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ORIGINAL RESEARCH

Effects of Remote Ischemic Preconditioning on Postoperative Cognitive Dysfunction in Elderly Patients with Laparoscopic Cholecystectomy

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Purpose: We hypothesized that remote ischemic preconditioning (RIPC) could improve postoperative cognitive dysfunction (POCD) in elderly patients following laparoscopic cholecystectomy (LC).

Patients and Methods: Eighty-eight patients were randomly assigned to either the control or the RIPC group. The RIPC was applied on the right upper limb using a blood pressure cuff inflating 200 mmHg, consisting of 3 cycles of 5 min ischemia and 5 min reperfusion. Serum concentrations of Neuron-specific Enolase (NSE) and Brain-Derived Neurotrophic Factor (BDNF) were collected at one-day preoperative (T0), at the end of the operation (T4) and one-day postoperative (T5). *Z* score was tested at T0 and 3 days after the operation (T6). POCD was determined if there were two *Z* scores ≥1.96 at the same time or an average *Z* score ≥1.96.

Results: There was no significant difference in the *Z* score of each test between the two groups at T0 ($P > 0.05$). Notably, the duration of Stroop test C was significantly shorter in the RIPC group than that in the Control group at T6 ($P = 0.01$). POCD occurred in 1/44 (2.3%) patients in the RIPC group and 8/44 (18.2%) patients in the control group at T6 (P=0.035). In addition, serum NSE concentration was significantly decreased, but serum BDNF concentration was increased compared with the control group at T4 and T5 (P<0.001).

Conclusion: RIPC could reduce the incidence of POCD in elderly patients after laparoscopic cholecystectomy.

Keywords: postoperative cognitive dysfunction, remote ischemic preconditioning, regional cerebral oxygen saturation, elderly patients

Introduction

Cholecystitis accompanied by gallstones is a frequent occurrence in the biliary tract system. It was predicted that an increasing number of elderly patients would suffer from cholecystolithiasis with population aging.[1] Laparoscopic cholecystectomy (LC) had become the "gold standard" for the treatment of gallbladder diseases requiring surgical removal.[2] However, short-term laparoscopy was reported to be associated with ischemia-reperfusion changes,[3] while the anti-Trendelenburg position adopted intraoperatively might exacerbate cerebral hypoperfusion and lead to central nervous system complications.

Postoperative cognitive dysfunction (POCD) is a common central nervous system complication after surgery, especially in elderly patients. The main clinical manifestations of POCD were changes in consciousness, memory and sleep disabilities.[4] Moreover, cognitive deterioration resulted in prolonged hospital stays and increased health-care costs, in the long run, it reduced the possibility of patients returning to independent living and brought heavy burdens to families and society.[5–7] However, the exact pathophysiological mechanism of POCD remained unknown, and its occurrence was related to abnormal oxygen metabolism in the brain.[8] In the meantime, the identification of biomarkers associated with POCD could help clinicians intervene early in patients. One of the biomarkers of nerve damage was Neuron-specific Enolase (NSE), and previous animal and clinical studies illustrated that elevated concentrations of NSE

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might help predict POCD.[9,10] Brain-derived neurotrophic factor (BDNF) also received more attention recently, and it played a crucial role in the recovery of cognitive function in many studies.[11,12] These biomarkers could provide clues to help clarify the underlying mechanism of POCD. Currently, specific interventions were unavailable to treat POCD, and the most economical and effective solution seemed to be prevention.

Remote ischemic preconditioning (RIPC) is an approach to protect against subsequent vital organ damage through nonlethal ischemic-reperfusion of distal ischemic-tolerant tissues. Furthermore, RIPC was not only safe and non-invasive but also convenient and feasible, so it had significant clinical application value.[13,14] To date, the protective mechanism of RIPC against ischemia-reperfusion injury was still unclear. A recent experimental study confirmed that RIPC improved the tolerance to ischemic injury in the brain.[15] In clinical studies, RIPC improved postoperative cognitive function following a colon or cardiac surgery, with no reported adverse effects.[16,17] Although controversial data were published on the influence of RIPC on POCD undergoing cardiac surgery, RIPC remained an appealing strategy.[18] In addition, a latest secondary analysis of a randomized controlled study verified that monitoring regional cerebral oxygen saturation (rSO_2) was helpful in detecting ischemia and evaluating the effect of RIPC.[19] Meanwhile, multiple meta-analyses indicated that rSO_2 monitoring was associated with a reduction in perioperative neurocognitive disorders.[20–22]

So far, it has not been examined whether the effect of RIPC on rSO_2 during the anti-Trendelenburg position is related to reducing the occurrence of POCD after LC. Thus, we conducted this study to observe the effectiveness of RIPC on rSO_2 and POCD in elderly patients undergoing LC and to explore the relevant mechanisms further.

Materials and Methods

Study Population

Between October 2022 and December 2022, patients scheduled for LC were enrolled in this prospective, randomized, double-blind clinical trial (ChiCTR2200066377). The informed consent and study protocol were approved by the Ethics Committee of the Hebei General Hospital, China (Ethics No. 2022-407). This study complied with the Declaration of Helsinki. Participants were given adequate time to consider whether to take part in this trial. Enrolled patients were randomly assigned to either a control or a RIPC group according to a table of random numbers. The personnel involved in this study were blinded to randomization, cognitive test results and peripheral blood collection. All patients received standard perioperative care.

Inclusion criteria in this present study were as follows: age ≥65 years, New York Heart Association (NYHA) classification I–III, American Society of Anesthesiologists (ASA) classification levels II–III and patients undergoing LC under general anesthesia. Exclusion criteria were as follows: patients with central nervous system disease; a personal history of drug or alcohol abuse; there was a skin disease or local infection in the right upper limb; patients with hepatic or renal insufficiency or sepsis; perioperative hemorrhage or severe electrolyte disturbance; hearing, visual and speech communication impairments that prevent cooperation; participated in other clinical trials; preoperative MMSE scores were <21 points for primary school and <24 points for junior high school and above.

Study Design

Patients entered the operating room with continuous monitoring, which included an electrocardiogram, noninvasive blood pressure, oxygenation saturation (SpO_2), rSO_2 and bispectral index (BIS). Prior to anesthesia, the patient was given a crystal fluid infusion on the basis of individual physiological requirements. Midazolam (0.04 $mg \cdot kg^{-1}$), sufentanil (0.3 $\mu g \cdot kg^{-1}$), etomidate (0.2–0.4 $mg \cdot kg^{-1}$) and cisatracurium (0.3–0.4 $\mu g \cdot kg^{-1}$) were used to induce anesthesia. After 5 min of pure oxygen inhalation, we performed tracheal intubation and connected the anesthesia machine for mechanical ventilation. After confirming that the depth of the tracheal tube was appropriate, a pressure-controlled volume-guaranteed ventilation mode (PCV-VG) was adopted. Respiratory parameters were adjusted to maintain the end-tidal CO_2 partial pressure at 35–45 mmHg according to the intraoperative situation. Anesthesia was maintained with remifentanil target concentration (1.5–3.0 $\mu g \cdot mL^{-1}$), propofol (2.0–2.5 $\mu g \cdot mL^{-1}$), sevoflurane (1–2%) to maintain BIS values at 40–60.

The intervention was performed after anesthesia induction. Participants in the RIPC group were wrapped with a blood pressure cuff around their right upper limb and were pressurized to 200mmHg for three cycles, 5 min of ischemia and 5

min of reperfusion each time. The blood pressure cuff was placed in the same position in the Control group, but ischemic preconditioning was not performed. The standard pneumoperitoneum insufflation pressure used during surgery was 12–15mmHg.

The management of intraoperative hypotension, low output and bradycardia were determined by the chief anesthesiologist. The following was recommended: norepinephrine should be given when the mean arterial blood pressure was less than 50 mmHg, atropine should be given when the heart rate was less than 45 bpm, and crystalloid and colloidal fluids were used to maintain a proper blood volume.

Endpoints

The main outcome was the incidence of POCD at T6. Neuropsychological tests were performed by a researcher who was unaware of the groupings, which included the mini-mental state examination (MMSE), picture recall test (PRT), Stroop color test (Stroop test), digit-symbol test (DST), number-connecting test (NCT) and numerical symbol conversion test (DSST). Enrolled patients completed the above tests 1 day before the operation (T0) and 3 days after the operation (T6), each score was recorded. Postoperative cognitive dysfunction was defined if the Z score was ≥1.96 on 2 tests or an average Z score ≥1.96.

Secondary endpoints were changes of rSO_2 at the time of admission (T1), in the anti-Trendelenburg position (T2), in the horizontal position (T3) and at the end of the operation (T4). Arterial blood gas analysis was performed at the above 4 time points. Moreover, NSE and BDNF were measured at 1-day preoperative (T0), at the end of the operation (T4) and 1-day postoperative (T5). Blood samples were clotted at room temperature and then immediately centrifugation for 20 min at approximately 1000×g. Collected the supernatant and stored it at −80°C for further analysis. Based on the manufacturer's instructions, serum levels of NSE (EH0370-HS, FineTest, China) and BDNF (EH0043, FineTest, China) were measured using enzyme-linked immunosorbent assay (ELISA) kits.

Statistical Analysis

Pass 15.0 software was used to calculate the sample size, according to the data from the MMSE score on the third postoperative day, which was obtained from our previous pretest. A sample size of 82 patients (41 in each group) was required to ensure a minimum 90% probability of using a two-sided t-test to detect a difference of 0.05 significance levels. At least 106 samples should be included for a 20% loss-to-follow rate. As a result, 110 patients were ultimately enrolled in this study.

SPSS 26 was used for data sorting and statistical analysis. Qualitative variables were expressed as numbers and analyzed using the χ^2 test. Continuous variables were expressed as mean ± standard deviation and analyzed by t-test if the assumptions of normal distribution and chi-squareness were satisfied; otherwise, the Wilcoxon rank sum test was used. Within-group comparisons were analyzed using one-way ANOVA. Pearson's correlation coefficient represented the linear relationship between two continuous variables. $P < 0.05$ was considered statistically significant.

The formula for calculating the Z score in the neuropsychological test was as follows: Z score = (postoperative score - preoperative score - learning effect)/standard deviation of the preoperative score in the normal population. In our case, the normal population consisted of 20 non-surgical family volunteers. The learning effect was the average of postoperative score minus preoperative score of the normal population.

Results

Characteristics of Patients

A total of 110 patients met the inclusion criteria of this trial. Twenty-two were excluded, of which, four declined to participate and 18 were excluded according to the exclusion criteria. As shown in Figure 1, the remaining 88 patients were randomly grouped and statistically analyzed. As Table 1 presents, the demographic characteristics and perioperative data between the two groups in baseline were comparable, with no significant or clinically meaningful difference.

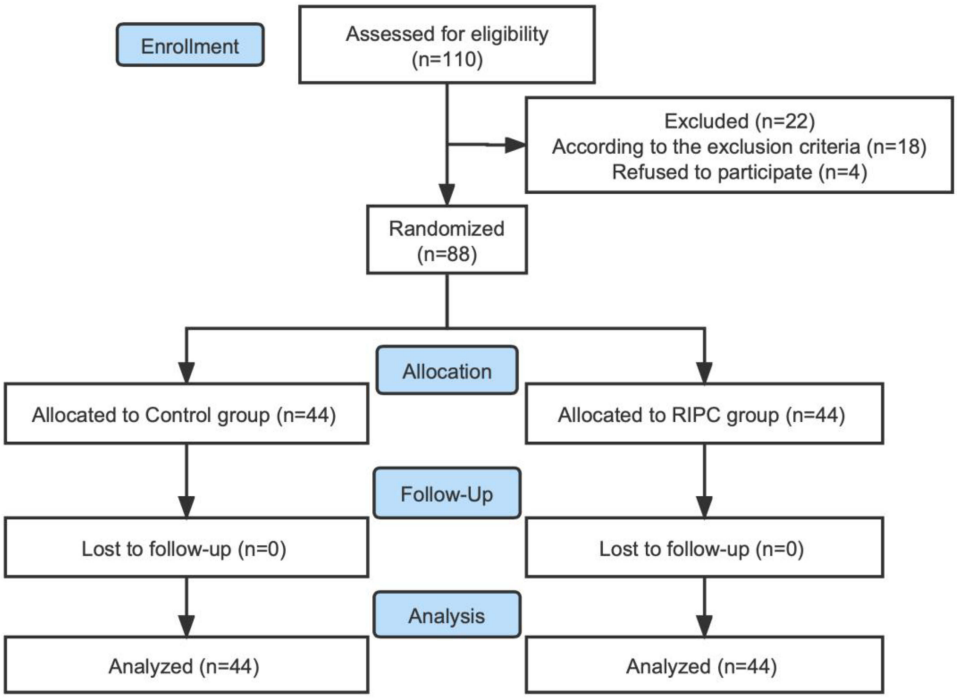

Figure 1 Flow chart of the study inclusion process.

Cognitive Function Assessment and the Incidence of POCD

All 88 participants underwent neurocognitive assessment and the *Z* score of each neuropsychological test in both groups is shown in Table 2. The *Z* score for each test was not statistically significant in either group at T0. However, compared

Table 1 Demographic Characteristics and Perioperative Data

Variable	Control Group (n = 44)	RIPC Group (n = 44)	P value
Age, years	69.23±2.01	68.82±2.41	0.39
Sex (male, %)	15(34)	21(47)	0.19
BMI (kg/m^2)	23.92±3.18	23.91±2.80	0.98
ASA, II/III	20/24	21/23	0.83
Educational level			0.94
Primary, n(%)	2(5)	3(7)	
Junior high school, n(%)	18(41)	17(39)	
Senior high school, n(%)	19(43)	20(45)	
College degree, n(%)	5(11)	4(9)	
Smoking history, n(%)	8(18)	10(23)	0.59
Drinking history, n(%)	3(6)	2(4)	0.64
Hypertension, n(%)	31(70)	33(75)	0.63
Coronary heart disease, n(%)	5(11)	6(13)	0.74
Diabetes, n(%)	4(9)	5(11)	0.72
Lactated Ringer solution (mL)	826.36±208.40	807.05±185.10	0.65
Intraoperative bleeding (mL)	5.73±2.20	5.32±2.13	0.38
Anesthesia duration (min)	72.75±15.26	75.39±19.51	0.48
Pneumoperitoneum pressure	13(12,14)	13(12,14)	0.53
Surgery duration (min)	104.27±27.00	103.32±24.72	0.86
Length of stay (day)	6.86±1.52	6.66±1.74	0.56

Note: Data are expressed as mean ± SD or number or median (interquartile range) (%).
Abbreviations: RIPC Group, Remote ischemic preconditioning group; BMI, Body mass index; ASA, American Society of Anesthesiologists.

Table 2 *Z* Score in Each Neuropsychological Test

		Control Group (n = 44)	RIPC Group (n =44)	*P* value
MMSE	T0	25.05±1.41	25.32±1.43	0.37
	T6	24.55±1.53	24.80±1.58	0.45
PRT				
PRT-A	T0	5.16±1.10	4.98±0.90	0.40
	T6	5.05±1.10	4.95±1.12	0.70
PRT-B	T0	5.16±1.12	5.09±1.18	0.78
	T6	5.18±1.15	5.00±0.99	0.43
PRT-C	T0	5.02±1.19	5.00±1.24	0.93
	T6	5.00±1.08	5.05±1.14	0.85
Stroop test				
Stroop test-A	T0	29.05±2.98	28.50±2.73	0.37
	T6	29.36±2.55	28.91±3.09	0.45
Stroop test-B	T0	50.59±3.66	50.27±3.68	0.69
	T6	50.61±4.61	50.39±4.44	0.81
Stroop test-C	T0	113.00±6.70	110.18±7.70	0.07
	T6	115.86±7.06	110.91±8.69*	0.01
NCT	T0	47.84±5.81	48.25±5.92	0.74
	T6	49.52±5.51	49.70±5.82	0.88
DST	T0	211.86±22.15	212.27±19.70	0.93
	T6	213.80±21.36	211.86±23.10	0.69
DSST	T0	15.23±2.44	15.50±2.42	0.60
	T6	16.11±2.05	15.89±2.17	0.62

Notes: Data are expressed as mean ± SD. *$P < 0.05$, vs the Control group.
Abbreviations: RIPC, Remote ischemic preconditioning; MMSE, Mini-mental state examination; PRT, Picture recall test; Stroop Test, Stroop the color test; NCT, Number connecting test; DST, Digit-symbol test; DSST, Digit symbol substitution test.

with the control group, patients in the RIPC group took significantly less time in the Stroop test C at T6 ($P = 0.03$). In the remaining tests, the *Z* score of the RIPC group had no significant difference compared with the Control group at T6. There were no significant differences in postoperative *Z* score compared with preoperative *Z* score in the two groups, respectively. As displayed in Figure 2, the incidence of POCD in the control group was 18.2%, which was higher than in the RIPC group (2.3%) (P=0.035).

Operation-Related Data and Values of rSO_2 (%) During Surgery

As shown in Table 3, there were no significant differences in heart rate (HR) and mean arterial pressure (MAP) between the two groups at T1, T2, T3 and T4. Blood gas indexes such as PaO_2, $PaCO_2$, lactic acid (Lac), hemoglobin (Hb) and glucose (Glu) also showed no statistical difference between the two groups at the above four time points.

The trends of rSO_2 at T1, T2, T3 and T4 in the two groups are shown in Figure 3. The values of rSO_2 in the control group at T2 were significantly lower than those in the RIPC group ($P < 0.05$).

Serum Concentrations of NSE and BDNF

As Figure 4 presents, the serum concentrations of NSE and BDNF were not significantly different between groups at T0. Serum NSE concentrations were significantly increased at T4 and T5 in both groups compared with T0 ($P < 0.001$). At T4 and T5, the serum NSE concentration in the RIPC group was lower compared with the control group ($P < 0.001$). Compared with T0, serum concentrations of BDNF were significantly increased at T4 and T5 in the two groups ($P < 0.001$). In the RIPC group, serum BDNF concentrations were significantly higher at T4 and T5 ($P < 0.001$).

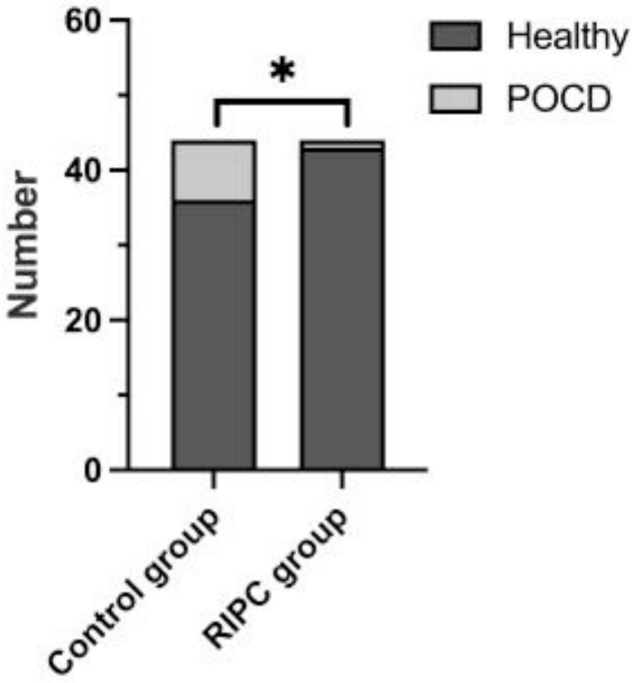

Figure 2 A histogram of the number of POCD and healthy people in both groups. *P<0.05, vs the Control group.
Abbreviation: POCD, Postoperative cognitive dysfunction.

Correlation Analysis

Correlation Analysis of rSO_2 and Neuropsychological Tests

By using rSO_2 as an independent variable, the correlation of MMSE, PRT-A, PRT-B, PRT-C, Stroop test-A, Stroop test-B, Stroop test-C, NCT, DST and DSST was analyzed. The results showed that rSO_2 was not correlated to neuropsychological tests and the correlation coefficient is shown in Table 4. The difference has no statistical significance ($P > 0.05$).

Correlation Analysis of MMSE and Serological Indexes

We used MMSE as an independent variable and analyzed the correlation of NSE and BDNF. As shown in Table 5, the MMSE was not correlated to serological indexes. The difference has no statistical significance ($P > 0.05$).

Table 3 Surgery-Related Data

		Control Group (n = 44)	RIPC Group (n = 44)	*P* value
MAP (mmHg)	T1	94.39±9.05	93.73±9.08	0.73
	T2	81.98±7.62	82.02±4.23	0.97
	T3	79.48±6.53	81.14±3.05	0.13
	T4	87.59±7.04	85.45±3.62	0.07
HR (bpm)	T1	86.00 (85.00, 88.75)	88.00 (83.00, 89.00)	0.91
	T2	63.00 (60.00, 65.00)	62.00 (61.00, 66.75)	0.91
	T3	60.00 (55.25, 69.00)	59.00 (55.00, 64.75)	0.16
	T4	68.00 (65.00, 72.00)	67.00 (63.00, 74.00)	0.26
PaO2 (mmHg)	T1	87.0 (81.00, 91.00)	88.0 (82.50, 90.75)	0.58
	T2	156.5 (129.50, 186.75)	161.5 (145.50, 184.50)	0.36
	T3	133.0 (117.75, 166.50)	135.0 (116.25, 196.75)	0.43
	T4	111.0 (100.25, 130.75)	113.0 (101.00, 134.00)	0.54
PaCO2 (mmHg)	T1	38.0 (35.00, 39.00)	38.0 (36.00, 39.00)	0.52
	T2	38.0 (36.00, 39.75)	39.0 (36.00, 42.00)	0.27
	T3	40.0 (39.00, 42.75)	40.5 (38.00, 45.00)	0.67

(*Continued*)

Table 3 (Continued).

		Control Group (n = 44)	RIPC Group (n = 44)	*P* value
	T4	39.0 (36.00, 44.00)	40.0 (38.00, 43.00)	0.59
Lac (mg/dL)	T1	1.30 (1.20, 1.68)	1.30 (1.20, 1.58)	0.78
	T2	0.90 (0.80, 1.28)	0.90 (0.73, 1.40)	0.73
	T3	0.90 (0.70, 1.20)	0.90 (0.80, 1.20)	0.79
	T4	0.85 (0.70, 1.10)	0.85 (0.60, 1.30)	0.83
Hb (g/L)	T1	12.82±1.61	13.26±1.60	0.21
	T2	12.46±1.61	12.45±1.61	0.98
	T3	12.22±1.61	12.58±1.47	0.27
	T4	12.43±1.65	12.89±1.33	0.19
Glu (mmol/L)	T1	5.97±0.80	5.81±1.08	0.41
	T2	6.43±1.01	6.25±1.34	0.48
	T3	7.01±1.27	6.86±1.44	0.62
	T4	7.44±1.59	7.21±1.70	0.51

Note: Data are presented as mean ± SD or median (interquartile range).
Abbreviations: RIPC, Remote ischemic preconditioning; MAP, Mean arterial pressure; HR, Heart rate; Lac, Lactic acid; Hb, Hemoglobin; Glu, Glucose.

Discussion

As far as we knew, this trial was the first to investigate the effect of RIPC on POCD in elderly patients following LC. We found that RIPC reduced the incidence of POCD, but the MMSE test was not associated with NSE or BDNF. Moreover, the decrease in rSO_2 was related to the change of posture during the operation.

With the increasing trend of the aging population, more and more elderly patients are undergoing surgery. POCD, as a common postoperative complication, is known to occur more frequently in older patients. Moreover, POCD could lead to loss of speech, personality changes, and even permanent illnesses such as Alzheimer's, which might persist for weeks, months, or even longer after surgery.[23] Although many interventions were undertaken to reduce the occurrence of POCD, definitive guidelines were not yet published. Recently, a number of studies showed the safety of RIPC and its protective effects on the brain.[14,24]

In our present study, compared with the control group, the incidence of POCD was significantly lower in the RIPC group ($P = 0.03$) and patients in the RIPC group took significantly less time in the postoperative Stroop test C, suggesting that RIPC improved early POCD in elderly patients undergoing LC. The above results were consistent with a previous study showing that RIPC improved POCD in elderly patients after colon surgery.[17] However, a recent study from cardiac surgery confirmed that RIPC could not reduce the incidence of POCD, which was associated with the lack of a non-

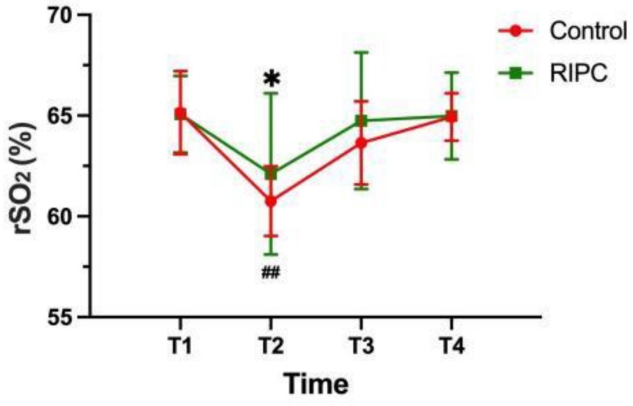

Figure 3 Line chart of rSO_2 changes at different time points. *P<0.001, vs the Control group. ##P<0.001, vs baseline in either group.
Abbreviation: rSO_2, Regional cerebral oxygen saturation.

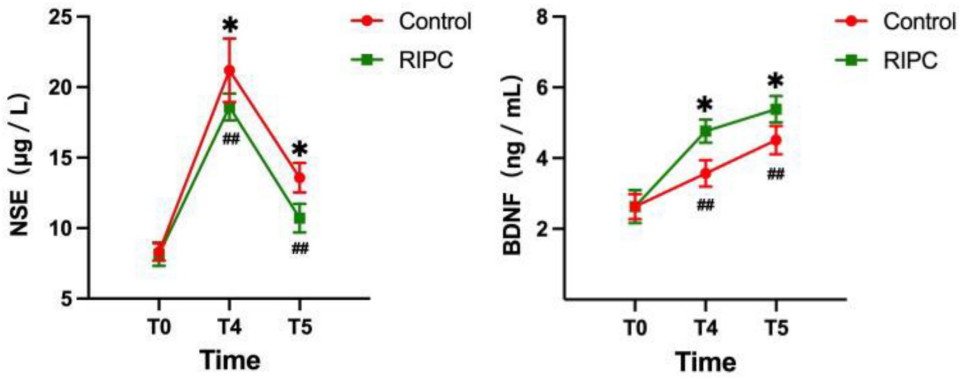

Figure 4 Changes in NSE and BDNF (mean ± SD) between the two groups. *P<0.001, vs the Control group. ##P<0.001, vs baseline in either group.
Abbreviations: NSE, Neuron-specific Enolase; BDNF, Brain-Derived Neurotrophic Factor.

surgical control group receiving neuropsychological tests.[18] Whereas in our study, we chose healthy family members of the same age group to be tested at the same time, so the learning effect was well excluded.

The changes in rSO_2 were considered to be associated with the development of POCD and might help predict POCD.[25] In this study, we found that when the surgical position was changed to anti-Trendelenburg, the decrease of rSO_2 was measured in the control group ($P < 0.05$). However, the hemodynamics were stable, and blood gas analysis showed no significant changes in relevant oxygenation indexes. The decrease in rSO_2 might be due to a change in surgical position, which resulted in a transient decrease in the amount of blood returning to the heart. The latest meta-analysis showed that the mean intraoperative brain oxygen saturation was significantly lower in POCD patients than in non-POCD patients ($I^2 = 55\%$, SMD = - 0.57).[22] As described in this study, the values of rSO_2 in the control group were significantly lower at T2 ($P < 0.05$), which was similar to the previous study.[26]

To date, the underlying mechanism of POCD development remains unclear, and neurotrophic factors were critical in the development of POCD. In this trial, we found that serum BDNF concentrations were significantly increased after surgery in both groups. However, the BDNF concentration in the RIPC group was higher at T4 and T5 ($P < 0.05$). BDNF was mediated by tyrosine kinase B (TrkB) and widely expressed in the nervous system, which played a role in synaptic plasticity and neuronal survival in the brain.[27] Multiple studies demonstrated that BDNF could cross the blood–brain barrier, and the level of BDNF in blood correlated with the level of BDNF in the brain.[28,29] Previous studies reported that POCD was more likely to occur in laboratory animals with lower BDNF concentrations.[30,31] However, a clinical study showed that there was no difference in the level of BDNF between POCD and non-POCD groups.[32] Therefore, the

Table 4 Correlation Analysis of rSO_2 and Neuropsychological Tests

Test	MMSE	PRT-A	PRT-B	PRT-V	Stroop Test-A	Stroop Test-B	Stroop Test-C	NCT	DST	DSST
rSO_2										
r	0.08	0.09	0.14	−0.04	−0.02	−0.06	−0.07	−0.05	−0.05	0.08
p	0.46	0.43	0.21	0.75	0.84	0.55	0.54	0.67	0.64	0.48

Table 5 Correlation Analysis of MMSE and Serological Indexes

Index	NSE	BDNF
MMSE		
r	−0.02	−0.15
p	0.86	0.17

correlation analysis between BDNF and MMSE was further conducted in this study and the results showed that there was no correlation between them.

To further explore the effect that RIPC improved postoperative cognitive function, we also measured the levels of NSE. NSE, one of the markers of brain injury, was found in neurons, neuroectodermal cells and red blood cells. Under normal conditions, plasma NSE levels were deficient, but increased in cerebrospinal fluid and blood when neurons were damaged.[33] Several studies demonstrated that expression levels of NSE in patients with POCD increased.[10,34] In this study, serum NSE concentrations increased significantly at T4 and T5 in both groups, which suggested that patients experienced an injury to the Central Nervous System (CNS) after surgery. Notably, the serum NSE concentration in the RIPC group was lower after surgery ($P < 0.05$), which proved that RIPC could inhibit CNS injury. In addition, previous studies showed that the relationship between NSE and POCD had different results. There was a relationship between NSE and POCD in patients undergoing non-cardiac surgery, but not in cardiac surgery.[35,36] Therefore, similar to the existing literature, we found no correlation between NSE and MMSE.

Nonetheless, there were some limitations in our trial. Firstly, the sample size was relatively small, and the Z score difference was insignificant except for the Stroop test C. Multi-center trials with larger sample sizes are needed in the future. In addition, the follow-up time was too short to investigate the long-term development rule of POCD. Whether there are long-term adverse reactions in RIPC can be further explored in future trials.

Conclusions

To sum up, this study indicated that RIPC could improve POCD in elderly patients undergoing LC. In addition, NSE and BDNF concentrations were not effective markers for identifying POCD. Further studies are still needed to confirm if RIPC contributes to long-term improvements in the quality of life for patients undergoing LC.

Data Sharing Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Ethics Approval Statement

The study was approved by the Ethics Committee of the Hebei General Hospital (Ethics No. 2022-407) and written according to the CONSORT 2010 checklist (see Supplementary file).

Patient Consent Statement

All patients signed informed consent forms.

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Disclosure

All authors have no conflict of interest to declare for this work.

References

1. Pisano M, Ceresoli M, Cimbanassi S, et al. WSES and SICG guidelines on acute calculous cholecystitis in elderly population. *World J Emerg Surg*. 2017;2019(14):10. doi:10.1186/s13017-019-0224-7
2. Kamarajah SK, Karri S, Bundred JR, et al. Perioperative outcomes after laparoscopic cholecystectomy in elderly patients: a systematic review and meta-analysis. *Surg Endosc*. 2020;34(11):4727–4740. doi:10.1007/s00464-020-07805-z
3. Bickel A, Khatib S, Kakiashvilli E, Palzur E. Reappraisal of ischemia-reperfusion injury in a short duration laparoscopic surgery, a pilot study. *BMC Surg*. 2021;21(1):346. doi:10.1186/s12893-021-01339-4
4. Tan XX, Qiu LL, Sun J, Tan S. Research progress on the role of inflammatory mechanisms in the development of postoperative cognitive dysfunction. *Biomed Res Int*. 2021;2021:3883204. doi:10.1155/2021/3883204
5. Thiele RH, Theodore DJ, Gan TJ. Outcome of organ dysfunction in the perioperative period. *Anesth Analg*. 2021;133(2):393–405. doi:10.1213/ane.0000000000005603

6. Liu B, Huang D, Guo Y, et al. Recent advances and perspectives of postoperative neurological disorders in the elderly surgical patients. *CNS Neurosci Ther*. 2022;28(4):470–483. doi:10.1111/cns.13763
7. Wang CM, Chen WC, Zhang Y, Lin S, He HF. Update on the mechanism and treatment of sevoflurane-induced postoperative cognitive dysfunction. *Front Aging Neurosci*. 2021;13:702231. doi:10.3389/fnagi.2021.702231
8. Glumac S, Kardum G, Karanović N. Is it time to redefine cognitive dysfunction after cardiac surgery? The importance of methodological consistency. *Acta Clin Croat*. 2021;60(1):127–130. doi:10.20471/acc.2021.60.01.18
9. Zbóril S, Schmidt AP, Oses JP, et al. S100B protein and neuron-specific enolase as predictors of postoperative cognitive dysfunction in aged dogs: a case-control study. *Vet Anaesth Analg*. 2020;47(6):740–747. doi:10.1016/j.vaa.2020.06.002
10. Wan Z, Li Y, Ye H, Zi Y, Zhang G, Wang X. Plasma S100β and neuron-specific enolase, but not neuroglobin, are associated with early cognitive dysfunction after total arch replacement surgery: a pilot study. *Medicine*. 2021;100(15):e25446. doi:10.1097/md.0000000000025446
11. Jiang W, Liu F, Li H, et al. TREM2 ameliorates anesthesia and surgery-induced cognitive impairment by regulating mitophagy and NLRP3 inflammasome in aged C57/BL6 mice. *Neurotoxicology*. 2022;90:216–227. doi:10.1016/j.neuro.2022.04.005
12. Trubnikova OA, Tarasova IV, Moskin EG, et al. Beneficial effects of a short course of physical prehabilitation on neurophysiological functioning and neurovascular biomarkers in patients undergoing coronary artery bypass grafting. *Front Aging Neurosci*. 2021;13:699259. doi:10.3389/fnagi.2021.699259
13. Sangeetha RP, Venkatapura RJ, Kamath S, et al. Effect of remote ischemic preconditioning on cerebral vasospasm, biomarkers of cerebral ischemia, and functional outcomes in aneurysmal subarachnoid hemorrhage (ERVAS): a randomized controlled pilot trial. *Brain Circ*. 2021;7(2):104–110. doi:10.4103/bc.bc_13_21
14. Zhao W, Meng R, Ma C, et al. Safety and efficacy of remote ischemic preconditioning in patients with severe carotid artery stenosis before carotid artery stenting: a proof-of-concept, randomized controlled trial. *Circulation*. 2017;135(14):1325–1335. doi:10.1161/circulationaha.116.024807
15. Jiao Y, Wang J, Jia Y, Xue M. Remote ischemic preconditioning protects against cerebral ischemia injury in rats by upregulating miR-204-5p and activating the PINK1/Parkin signaling pathway. *Metab Brain Dis*. 2022;37(4):945–959. doi:10.1007/s11011-022-00910-z
16. Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Pagel PS. Remote ischemic preconditioning prevents deterioration of short-term postoperative cognitive function after cardiac surgery using cardiopulmonary bypass: results of a pilot investigation. *J Cardiothorac Vasc Anesth*. 2015;29(2):382–388. doi:10.1053/j.jvca.2014.07.012
17. He Z, Xu N, Qi S. Remote ischemic preconditioning improves the cognitive function of elderly patients following colon surgery: a randomized clinical trial. *Medicine*. 2017;96(17):e6719. doi:10.1097/md.0000000000006719
18. Meybohm P, Renner J, Broch O, et al. Postoperative neurocognitive dysfunction in patients undergoing cardiac surgery after remote ischemic preconditioning: a double-blind randomized controlled pilot study. *PLoS One*. 2013;8(5):e64743. doi:10.1371/journal.pone.0064743
19. Sangeetha RP, Ramesh VJ, Kamath S, et al. Effect of remote ischemic preconditioning on cerebral oxygen saturation in aneurysmal subarachnoid hemorrhage: secondary analysis of a randomized controlled trial. *J Clin Neurosci*. 2022;98:78–82. doi:10.1016/j.jocn.2022.01.035
20. Wong ZZ, Chiong XH, Chaw SH, et al. The use of cerebral oximetry in surgery: a systematic review and meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth*. 2022;36(7):2002–2011. doi:10.1053/j.jvca.2021.09.046
21. Ding L, Chen DX, Li Q. Effects of electroencephalography and regional cerebral oxygen saturation monitoring on perioperative neurocognitive disorders: a systematic review and meta-analysis. *BMC Anesthesiol*. 2020;20(1):254. doi:10.1186/s12871-020-01163-y
22. Chen N, Lu J. Meta-analysis of the correlation between postoperative cognitive dysfunction and intraoperative cerebral oxygen saturation. *Comput Math Methods Med*. 2022;2022:3731959. doi:10.1155/2022/3731959
23. Migirov A, Chahar P, Maheshwari K. Postoperative delirium and neurocognitive disorders. *Curr Opin Crit Care*. 2021;27(6):686–693. doi:10.1097/mcc.0000000000000882
24. Raval RN, Small O, Magsino K, et al. Remote ischemic pre-conditioning in subarachnoid hemorrhage: a prospective pilot trial. *Neurocrit Care*. 2021;34(3):968–973. doi:10.1007/s12028-020-01122-y
25. Soenarto RF, Hidayat JK, Eureka O, Auerkari AN. Can Near-Infrared Spectroscopy (NIRS) monitoring prevent post-operative cognitive dysfunction following open- heart surgery? *J Pak Med Assoc*. 2021;71(Suppl 2):S10–S13.
26. Larsen JR, Kobborg T, Shahim P, Blennow K, Rasmussen LS, Zetterberg H. Serum-neuroproteins, near-infrared spectroscopy, and cognitive outcome after beach-chair shoulder surgery: observational cohort study analyses. *Acta Anaesthesiol Scand*. 2021;65(1):26–33. doi:10.1111/aas.13691
27. Qiu LL, Pan W, Luo D, et al. Dysregulation of BDNF/TrkB signaling mediated by NMDAR/Ca(2+)/calpain might contribute to postoperative cognitive dysfunction in aging mice. *J Neuroinflammation*. 2020;17(1):23. doi:10.1186/s12974-019-1695-x
28. Fang FA, Meng YQ. Effects of distant ischemic preconditioning on cognitive function in patients with mild cognitive impairment after off-pump coronary artery bypass grafting. *Int Med Health Guid News*. 2019;25(18):3027–3030.
29. Xue FX, Zhou SS. Protective effect of hyperbaric oxygen pretreatment and the expression of BDNF and GDNF genes in hippocampus of rats after cerebral ischemia reperfusion. *Prog Mod Biomed*. 2020;20(15):2813–2816. doi:10.13241/j.cnki.pmb.2020.15.003
30. Xue Z, Shui M, Lin X, et al. Role of BDNF/ProBDNF imbalance in postoperative cognitive dysfunction by modulating synaptic plasticity in aged mice. *Front Aging Neurosci*. 2022;14:780972. doi:10.3389/fnagi.2022.780972
31. Wei FS, Rao MW, Huang YL, Chen SB, Wu YQ, Yang L. miR-182-5p delivered by plasma exosomes promotes sevoflurane-induced neuroinflammation and cognitive dysfunction in aged rats with postoperative cognitive dysfunction by targeting brain-derived neurotrophic factor and activating NF-κB pathway. *Neurotox Res*. 2022;40(6):1902–1912. doi:10.1007/s12640-022-00597-1
32. Ji MH, Yuan HM, Zhang GF, et al. Changes in plasma and cerebrospinal fluid biomarkers in aged patients with early postoperative cognitive dysfunction following total hip-replacement surgery. *J Anesth*. 2013;27(2):236–242. doi:10.1007/s00540-012-1506-3
33. Barbu M, Jónsson K, Zetterberg H, et al. Serum biomarkers of brain injury after uncomplicated cardiac surgery: secondary analysis from a randomized trial. *Acta Anaesthesiol Scand*. 2022;66(4):447–453. doi:10.1111/aas.14033
34. Wei H, Huang JS, Zhao F, Xie ZQ, Xia ZY, Gan JH. Transcutaneous electrical acupoint stimulation improves postoperative cognitive function in senior patients undergoing video-assisted thoracoscopic surgery: a randomized controlled trial. *Chin J Integr Med*. 2022;28(8):730–735. doi:10.1007/s11655-022-3516-1
35. Rasmussen LS, Christiansen M, Rasmussen H, Kristensen PA, Moller JT. Do blood concentrations of neurone specific enolase and S-100 beta protein reflect cognitive dysfunction after abdominal surgery? ISPOCD group. *Br J Anaesth*. 2000;84(2):242–244. doi:10.1093/oxfordjournals.bja.a013410
36. Rasmussen LS, Christiansen M, Eliasen K, Sander-Jensen K, Moller JT. Biochemical markers for brain damage after cardiac surgery – time profile and correlation with cognitive dysfunction. *Acta Anaesthesiol Scand*. 2002;46(5):547–551. doi:10.1034/j.1399-6576.2002.460512.x