical variables. A P value less than 0.1 was considered a significant difference. The potential association between N_2O inhalation and primary or secondary endpoints was analyzed using multivariable odds ratios (ORs) and 95% confidence intervals (CIs) that were adjusted for age, sex, BMI, surgery duration, intraoperative NSAIDS, opioid consumption after discharge, ASA score, duration of chest tube drainage, PCA, intercostal nerve block, NRS at discharge, preoperative Hb and WBC, employment and marital status using multivariable logistic regression or multivariable linear regression.

We assessed the differences in outcomes in 4 subgroups (age, sex, surgery type, and intercostal nerve block) by adding a treatment-by-subgroup interaction term to the multivariate regression. We also explored the association between patient characteristics and several endpoints using the stepwise method of multivariate logistic regression models and linear regression models.

Data analysis was conducted using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided P value less than 0.05 was considered statistically significant.

Results

A total of 1,142 patients received VATS in our medical centre during the previously designed time period, of whom 859 met our selection criteria. Twenty-six (3.1%) patients

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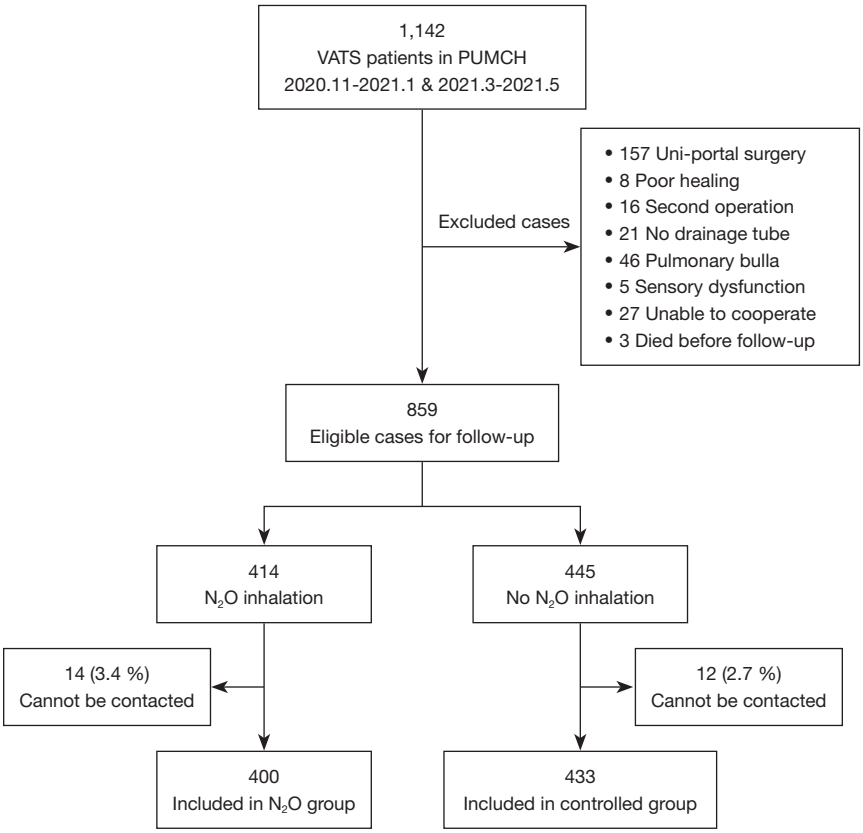

Figure 1 Flow chart for patients enrolment. VATS, video-assisted thoracoscopic surgery; PUMCH, Peking Union Medical College Hospital; N_2O, nitrous oxide.

could not be contacted despite multiple attempts. The remaining 833 patients were interviewed by telephone, among whom 400 (48.0%) patients received N_2O during anaesthesia and 433 (52.0%) did not receive N_2O inhalation (*Figure 1*).

Baseline and surgical characteristics

The mean age was 56.3 years, with 66.4% of female patients and 58.1% of patients aged ≥60 years. Over 80% of patients were classified as ASA II (*Table 1*). The average operation time was 1.7 hours, and the average length of stay was 6.4 days (*Table 2*). A total of 419 (50.3%) patients underwent intercostal nerve block, and 162 (19.4%) patients underwent PCA after surgery. At the 6-month follow-up, 387 (46.5%) patients developed CPSP, of whom 79 (20.4%) complained of moderate to severe pain with NRS ≥3, and 158 (40.8%) developed neuropathic pain (*Table 3*).

The baseline age and sex showed no significant difference between the two groups. Patients in the N_2O group had lower ASA scores, less duration of chest tube drainage and lower pain severity at discharge. More patients received PCA after surgery, and fewer patients received intercostal nerve block in the N_2O group. Preoperative Hb and WBC were slightly lower in the N_2O group, with no clinical significance. Furthermore, there were more patients with full-time employment and fewer patients who were married in the exposed group.

N_2O inhalation and CPSP

A total of 160 (40.0%) patients in the N_2O group and 227

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Table 1 Patient demographic characteristics

Variables	Overall (n=833)	N_2O group (n=400)	Control group (n=433)	P value
Age (years), mean (SD)	56.3 (11.1)	56.1 (11.5)	56.5 (10.8)	0.57
Sex, n (%)				0.30
Male	280 (33.6)	127 (31.8)	153 (35.3)	
Female	553 (66.4)	273 (68.2)	280 (64.7)	
BMI (kg/m^2), mean (SD)	23.9 (3.2)	23.9 (3.2)	24.0 (3.3)	0.77
ASA, n (%)				0.02
I	106 (12.7)	63 (15.8)	43 (9.9)	
II	672 (80.7)	316 (79.0)	356 (82.2)	
III	55 (6.6)	21 (5.2)	34 (7.9)	
History of smoking, n (%)	182 (21.8)	81 (20.3)	101 (23.3)	0.31
Blood type, n (%)				0.14
A	215 (25.8)	113 (28.2)	102 (23.6)	
B	285 (34.2)	122 (30.5)	163 (37.6)	
O	252 (30.3)	127 (31.8)	125 (28.9)	
AB	81 (9.7)	38 (9.5)	43 (9.9)	
Hypertension, n (%)	245 (29.4)	110 (27.5)	135 (31.2)	0.25
Diabetes, n (%)	103 (12.4)	55 (13.8)	48 (11.1)	0.25
Coronary heart disease, n (%)	46 (5.5)	19 (4.8)	27 (6.2)	0.37
History of allergy, n (%)	136 (16.3)	71 (17.8)	65 (15.0)	0.30
Full-time employment, n (%)	361 (43.3)	188 (47.0)	173 (40.0)	0.04
Married, n (%)	762 (91.5)	358 (89.5)	404 (93.3)	0.06

N_2O, nitrous oxide; SD, standard deviation; BMI, body mass index; ASA, American Society of Anaesthesiologists.

(52.4%) patients in the control group reported CPSP at 6 months after surgery. After univariate analysis, N_2O inhalation was negatively associated with CPSP (OR =0.76; 95% CI: 0.66–0.89; P<0.001). N_2O inhalation was independently associated with CPSP (OR =0.65; 95% CI: 0.48–0.89; P=0.007) (*Table 4*). N_2O inhalation was found to decrease the odds of CPSP at 3 months after surgery (OR =0.72; 95% CI: 0.52–0.99; P=0.045) (*Table 5*), as well as neuropathic pain (OR =0.44; 95% CI: 0.30–0.63; P<0.001) (*Table 6*).

Subgroup analyses for CPSP indicated significant interaction in the sex subgroup suggesting that N_2O inhalation reduced the risk of CPSP more in females than in males (OR =0.57; 95% CI: 0.38–0.83, P for interaction =0.04) (*Figure 2*). There were no significant interaction effects in the subgroups of age, surgery type and intercostal nerve block.

Risk factors for CPSP

A higher NRS score at discharge and previous coronary artery disease were risk factors for 6-month CPSP, while N_2O inhalation and full-time employment were protective factors (*Table 7*). For the 3-month CPSP, a higher NRS score at discharge, prolonged duration of drainage and female sex were risk factors, while full-time employment,

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Table 2 Surgical and perioperative characteristics

Variables	Overall (n=833)	N_2O group (n=400)	Control group (n=433)	P value
Surgery type, n (%)				>0.99
Lobectomy	636 (76.4)	305 (76.2)	331 (76.4)	
Wedge resection	197 (23.6)	95 (23.8)	102 (23.6)	
Blood loss (mL), mean (SD)	41.0 (77.4)	41.7 (93.9)	40.3 (58.3)	0.80
Length of incision (mm), mean (SD)	31.1 (4.8)	30.9 (4.8)	31.3 (4.8)	0.15
Surgery duration (hours), mean (SD)	1.7 (0.7)	1.7 (0.7)	1.7 (0.8)	0.93
Chest tube drainage (days), mean (SD)	2.7 (1.8)	2.8 (1.9)	2.6 (1.6)	0.06
LOS (days), mean (SD)	6.4 (3.6)	6.3 (2.4)	6.4 (4.5)	0.55
Malignant tumor, n (%)	690 (82.8)	327 (81.8)	363 (83.8)	0.46
Perioperative chemotherapy, n (%)	49 (5.9)	28 (7.0)	21 (4.8)	0.24
Preoperative Hb (g/L), mean (SD)	137.4 (15.1)	136.3 (14.7)	138.4 (15.4)	0.04
Preoperative WBC ($\times10^9$/L), mean (SD)	5.9 (1.6)	5.7 (1.5)	6.0 (1.7)	0.02
Postoperative WBC ($\times10^9$/L), mean (SD)	11.3 (3.2)	11.3 (3.1)	11.4 (3.3)	0.47
△WBC ($\times10^9$/L), mean (SD)	5.5 (2.8)	5.5 (2.7)	5.4 (2.9)	0.63

N_2O, nitrous oxide; SD, standard deviation; LOS, length of stay; Hb, haemoglobin; WBC, white blood cell; △WBC, postoperative WBC count – preoperative WBC count.

Table 3 Analgesia and postoperative pain characteristics

Variables	Overall (n=833)	N_2O group (n=400)	Control group (n=433)	P value
Intercostal nerve block, n (%)	419 (50.3)	171 (42.8)	248 (57.3)	<0.001
Intraoperative NSAIDs, n (%)	119 (14.3)	61 (15.3)	58 (13.4)	0.49
Postoperative PCA, n (%)	162 (19.4)	90 (22.5)	72 (16.6)	0.04
NRS score on POD 1, mean (SD)	5.9 (2.3)	5.9 (2.6)	5.9 (2.1)	0.73
NRS score at discharge, mean (SD)	3.3 (1.7)	3.2 (1.9)	3.5 (1.6)	0.01
CPSP at 6 months, n (%)	387 (46.5)	160 (40.0)	227 (52.4)	<0.001
CPSP at 3 months, n (%)	479 (57.5)	209 (52.3)	270 (62.4)	0.003
Neuropathic pain, n (%)	182 (21.8)	59 (14.8)	123 (28.4)	<0.001
Opioids after discharge, n (%)	225 (27.0)	105 (26.3)	120 (27.7)	0.64
NRS score of CPSP at 6 months, mean (SD)	2.02 (0.91)	1.87 (1.07)	2.05 (0.81)	0.053

N_2O, nitrous oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; PCA, patient-controlled analgesia; NRS, numeric rating scales; POD 1, postoperative day 1; SD, standard deviation; CPSP, chronic post-surgical pain.

opioid consumption and perioperative chemotherapy were protective factors (*Table 7*). Regarding the development of neuropathic pain, N_2O, intraoperative use of NSAIDs and opioid consumption were protective factors, while female sex, history of smoking and higher NRS at discharge were associated with higher odds of neuropathic pain (*Table 7*).

Discussion

In our study, chronic pain in thoracoscopy surgeries

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Table 4 Full multivariate regression model of N_2O for CPSP at 6 months

Variables	Adjusted OR	95% CI	P value
N_2O inhalation	0.654	0.480–0.890	0.007
Age	1.005	0.987–1.023	0.58
Female	1.187	0.787–1.790	0.41
BMI	0.990	0.942–1.041	0.70
ASA	–	–	0.87
II	1.135	0.708–1.818	0.60
III	1.091	0.509–2.430	0.82
Surgery duration	1.035	0.833–1.287	0.76
Chest tube drainage time	1.042	0.952–1.142	0.37
Preoperative Hb	1.004	0.991–1.017	0.60
NRS at discharge	1.626	1.458–1.814	<0.001
PCA	0.855	0.582–1.256	0.43
Preoperative WBC	0.938	0.850–1.035	0.20
Opioids consumption	0.846	0.587–1.220	0.37
Intercostal nerve block	0.894	0.659–1.213	0.47
Intraoperative NSAIDs	0.895	0.577–1.388	0.62
Married	1.170	0.681–2.009	0.57
Full-time employment	0.791	0.544–1.388	0.62

N_2O, nitrous oxide; CPSP, chronic postsurgical pain; OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anaesthesiologists; Hb, haemoglobin; NRS, numeric rating scales; PCA, patient-controlled analgesia; WBC, white blood cell; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 5 Full multivariate regression model of N_2O for CPSP at 3 months

Variables	Adjusted OR	95% CI	P value
N_2O inhalation	0.722	0.524–0.993	0.045
Age	1.003	0.985–1.022	0.72
Female	1.696	1.113–2.582	0.01
BMI	1.015	0.964–1.068	0.58
ASA	–	–	0.45
II	1.210	0.751–1.951	0.43
III	0.869	0.399–1.894	0.72
Surgery duration	0.959	0.767–1.198	0.71
Chest tube drainage time	1.113	1.007–1.231	0.04
Preoperative Hb	1.006	0.992–1.019	0.41
NRS at discharge	1.798	1.594–2.028	<0.001
PCA	1.018	0.688–1507	0.93
Preoperative WBC	0.945	0.853–1.046	0.27
Opioids consumption	0.694	0.470–1.026	0.07
Intercostal nerve block	0.552	0.663–1.246	0.55
Intraoperative NSAIDs	0.657	0.704–1.744	0.66
Married	0.846	0.486–1.474	0.56
Full-time employment	0.662	0.449–0.975	0.04

N_2O, nitrous oxide; CPSP, chronic postsurgical pain; OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anaesthesiologists; Hb, haemoglobin; NRS, numeric rating scales; PCA, patient-controlled analgesia; WBC, white blood cell; NSAIDs, nonsteroidal anti-inflammatory drugs.

remains common, with an overall incidence of CPSP 46.5% 6 months after surgery, and one-fifth of them experienced moderate to severe pain, which is consistent with previous studies (4,5). We observed a reduction in CPSP occurrence in our center, whereas the incidence of CPSP was 64.5% in a retrospective case-control study in PUMCH in 2009, in which most patients received thoracotomy (16).

Our study confirms that N_2O administration may have protective effects on CPSP in thoracoscopic surgeries, reducing the incidence of CPSP by 35% at 6 months. The same remains true when exploring the association between N_2O and CPSP at 3 months, suggesting that the result is rather stable. Furthermore, the administration of N_2O reduced the severity of CPSP at 6 months. Intraoperative inhalation of N_2O also reduced the incidence of neuropathic pain after surgery, in accordance with a previous study showing that a single 50% N_2O exposure induced a persistent reduction in hyperalgesia-allodynia in a rat neuropathic pain model (17).

The analgesic mechanisms of N_2O include activating TWIK-related K^+ channel 1 potassium channels on first-order neurons, blocking voltage-dependent calcium channels to attenuate neuronal excitability, attenuating postsynaptic glutamatergic receptor activation, and possibly blocking voltage-dependent sodium channels in the ascending pathway. In the descending pathway, N_2O induces the release of endogenous opioid ligands and stimulates norepinephrine release. In addition, N_2O may

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Table 6 Full multivariate regression model of N_2O for neuropathic pain

Variables	Adjusted OR	95% CI	P value
N_2O inhalation	0.436	0.301–0.632	<0.001
Age	1.003	0.985–1.022	0.29
Female	1.696	1.113–2.582	0.07
BMI	1.015	0.964–1.068	0.55
ASA	–	–	0.50
II	1.210	0.751–1.951	0.34
III	0.869	0.399–1.894	0.98
Surgery duration	0.959	0.767–1.198	0.07
Chest tube drainage time	1.113	1.007–1.231	0.13
Preoperative Hb	1.006	0.992–1.019	0.68
NRS at discharge	1.798	1.594–2.028	<0.001
PCA	1.018	0.688–1507	0.67
Preoperative WBC	0.945	0.853–1.046	0.82
Opioids consumption	0.694	0.470–1.026	0.02
Intercostal nerve block	0.552	0.663–1.246	0.25
Intraoperative NSAIDs	0.657	0.704–1.744	0.01
Married	0.846	0.486–1.474	0.11
Full-time employment	0.662	0.449–0.975	0.07

N_2O, nitrous oxide; OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anaesthesiologists; Hb, haemoglobin; NRS, numeric rating scales; PCA, patient-controlled analgesia; WBC, white blood cell; NSAIDs, nonsteroidal anti-inflammatory drugs.

mediate epigenetic changes by inhibiting methionine synthase (18).

Consistent with our findings, in the ENIGMA (evaluation of N_2O in the gas mixture for anaesthesia) randomized controlled trial (11), 640 Hong Kong patients with noncardiac surgery lasting more than 2 hours were subjected to N_2O-based or N_2O-free general anaesthesia. After multivariate analysis, N_2O reduced the risk of postoperative chronic pain (OR =0.43; 95% CI: 0.23–0.83; P=0.01). The ENIGNA-II trials (13) further confirmed this relationship in a predesigned subgroup analysis of 909 patients, in which N_2O reduced the risk of postoperative chronic pain in Asian populations [relative risk (RR) =0.70; 95% CI: 0.50–0.98; P=0.03], probably due to specific polymorphisms in the tetrahydrofolate reductase system in Asian populations, which may be more sensitive to the inhibitory effect of N_2O on the methyl donor activity of methionine synthase, thereby inhibiting DNA synthesis related to chronic postoperative pain and reducing neural plasticity, central nervous sensitivity and neuroinflammation (19,20).

Subgroup analysis showed that intraoperative N_2O was more significant in preventing CPSP in female patients than in male patients, suggesting that more administration of N_2O should be considered in female patients. There were no significantly different impacts of N_2O in the young or older populations, in cases of lobectomy or wedge section and in patients with or without intercostal nerve block.

Although previous research showed that younger age is a risk factor for CPSP after lobectomy (21-23), we did not find any significant impact of age while exploring risk factors for CPSP. Being female is generally considered to be associated with a higher incidence of CPSP (4). In our study, female sex was found to be a risk factor for neuropathic pain and CPSP at 3 months after surgery but was not associated with CPSP at 6 months. Studies suggest that marriage, full-time employment, drinking and smoking may show protective effects in breast surgery (24), whereas our study suggested that a full-time job was a protective factor against CPSP at both 3 and 6 months after surgery and that smoking was a risk factor for neuropathic pain. Postoperative acute pain shares the same molecular mechanism, including peripheral and central sensitization, and is a widely recognized independent risk factor for CPSP (24-27). The findings of this study are consistent with those in previous studies. Although intercostal nerve block reduces the severity of pain at discharge (28,29), there is no clinical evidence of its preventing CPSP. Delayed removal of the thoracic drainage tube is a risk factor for CPSP at 3 months, in accordance with a previous study (30,31). Although NSAIDs have no proven efficacy against neuropathic pain (32), the combination of opioids with NSAIDs produces synergistic analgesic effects on neuropathic pain (33), and intraoperative usage of NSAIDs was a protective factor against neuropathic pain in our research. Interestingly, coronary heart disease was a risk factor for chronic pain, which had no relevant research evidence to explain this phenomenon. This result may be

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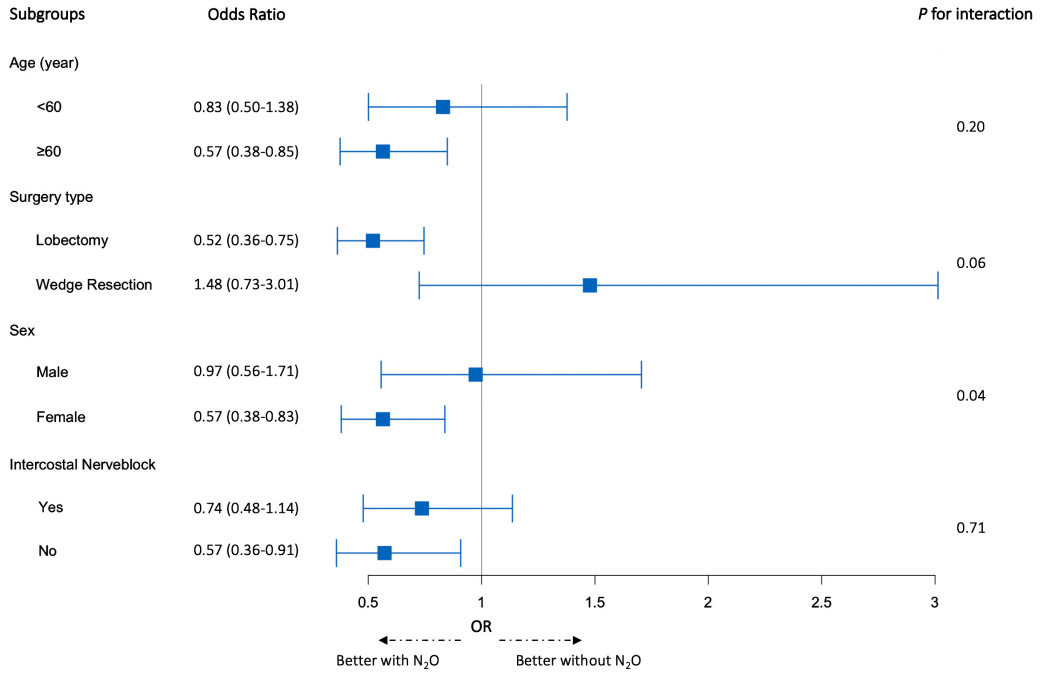

Figure 2 Odds ratios for chronic postsurgical pain associated with the use of N_2O in selected subgroups. OR, odds ratio; N_2O, nitrous oxide.

attributed to fewer options regarding pain-control methods in patients with coronary heart disease, as NSAID use is relatively contraindicated in such patients. Perioperative chemotherapy was a protective factor in our study, in contrast with a prior investigation (6), and these findings still need further research and testing.

Although our study included a relatively large sample of patients to evaluate the effect of N_2O on CPSP, there are several limitations. First, this was a single-centre observational study with no randomization, and several components of multimodal analgesia including paracetamol, thoracic epidural, thoracic paravertebral block, or local anesthesia infiltration, were not routinely used in our institution. The exposed and control groups were chosen by time period, which eliminated the confounding of anaesthesiologists' subjective choice on analgesics but also led to some confounding factors that cannot be adjusted, such as the surgeon's choice of patients, surgical technical improvements and the season. We collected as much baseline information as possible to attenuate the difference. Second, the endpoints were mainly obtained through telephone follow-up. Pain and NRS scores were evaluated by patients' subjective answers and may not have been precise or were influenced by physiological and psychological states (34), which we did not explore in this study. Nevertheless, our predesigned standard operating procedure and brief verbal questionnaire enabled nearly all participants to cooperate, including uneducated and elderly patients, ensuring the generalizability of the data. Third, we did not include uniportal VATS, which exhibited a significantly lower incidence of post-thoracotomy pain syndrome (35). To some extent, the generalisability of the study was limited (36). Finally, we did not adjust the subgroup analyses for multiple testing, and this may have increased the type I error. Therefore, the results need to be interpreted with caution.

Conclusions

In summary, in this prospective cohort of patients who underwent thoracoscopic surgery, intraoperative inhalation of N_2O was found to be significantly associated with decreased chronic postoperative pain. This rotective effect was more obvious in female patients. Considering the CPSP

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Table 7 Factors that were associated with the development of CPSP and secondary endpoints

Endpoints	Variable	OR/regression coefficient	95% CI	P value
CPSP at 6 months	N_2O inhalation	0.67	0.49–0.89	0.009
	Full-time employment	0.73	0.54–0.99	0.04
	NRS at discharge	1.60	1.45–1.77	<0.001
	Coronary artery disease	2.27	1.15–4.46	0.02
CPSP at 3 months	Female	1.48	1.07–2.04	0.02
	Perioperative chemotherapy	0.49	0.26–0.93	0.03
	Full-time employment	0.61	0.45–0.83	0.002
	Opioid consumption	0.68	0.46–1.00	0.05
	NRS at discharge	1.83	1.62–2.06	<0.001
	Duration of drainage tube	1.10	1.01–1.21	0.04
Neuropathic pain	N_2O inhalation	0.43	0.30–0.62	<0.001
	Opioid consumption	0.61	0.40–0.93	0.02
	NSAIDs	0.50	0.28–0.88	0.02
	Female	2.71	1.43–5.12	0.002
	Smoking	2.20	1.09–4.40	0.03
	NRS at discharge	1.37	1.22–1.53	<0.001
	Blood loss	1.00	1.00–1.00	0.03

CPSP, chronic postsurgical pain; OR, odds ratio; CI, confidence interval; N_2O, nitrous oxide; NRS, numeric rating scales; NSAIDs, nonsteroidal anti-inflammatory drugs.

in thoracoscopic surgery patients, perioperative analgesia could be improved by administrating N_2O and applying multimodal analgesia with the combination of different anesthesia methods.

Acknowledgments

We would like to thank all the clinical practitioners who took the time to participate in this research. We would also like to thank the presentation of the manuscript in Research Square.

Funding: This work was supported by National High Level Hospital Clinical Research Funding (No. 2022-PUMCH-B-007).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-556/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-556/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-556/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-556/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethical Committee of Peking Union Medical College Hospital (Ethical Committee No. JS-2409), Beijing, China (Chairperson Prof. Zhaohui Zhu) on June 23, 2020. The

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Ethical Committee waived the need for written informed consent due to the observational nature of the study, and verbal consent was attained through verbal questionnaire.

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References

1. Schug SA, Lavand'homme P, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain 2019;160:45-52.
2. Fiorelli S, Cioffi L, Menna C, et al. Chronic Pain After Lung Resection: Risk Factors, Neuropathic Pain, and Quality of Life. J Pain Symptom Manage 2020;60:326-35.
3. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet 2019;393:1537-46.
4. Bayman EO, Parekh KR, Keech J, et al. A Prospective Study of Chronic Pain after Thoracic Surgery. Anesthesiology 2017;126:938-51.
5. Wildgaard K, Ringsted TK, Hansen HJ, et al. Persistent postsurgical pain after video-assisted thoracic surgery--an observational study. Acta Anaesthesiol Scand 2016;60:650-8.
6. Nelson DB, Niu J, Mitchell KG, et al. Persistent Opioid Use Among the Elderly After Lung Resection: A SEER-Medicare Study. Ann Thorac Surg 2020;109:194-202.
7. Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 2019;160:53-9.
8. Rabbitts JA, Fisher E. Postsurgical pain in children: unraveling the interplay between child and parent psychosocial factors. Pain 2017;158:1847-8.
9. Weinrib AZ, Azam MA, Birnie KA, et al. The psychology of chronic post-surgical pain: new frontiers in risk factor identification, prevention and management. Br J Pain 2017;11:169-77.
10. Nagele P, Zeugswetter B, Wiener C, et al. Influence of methylenetetrahydrofolate reductase gene polymorphisms on homocysteine concentrations after nitrous oxide anesthesia. Anesthesiology 2008;109:36-43.
11. Chan MTV, Wan ACM, Gin T, et al. Chronic postsurgical pain after nitrous oxide anesthesia. Pain 2011;152:2514-20.
12. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anesthesiology 2008;109:707-22.
13. Chan MT, Peyton PJ, Myles PS, et al. Chronic postsurgical pain in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial. Br J Anaesth 2016;117:801-11.
14. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-7.
15. Wang X, Ida M, Uyama K, et al. Impact of different doses of remifentanil on chronic postsurgical pain after video-assisted thoracic surgery: A propensity score analysis. Medicine (Baltimore) 2023;102:e34442.
16. Wang HT, Liu W, Luo AL, et al. Prevalence and risk factors of chronic post-thoracotomy pain in Chinese patients from Peking Union Medical College Hospital. Chin Med J (Engl) 2012;125:3033-8.
17. Bessière B, Laboureyras E, Chateauraynaud J, et al. A single nitrous oxide (N2O) exposure leads to persistent alleviation of neuropathic pain in rats. J Pain 2010;11:13-23.
18. Bessiere B, Iris F, Milet A, et al. A new mechanistic approach for the treatment of chronic neuropathic pain with nitrous oxide integrated from a systems biology narrative review. Med Gas Res 2021;11:34-41.
19. Crow M, Denk F, McMahon SB. Genes and epigenetic processes as prospective pain targets. Genome Med 2013;5:12.
20. Buchheit T, Van de Ven T, Shaw A. Epigenetics and the transition from acute to chronic pain. Pain Med 2012;13:1474-90.
21. Wong J, Cooper J, Thomas R, et al. Persistent Postsurgical Pain Following Thoracotomy: A Comparison of Thoracic Epidural and Paravertebral Blockade as Preventive Analgesia. Pain Med 2019;20:1796-802.
22. Montes A, Roca G, Sabate S, et al. Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and Thoracotomy: A Two-year Multicenter Cohort Study. Anesthesiology 2015;122:1123-41.
23. Hah JM, Cramer E, Hilmoe H, et al. Factors Associated With Acute Pain Estimation, Postoperative Pain Resolution, Opioid Cessation, and Recovery: Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open 2019;2:e190168.

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24. Humble SR, Varela N, Jayaweera A, et al. Chronic postsurgical pain and cancer: the catch of surviving the unsurvivable. Curr Opin Support Palliat Care 2018;12:118-23.
25. Liu CW, Page MG, Weinrib A, et al. Predictors of one year chronic post-surgical pain trajectories following thoracic surgery. J Anesth 2021;35:505-14.
26. Wang S, Li Y, Fei M, et al. Clinical Analysis of the Effects of Different Anesthesia and Analgesia Methods on Chronic Postsurgical Pain in Patients With Uniportal Video-Assisted Lung Surgery. J Cardiothorac Vasc Anesth 2020;34:987-91.
27. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000;93:1123-33.
28. Kelley TM Jr, Bailey DW, Sparks P, et al. Intercostal Nerve Blockade with Exparel® Results in Lower Opioid Usage during the First 24 Hours after Video-Assisted Thorascopic Surgery. Am Surg 2018;84:1433-8.
29. Clephas PRD, Hoeks SE, Singh PM, et al. Prognostic factors for chronic post-surgical pain after lung and pleural surgery: a systematic review with meta-analysis, meta-regression and trial sequential analysis. Anaesthesia 2023;78:1005-19.
30. Kar P, Sudheshna KD, Padmaja D, et al. Chronic pain following thoracotomy for lung surgeries: It's risk factors, prevalence, and impact on quality of life - A retrospective study. Indian J Anaesth 2019;63:368-74.
31. Chen WC, Bai YY, Zhang LH, et al. Prevalence and Predictors of Chronic Postsurgical Pain After Video-Assisted Thoracoscopic Surgery: A Systematic Review and Meta-analysis. Pain Ther 2023;12:117-39.
32. Haanpää ML, Backonja MM, Bennett MI, et al. Assessment of neuropathic pain in primary care. Am J Med 2009;122:S13-21.
33. Shinozaki T, Yamada T, Nonaka T, et al. Acetaminophen and non-steroidal anti-inflammatory drugs interact with morphine and tramadol analgesia for the treatment of neuropathic pain in rats. J Anesth 2015;29:386-95.
34. Giusti EM, Lacerenza M, Manzoni GM, et al. Psychological and psychosocial predictors of chronic postsurgical pain: a systematic review and meta-analysis. Pain 2021;162:10-30.
35. Gu Y, Li X, Zhou Q, et al. Uniportal video-assisted thoracic surgery versus open thoracotomy for chronic pain after surgery: a prospective cohort study. J Anesth 2024;38:525-36.
36. Hirai K, Usuda J. Uniportal video-assisted thoracic surgery reduced the occurrence of post-thoracotomy pain syndrome after lobectomy for lung cancer. J Thorac Dis 2019;11:3896-902.

Cite this article as: Yuan Y, Zhang L, Zhang Y, Shen L, Huang Y. Intraoperative nitrous oxide inhalation to prevent chronic postsurgical pain in video-assisted thoracoscopic surgery: a prospective observational cohort study. J Thorac Dis 2024;16(8):5110-5121. doi: 10.21037/jtd-24-556

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