Effects of Intraoperative Lung-Protective Ventilation on Clinical Outcomes in Patients With Traumatic Brain Injury: A Randomized Controlled Trial

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Abstract

Background: Secondary lung injury is the most common non-neurological complication after traumatic brain injury (TBI). Lung-protective ventilation (LPV) has been proven to improve perioperative oxygenation and lung compliance in some critical patients. This study aimed to investigate whether intraoperative LPV could improve respiratory function and prevent postoperative complications in emergency TBI patients.

Methods: Ninety TBI patients were randomly allocated to three groups (1:1:1): Group A, conventional mechanical ventilation [tidal volume (VT) 10mL/kg only]; Group B, small VT (8mL/kg) + positive end-expiratory pressure (PEEP) (5cmH₂O); Group C, small VT (8mL/kg) + PEEP (5cmH₂O) + recruitment maneuvers (RMs). Primary outcomes were intraoperative respiratory mechanics parameters and incidences of postoperative pulmonary complications; Secondary outcomes were serum levels of brain injury markers and incidences of postoperative neurological complications.

Results: Seventy-nine patients completed final analysis. Intraoperative PaO₂ and dynamic pulmonary compliance of Group B and C were higher than those of Group A ($P=0.028$; $P=0.005$), while their airway peak pressure and plateau pressure were lower than those of group A ($P=0.004$; $P=0.005$). Compared to Group A, postoperative 30-day incidences of hypoxemia, pulmonary infection and atelectasis of the other two groups significantly decreased (52.0% vs. 14.3% vs. 19.2%, $P=0.005$; 84.0% vs. 50.0% vs. 42.3%, $P=0.006$; 24.0% vs. 3.6% vs. 0.0%, $P=0.004$). Moreover, intraoperative hypotension in Group C was more frequent than that in Group A and B ($P=0.007$). At the end of surgery, serum levels of glial fibrillary acidic protein and ubiquitin carboxyl-terminal hydrolase isozyme L1 in Group B were lower than those in group A and C ($P=0.002$; $P<0.001$). Postoperative incidences of neurological complications among three groups were comparable.

Conclusions: Intraoperative continuous administration of small VT + PEEP is beneficial to TBI patients. Additional RMs with caution can be performed to prevent the disturbance of the stability of cerebral hemodynamics.

Trial registration: Chinese Clinical Trial Registry (ChiCTR2000038314), retrospectively registered on September 17, 2020.

Background

Traumatic brain injury (TBI) is a major medical and socioeconomic problem. Over 50 million people worldwide develop TBI every year, and the morbidity has increased in the past decade [1]. TBI causes a wide range of systemic effects. It was reported that 89% of severe TBI patients experienced at least one non-neurological complication, of which 81% developed respiratory dysfunction, involving 23% of respiratory failure cases. Hence, respiratory complications were prevalent non-neurological disorders after TBI [2]. Besides, neural and humoral regulation after injury leads to an attenuated response of lung

tissues to stress [3, 4], thus increasing the risk of pulmonary complications, especially pulmonary infection, neurogenic pulmonary edema (NPE), ventilator-associated lung injury (VALI), and atelectasis.

Tidal volume (VT) in general anesthesia is usually set 10–15 mL/kg corrected body weight (CBW), which is higher than that of most mammals with spontaneous respiration. High VT ventilation may cause alveolar overdistention, inflammatory mediator spillover, and VALI. Now, lung-protective ventilation (LPV) is defined as $VT \leq 8$ mL/kg, positive end-expiratory pressure (PEEP) ≥ 5 cmH₂O, and airway plateau pressure (Pplat) ≤ 30 cmH₂O, which is recognized as the optimal ventilation mode for patients with acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU) [5]. In view of satisfactory practices of LPV in ARDS patients, perioperative lung protection in operating room has also been highlighted by more anesthesiologists.

Various factors attribute to the complex interactions between mechanical ventilation (MV) and cerebral hemodynamics during operation. Plenty of clinical trials or meta-analysis have found that perioperative application of LPV can improve intraoperative oxygenation and lung compliance, and relieve postoperative pulmonary complications (PPCs). However, PEEP or recruitment maneuvers (RMs) may disrupt the stability of cerebral hemodynamics in emergency TBI patients, who are often excluded from these studies. Whether perioperative LPV is also beneficial to these patients requires explorations. A recent retrospective study involving 28,644 TBI patients in ICU showed no significant changes in intracranial pressure (ICP) and cerebral perfusion pressure (CPP) after applying LPV, indicating its safety of respiratory support in TBI patients [6].

Here, we conducted a randomized controlled trial with the hypothesis that intraoperative use of LPV can improve respiratory function and prevent postoperative complications in TBI patients. The primary aim was to assess intraoperative respiratory mechanics parameters and incidences of PPCs in TBI patients intervened with LPV. Secondary aims investigated their serum levels of brain injury markers and incidences of postoperative neurological complications.

Methods

Study Design, approvals and registration

A single-center, randomized controlled study involving 90 TBI patients was approved by the Ethics Committee of Northern Jiangsu People's Hospital (2019113). Informed consent was obtained from patients or their relatives. The trial was retrospectively registered at Chinese Clinical Trial Registry (ChiCTR2000038314) on 17/09/2020.

Patients

TBI patients aging 18–65 years who underwent emergency intracranial evacuation of hematoma were enrolled. No limitation in gender was set. Their body mass index (BMI) ranged from 18.5 to 29.9 kg/m² with the American Society of Anesthesiologists (ASA) Classification I or II.

Patients with a history of mental diseases or other neurological disorders (epilepsy, dementia, cerebrovascular malformation, etc.), severe cardiovascular diseases (valvular heart disease, pericarditis, cor pulmonale, etc.), and severe hepatic or renal insufficiency (cirrhosis, chronic renal failure, nephrotic syndrome, etc.), were excluded. Patients who had stroke, myocardial infarction or major surgery within three months and refused to participate were also excluded.

Patients were assigned by computer-generated randomized sequence to three groups (1:1:1): Group A (conventional MV), Group B (small VT + 5cmH₂O PEEP), Group C (small VT + 5cmH₂O PEEP + RMs). The random allocation scheme was sealed by the principal investigator in opaque envelopes. Two experienced anesthesiologists blinded to the random allocation enrolled eligible participants, and the other two assigned participants to interventions.

Anesthesia

Midazolam (0.05 mg/kg), sufentanil (0.5ug/kg), propofol (1–2 mg/kg), cis-atracurium (0.15–0.20 mg/kg) were intravenously injected for anesthesia induction. After tracheal intubation, the anesthesia machine was connected to start MV.

Inhalation of 2% sevoflurane during operation, and intravenous pump injection of remifentanyl (0.1–0.3 µg/kg/min), dexmedetomidine (0.01 µg/kg/min), cis-atracurium (5 µg/kg/min) were performed for anesthesia maintenance, the dose of which was adjusted according to the depth of anesthesia. Vasoactive drugs were applied if cyclic fluctuations occurred during surgery.

Mechanical ventilation

All patients received MV after tracheal intubation under the same general anesthesia management. Immediately after intubation, volume-controlled ventilation was applied in three groups with VT 10 mL/kg CBW, inspiration/expiration 1:2, fraction of inspired oxygen 100%, oxygen flow 2L/min, no PEEP and RMs. Five minutes later, the parameters of Group B and C were adjusted to 8 mL/kg CBW of VT and 5cmH₂O PEEP continuously. Patients in Group C received twice RMs before opening and after closing the endocranium. Briefly, RMs were performed to maintain the airway pressure 30cmH₂O for 30 s. During operation, respiratory rate was adjusted according to arterial blood gas analysis to maintain end-tidal carbon dioxide partial pressure (P_{ET}CO₂) at 30–35 mmHg.

Removal of the tracheal catheter postoperatively was discussed by the anesthesiologist and the attending physician. When patients recovered spontaneous breath, swallow, cough reflex, VT > 6 mL/kg, oxygen saturation (SpO₂) > 95% for 10 min, a gentle suction to clean the tube and oropharyngeal secretions, removal of the tracheal catheter, and delivery of oxygen by mask with 5L/min were performed. The mask was removed 10 min later, followed by 20-min observation and then patients were sent to the ward. Others with tracheal catheter were directly sent to ICU in the case of sedation, analgesia and ventilator.

Outcomes

Primary outcomes were: 1) intraoperative oxygenation and respiratory mechanics parameters [arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide (PaCO_2), pulmonary dynamic compliance (C_{dyn}), airway peak pressure (P_{peak}), P_{plat} , heart rate (HR), mean arterial pressure (MAP)]; 2) the incidences of intraoperative pulmonary and cardiovascular adverse reactions [$\text{SpO}_2 < 90\%$ or $\text{P}_{\text{ETCO}_2} > 45 \text{ mmHg}$ or systolic blood pressure (SBP) $< 90 \text{ mmHg}$ for more than 1 min, any arrhythmia]; 3) the incidences of postoperative 30-day pulmonary complications (hypoxemia, pulmonary infection, atelectasis, ARDS, VALI, NPE).

Secondary outcomes were intraoperative serum levels of brain injury markers [glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL1)] and the incidences of postoperative 30-day neurological complications (intracranial infection, intracranial hypertension, epilepsy, encephaledema, reoperation).

Other outcomes included intraoperative optic nerve sheath diameter (ONSD), postoperative duration of MV, length of stay, 30-day Glasgow Outcome Scale Extended (GOSE).

Data collection

The baseline characteristics were sex, age, BMI, ASA class, preoperative Glasgow Coma Scale (GCS) and hemoglobin concentration, intraoperative bleeding volume and infusion quantity, total operative and anesthesia time.

Blood gas analysis was performed on 1 mL radial artery blood sample at the onset of MV (T_1), ventilation for 60 min (T_2), and the end of surgery (T_3). The ONSD was measured by color Doppler ultrasound at anesthesia induction (T_0), T_1 , after applying PEEP (t_0), before the first RM (t_1), after the first RM (t_2), before the second RM (t_3), after the second RM (t_4) and T_3 . 5 mL internal jugular vein blood sample of each patient at T_1 , T_2 and T_3 was placed in vacuum blood collection tubes, whose supernatant was collected and detected by ELISA Kit of GFAP and UCHL1 (ab223867, Abcam; CY-8092, CircuLex) according to corresponding instructions.

Statistical analysis

Sample size was calculated as previously reported [7] and our pilot trial. According to the calculation formula for comparison of multiple sample rates [8], 24 patients per group were needed to detect a significant change in the incidence of PPC after applying LPV, with type I error of 0.05, 90% power and dropout rate of 20%.

Statistical Package for the Social Sciences version 22.0 was used for data processing. Normally distributed measurement data were expressed as mean $\pm$ standard deviation, and Levene test was conducted for assessing the homogeneity. If the data met the hypothesis of equal variance, Student-Newman-Keuls was applied to compare differences between any two samples; Otherwise, after performing Kruskal-Wallis H test, Bonferroni method was utilized to correct the significance level for post-hoc multiple comparison. Measurement data of skew distribution were expressed as median and

interquartile range, which were compared in the same way as data with unequal variances. Enumeration data expressed as percentages were analyzed by Chi-square test for $R \times C$ table data. Pairwise comparison was conducted if all theoretical frequencies were greater than 5; Otherwise, Fisher exact probability test and pairwise comparisons were conducted. $P < 0.05$ was considered statistically significant.

Results

From December 2019 to September 2020, we recruited 90 eligible TBI patients and equally assigned them to conventional MV (Group A), small VT + 5cmH₂O PEEP (Group B), small VT + 5cmH₂O PEEP + RMs (Group C). Finally, there were 79 participants completed final analysis, as 5, 2 and 4 patients died within postoperative 30 days in Group A, B and C, respectively (Fig. 1). Baseline characteristics of participants were comparable (Table 1).

Table 1
Baseline characteristics by randomized group

	Group A (n = 25)	Group B (n = 28)	Group C (n = 26)	<i>P</i>
Sex, n (%)				
Male	17 (68.0)	20 (71.4)	20 (76.9)	0.772
Female	8 (32.0)	8 (28.6)	6 (23.1)	
Age, years, median (IQR)	55.0 (45.0–60.0)	52.5 (45.3–56.0)	50.0 (43.5–56.0)	0.500
BMI, kg/m ² , mean ± SD	23.3 ± 2.1	22.9 ± 1.8	22.6 ± 1.8	0.469
ASA Class, n (%)				
I	9 (36.0)	7 (25.0)	7 (26.9)	0.649
II	16 (64.0)	21 (75.0)	19 (73.1)	
Glasgow Coma Scale, n (%) ^a				
13–15	1 (4.0)	3 (10.7)	3 (11.5)	0.911
9–12	9 (36.0)	9 (32.1)	8 (30.8)	
≤8	15 (60.0)	16 (57.1)	15 (57.7)	
Preoperative hemoglobin, g/dL, median (IQR)	12.0 (10.0–13.0)	13.0 (11.3–13.8)	12.0 (11.0–13.3)	0.462
Intraoperative amount of bleeding, mL, median (IQR)	300.0 (200.0–400.0)	300.0 (200.0–437.5)	300.0 (200.0–500.0)	0.440
Intraoperative fluid infusion volume, mL, median (IQR)	2500.0 (1975.0–3175.0)	2500.0 (2000.0–3000.0)	2500.0 (2000.0–3000.0)	0.810
Operative time, min, median (IQR)	200.0 (150.0–237.5)	177.5 (156.3–199.5)	162.5 (150.0–222.5)	0.379
Anesthesia time, min, median (IQR)	245.0 (200.0–285.0)	220.0 (201.3–253.8)	202.5 (193.8–270.0)	0.508
ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; SD, standard deviation.				
^a Glasgow Coma Scale is an indicator to assess the coma of a patient. It ranges from 3 to 15, and the higher the score, the better consciousness. A score of 13–15, 9–12 and ≤ 8 classify mild, moderate and severe traumatic brain injury, respectively.				

Figure 2 showed the timeline of intraoperative LPV strategy. Table 2 summarized intraoperative blood gas analysis, respiratory mechanics and hemodynamics. At T_1 , no significant differences in PaO_2 , $PaCO_2$, C_{dyn} , P_{peak} and P_{plat} were detected among three groups. At T_2 , compared to Group A, the median PaO_2 and C_{dyn} increased significantly in Group B and C (336.0 vs. 375.5 vs. 388.0 mmHg, $P=0.028$; 320.0 vs. 360.0 vs. 350.0 mL/cmH₂O, $P=0.005$), while their median P_{peak} and P_{plat} decreased significantly (18.0 vs. 17.0 vs. 17.0 cmH₂O, $P=0.004$; 14.0 vs. 13.0 vs. 13.0 cmH₂O, $P=0.005$). No significant difference in $PaCO_2$ was detected. At T_3 , the median PaO_2 , $PaCO_2$, C_{dyn} in Group B and C were higher than those in Group A (340.0 vs. 397.5 vs. 402.5 mmHg, $P=0.005$; 40.0 vs. 44.0 vs. 42.0 mmHg, $P=0.025$; 330.0 vs. 340.0 vs. 340.0 mL/cmH₂O, $P=0.009$), which were opposite to the median P_{peak} and P_{plat} (19.0 vs. 17.0 vs. 17.0 cmH₂O, $P=0.012$; 16.0 vs. 13.0 vs. 14.0 cmH₂O, $P=0.003$). There were no significant differences in aforementioned indicators between Group B and C both at T_2 and T_3 . Meanwhile, HR and MAP among three groups were comparable throughout the surgery.

Table 2
Intraoperative blood gas analysis, respiratory mechanics and hemodynamics

		Group A (n = 25)	Group B (n = 28)	Group C (n = 26)	P
PaO ₂ , mmHg	T ₁	419.0 (381.5–486.0)	426.0 (400.8-450.3)	433.5 (367.5-487.3)	0.781
	T ₂	436.0 (382.0-487.0)	475.5 (447.3-496.8)*	488.0 (409.8-527.3)*	0.028
	T ₃	440.0 (394.5-493.5)	497.5 (486.8-534.5)#	502.5 (441.3–554.0)*	0.005
PaCO ₂ , mmHg	T ₁	45.0 (39.5–50.0)	46.0 (40.3–49.0)	46.0 (37.0–49.0)	0.881
	T ₂	42.0 (39.0–46.0)	42.0 (40.0-47.8)	42.0 (38.8–47.3)	0.970
	T ₃	40.0 (38.0–42.0)	44.0 (39.3–47.8)*	42.0 (39.0-46.3)*	0.025
Cdyn, mL/cmH ₂ O	T ₁	320.0 (300.0-335.0)	320.0 (310.0-350.0)	310.0 (300.0-322.5)	0.080
	T ₂	320.0 (295.0-355.0)	360.0 (332.5–370.0)#	350.0 (340.0-360.0)*	0.005
	T ₃	330.0 (305.0-345.0)	340.0 (330.0-360.0)*	340.0 (330.0-370.0)*	0.009
Ppeak, cmH ₂ O	T ₁	17.0 (16.0–20.0)	18.0 (16.0–19.0)	19.0 (17.0–20.0)	0.379
	T ₂	18.0 (17.5–21.0)	17.0 (16.0-18.8)#	17.0 (15.8–19.0)*	0.004
	T ₃	19.0 (18.0–21.0)	17.0 (15.3–20.0)*	17.0 (16.0–19.0)*	0.012
Pplat, cmH ₂ O	T ₁	13.0 (11.5–14.5)	14.0 (12.0-15.8)	15.0 (13.0-16.3)	0.068
	T ₂	14.0 (13.0–17.0)	13.0 (11.3–14.8)*	13.0 (11.0–15.0)*	0.005
	T ₃	16.0 (13.5–17.0)	13.0 (11.0–15.0)#	14.0 (11.8–15.3)*	0.003
Heart rate, min ⁻¹	T ₁	81 (65–102)	80 (65–93)	76 (72–92)	0.779

Data are presented as median (interquartile range).

Cdyn, pulmonary dynamic compliance; DBP, diastolic blood pressure; MAP, mean arterial pressure; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; Ppeak, airway peak pressure; Pplat, airway plateau pressure; SBP, systolic blood pressure.

^a MAP=(SBP + DBP*2)/3.

*P< 0.05, #P< 0.01 compared to Group A at the same point in time.

		Group A (n = 25)	Group B (n = 28)	Group C (n = 26)	<i>P</i>
	T ₂	66 (58–92)	70 (62–87)	68 (62–83)	0.891
	T ₃	64 (56–93)	65 (59–80)	68 (63–85)	0.421
MAP, mmHg ^a	T ₁	88.0 (77.0–101.5)	93.0 (85.0–101.8)	93.5 (88.5–109.0)	0.419
	T ₂	79.0 (73.5–90.0)	86.0 (77.0–95.0)	82.0 (73.8–86.5)	0.210
	T ₃	77.0 (71.0–92.5)	78.0 (71.3–84.3)	81.0 (72.0–91.5)	0.802
Data are presented as median (interquartile range).					
Cdyn, pulmonary dynamic compliance; DBP, diastolic blood pressure; MAP, mean arterial pressure; PaCO ₂ , arterial partial pressure of carbon dioxide; PaO ₂ , arterial partial pressure of oxygen; Ppeak, airway peak pressure; Pplat, airway plateau pressure; SBP, systolic blood pressure.					
^a MAP=(SBP + DBP*2)/3.					
* <i>P</i> < 0.05, # <i>P</i> < 0.01 compared to Group A at the same point in time.					

Furthermore, intraoperative respiratory and cardiovascular adverse reactions were recorded and a 30-day postoperative follow-up was conducted (Table 3). Compared with Group A and B, the incidence of intraoperative hypotension (SBP < 90 mmHg) increased significantly in Group C (32.0% vs. 39.3% vs. 73.1%, *P* = 0.007), whilst no significant differences in the incidences of arrhythmia, SPO₂ < 90% and P_{ET}CO₂ > 45 mmHg were found among three groups. Our follow-up results showed that the incidences of hypoxemia, pulmonary infection and atelectasis in Group B and C were significantly lower than those in Group A (52.0% vs. 14.3% vs. 19.2%, *P* = 0.005; 84.0% vs. 50.0% vs. 42.3%, *P* = 0.006; 24.0% vs. 3.6% vs. 0.0%, *P* = 0.004). However, the incidences of ARDS, VALI and NPE among three groups were comparable. Besides, there were no significant differences in PPCs between Group B and C. Postoperative incidences of neurological complications of three groups were similar. The median postoperative ventilation time in Group A was significantly longer than that of Group B and C (72.0 vs. 24.0 vs. 24.0 h, *P* = 0.006), which was comparable between the latter two groups. Likewise, there were no significant differences in GOSE score and hospital stay in three groups.

Table 3
Intraoperative adverse reactions and postoperative 30-day follow-up

	Group A (n = 25)	Group B (n = 28)	Group C (n = 26)	<i>P</i>
Intraoperative adverse reactions, n (%)				
SpO ₂ < 90%	2 (8.0)	1 (3.6)	1 (3.8)	0.685
P _{ET} CO ₂ >45 mmHg	1 (4.0)	5 (17.9)	5 (19.2)	0.213
SBP < 90 mmHg	8 (32.0)	11 (39.3)	19 (73.1) ^{ab}	0.007
Arrhythmia	2 (8.0)	5 (17.9)	4 (15.4)	0.609
Postoperative respiratory complications, n (%)				
Hypoxemia	13 (52.0)	4 (14.3) ^a	5 (19.2) ^a	0.005
Pulmonary infection	21 (84.0)	14 (50.0) ^a	11 (42.3) ^a	0.006
Atelectasis	6 (24.0)	1 (3.6) ^a	0 (0.0) ^a	0.004
Acute respiratory distress syndrome	1 (4.0)	1 (3.6)	0 (0.0)	0.764
Ventilator-associated lung injury	3 (12.0)	3 (10.7)	2 (7.7)	0.902
Neurogenic pulmonary edema	1 (4.0)	0 (0.0)	1 (3.9)	0.537
Postoperative neurological complications, n (%)				
Intracranial infection	3 (12.0)	3 (10.7)	4 (15.4)	0.915
Intracranial hypertension	6 (24.0)	7 (25.0)	7 (26.9)	1.000
Epilepsy	2 (8.0)	2 (7.1)	3 (11.5)	0.890
Encephaledema	5 (20.0)	5 (17.9)	6 (23.1)	0.939
Reoperation	2 (8.0)	1 (3.6)	2 (7.7)	0.733
Other				
Mechanical ventilation time, h, median (interquartile range)	72.0 (36.0-105.0)	24.0 (3.0-62.0) ^a	24.0 (9.1-66.0) ^a	0.006

GOSE, Glasgow Outcome Scale Extended; P_{ET}CO₂, end-tidal carbon dioxide partial pressure; SBP, systolic blood pressure; SD, standard deviation; SpO₂, oxygen saturation.

^a*P*<0.05 compared to Group A; ^b*P*<0.05 compared to Group B.

^c GOSE is used to assess outcomes of patients with brain damage, which is divided into 8 levels. The higher the grade, the better the patient's prognosis.

	Group A (n = 25)	Group B (n = 28)	Group C (n = 26)	<i>P</i>
Length of stay, days, mean $\pm$ SD	21.5 $\pm$ 10.4	21.9 $\pm$ 8.3	22.0 $\pm$ 7.5	0.975
GOSE score, mean $\pm$ SD ^c	5 $\pm$ 1.6	6 $\pm$ 1.3	5 $\pm$ 1.2	0.768
GOSE, Glasgow Outcome Scale Extended; P _{ET} CO ₂ , end-tidal carbon dioxide partial pressure; SBP, systolic blood pressure; SD, standard deviation; SpO ₂ , oxygen saturation.				
^a <i>P</i> <0.05 compared to Group A; ^b <i>P</i> <0.05 compared to Group B.				
^c GOSE is used to assess outcomes of patients with brain damage, which is divided into 8 levels. The higher the grade, the better the patient's prognosis.				

As for ONSD (Table 4), there were no significant differences among three groups at T₀, T₁ and T₃. When compared within each group, the differences in Group A or B were comparable at any time. Comparisons in Group C were interesting. In detail, after performing each RM, the mean ONSD (mm) at t₂ or t₄ was not only significantly higher than that before carrying out each RM (t₁ vs. t₂: 5.38 vs. 5.65; t₃ vs. t₄: 5.38 vs. 5.61; *P*<0.05), but it was higher than that at T₀ or T₃ (T₀ vs. t₂: 5.26 vs. 5.65; T₀ vs. t₄: 5.26 vs. 5.61; T₃ vs. t₂: 5.34 vs. 5.65; T₃ vs. t₄: 5.34 vs. 5.61; *P*<0.05).

Table 4
Ultrasound measurement of ONSD

	T ₀	T ₁	t ₀	t ₁	t ₂	t ₃	t ₄	T ₃	<i>P</i>
Group A (n = 25)	5.32 $\pm$ 0.36	5.37 $\pm$ 0.32	NA	NA	NA	NA	NA	5.32 $\pm$ 0.30	0.864
Group B (n = 28)	5.33 $\pm$ 0.32	5.37 $\pm$ 0.30	5.44 $\pm$ 0.31	NA	NA	NA	NA	5.38 $\pm$ 0.29	0.527
Group C (n = 28)	5.26 $\pm$ 0.28	5.32 $\pm$ 0.30	5.37 $\pm$ 0.31	5.38 $\pm$ 0.29	5.65 $\pm$ 0.28 ^{abcd}	5.38 $\pm$ 0.30	5.61 $\pm$ 0.28 ^{abcd}	5.34 $\pm$ 0.29	< 0.001
Data are presented as mean $\pm$ standard deviation (mm).									
NA, not applicable; ONSD, optic nerve sheath diameter									
^a <i>P</i> <0.05, ^b <i>P</i> <0.05, ^c <i>P</i> <0.05, ^d <i>P</i> <0.05 compared to T ₀ , T ₃ , t ₁ , t ₃ , respectively.									

Table 5 showed serum levels of GFAP and UCHL1 in three groups at different time points. Both of them increased significantly in each group with the prolongation of operative time (*P*<0.001, each). At T₁, there were no significant differences in GFAP and UCHL1 levels among three groups. At T₂, the mean serum level of GFAP in Group B was the lowest (399.16 vs. 360.93 vs. 389.12 pg/mL, *P*=0.042), but significant difference was only detected between Group A and B. The mean serum level of UCHL1 in Group B was

significantly lower than that of the other two groups (828.16 vs. 661.96 vs. 782.00 pg/mL, $P = 0.001$), which was comparable between Group A and C. Similarly, at T_3 , the mean serum level of GFAP was significantly lower in Group B than the other groups (459.24 vs. 396.68 vs. 431.96 pg/mL, $P = 0.002$), which was comparable in the latter two groups. The mean serum level of UCHL1 was the highest in Group A, which was the lowest in Group B (1223.00 vs. 849.21 vs. 1068.50 pg/mL, $P < 0.001$).

Table 5
Intraoperative serum levels of GFAP and UCHL1

		Group A (n = 25)	Group B (n = 28)	Group C (n = 26)	<i>P</i>
GFAP	T_1	328.68 ± 54.50	325.79 ± 55.82	336.58 ± 61.04	0.776
	T_2	399.16 ± 55.40 [*]	360.93 ± 56.71 ^{a*}	389.12 ± 57.32 [*]	0.042
	T_3	459.24 ± 56.37 ^{*#}	396.68 ± 55.78 ^{a*#}	431.96 ± 71.44 ^{b*#}	0.002
UCHL1	T_1	422.60 ± 165.27	413.43 ± 172.77	434.58 ± 186.98	0.906
	T_2	828.16 ± 134.20 [*]	661.96 ± 166.73 ^{a*}	782.00 ± 177.36 ^{b*}	0.001
	T_3	1223.00 ± 126.37 ^{*#}	849.21 ± 175.51 ^{a*#}	1068.50 ± 167.71 ^{ab*#}	< 0.001
Data are presented as mean ± standard deviation (pg/mL).					
GFAP, glial fibrillary acidic protein; UCHL1, ubiquitin carboxyl-terminal hydrolase isozyme L1.					
^a $P < 0.05$ compared to Group A, ^b $P < 0.05$ compared to Group B at the same point in time.					
[*] $P < 0.05$, [#] $P < 0.05$ compared to T_1 , T_2 within each group, respectively.					

Discussion

Our study investigated effects of intraoperative LPV on respiratory function and the incidences of postoperative complications in emergency TBI patients. The results demonstrated that intraoperative continuous administration of small VT + PEEP could improve oxygenation and respiratory mechanics parameters, decrease incidences of PPCs, and lower increase in posttraumatic serum levels of brain injury markers. However, implementing intermittent RMs might disturb intraoperative cerebral hemodynamics, leading to the fluctuation of ICP.

Small VT ventilation (6–8 mL/kg CBW) is now served as the respiratory care standard for ARDS patients in ICU. A consensus has been formed that it is also suitable for patients with healthy lungs in operating room [9, 10]. An animal experiment showed that small VT ventilation could more effectively promote the oxygenation of rats with brain injury than large VT ventilation [11]. Furthermore, large VT ventilation in TBI patients might be associated with the occurrence of ARDS, and its incidence increased to some extent with the VT [12]. However, a single use of small VT causes periodic alveolar collapse of local lung

tissues, thus increasing the risk of atelectasis. Interestingly, this adverse effect can be offset by combining PEEP and/or RMs, which would inevitably involve positive pressure ventilation and might adversely affect ICP and CPP [13–15]. However, another study showed that high PEEP (5-15cmH₂O) could improve PaO₂ of local brain tissue without affecting ICP and CPP in patients with TBI and ARDS [16]. In summary, the interaction between the lung and the brain poses an important challenge to the ventilation management in TBI patients. An optimal ventilation strategy for TBI patients requires in-depth discussion.

In this study, two groups of TBI patients were treated with LPV: small VT (8 mL/kg CBW), intraoperative continuous administration of 5cmH₂O PEEP. And some were given RMs before opening and after closing the endocranium. Our results showed that intraoperative application of small VT + PEEP or small VT + PEEP + RMs improved oxygenation and pulmonary compliance in TBI patients compared to those treated with conventional MV. However, no significant differences in PaO₂ and Cdyn were found between two intervention groups, suggesting that RMs might not provide further improvement on the basis of PEEP. Ppeak, close to airway pressure, reflects the dynamic compliance of respiratory system. Recently, Pplat was recommended as a better predictor of barotrauma and VALI, which was closer to alveolar pressure and reflects the static compliance of respiratory system [17]. Our results showed that patients intervened with LPV had lower Ppeak and Pplat than those receiving conventional MV, suggesting that the implementation of LPV improved respiratory mechanics parameters, and contributed to relieve barotrauma and PPCs. However, there was a rise in PaCO₂ at the end of surgery in patients receiving LPV, which may be explained by CO₂ retention resulted from reduced periodic alveolar collapse and expansion following small VT. But the little rise could be considered as a compensatory state that would not cause obvious pathological damage [18]. The incidence of intraoperative hypoxemia was lower in two intervention groups, while the cardiovascular adverse reactions in small VT + PEEP + RMs group were more frequently observed. Since intrathoracic pressure increased rapidly in a short time, RMs-treated patients generated a decrease in blood volume returning to the heart, and the cardiac output [13]. Collectively, although small VT + PEEP + RMs can improve intraoperative oxygenation and respiratory mechanics parameters in TBI patients, RMs may cause adverse effects on hemodynamics, while small VT only combined with PEEP can improve lung function without affecting their circulatory stability.

Another primary outcome was the incidence of PPCs in three groups. PPCs are the most common mid-term complications after major surgery and strongly linked to clinical prognosis [19]. An observational study in 29 countries named LAS VEGAS showed that 80% severe TBI patients developed PPCs [20]. Serious pulmonary complications, like ARDS, NPE or VALI, are associated with high mortality, unfavorable neurological outcomes, longer ICU retention and hospital stays in TBI patients [21]. We investigated the incidence of pulmonary complications within postoperative 30 days. The incidences of hypoxemia, pulmonary infection, and atelectasis in LPV-intervened patients were significantly lower than those of patients receiving conventional MV, which was consistent with Marret E et al [22] study. Moreover, using LPV significantly reduced postoperative ventilation time, which might be attributed to the improvement of intraoperative respiratory function and decreased risk of PPCs by small VT combined with PEEP and

RMs. The GOSE score is usually used to evaluate the degree of disability and neurological prognosis of TBI patients [23]. Our results showed no statistical differences in GOSE score among three groups after 30 days, probably owing to a short follow-up time and limited sample size. Postoperative neurological complications and hospital stays were comparable among three groups, possibly because improving ventilation strategy alone hardly achieved a breakthrough in neurological outcomes of TBI patients. Surgical factors, the quality of nursing, and family economical state, are all needed to be considered comprehensively.

The biggest concern about TBI patients with perioperative LPV is that it may have an adverse effect on ICP and CPP. Ultrasound measurement of ONSD is a novel non-invasive method, widely used to dynamically and rapidly assess changes in ICP. It has a close correlation with canonical direct intubation in ventricle to estimate intracranial hypertension [24, 25]. Our ultrasound results showed no significant changes in ONSD at any time both in conventional MV and small VT + PEEP group, suggesting that intraoperative continuous administration of 5cmH₂O PEEP did not affect patients' ICP. Mascia et al [26] randomly applied 5cmH₂O or 10cmH₂O PEEP in 12 patients along with brain injury and ARDS. They found that the PEEP level, which was insufficient to give rise to excessive alveolar expansion or an evident increase in PaCO₂, had no significant impact on ICP, and could safely improve oxygenation. Likewise, if the PEEP value was lower than that of ICP during MV, the elevation of intrathoracic pressure within a certain range would not increase ICP [27]. Therefore, 5cmH₂O PEEP was applied in our study not lifting ICP visibly, because it did not cause alveolar hyperinflation or it was less than patients' ICP. However, RMs could rapidly expand the alveoli in a short period and increase the pressure in the thoracic cavity, which blocked the return of systemic circulation to the right atrium (cerebral venous reflux) and eventually increased ICP. After ceasing RMs, the intrathoracic pressure dropped to normal, and patient's ICP decreased accordingly [28]. Consistent with previous finding [29], a single RM transiently increased ONSD, which returned to the baseline within 5–10 minutes, indicating that RMs had the risk of elevating ICP of TBI patients.

Immediately after acute brain injury, astrocytes undergo mechanical deformation or local necrosis, leading to increased serum concentration of GFAP [30–32]. UCHL1 is a neuron-specific cytosolic enzyme and its serum level in acute phase of cerebral injury strongly correlated with the severity of damage [33]. Combined testing of GFAP and UCHL1 could more accurately diagnose the severity of brain damage and predict the long-term prognosis [34]. Here, postoperative serum levels of GFAP and UCHL1 in each group were higher than before. Possibly because they were released from necrotic cells and accumulated with the posttraumatic time course [35]. Furthermore, both serum levels of GFAP and UCHL1 in Group B were lower than the others at T₃. It is considered that PEEP can improve oxygenation, reduce the release of inflammatory mediators of the lung and brain, thereby alleviating secondary injuries. Interestingly, additional RMs posed a large continuous positive airway pressure in a short time, which had an adverse effect on cerebral hemodynamics that neutralized favorable results of implementing PEEP. Hence, intraoperative application of small VT + PEEP could prevent further brain damage in TBI patients to some extent. Whether RMs played the same role remained further exploration.

Several limitations in our study should be noteworthy. First, actual values and accurate changes in ICP were unable to be obtained from ultrasound measurement of ONSD. Second, our results may not be applicable to other neurosurgical patients, like intracranial tumors, craniocerebral injury in sitting position during operation, spontaneous cerebral hemorrhage, etc. Third, during the study period, especially before operation, some severe patients were treated with mannitol and dexamethasone due to their conditions, which might affect the results consequently. Fourth, a 30-day postoperative follow-up was unable to accurately evaluate long-term survival and life quality of TBI patients. Last, it was a single-center study with limited sample size. Large-scale clinical trials are needed in the future to validate the impact of intraoperative LPV on TBI patients.

Conclusions

Intraoperative continuous administration of small VT + PEEP is beneficial to TBI patients, manifesting as improved oxygenation and respiratory mechanics parameters, decreased incidences of PPCs, and lowered increase in posttraumatic serum levels of brain injury markers. However, additional RMs should be cautiously applied in these patients, since it is prone to disturbing intraoperative cerebral hemodynamics.

Abbreviations

TBI

Traumatic brain injury; NPE:Neurogenic pulmonary edema; VALI:Ventilator-associated lung injury; VT:Tidal volume; CBW:Corrected body weight; LPV:Lung-protective ventilation; PEEP:Positive end-expiratory pressure; Pplat:Airway plateau pressure; ARDS:Acute respiratory distress syndrome; ICU:Intensive care unit; MV:Mechanical ventilation; PPCs:Postoperative pulmonary complications; RMs:Recruitment maneuvers; ICP:Intracranial pressure; CPP:Cerebral perfusion pressure; BMI:Body mass index; ASA:American Society of Anesthesiologists; $P_{ET}CO_2$:End-tidal carbon dioxide partial pressure; SpO_2 :Oxygen saturation; PaO_2 :Arterial partial pressure of oxygen; $PaCO_2$:Arterial partial pressure of carbon dioxide; Cdyn:Pulmonary dynamic compliance; Ppeak:Airway peak pressure; HR:Heart rate; MAP:Mean arterial pressure; SBP:Systolic blood pressure; GFAP:Glial fibrillary acidic protein; UCHL1:Ubiquitin carboxyl-terminal hydrolase isozyme L1; ONSD:Optic nerve sheath diameter; GOSE:Glasgow Outcome Scale Extended; GCS:Glasgow Coma Scale

Declarations

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Authors' contributions

JG, LLJ and YJW have given substantial contributions to the conception and design of the manuscript, YZ, DHL and KSY to acquisition, analysis and interpretation of the data. All authors have participated in drafting the manuscript, JG and LLJ revised it critically. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Northern Jiangsu People's Hospital (2019113). All procedures performed involving human participants were in accordance with the ethical standards of the Declaration of Helsinki 1964 and its later amendments. Informed consent was obtained from all individual participants included in the study or their relatives.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Consolidated Standards of Reporting Trials (CONSORT) flow diagram. PEEP, positive end-expiratory pressure; RMs, recruitment maneuvers; VT, tidal volume.

Figure 2

Timeline of intraoperative lung-protective ventilation strategy implementation. PEEP, positive end-expiratory pressure; RM, recruitment maneuver.