The Potential Role of Lung-Protective Ventilation in Preventing Postoperative Delirium in Elderly Patients Undergoing Prone Spinal Surgery: A Preliminary Study

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background:
Postoperative delirium (POD) is a frequent complication in elderly patients, usually occurring within a few days after surgery. This study investigated the effect of lung-protective ventilation (LPV) on POD in elderly patients undergoing spinal surgery and the mechanism by which LPV suppresses POD.

Material/Methods:
Seventy-one patients aged ≥65 years were randomized to receive LPV or conventional mechanical ventilation (MV), consisting of intermittent positive pressure ventilation following induction of anesthesia. The tidal volume in patients who received MV was 8 ml/kg predicted body weight (PBW), and the ventilation frequency was 12 times/min. The tidal volume in patients who received LPV was 6 ml/kg PBW, the positive end-expiratory pressure was 5 cmH_2O, and the ventilation frequency was 15 times/min, with a lung recruitment maneuver performed every 30 min. Blood samples were collected immediately before anesthesia induction (T_0), 10 min (T_1) and 60 min (T_2) after turning over, immediately after the operation (T_3), and 15 min after extubation (T_4) for blood gas analysis. Simultaneous cerebral oxygen saturation (rSO_2) and cerebral desaturation were recorded. Preoperative and postoperative serum concentrations of interleukin (IL)-6, IL-10 and glial fibrillary acidic protein (GFAP) were measured by ELISA. POD was assessed by nursing delirium screening score.

Results:
Compared with the MV group, pH was lower and $PaCO_2$ higher in the LPV group at T_2. In addition PaO_2, SaO_2, and PaO_2/FiO_2 were higher at T_1, and T_4, and rSO_2 was higher at T_3, and T_4 in the LPV than in the MV group ($P<0.05$ each). Postoperative serum GFAP and IL-6 were lower and IL-10 higher in the LPV group. The incidences of cerebral desaturation and POD were significantly lower in the LPV group ($P<0.05$).

Conclusions:
LPV may reduce POD in elderly patients undergoing spinal surgery by inhibiting inflammation and improving cerebral oxygen metabolism.

MeSH Keywords:
Aged • Cerebral Cortex • Delirium • Inflammation • Prone Position • Ventilation

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Background

Postoperative delirium (POD) is an acute and fluctuating dysfunction of consciousness caused by surgically-associated and individual patient factors. It is a common postoperative complication in the elderly, usually occurring within a few days after surgery [1]. POD is characterized by disorientation, reduce attention, and changes in cognitive function. Delirium can increase postoperative complications, prolong hospital stay, and increase financial costs. Measures to deal with delirium include prevention, monitoring, and early treatment, with prevention being better than earliest possible treatment [2,3].

The incidence of POD increases with increasing number of operations, especially in elderly patients after spinal surgery [4]. Spinal surgery is complex, delicate, and time-consuming, resulting in an incidence of POD that can be as high as 40.5% [5]. Patients undergoing spinal surgery are usually placed in a prone position, as the operating field is clear and convenient for surgery. However, this position is non-physiological, reducing cerebral oxygen saturation (rSO_2). Decreased rSO_2 is more likely to occur when patients are in the prone than in the supine position or when they change from the supine to the prone position [6].

Intraoperative cerebral blood flow and inadequate oxygen supply are the main risk factors for POD and cognitive dysfunction [6]. Spinal surgery in the prone position increases the risk of changes in cerebral blood perfusion, which may affect the oxygen supply to the brain [7]. The prone position also increases intra-abdominal pressure because of direct compression of the inferior vena cava and increased intrathoracic pressure. Left ventricular compliance and filling are also reduced, leading to hypotension and decreased cerebral perfusion. Reduced blood supply to the brain reduces its oxygen supply [8]. Imbalances between oxygen supply and consumption in the brain can induce brain cell hypoxia and metabolic dysfunction in brain tissue. This, in turn, can reduce the number of neurons in the brain and induce imbalances in central neurotransmitters, such as acetylcholine and dopamine, and leading to delirium [9,10].

Inflammation is also a major risk factor for POD [10–12]. Mechanical ventilation can cause ventilator-associated lung injury, which can promote the release of inflammatory factors in the lungs and throughout the body [13–15]. Because respiratory function and lung compliance are generally reduced in elderly patients, mechanical ventilation under general anesthesia is more likely to cause lung injury such as barotraumas and induce peripheral inflammatory responses. Peripheral inflammatory factors can interact with endothelial cells at the blood-brain barrier (BBB) and induce the release of other inflammatory molecules into the brain. Peripheral inflammatory factors can also activate mast cells to release pro-inflammatory factors and neurotoxic substances, which can cause the destruction of the BBB. When the BBB is destroyed, these mediators can enter the brain and activate glial cells and neurons to release various neuroinflammatory mediators. In addition, activation of microglia and astrocytes in the brain can induce their release of inflammatory mediators, which can cross the defective BBB into the peripheral system. These mediators can recruit and activate inflammatory cells near the site of brain inflammation site, exacerbating the inflammation and neurodegeneration of the brain. This, in turn can cause ischemia, hypoxia, and even edema of brain tissue, eventually resulting in neuronal injury and neurodegeneration [16–18].

Lung-protective ventilation (LPV) includes low tidal volume, a certain level of positive end-expiratory pressure (PEEP), and hypercapnia, with or without a lung recruitment maneuver [19]. LPV is mainly used in patients with acute respiratory distress syndrome (ARDS) and is increasingly used in anesthetized patients undergoing surgery. LPV can benefit patients without lung injury who require mechanical ventilation during surgery, significantly reducing the incidence of postoperative pulmonary complications [20]. Moreover, LPV during general anesthesia can improve pulmonary compliance, effectively avoid barotrauma, and ensure oxygenation [21]. The present study therefore evaluated the effect of LPV on POD in elderly patients undergoing spinal surgery in the prone position and assessed the relationships among LPV, neuroinflammation, rSO_2, and POD. These results may provide clinical evidence of methods to prevent POD.

Material and Methods

This prospective, randomized, double-blind controlled study was performed in compliance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Third Hospital of Hebei Medical University (2018-033-1). All enrolled patients provided written informed consent. In addition, this study has been registered in the Chinese Clinical Trial Registry (ChiCTR1900021155). In this study, all invasive procedures were routine intraoperative procedures, and the use of a cerebral oxygen monitor was free of charge. Thus, none of these patients experienced additional pain or expenses due to enrollment in this study.

Participants

Using a random numbers table method, patients were randomly assigned by 2 individuals not involved in this study to undergo conventional mechanical ventilation (MV) or LPV during surgery. The anesthesiologists were not involved in the study, and the data collectors and medical staff members responsible

for the preoperative and postoperative management of the patient were unaware of the intraoperative method of mechanical ventilation used for each patient. All patients underwent posterior lumbar decompression and interbody fusion with internal fixation under general anesthesia from March to September 2019 in the Third Hospital of Hebei Medical University. Patients were included if they were aged ≥65 years; had a body mass index (BMI) <28 kg/m^2, an American Society of Anesthesiologists (ASA) physical status ≤III; and a score ≥23 points on the mini-mental state examination (MMSE) performed 1 day before surgery. Patients were required to have had no history of anemia, hypoalbuminemia, central nervous system disorders, mental illness, hypoxemia, chronic lung disease, asthma, or treatment with antidepressant or sedative drugs. Patients were excluded if they had baseline rSO_2 <60% before anesthesia induction; their surgical plan was changed; they refused blood donations; the operation time was >4 h, or intraoperative blood loss was > 800 ml.

Anesthesia and surgical management

All patients were anesthetized by experienced anesthesiologists and all operations were performed by experienced spinal surgeons. After entering the operating room, blood pressure, electrocardiogram, digital pulse oxygen saturation, $P_{ET}CO_2$, and rSO_2 were monitored. Cerebral oxygen electrodes were placed on the forehead 4 cm from the eyebrow arch to avoid the frontal sinus. Measurements of rSO_2 were concealed from the anesthetist so that anesthetic management was not influenced by rSO_2. Intravenous anesthesia was rapidly introduced, oral visual tracheal intubation was performed for complete muscle relaxation, and intermittent positive pressure was applied for mechanical ventilation. Body temperature was maintained by intraoperative blood transfusion and infusion thermostats. Depth of anesthesia was monitored to maintain bispectral index (BIS) at 45 to 60, and doses of anesthetic drugs and fluids were adjusted based on changes in BIS and hemodynamics. Blood pressure fluctuation did not exceed 20% of its baseline amplitude. Atropine was administered only to reverse bradycardia. After extubation, all patients were transferred to the surgical intensive care unit and received inhaled oxygen at a flow of 2 L/min through a nasal catheter.

Intervention methods

The tidal volume of patients in the control (MV) group was set at 8 ml/kg predicted body weight (PBW), and the initial ventilation frequency was 12 times/min. In the LPV group, tidal volume was set at 6 ml/kg PBW, low-level PEEP at 5 cmH$_2$O or 0.490 kPa, and the initial ventilation frequency at 15 times/min, with a lung recruitment maneuver performed every 30 min. Other parameters of the ventilator were the same in the 2 groups, including I: E of 1: 2, oxygen concentration of 100%, and oxygen flow of 2 L/min. $P_{ET}CO_2$ was maintained at 35-45 mmHg (4.655–5.985 kPa) by adjusting the ventilation frequency. For lung recruitment during surgery, the peak inspiratory pressure was initially set at 45 cmH$_2$O, tidal volume set at 8 ml/kg PBW, ventilation frequency at 6-8 times/min, I: E at 1: 2, and PEEP at 5 cmH$_2$O [23]. The tidal volume was gradually increased by 4 ml/kg PBW until the average airway pressure was 30–35 cmH$_2$O, and 3 consecutive breaths were taken. After the end of the operation, PEEP was maintained at 5 cmH$_2$O, and the remaining parameters were set identical to those before lung recruitment.

Blood samples

Venous blood samples were drawn into sterile EDTA-containing test tubes before the induction of anesthesia and 3 days after surgery. Four ml aliquots were allowed to coagulate at room temperature for 30 min and centrifuged at 1,000×g for 10 min, and the serum stored at -70°C. In addition, 2 ml aliquots were allowed to coagulate for 2 hours at room temperature and centrifuged at 1,000×g for 15 min, and the serum stored at −80°C.

Date collection and serum index detection

Blood samples from the radial artery were collected immediately before induction of anesthesia (T_0), 10 min (T_1) and 60 min (T_2) after turning over, immediately after the operation (T_3), and 15 min after extubation (T_4). Blood gasses were analyzed; pH, PaO_2, $PaCO_2$, and SaO_2 were recorded; and PaO_2/SaO_2 was calculated. Simultaneously, rSO_2 and the incidence of cerebral desaturation during surgery were recorded. Serum concentrations of interleukin (IL)-6, IL-10, and glial fibrillary acidic protein (GFAP) were determined by commercial IL-6 (ABclonal, Woburn, MA, USA), IL-10 (ABclonal) and GFAP (CUSABIO, Houston, TX, USA) ELISA kits, respectively.

Calculation of PBW

PBW was calculated as 50 kg+0.91 kg×(height [cm]-152.4) for men and as 45.5 kg+0.91 kg×(height [cm]-152.4) for women [24].

Definitions of baseline rSO_2 and cerebral desaturation

The rSO_2 values of each cerebral oxygen electrode were recorded within 2 minutes prior to anesthesia induction and averaged. The lower of the 2 averages was defined as the baseline rSO_2 value of that patient [25]. Cerebral desaturation was defined as a reduction in rSO_2 value >20% from baseline value or intraoperative rSO_2 value <40% lasting for more than 1 min [26].
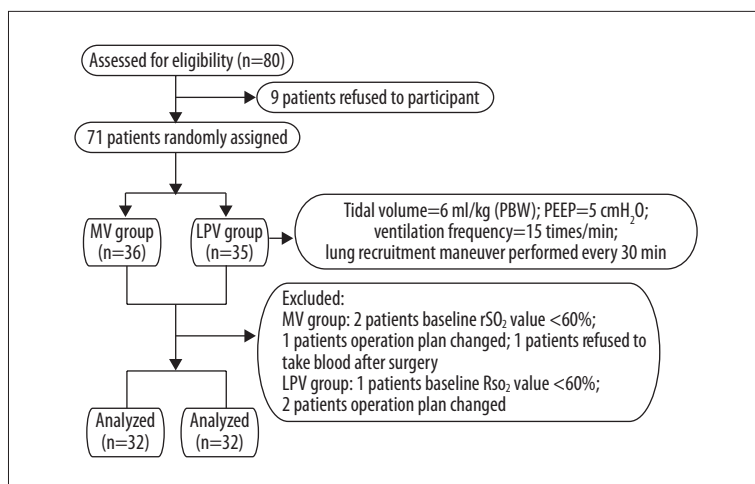
Figure 1. Patient flow diagram of this study. Studies have found that preoperative rSO_2 value less than 60% is closely related to the occurrence of postoperative mental state dysfunction in elderly patients, therefore, patients with baseline rSO_2 value <60% before anesthesia induction were removed from the trial. MV – conventional mechanical ventilation; LPV – lung-protective ventilation; rSO_2 – cerebral oxygen saturation.

Evaluation of delirium

POD was determined by a bedside nurse trained in neurology department using the nursing delirium screening score (Nu-DESC), performed 1–3 days postoperatively. Five parameters were captured: disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations, and psychomotor retardation, with each graded as 0–2 points. Delirium was defined as a score of ≥2 points on one of the 3 days [27].

Statistical analysis

Calculation of sample size

To compare the effects of LPV and conventional MV on POD in elderly patients undergoing spinal surgery, the standard deviations in the 2 groups were assumed to be equal, with a between-group difference in cognitive function defined at 75% of the standard deviation. If $\alpha=0.05$ and $\beta=0.10$, then $\delta/\sigma=0.75$, the formula for comparing the mean of 2 sample sizes, indicated that 31 patients were needed for each group [22]. Assuming a dropout rate of 20%, at least 74 patients should be included in both groups to ensure that 62 patients completed the study.

All data were analyzed using SPSS version 21.0 software for Windows (SPSS Inc, Chicago, IL, USA). Normally distributed data were expressed as mean±standard deviation and compared by independent-samples t tests. Non-normally distributed data were expressed as median (interquartile range) and compared by Mann-Whitney U-tests. Categorical data were expressed as numbers or numbers and percentages and compared by χ^2 tests. Univariate repeated measures ANOVA was used for intra-group comparisons. Associations were calculated, along with their 95% confidence intervals (CI). P-values <0.05 were considered statistically significant.

Results

Of the 80 patients screened for this study, 9 did not agree to take part and 7 were excluded, including 3 with baseline rSO_2 <60% before anesthesia induction; 3 because operation plans changed; and 1 who refused to supply a blood sample after the operation. Thus, this study included 64 patients, 32 in each group (Figure 1, flow diagram). Demographic and clinical characteristics did not differ significantly in the 2 groups (P>0.05 each). However, the rates of cerebral desaturation (P=0.030) and POD (P=0.039) were significantly lower in the LPV than in the MV group (Table 1).

Blood gas analysis, showed no significant between-group differences at T_0. In contrast, pH was significantly lower (P=0.021) and $PaCO_2$ higher (P=0.005) at T_2 in the LPV than in the MV group. In addition PaO_2, SaO_2, and PaO_2/FiO_2 were significantly higher in the LPV than in the MV group at both T_1 (P=0.026, P=0.044, and P=0.026, respectively) and T_4 (P=0.005, P=0.001, and P=0.005, respectively) (Table 2).

Prior to surgery, there were no significant between-group differences in IL-6, IL-10, and GFAP concentrations. Three days after surgery, however, serum concentrations of GFAP (P=0.000) and IL-6 (P=0.000) were significantly lower, and IL-10 (P=0.001) significantly higher, in the LPV than in the MV group (Table 3). Comparisons of points on the left and right sides of patients in the 2 groups showed no statistically significant differences in rSO_2 values at baseline. In contrast, rSO_2 values were significantly higher on the left and right sides of patients in the LPV than in the MV group at T_3 (P=0.042 and P=0.012, respectively) and T_4 (P=0.012 and P=0.005, respectively) (Figure 2), with the change of rSO_2 over time being significant on the left (P=0.000) and right (P=0.000) sides.

Comparisons of rSO_2 values in the MV group showed that, when compared with T_0 on the same side, rSO_2 values were

Table 1. Demographic and clinical characteristics of patients who received LPV or conventional MV and rates of cerebral desaturation and postoperative delirium (POD).

Characteristics	MV Group (n=32)	LPV Group (n=32)	*P*-value
Age (years), mean±SD	68.8±2.2	69.4±3.0	0.350
Sex (Male/Female), n	11/21	12/20	0.794
ASA (I/II/III), n	9/21/2	11/17/4	0.607
Preoperative MMSE score, mean±SD	26.8±1.9	26.5±1.5	0.519
BMI (kg/m^2), mean±SD	24.0±1.5	23.9±1.7	0.846
PBW (kg), M (Q)	57 (14)	54 (16)	0.710
Hypertension, n (%)	14 (44)	15 (47)	0.802
Diabetes, n (%)	7 (22)	6 (19)	0.756
Coronary heart disease, n (%)	4 (13)	4 (13)	1.000
Blood loss (ml), mean±SD	438±133	409±132	0.388
Urine output (ml), mean±SD	499±176	507±222	0.877
Infusion volume (ml), mean±SD	1902±263	1909±201	0.894
Anesthesia duration (min), mean±SD	153±27	159±26	0.392
Operation duration (min), mean±SD	114±27	117±25	0.690
Prevalence of cerebral desaturation, n (%)	10 (31)	3 (9)	0.030
Prevalence of POD, n (%)	8 (25)	2 (6)	0.039

ASA – American Society of Anesthesiologists; MMSE – Mini-mental State Examination; BMI – body mass index; PBW – predicted body weight; POD – postoperative delirium; SD – standard deviation; M(Q) – median (interquartile range); n – number of patients; MV – conventional mechanical ventilation; LPV – lung-protective ventilation.

Table 2. Blood gas parameters over time in patients who received LPV or conventional MV (n=32 each).

	Group	T0	T1	T2	T3	T4
pH	MV	7.43±0.04	7.41±0.05	7.41±0.04	7.38±0.05	7.33±0.06
	LPV	7.43±0.05	7.40±0.07	7.38±0.05*	7.37±0.05	7.33±0.08
PaO$_2$ (mmHg)	MV	95 (16)	344 (131)	371 (128)	372 (164)	112 (48)
	LPV	92 (15)	406 (103)*	417 (95)	407 (118)	162 (138)*
PaCO$_2$ (mmHg)	MV	36±4	36±6	36±5	39±6	45±8
	LPV	36±4	38±7	40±6*	40±5	45±10
SaO$_2$ (%)	MV	97.1 (1.7)	99.6 (0.3)	99.6 (0.5)	99.6 (0.5)	97.6 (2.5)
	LPV	97.0 (2.0)	99.7 (0.4)*	99.7 (0.4)	99.7 (0.3)	98.8 (1.9)*
PaO$_2$/FiO$_2$ (mmHg)	MV	95 (16)	344 (131)	371 (128)	372 (164)	112 (48)
	LPV	92 (15)	406 (103)*	417 (95)	407 (118)	162 (138)*

Values expressed as mean±standard deviation or as median (interquartile range). * $P<0.05$ compared with the MV group.
T_0 – immediately before anesthesia induction; T_1 – 10 min after turning over; T_2 – 60 min after turning over; T_3 – immediately after the operation; T_4 – 15 min after extubation; MV – conventional mechanical ventilation; LPV – lung-protective ventilation.

Table 3. Preoperative and postoperative concentrations of GFAP, IL-6, and IL-10 in patients who received LPV or conventional MV (n=32 each).

	Group	Preoperative	Postoperative
GFAP (ng/ml)	MV	0.159±0.030	1.080±0.303
	LPV	0.162±0.029	0.703±0.225*
IL-6 (pg/mL)	MV	8.5±2.4	31.5±7.2
	LPV	8.5±2.1	23.1±4.7*
IL-10 (pg/mL)	MV	18±9	58±16
	LPV	18±10	75±24*

Values expressed as mean±standard deviation. * $P<0.05$ compared with the MV group. IL-6 – interleukin-6; IL-10 – interleukin-10; GFAP – glial fibrillary acidic protein; MV – conventional mechanical ventilation; LPV – lung-protective ventilation.
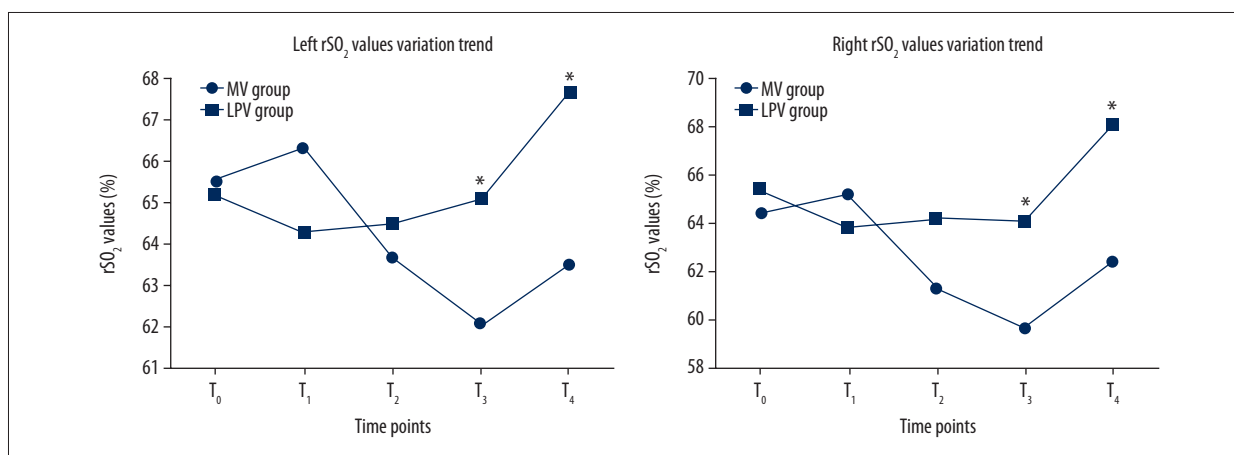

Figure 2. Changes over time in rSO_2 values on the left and right sides in patients who received LPV or conventional MV. Compared with MV group, * $P<0.05$. MV – conventional mechanical ventilation; LPV – lung-protective ventilation; rSO_2 – cerebral oxygen saturation; T_0 – immediately before anesthesia induction; T_1 – 10 min after turning over; T_2 – 60 min after turning over; T_3 – immediately after operation; T_4 – 15 min after extubation.

significantly lower on the right side at T_2 ($P=0.009$) and on the left ($P=0.004$) and right ($P=0.001$) sides at T_3. Compared with T_1, rSO_2 values were significantly lower on the left and right sides at T_2 ($P=0.026$ and $P=0.004$, respectively) and T_3 ($P=0.001$ and $P=0.000$, respectively), but rSO_2 values at T_3 and T_4 did not differ significantly from those at T_2 and did not differ significantly at T_3 and T_4.

Comparisons of rSO_2 values in the LPV group showed that rSO_2 values at T_4 were significantly higher on the left side than at T_0 ($P=0.036$), on the left ($P=0.013$) and right ($P=0.011$) sides than at T_1, on the left ($P=0.023$) and right ($P=0.033$) sides than at T_2, and on the right side than at T_3 ($P=0.020$). The trends of rSO_2 values over time were different in the 2 groups on both the left ($P=0.000$) and right ($P=0.002$) sides, with the MV group showing a downward trend and the LPV group showing an upward trend (Figure 2).

Discussion

This study found that the incidence of POD was significantly lower in patients who received LPV than in those who received conventional MV, suggesting that LPV, consisting of low tidal volume+5 cmH$_2$O PEEP combined with lung recruitment, may reduce the incidence of POD in elderly patients after spinal surgery in the prone position. This strategy may lower POD by inhibiting systemic inflammation caused by lung injury and improving cerebral oxygen metabolism.

Low tidal volume and proper PEEP has significant benefits on mortality in ARDS patients [28], with patients who underwent various surgical procedures benefitting from LPV [29–31]. A ventilation mode consisting of low tidal volume (6 ml/kg) combined with low PEEP (5 cmH$_2$O) during general anesthesia was found to effectively avoid lung injury, ensure patient oxygenation, and improve lung compliance [21]. Lung recruitment can also improve oxygenation and pulmonary compliance [32]. This

preliminary study investigating the relationship between LPV and POD suggests the need for further large-scale clinical trials.

Cerebral oxygen monitoring uses near-infrared spectroscopy (NIRS) to non-invasively measure the oxygenation state of the frontal lobe of the brain, enabling evaluation of the balance between cerebral oxygen supply and consumption, as well as changes in cerebral blood flow [6,33,34]. Cerebral desaturation has been associated with postoperative cognitive dysfunction following general surgery [35,36]. Dynamic monitoring of intraoperative changes in rSO_2 values, focusing on fluctuations at baseline, is of greater clinical significance than simply recording absolute rSO_2 values [34]. The present study therefore measured rSO_2 values at different time points and associated changes, confirming the relationships among LPV, cerebral desaturation in the prone position, and POD.

Blood acidity and $PaCO_2$ affect the affinity of hemoglobin to oxygen, known as the Bohr effect. A reduction in pH or an increase in $PaCO_2$ reduces the affinity of hemoglobin to oxygen, increasing the oxygen supply to tissues. At the same time, increased $PaCO_2$ can relax cerebral blood vessels and increase cerebral blood flow [37], delivering more oxygen to brain tissues. This study found that, under conditions of ensured oxygenation, the $PaCO_2$ of arterial blood in the LPV group increased and the pH decreased at T_2. Although rSO_2 did not change significantly at T_2, it showed an upward trend, with significant increases at T_3 and T_4. These results suggest that LPV may improve cerebral oxygen metabolism through the Bohr effect.

Elevated levels of inflammatory response markers are strongly associated with delirium [38–40]. IL-6 is an acute reactive protein that can serve as a marker for surgical injury and lung injury due to ventilation [41]. High levels of IL-6 correlate with nosocomial mortality, as well as various baseline characteristics, such as poor functional status, cognitive disorders, and emergency admissions [40]. IL-10, which is mainly produced by monocytes and macrophages, can inhibit the release of pro-inflammatory factors such as tumor necrosis factor (TNF)-α, IL-6, and IL-8. Both the pro-inflammatory factor IL-6 and the anti-inflammatory factor IL-10 are closely related to POD [42].

Inflammation can increase metabolic load in the brain. Studies of premature infants have shown that exposure to inflammation in the womb leads to increased brain oxygen consumption, increasing their risk of severe hypoxia and ischemia [42]. Perinatal inflammation is associated with poor neural development, which may be due to changes in oxygen supply and consumption in the brain [43]. This study showed that LPV reduced inflammatory responses and increased rSO_2 values in patients who underwent spinal surgery in the prone position, suggesting that LPV may reduce tissue oxygen consumption

by reducing inflammatory responses, thereby increasing brain oxygen and reducing delirium.

Severe systemic inflammation has a strong effect on neurocognitive functions of the brain. Damage to the hippocampus appears to be directly involved in this process, while astrocytes play an important role in neuroinflammation and neuroimmune responses [44]. GFAP is a structural protein in astrocytes of the central nervous system, and its release is usually associated with stroke or acute brain injury. High levels of GFAP in the brain have been reported to correlate with the occurrence of POD [45,46]. This study found that, along with reducing the incidence of POD, LPV significantly reduced the postoperative serum concentration of GFAP compared with the conventional MV group, providing further evidence for the relationship between GFAP and delirium.

POD is thought to be caused by neurotransmitter imbalance and inflammation [47–49]. Brain tissue ischemia and hypoxia can alter central neurotransmitter content. Acetylcholine levels were shown to be reduced and dopamine levels elevated in plasma and cerebrospinal fluid of patients with delirium [50–52]. Release of acetylcholine inhibits the release of TNF-α, IL-6, and IL-8, suggesting that cholinergic anti-inflammatory effects may protect the brain from inflammatory responses. Therefore, decreased cholinergic activity can lead to neuroinflammatory responses and further cognitive impairment. Elevated dopamine can induce changes in the neurological behavior of patients with delirium by directly stimulating the central nervous system and other pathways [48]. Inflammatory mediators, which are inversely associated with the number of synapses in mouse brain, can significantly activate microglia, which are closely related to neurodegeneration [53]. During systemic inflammation, white blood cells adhere to endothelial cells, leading to the release of free radicals and enzymes, increasing BBB permeability. This allows the central nervous system to respond to surrounding immune signals, resulting in the production of cytokines and other inflammatory mediators in the brain [48,54]. This process can aggravate the inflammation of the central nervous system, resulting in cognitive function and behavioral disorders.

Because older patients with preexisting cognitive impairment are at greatest risk of delirium [47], the MMSE test was administered before surgery to eliminate patients with dementia. Moreover, lung compliance in general anesthesia is affected by many factors, resulting in the exclusion of patients with obvious thoracic and pulmonary diseases and those taking drugs that could affect lung function. Because obesity can affect ventilation mechanics in the prone position, patients with BMI >28 kg/m^2 were excluded. In addition, low preoperative rSO_2 (<60%) has been associated with delirium [25]; therefore,

patients with baseline rSO_2 value <60% before anesthesia induction were excluded from this study.

This study had several limitations. Because of the strict exclusion criteria, the number of patients enrolled was small. Changes in cognitive function may also result from preoperative medication, pain, and postoperative use of analgesics or other medications. This pilot study utilized univariate analysis to study the relationship between LPV and POD. A larger clinical trial is needed, enabling multivariate analysis that can control for potential confounders. Inflammatory indicators in bronchoalveolar lavage fluid can better reflect the degree of lung injury, as can serum CC16 [55], suggesting that future clinical studies should assess additional numbers of lung injury indicators. It is also necessary to monitor indicators of respiratory mechanics during ventilation. The patient follow-up time of this study was short, suggesting that prolonged observation may help better guide the management of delirium in these patients. The ability to assess cognitive status in elderly patients is also limited. The Nu-DESC test, which has high sensitivity but low specificity, is administered by a nurse at the bedside as part of their daily practice of clinical management [27]. Although serum concentrations of inflammatory factors were measured, serum may not adequately reflect the concentrations of these factors in cerebrospinal fluid. Peripheral inflammation may alter the inflammation of the central nervous system by means other than increasing BBB permeability. This study did not measure changes in central neurotransmitter content, suggesting the need for further clinical studies to confirm the relationships of LPV, delirium after surgery in the prone position, and neurotransmitter imbalances.

Conclusions

LPV is potentially beneficial for elderly patients undergoing spinal surgery in the prone position, via a mechanism that involves reduced inflammatory responses and improved cerebral oxygen metabolism. The beneficial role of LPV in improving long-term treatment outcomes is unclear, indicating a need for further research to elucidate the mechanisms by which LPV inhibits the development of POD.

Acknowledgments

Conflicts of interest

None.

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