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Impact of Permissive Hypercapnia on Postoperative Early Plasma Neurofilament Light Chain in Elderly Patients Undergoing Laparoscopic Surgery: A Prospective, Randomized Controlled Trial

Ya-zhi Xi[1,2], Xue-lian Wei[1,2], Lei Xie[1,2], Xiao-yu Jia[2], Zhen-ping Li[2], Qing-he Zhou[2]

[1]Anesthesia Medicine, Zhejiang Chinese Medical University, Hangzhou City, Zhejiang Province, People's Republic of China; [2]Department of Anesthesiology and Pain Medicine, the Affiliated Hospital of Jiaxing University, Jiaxing City, Zhejiang Province, People's Republic of China

Correspondence: Qing-he Zhou, Department of Anesthesiology and Pain Medicine, the Affiliated Hospital of Jiaxing University, No. 1882, South of the Second Ring Road, Jiaxing City, Zhejiang Province, 314000, People's Republic of China, Tel +8613732573379, Fax +86057389997760, Email zqh10980@zjxu.edu.cn

Background: The effects of intraoperative permissive hypercapnia ($PaCO_2$ of 45–55 mmHg) on the central nervous system remain unclear. Neurofilament light chain (NfL, a protein found in the axons and nerve fibers of neurons) has been associated with central nervous system disorders. This study investigated the effect of intraoperative permissive hypercapnia on plasma NfL concentration 1 day postoperatively, and in turn on the central nervous system, during laparoscopic surgery.

Methods: This investigation was a prospective, single-blind randomized controlled trial. Eighty-four individuals aged above 60 years were randomly allocated to either the normocapnia group with an $PaCO_2$ of 35–45 mmHg (n=42) or the hypercapnia group with a $PaCO_2$ of 45–55 mmHg (n=42). The primary outcome was the 1-day postoperative plasma NfL concentration. Secondary outcomes included the area under the curve (AUC) values for $PaCO_2$ and regional cerebral oxygen saturation (rSO_2). The Mann–Whitney *U*-test was mainly used to analyze the outcomes.

Results: The final analysis included 38 and 40 patients in the normocapnia and hypercapnia groups, respectively. There was no statistically significant difference observed between the groups regarding the preoperative and 1-day postoperative plasma NfL concentration (14.0 [11.1, 19.9] vs 16.3 [9.06, 19.9] pg/mL, $P>0.05$; 23.4 [16.8, 32.3] vs 21.5 [15.6, 29.9] pg/mL, $P>0.05$, respectively). However, in both groups, the postoperative plasma concentration of NfL showed a significant increase when compared with the preoperative levels (both $P < 0.001$). The AUCs of $PaCO_2$ and rSO_2 from the beginning to the end of the pneumoperitoneum were significantly higher in the hypercapnia group compared with the normocapnia group (both $P<0.05$).

Conclusion: Our results indicate that intraoperative permissive hypercapnia targeting a $PaCO_2$ of 45–55 mmHg does not significantly influence postoperative early plasma NfL elevation levels in elderly patients undergoing laparoscopic surgery. During general anesthesia, intraoperative permissive hypercapnia might not significantly impact the central nervous system.

Keywords: hypercapnia, laparoscopic surgery, neurofilament light chain, general anesthesia

Introduction

Laparoscopic surgery is generally preferred because it causes less trauma compared with open surgery.[1] However, there is a potential concern with laparoscopic surgery known as hypercapnia. It occurs due to the contrast in carbon dioxide (CO_2) pressure between the abdominal cavity and the blood, along with the high CO_2 solubility in the blood, which allows for rapid CO_2 absorption through the peritoneum when creating a pneumoperitoneum.[2] Concerning major abdominal surgeries, anesthetists have observed that maintaining the arterial partial pressure of carbon dioxide

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($PaCO_2$) within a normal range is challenging for certain patients. This has resulted in the practice of permissive hypercapnia, in which a higher-than-normal $PaCO_2$ is tolerated intraoperatively.[3]

Permissive hypercapnia is a ventilation strategy that involves using low tidal volume ventilation, enabling a slight increase in $PaCO_2$ concentration and permitting a certain acidosis level.[4] CO_2 plays a crucial role in regulating cerebral vascular tension. It has been found that a 1 mmHg increase in $PaCO_2$ is typically accompanied by a 2%-4% increase in cerebral blood flow in healthy individuals.[5] A continuous increase in CO_2 concentration can cause brain swelling and intracranial pressure elevation.[4,6] The maintenance of mild hypercapnia during surgical operations has demonstrated improved regional cerebral oxygen saturation (rSO_2)[7] and a lower incidence of postoperative cognitive impairment.[8] While a study conducted by Wang et al revealed that the presence of hypercapnia during orthopedic surgery in elderly patients is associated with the emergence and development of postoperative cognitive impairment.[9] Therefore, understanding the potential effects of permissive hypercapnia on the central nervous system intraoperatively is essential.

Neurofilament light chain (NfL), a protein found in the axons and nerve fibers of neurons, a protein found in the axons and nerve fibers of neurons, has been associated with a range of central nervous system disorders.[10–12] An increase in NfL concentration has been observed in instances of axonal damage resulting from cerebral hypoperfusion.[13] According to reports, the cerebrospinal fluid to plasma ratio of NfL is 40:1.[14] With the development of the fourth-generation immunoassay technology Simoa, plasma NfL concentration can be measured in picograms, enabling even the slightest changes to be detected.[15,16] An increase in NfL concentration can serve as a noninvasive biomarker for identifying patients with brain injuries.[17] Observational studies have shown that NfL levels increase in cases of acute injuries (such as traumatic brain injury)[18] and post-surgery,[19] and are higher in patients with chronic neurological disorders.[20,21]

The influence of intraoperative permissive hypercapnia on the central nervous system remains uncertain. Therefore, we conducted a randomized controlled trial to investigate the effects of permissive hypercapnia on the central nervous system in elderly patients undergoing laparoscopic surgery by measuring alterations in postoperative plasma NfL levels.

Material and Methods

Trial Design

This single-center, prospective, randomized controlled trial was conducted at the Affiliated Hospital of Jiaxing University between April 2023 and January 2024. The study was approved by the ethics committee of the affiliated hospital of Jiaxing University, China, on February 14, 2023 (reference number 2023-KY-050) and registered with ClinicalTrials.gov (https://clinicaltrials.gov/study/ NCT05793437, principal investigator: Qing-he Zhou, date of registration: March 31, 2023). All participants enrolled in the trial signed written informed consent before enrollment.

Sample Size Calculation

The sample size was calculated using PASS software (Version 15.0). The preliminary study revealed that the plasma NfL concentrations were 21.1 ± 7.3 and 26.8 ± 8.2 pg/mL in the hypercapnia group (unpublished data, n = 14) and the normocapnia group (unpublished data, n = 14) within 24 h postoperatively, respectively. A sample size of 34 patients per group was needed to provide a power of 80% and a two-sided significance level of 0.05. Considering a dropout rate of approximately 20%, the sample size was increased to 84.

Participants and Baseline Data Collection

This study included participants aged 60 years or older who underwent laparoscopic surgery, with an expected pneumoperitoneum duration of > 1 h and required a hospital stay of at least 72 h postoperatively. The selection of the age criterion was based on the guidelines provided by the World Health Organization (https://www.who.int/health-topics/ageing) and recent research conducted on elderly individuals.[22–24] Only patients with a body mass index (BMI) of 18–28 kg/m^2, who were conscious and able to think independently, and an American Society of Anesthesiologists (ASA) physical status classification of II, or III were included in the study.

The exclusion criteria encompassed severe heart failure defined by New York Heart Association class III or IV, arrhythmia or atrial fibrillation; moderate or severe obstructive lung disease as determined by the preoperative lung function test; renal dysfunction with blood creatinine level > 177 μmol/L or active liver disease; evident neurological and psychiatric disorders; recent use of sedative-hypnotics, analgesics, and antidepressants; intracranial hypertension (including hydrocephalus, brain tumors, and brain-occupying lesions); severe hypertension or hypotension; severe preoperative metabolic acidosis and hypercapnic respiratory failure; undergoing an emergency surgical procedure or being required to convert to an open surgical approach because of unanticipated circumstances; refusal to follow-up postoperatively; serious complications during the procedure, including subcutaneous emphysema; transfer to the intensive care unit after surgery; current participation in other clinical studies that may potentially impact the outcomes of this study.

Following the acquisition of written informed consent, fundamental patient data was gathered. Patients completed the questionnaires at their own convenience, both preoperatively and 1 day postoperatively. The study employed the Confusion Assessment Method (CAM) as a questionnaire to assess delirium, with scores of ≤19 indicating the absence of delirium, scores ranging from 20 to 22 indicating the possibility of delirium, and scores of ≥22 indicating the presence of delirium. Another questionnaire utilized was the quality of recovery (QoR-40), which consisted of 40 questions and evaluated five areas of rehabilitation. Additionally, pain intensity was measured using an 11-point numerical rating scale (NRS) as the third questionnaire.

Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio using random numbers generated from www.random.org and block randomization (block size of 4) to either the normocapnia or hypercapnia group. Assignments were contained in prepared opaque envelopes that were opened on the day of the operation. Each block had a random arrangement of two patients receiving the normocapnia intervention and two patients receiving the hypercapnia intervention. All participants involved with patient care and study data collection/data analysis, including the surgeons, operating room and postanesthesia care unit nurses, research assistants, and statisticians were blinded to the group assignment. Only the attending anesthesiologists performing the anesthesia procedure were not blinded to the study.

Intervention, Anesthesia, and Perioperative Care

Before the procedure, the end-expiratory carbon dioxide ($EtCO_2$) was calibrated. Radial artery catheterization was performed to monitor arterial blood pressure. $PaCO_2$ and arterial partial pressure of oxygen (PaO_2) were assessed via arterial blood gas (ABG) analysis before preoxygenation (T0). Rapid anesthesia induction was achieved by intravenous injection of propofol (2.0–2.5 mg/kg), sufentanil (0.3–0.5 μg/kg), and cisatracurium (0.15 mg/kg). Endotracheal intubation and volume control ventilation mode (Carestation 650; General electric medical system Co., Ltd., Wuxi, China) were subsequently performed. The $PaCO_2$ was maintained at 35 to 45 mmHg for the normocapnia group and at 45 to 55 mmHg for the hypercapnia group[8] by adjusting respiratory parameters based on the values of $PaCO_2$. The tidal volume (Vt, 6–8 mL/kg of predicted body weight) and respiratory rate (RR, 12–16 times/min) were set in the hypercapnia group; the Vt (8–10 mL/kg of predicted body weight) and RR (12–16 times/min) were set in the normocapnia group. The calculation of predicted body weight (PBW) was calculated as 50+0.91 × (height [cm] −152.4) for man and 45.5+0.91 × (height [cm]−152.4) for women. Remifentanil (0.1–0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was intravenously infused, and the anesthesiologist titrated sevoflurane to maintain the BIS within 40–60. ABG analysis was also measured at 30 min (T1), 60 min (T2), and 90 min (T3; in case the pneumoperitoneum time falls short of 90 min, there is no data for T3) after pneumoperitoneum. The intra-abdominal pressure used during surgery was standardized at 10–12 mmHg. ABG was measured again and determined if $PaCO_2$ was within the target range before deflation (T4). The ventilation parameter settings were adjusted if the $PaCO_2$ concentration deviated from the research requirements, and additional ABG samples were collected at the discretion of the anesthetist. Additionally, the lowest pH limit was set to 7.2 for the hypercapnia group. Mean arterial pressure (MAP), blood oxygen saturation, regional cerebral oxygen saturation (rSO_2), included heart rate (HR), and $PetCO_2$ were also recorded at five time points (T0-T4).

If the mean arterial pressure was less than 65 mmHg, or there was a decrease in systolic blood pressure of less than 20%, or the systolic blood pressure dropped below 100 mmHg,[25] a single intravenous dose of 10–20

micrograms of norepinephrine would be administered. If the systolic blood pressure was above 140 mmHg and the diastolic blood pressure was greater than 90 mmHg, or if there was an increase of more than 20% from the baseline, 5–10 milligrams of urapidil would be given intravenously. If the heart rate was over 100 beats/min, 20–30 mg of esmolol would be administered. If the heart rate was below 50 beats/min, 0.5 mg of atropine would be given intravenously. In cases of oxygen saturation below 90%, respiratory parameters should be adjusted to increase oxygen concentration.

Outcomes Measurement

The primary outcome of this study was the plasma NfL concentration 1 day postoperatively. Furthermore, we observed the following outcomes: the abnormal rate of NfL concentration 1 day postoperatively (referring to the literature[26]), rSO_2, QoR-40, CAM scores, and postoperative delirium (POD) incidence 1 day postoperatively. The area under the curve (AUC) values of $PaCO_2$, rSO_2, pH, and MAP from T0 to T4 for the participant were calculated.

Measurement of NfL

Before the surgical procedure, blood samples with a volume of 5 mL were collected. Similarly, blood samples were obtained once again 24 h after the operation. These samples were stored in vacutainer tubes produced by Kang Wei Shi Medical Device Co, LTD, which were equipped with the anticoagulant ethylenediaminetetraacetic acid (EDTA). Subsequently, the tubes were subjected to centrifugation at a speed of 3000 rpm for a duration of 10 minutes within an hour. Following this, the tubes were transferred into 500-μL aliquots using Eppendorf tubes (AXYGEN). The samples were initially preserved at a temperature of −80°C within the laboratory of the affiliated hospital of Jiaxing University. The samples were subsequently transported using dry ice for analysis. The evaluation of NfL concentration was performed using the ultrasensitive Simoa technology on the automated Simoa HD-X platform (Quanterix, MA, US) at GBIO Laboratory in Hangzhou, Zhejiang Province, China. Dilute blood samples at a ratio of 1:4. Measure calibrator and quality control samples in duplicate. All sample measurements should be carried out by laboratory technicians accredited by the committee in a single experiment using the same batch of reagents. The operator should have no knowledge of the participants' disease status. The coefficients of variation of intra-assay were 5.78% for a quality control sample containing 3.940 pg/mL of NfL and 0.96% for a quality control sample with 177.241 pg/mL of NfL. The lower limit of quantification was recorded as 0.3080 pg/mL.

Measurement of $PaCO_2$ and rSO_2

$PaCO_2$ was measured by the Roche Cobas b 123 (Roche Diagnostics, Shanghai, China) in whole blood. The use of exclusively sodium heparin as the anticoagulant for analysis is essential. Additionally, it is crucial to collect the blood sample for analysis from eligible individuals' blood vessels and immediately send it for analysis, ideally within 15 minutes.

In order to collect rSO_2, a FORE-SIGHT regional oximeter manufactured by Gloryway Medical, Beijing, China was used. NIRS sensors were installed on the bilateral regions of the patient's forehead, facilitating the measurement of rSO_2 in both hemispheres of the brain.

Statistical Analysis

The analysis was conducted using SPSS version 23.0 (IBM, Armonk, NY, USA). Continuous data were inspected and tested for distribution using the Shapiro–Wilk test. Normally distributed data were presented as mean (Standard deviation; SD) and analysed by unpaired Student's *t*-test between the groups. Non-normally distributed data were expressed as median (25%–75% range) and analysed by the Mann–Whitney *U*-test between the groups. For intra-group comparisons, Wilcoxon-tests or paired Student's *t*-test are used to analyze. The χ^2-test, continuity correction χ^2-test, or Fisher's exact test was employed to analyze categorical variables, as appropriate. A significance level of $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

From April 2023 to January 2024, we enrolled 131 elderly patients undergoing laparoscopic surgery. Of whom 84 patients signed the informed consent form and were enrolled in the study. 6 patients were lost to follow-up because 3 had the duration of the target range for $PaCO_2$ is <1 h and 3 were discontinued from the intervention (2 were converted to an open surgical approach because of unanticipated circumstances; 1 was transferred to the intensive care unit postoperatively). The final analysis included 78 individuals, including 38 and 40 in the normocapnia and hypercapnia group, respectively (Figure 1). The characteristics of the patients at baseline and peri-operation are shown in Table 1.

Neurofilament Light

The normocapnia group exhibited a significant increase in plasma NfL concentration from preoperatively to postoperatively (14.0 [11.1, 19.9] vs 23.4 [16.8, 32.3] pg/mL, $P < 0.001$; Figure 2). Similarly, the hypercapnia group showed a significant increase in plasma NfL concentration from preoperatively to postoperatively (16.3 [9.1, 19.9] vs 21.5 [15.6, 29.9] pg/mL, $P < 0.001$; Figure 2). However, there were no significant differences in plasma NfL

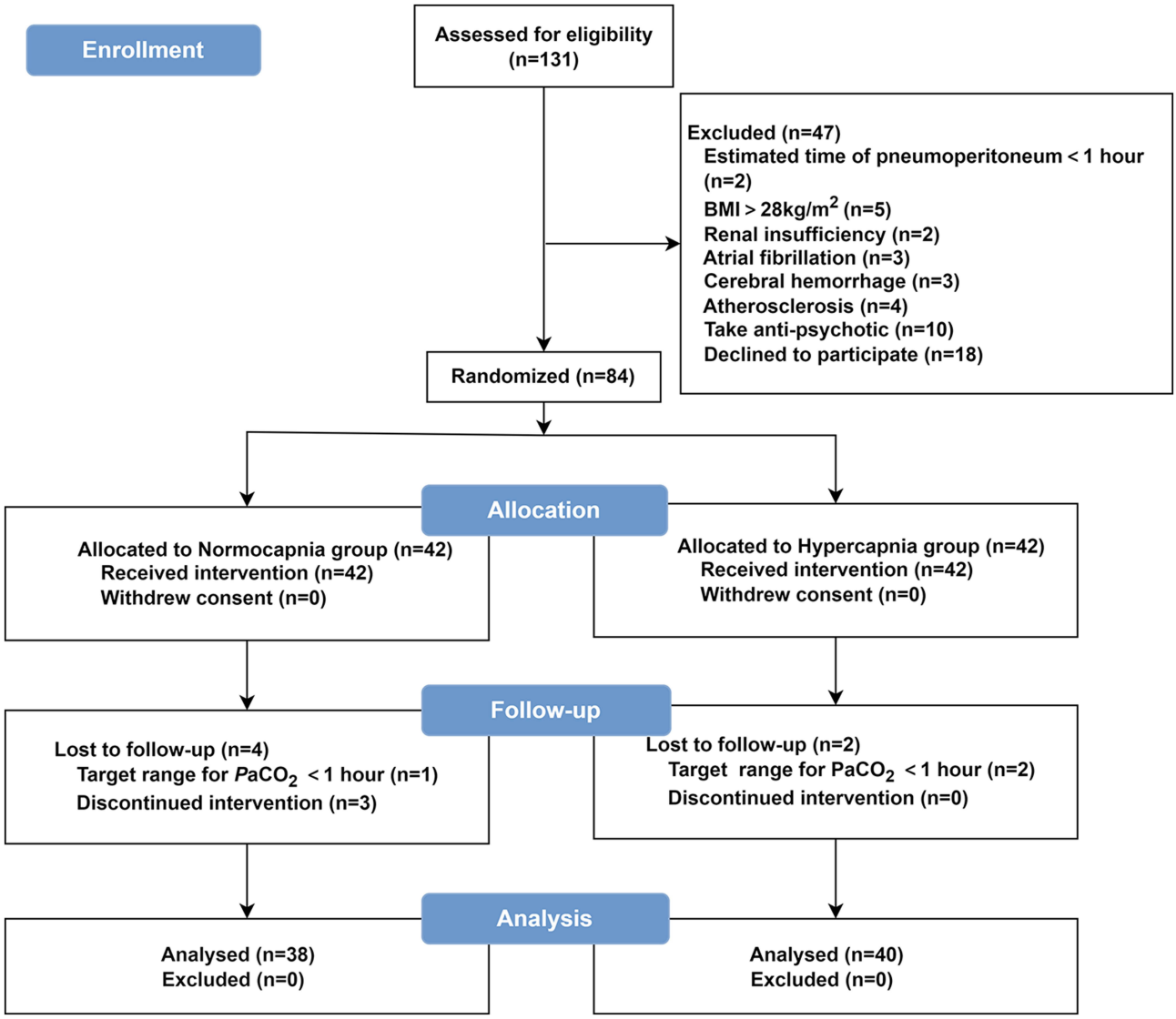

Figure 1 Patient flow through the study.

Table 1 Baseline and Perioperative Characteristics of the Included Patients

	Normocapnia (n=38)	Hypercapnia (n= 40)	*P* values
Age (years)	69.4 ± 5.2	69.1 ± 5.9	0.816
Male sex, *n* (%)	19 (50.0%)	27 (67.5%)	0.116
BMI (kg/m^2)	22.8 ± 2.6	22.8 ± 2.4	0.978
Education (years)	6 (0, 9)	6 (6, 9)	0.491
ASA physical status, *n* (%)			0.115
II	20 (52.6%)	28 (70.0%)	
III	18 (47.4%)	12 (30.0%)	
Comorbidities			
Hypertension, *n* (%)	20 (52.6%)	25 (62.5%)	0.378
Diabetes, *n* (%)	5 (13.2%)	5 (12.5%)	0.931
Heart disease, *n* (%)	5 (13.2%)	3 (7.5%)	0.653
Respiratory disease, *n* (%)	4 (10.5%)	5 (12.5%)	1.000
Perioperative characteristics			
PaO_2 (mmHg)	85.0 (77.0, 91.0)	81.0 (73.6, 87.4)	0.218
$PaCO_2$ (mmHg)	39.0 (36.3, 40.2)	39.4 (36.0, 44.0)	0.545
pH	7.43 (7.41, 7.45)	7.42 (7.41, 7.43)	0.287
Hb (g/L)	126 ± 21.3	127 ± 18.4	0.838
Scr (μmol/L)	73.8 (68.5, 85.4)	73.8 (66.3, 90.5)	0.795
BUN (mmol/L)	5.08 (4.31, 6.26)	5.47 (4.56, 6.71)	0.263
Surgery type, *n* (%)			0.549
Prostatic resection	0 (0.0)	2 (5.0%)	
Gastric resection	4 (10.5%)	3 (7.5%)	
Colorectal resection	34 (89.5%)	35 (87.5%)	

Note: Data are presented as the mean ± SD, median (interquartile range), or number of patients (%). *P*-value as a result of *t*-test, U Mann–Whitney or χ^2-test.

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; PaO_2, partial pressures of oxygen in arterial blood; $PaCO_2$, partial pressures of carbon dioxide in arterial blood; Hb, haemoglobin; Scr, serum creatinine; BUN, blood urea nitrogen.

concentration between the groups at baseline and 1 day postoperatively (both $P > 0.05$). Additionally, the abnormal rate of NfL 1 day postoperatively did not differ between the two groups (hypercapnia group, 15.0%; normocapnia group, 26.3%; RR: 0.57; 95% CI: 0.23–1.42; $P > 0.05$).

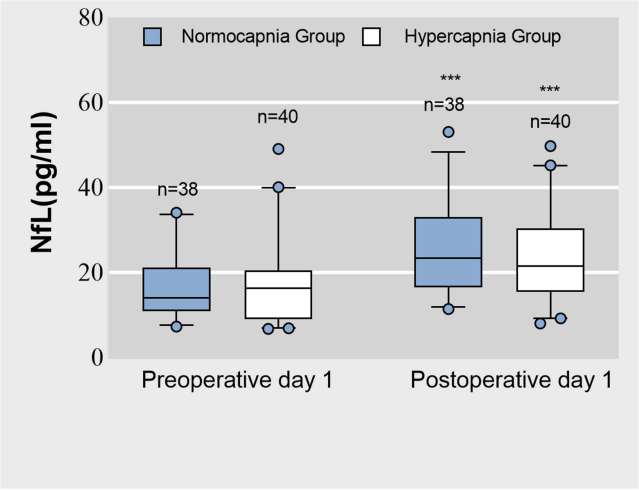

Figure 2 The plasma neurofilament light chain (NfL) concentration on preoperative and postoperative day 1. ***Compared with preoperative, postoperative plasma NfL concentration was significantly higher ($P < 0.001$, the Mann–Whitney *U*-test).

Postoperative Delirium

The CAM scores did not show a significant difference between the two groups ($P > 0.05$). Among the 78 analyzed patients, 3 (3.8%) developed delirium 1 day postoperatively. The association between the incidence of POD and the use of permissive hypercapnia was not significant, with the hypercapnia group showing an incidence of 5.0% compared to 2.6% in the normocapnia group (RR: 1.90; 95% CI: 0.18–20.1; $P > 0.05$; Table 2).

$PaCO_2$, rSO_2, pH, and MAP

The AUCs values of $PaCO_2$ and rSO_2 from the beginning to the end of the pneumoperitoneum were significantly higher in the hypercapnia group compared with the normocapnia group ($P < 0.05$). The two groups demonstrated no significant difference in the AUCs values of pH and MAP (both $P > 0.05$) (Table 3, supplementary Figure 1 and 2).

Other Intraoperative Characteristics and Postoperative Outcomes

The two groups showed no significant difference in the NRS scores ($P > 0.05$), as well as QoR-40 scores postoperatively ($P > 0.05$; Table 2). However, the normocapnia group had a significantly higher incidence of hypotension compared to the hypercapnia group ($P < 0.05$, Table 4). Other results did not differ between the two groups (all $P > 0.05$).

Table 2 Postoperative Data

	Normocapnia (n=38)	Hypercapnia (n=40)	*P* value
Extubation time (min)	19.8 (18.0, 30.0)	25.2 (16.5, 42.6)	0.606
PACU duration (min)	87.6 (71.4, 109)	95.0 (65.0, 110.0)	0.947
QoR-40 scores	173 ± 7.9	181 ± 6.2	0.079
NRS scores	2 (2.0, 3.0)	2 (2.0, 3.0)	0.503
Postoperative CAM	17 (14.0, 17.0)	17 (14.8, 20.8)	0.156
Presence of postoperative delirium, *n* (%)	1 (2.6%)	2 (5.0%)	1.000
Postoperative hospital duration (day)	9 (8.0, 10.0)	9 (8.0, 11.0)	0.245
Complications after surgery			
Abdominal infection, *n* (%)	7 (18.4%)	5 (12.5%)	0.469
Pleural effusion, *n* (%)	0 (0)	2 (5.0%)	0.241
Feeble, *n* (%)	5 (13.2%)	4 (10.0%)	0.935
Nausea and vomiting, *n* (%)	11 (28.9%)	7 (17.5%)	0.230
PPCs, *n* (%)	10 (26.3%)	7 (17.5%)	0.346
Fever, *n* (%)	10 (26.3%)	9 (22.5%)	0.695

Note: Data are presented as the mean ± SD, median (interquartile range), or number of patients (%). *P*-value as a result of *t*-test, U Mann–Whitney or χ^2-test.
Abbreviations: PACU, postanesthesia care unit; QoR-40, the quality of recovery-40 Questionnaire; NRS, numerical rating scale; CAM, the Confusion Assessment Method; PPCs, postoperative pulmonary complications.

Table 3 AUCs of $PaCO_2$, rSO_2, pH, MAP in the Two Groups

	Normocapnia (n=38)	Hypercapnia (n=40)	*P* value
AUC of $PaCO_2$	5888 (4390, 6754)	6645 (4971, 7805)	0.025
AUC of rSO_2	8775 (8415, 8948.0)	11,625 (10,283.0, 13,875.0)	0.012
AUC of pH	1069 (892.0, 1300.0)	1027 (770.0, 1172.0)	0.284
AUC of MAP	11955 (10,416.0, 15,108.0)	11,490 (9175.0, 13,658.0)	0.159

Note: Data are presented as median (interquartile range). *P*-value as a result of U Mann–Whitney.
Abbreviations: AUC, area under the curve; $PaCO_2$, partial pressures of carbon dioxide in arterial blood; rSO_2, regional cerebral oxygen saturation; MAP, mean arterial pressure.

Table 4 Intraoperative Data

	Normocapnia (n= 38)	Hypercapnia (n= 40)	*P* values
Duration of anesthesia (min)	171 (150, 201)	164 (135, 187)	0.358
Duration of surgery (min)	149 (121,174)	157 (135,187)	0.358
Duration of pneumoperitoneum (min)	143 (120, 170)	133 (105, 160)	0.322
Total fluid infusion			
Crystalloid solution (mL)	1000 (1000, 1300)	1000 (1000, 1500)	0.835
Colloidal solution (mL)	500 (500, 500)	500 (250, 500)	0.169
Red blood cells	0	0	
Urine output (mL)	275 (150, 400)	200 (150, 300)	0.556
Estimated blood loss (mL)	30 (30, 50)	50 (30, 50)	0.751
Intraoperative drugs			
Propofol (mg)	150 (120, 200)	150 (108, 200)	0.460
Sufentanil (μg)	25 (25, 30)	27 (20, 30)	0.747
Atracurium (mg)	22.2 ± 7.3	24.4 ± 4.3	0.207
Sevoflurane (mL/h)	16.6 (14.0, 19.8)	15.8 (12.3, 18.7)	0.351
Remifentanil (mg)	1.2 (1.0, 1.6)	1.2 (1.0, 1.4)	0.135
Atropine, *n* (%)	8 (21.1%)	13 (32.5%)	0.255
Vasopressor drugs, *n* (%)	24 (63.2%)	31 (77.5%)	0.165
Hypotensor, *n* (%)	0 (0)	0 (0)	
Adverse events, *n* (%)			
Hypotension	20 (52.6%)	8 (20.0%)	0.003
Hypertension	5 (13.2%)	6 (15.0%)	0.815
Bradycardia	15 (39.5%)	11 (27.5%)	0.262
Tachycardia	4 (10.5%)	1 (2.5%)	0.325
Hypoxemia	1 (2.6%)	1 (2.5%)	1.000

Note: Data are presented as the mean ± SD, median (interquartile range), or number of patients (%). *P*-value as a result of *t*-test, U Mann–Whitney or χ^2-test.

Discussion

The study primarily revealed that postoperative plasma NfL concentrations were notably elevated compared to preoperative levels in all patients. Nevertheless, there was no variation in plasma NfL concentration on postoperative day 1 between patients who underwent permissive hypercapnia with a target $PaCO_2$ of 45–55 mmHg and those who did not. Intraoperative permissive hypercapnia might not significantly impact the central nervous system during general anesthesia.

Our trial revealed that the NfL concentration 1 day postoperatively was associated with slightly and nonsignificantly lower postoperative plasma NfL elevation levels, indicating that permissive hypercapnia may not harm the central nervous system. The slightly lower postoperative plasma NfL levels during intraoperative permissive hypercapnia may be linked to the rise in $PaCO_2$ levels, which in turn activated the sympathetic adrenal mechanism and sympathetic nervous tension.[27] This ultimately led to an elevation in blood pressure and an enhancement in brain oxygen delivery caused by an increase in cerebral perfusion.[28] Physiologically, NfL is more easily detected in the axons of the brain white matter,[10] and radiological studies have shown that the brain white matter is particularly susceptible to ischemic damage.[29] Cerebral ischemia, caused by hypotension, can be decreased by permissive hypercapnia with increasing in cerebral perfusion,[30] which may be the anatomical basis for the above-mentioned results.

The AUC of $PaCO_2$ from T0-T4 was calculated for participants, and the $PaCO_2$ levels were significantly higher in patients with hypercapnia than with normocapnia during surgery. The current study revealed that higher rSO_2 levels are associated with permissive hypercapnia, which is congruent with previous data.[8] According to Wong et al,[8] hypercapnia ($PaCO_2$ 45–55mmHg) resulted in a stable increase in rSO_2 values in both hemispheres compared to the baseline, while the control group ($PaCO_2$ 35–40mmHg) showed a decrease in rSO_2. In our study, no statistically significant difference

was revealed in POD, which agrees with the primary outcome measure. The differences in result compared to Wang et al[9] may be attributed to the varying range of control for intraoperative hypercapnia.[4,6]

On postoperative day 1, the plasma NfL concentration indicates a significant increase compared to the baseline level. This observation is associated with the results of a previous study, which demonstrated that anesthesia and surgery are associated with neuronal damage and a notable rise in postoperative plasma NfL concentration.[19] Research revealed an independent correlation between the severity of delirium and NfL levels 1 day postoperatively.[19,31]

Our trial had several strengths. Previous studies have mainly focused on the effects of PetCO$_2$ on the central nervous system.[32–34] Our study continuously monitored changes in intraoperative blood gas parameters and adjusted the ventilator settings to maintain the target range of PaCO$_2$, ensuring the accuracy of the experiment. NfL, a component of the neuronal cytoskeleton, is increasingly recognized as a specific biomarker in the clinical evaluation of neurological patients.[10] Additionally, the high sensitivity of the Simoa technique allowed reliable quantification of NfL in blood, obviating the need for lumbar punctures and facilitating repeat assays in the perioperative period.[19]

The trial had some limitations. First, this study only set the range of PaCO$_2$ with hypercapnia intervention to be less than 55 mmHg, which is the common scope of laparoscopic surgery, without considering the effect of a higher PaCO$_2$ range on NfL. Second, blinding the procedure was not feasible in this trial as ventilation parameters had to be continuously adjusted according to PaCO$_2$ levels, resulting in an open-label design. Third, the trial only assessed NfL levels preoperatively and 1 day postoperatively. Bias development due to the short follow-up period could not be ruled out.

Conclusion

In conclusion, anesthesia and surgery can cause a significant increase in postoperative plasma NfL levels among all patients; intraoperative permissive hypercapnia targeting a PaCO$_2$ of 45–55 mmHg does not significantly influence postoperative early plasma NfL elevation levels in elderly patients undergoing laparoscopic surgery. These suggest that intraoperative permissive hypercapnia may not significantly affect the central nervous system, while anesthesia and surgery may have a certain influence.

Abbreviation

PaCO$_2$, arterial carbon dioxide partial pressure; CO$_2$, carbon dioxide; BMI, body mass index; ASA, American Society of Anesthesiologists; NfL, Neurofilament light chain; POD, postoperative delirium; QoR-40, quality of recovery-40; NRS, numerical rating scale; AUC, area under the curve; rSO$_2$, regional cerebral oxygen saturation; CAM, Confusion Assessment Method; EtCO$_2$, end-expiratory carbon dioxide; PetCO$_2$, end-expiratory carbon dioxide partial pressure; HR, heart rate; BIS, bispectral index; PaO$_2$, arterial partial pressure of oxygen; ABG, arterial blood gas; Vt, tidal volume; RR, respiratory rate; MAP, Mean arterial pressure; POD, postoperative delirium; PBW, predicted body weight (PBW); EDTA, ethylenediaminetetraacetic acid; SD, standard deviation.

Data Sharing Statement

All the data and material generated during the current study are available from the corresponding author upon reasonable request (zqh10980@zjxu.edu.en).

Ethics Approval and Informed Consent

The study was approved by the ethics committee of the affiliated hospital of Jiaxing University, China, on February 14, 2023 (reference number 2023-KY-050). This study was registered with clinicaltrials.gov (https://clinicaltrials.gov/study/NCT05793437, principal investigator: Qing-he Zhou, date of registration: March 31, 2023) before patient enrollment. All enrolled participants in the trial signed written informed consent preoperatively. The research protocol complied with the Consolidated Standards of Reporting Trials (CONSORT) statement and the Helsinki Declaration.

Consent for Publication

The details of any images, videos, recordings, etc can be published.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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