Drive Pressure-Guided Individualized Positive End-Expiratory Pressure in Traumatic Brain Injury Surgery: A Randomized Controlled Trial

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AIM: Intraoperative lung-protective ventilation strategies (LPVS) have been shown to improve lung oxygenation and prevent postoperative pulmonary problems in surgical patients. However, the application of positive end-expiratory pressure (PEEP)-based LPVS in emergency traumatic brain injury (TBI) has not been thoroughly explored. The purpose of this study is to evaluate the effects of drive pressure-guided individualized PEEP on perioperative pulmonary oxygenation, postoperative pulmonary complications, and recovery from neurological injury in patients with TBI.

METHODS: A total of 111 TBI patients who met the inclusion criteria at Northern Jiangsu People's Hospital were randomized into three groups: group A (0 PEEP, 50% inhaled oxygen concentration, and 6 mL/kg tidal volume), group B (5 cmH_2O PEEP, 50% inhaled oxygen concentration, and 6 mL/kg tidal volume), and group C (individualized PEEP guided by driving pressure, 50% inhaled oxygen concentration, and 6 mL/kg tidal volume). The primary endpoints were lung ultrasound score (LUS), optic nerve sheath diameter (ONSD), and serum levels of neuron-specific enolase (NSE) and High mobility group box 1 protein (HMGB1). Secondary endpoints included intraoperative hemodynamic and respiratory mechanics parameters, postoperative pulmonary complications, and clinical lung infection scores.

RESULTS: Eighty-nine patients completed the final analysis. LUS was significantly lower in group C compared to group A at T4 (least square mean [95% confidence interval (CI)]: 2.50 [1.35, 3.65] vs. 5.25 [4.10, 6.40], $p < 0.05$). Although ONSD increased gradually in group C, it did not differ substantially from group A postoperatively (least square mean [95% CI]: 5.09 [4.90, 5.27] vs 5.16 [4.97, 5.34] mm, $p > 0.05$). Serum NSE levels in group C were significantly lower on postoperative days 1 (4.40 [3.89, 4.41] vs. 10.95 [10.44, 11.46], $p < 0.05$) and 3 (2.79 [2.28, 3.30] vs. 10.95 [10.44, 11.46], $p < 0.05$). Additionally, serum HMGB1 levels in group C were significantly reduced on postoperative days 1 (229 [200, 258] vs. 662 [633, 691], $p < 0.05$) and 3 (166 [137, 195] vs. 662 [633, 691], $p < 0.05$).

CONCLUSIONS: Individualized PEEP guided by driving pressure can improve perioperative pulmonary oxygenation and reduce the incidence of postoperative pulmonary complications. Furthermore, this strategy did not significantly elevate intraoperative intracranial pressure (ICP) and promoted recovery from postoperative neurological injury, likely by reducing the inflammatory response.

CLINICAL TRIAL REGISTRATION: https://www.chictr.org.cn/ (clinical trial no. ChiCTR2200066795).

Keywords: traumatic brain injury; lung-protective ventilation strategy; lung ultrasound score; optic nerve sheath diameter; neuron-specific enolase

Introduction

Traumatic brain injury (TBI) is a major global health issue, affecting approximately 100 million people annually and imposing a substantial economic burden [1, 2]. Its prevalence is rising in developing countries, and it is anticipated to surpass many other diseases as the leading cause of disability and death by 2030 [3]. Patients with TBI often experience secondary pulmonary and cerebral complications due to compromised airway protection and disrupted defense barriers caused by direct craniocerebral injury and impaired consciousness. This can lead to lung injuries such as neurogenic pulmonary edema, acute respiratory distress syndrome (ARDS), and ventilation-associated pneumonia. Moreover, lung hypoxia may exacerbate intracranial hypertension, resulting in neurological problems [4, 5]. Surprisingly, this feedback loop can occur within 2–3 hours after the onset of TBI [6, 7]. Consequently, emergency perioperative anesthetics for TBI patients require careful management to improve their prognosis.

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Cerebro-pulmonary syndrome is a lung disease frequently associated with craniocerebral injury, with up to 70% of patients developing neurogenic pulmonary edema (NPE) [8]. Measuring the partial pressure of oxygen in brain tissue ($PbtO_2$) provides a suitable clinical approach to distinguish between ischemic and non-ischemic brain physiology disorders [9]. Systemic oxygenation and ventilation parameters, such as fraction of inspired oxygen (FiO_2) and arterial oxygen partial pressure (PaO_2), can help predict $PbtO_2$, assuming alveolar function is adequate [10, 11]. Furthermore, a study by Robba *et al*. [12] in an intensive care unit revealed that employing a lung-protective ventilation strategy (LPVS) reduced cerebral hypoxia and improved TBI patients' prognosis. Currently, mechanical ventilation (MV) with low tidal volume (VT) and moderate to high positive end-expiratory pressure (PEEP) is considered a protective strategy recommended for patients with ARDS and even for patients with healthy lungs [13]. This strategy becomes particularly relevant with neurosurgical patients, as they typically require prolonged mechanical ventilation due to extended cognitive impairment, susceptibility to hospital, acquired pneumonia, and higher mortality rates [14, 15].

The LPVS aims to minimize lung damage caused by mechanical ventilation. This is achieved by utilizing low tidal volumes to limit lung hyperinflation and applying PEEP and lung resuscitation techniques to prevent lung collapse and atelectasis [16]. LPVS has demonstrated enhanced pulmonary oxygenation and reduced postoperative pulmonary complications in various surgical procedures (e.g., thoracic and abdominal surgery) and critically ill patients [17, 18]. These positive outcomes suggest that employing LPVS in cranial surgery is feasible and safe. Recent studies have highlighted the potential of driving pressure (DP) as a suitable target for LPVS [19, 20]. DP is a physiologic variable of interest associated with pulmonary complications in patients with lung injury or ARDS in retrospective study [21]. A meta-analysis involving 17 randomized controlled trials with 2250 patients compared low PEEP with high PEEP settings during ventilation at different tidal volumes (TVs). The results indicated that ventilatory settings aimed at reducing DP in mechanical ventilation reduced postoperative pulmonary complications (PPC). Moreover, it is speculated that high DP may increase morbidity even in patients with healthy lungs [22]. As a result, a new direction of "minimum DP"-based ventilation has been proposed. However, there are limited trials evaluating the role of DP in early lung protection after TBI, necessitating further research in this area.

Implementing protective ventilation strategies in patients with TBI presents challenges. Although recent data suggest that the use of low tidal volume can improve outcomes without causing harm, even in this specific population [23], it is worth noting that such strategies may lead to increased CO_2 values and pose risks to intracranial pressure and cerebral hemodynamics. Consequently, the application of lung-protective strategies in patients with TBI is often inadequate, and they are frequently excluded from crucial trials investigating the impact of these strategies on patient outcomes. Therefore, it becomes clinically imperative to ascertain how to balance the benefits and risks of mechanical ventilation on both the lungs and the brain simultaneously. Given the feasibility and practicality of these methods, we hypothesize that individualized PEEP titration, based on the minimum driving pressure, can effectively reduce postoperative atelectasis, enhance intraoperative oxygenation, and improve postoperative lung function in patients with acute TBI. The role of LPVS in lung protection was assessed using the lung ultrasound score (LUS) and other relevant indicators. Simultaneously, the impact of PEEP on intracranial pressure (ICP) and neurology was analyzed by monitoring changes in patients' optic nerve sheath diameter (ONSD) and serum neuron-specific enolase (NSE) expression levels.

Patients and Methods

Study Design, Approvals, and Registration

This randomized, parallel, double-blind, single-center study was registered at https://www.chictr.org.cn/ (trial registration: ChiCTR2200066795). This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from patients with TBI undergoing emergency craniocerebral surgery after receiving approval from the Northern Jiangsu People's Hospital, (2019-KY180-1). If the patient was unconscious, written consent was obtained from the patient's relatives according to local regulations. The study adhered to the guidelines outlined in the Consolidated Standards of Reporting Trials (CONSORT).

Patients

Inclusion Criteria: (1) Age between 18 and 80 years; (2) American Society of Anesthesiologists (ASA) classification of II to IV; (3) Body mass index (BMI) between 17 and 36 kg/m^2; (4) Diagnosis confirmed by outpatient computed tomography (CT) or magnetic resonance imaging (MRI) within 6 hours post-trauma; (5) Immediate transfer to the operating room for emergency surgery; (6) Expected operating time exceeding 2 hours. Exclusion Criteria: (1) History of ocular trauma, ocular tumor, optic neuritis, glaucoma, or any other ocular diseases; (2) Presence of acute or chronic pulmonary diseases, or a history of thoracic surgery or trauma; (3) History of psychiatric or neurological disorders; (4) Presence of traumatic wet lung or severe organ damage unrelated to the current trauma; (5) Episodes of vomiting and aspiration; (6) Preoperative intubation.

Anesthesia

Following the patient's arrival in the operating room, oxygen was administered via a mask; the electrocardiogram (ECG), heart rate (HR), noninvasive blood pressure

(NIBP), and arterial oxygen partial pressure (SpO_2) were monitored. Peripheral venous access to the lower extremities was opened, and direct arterial pressure was measured using a radial artery puncture under local anesthesia. Before anesthesia induction, patients were administered oxygen via a mask at a flow rate of 6–8 L/min, with a fraction of inspired oxygen (FiO_2) of 100% for 10–15 minutes. The upper body was elevated by 40°. Anesthesia was induced using intravenous sufentanil 0.5 μg/kg, propofol 0.5–1.0 mg/kg, and rocuronium 0.6 mg/kg (ideal body weight), followed by tracheal intubation using a transoral visual laryngoscope. After successful tracheal intubation, mechanical ventilation was performed; all patients underwent femoral vein puncture after induction for central venous access.

After tracheal intubation, the patients were ventilated in the volume, controlled mode with the following parameters: tidal volume, 6 mL/kg; FiO_2, 50%; inspiratory, to, expiratory ratio, 1:2; and respiratory rate, 12–20 times/minute to maintain end-expiratory carbon dioxide ($EtCO_2$) between 35 and 45 mmHg. Combined intravenous, inhalation anesthesia was used, with intravenous pumping of dexmedetomidine 0.6–0.8 μg/kg/h, remifentanil 10–12 μg/kg/h, cis, benzene sulfonate atracurium 0.06–0.12 mg/kg/h, and inhalation of sevoflurane 1%–2% to achieve reasonable sedation, analgesia, and satisfactory muscle relaxation. The Anesthesiologist used vasoactive drugs as needed to maintain stable hemodynamics during surgery, based on the patient's circulatory parameters and clinical experience.

The Anesthesiologist and the attending physician discussed the removal of the postoperative tracheal tube. When the patient's spontaneous breathing, swallowing, and cough reflexes recovered; tidal volume (VT) was greater than 6 mL/kg; and oxygen saturation SpO_2 was above 95% for 10 minutes, light suctioning was performed to clean the catheter and oropharyngeal secretions. The tracheal tube was then removed, and oxygen was delivered at a rate of 5 L/min with a face mask. The mask was released after 10 minutes, the patient was observed for 20 minutes, and then admitted to the ward. Others with tracheal tubes were sent directly to the intensive care unit under sedation, analgesia, and ventilation.

Randomization

A trier used computer-generated numbers to allocate patients randomly; the assigned numbers were sealed in opaque envelopes. After anesthesia induction, the envelopes were opened by an Anesthesiologist controlling the ventilator parameters, and the ventilator parameters were set according to the randomized grouping results. Multiple specially trained investigators measured LUS and ONSD. The participating investigators and patients were blinded to the trial procedure. The patients were randomly assigned to one of the following three groups:

Group A: 0 cmH_2O PEEP (n = 37)

After tracheal intubation, the ventilator parameters were set throughout the procedure: inspired oxygen concentration, 50%; tidal volume, 6 mL/kg (ideal body weight); PEEP, 0; and volume, controlled ventilation mode [24].

Group B: 5 cmH_2O PEEP (n = 37)

After tracheal intubation, the ventilator parameters were set throughout the procedure: inspired oxygen concentration, 50%; tidal volume, 6 mL/kg (ideal body weight); PEEP, 5 cmH_2O; and volume, controlled ventilation mode.

Group C: Drive pressure-guided individualized PEEP (n = 37)

After tracheal intubation, the ventilator parameters were set during the operation: inspired oxygen concentration, 50%; tidal volume, 6 mL/kg (ideal body weight); PEEP, 5 cmH_2O; and volume, controlled ventilation mode. We implemented a PEEP titration strategy following established literature practices [25]. PEEP was incrementally increased from 2 cmH_2O to 10 cm H_2O, with each level (2, 3, 4, 5, 6, 7, 8, 9, and 10 cmH_2O) sustained for 10 respiratory cycles until the minimum driving pressure (platform airway pressure, PEEP) is achieved. The driving pressure for the final cycle is then recorded at each PEEP level.

Measurements and Endpoints

Primary Endpoints

LUS: Patients were placed supine; a convex array transducer with a 3.5–10 MHz frequency was used to perform a bedside lung ultrasound. Twelve zones of both lungs were scored, with the anterior and posterior axillary lines dividing each side of the lung into three zones: anterior, lateral, and rear. Each zone was divided into superior and inferior zones at the level of the nipple. Each examination area was scored from 0 to 3; the 12 examination area scores were summed to obtain the LUS score (0–36): 0, standard, normal lung glides, visible A, lines, or a small number of B lines (less than 2); 1, three or more B lines; 2, B lines and fusion; and 3, lung consolidation or air bronchogram sign. The scores for each area were summed to obtain the lung total ventilation score [26]. The LUS score was determined before anesthesia induction (T1), immediately after PEEP titration (T2, which corresponded to 10 minutes of ventilation in groups A and B), and at the end of the operation (T4). The comprehensive ultrasound examination, conducted using the Sonosite M, Turbo ultrasound machine and a 6–13 MHz linear transducer array (L25), lasted 10 minutes. This lung ultrasound measurement time was aligned with the timing of electrical impedance tomography (EIT) assessments. Trained Anesthesiologists with 1 and 3 years of LUS experience performed the LUS procedure.

ONSD: The patient was supine with both eyes closed and a transparent patch covering the eyelids and coated with gel. The ONSD was then measured twice on each side with a line array probe at a frequency of 5 to 10 MHz, at the appropriate angle, in the cross, sectional and sagittal positions

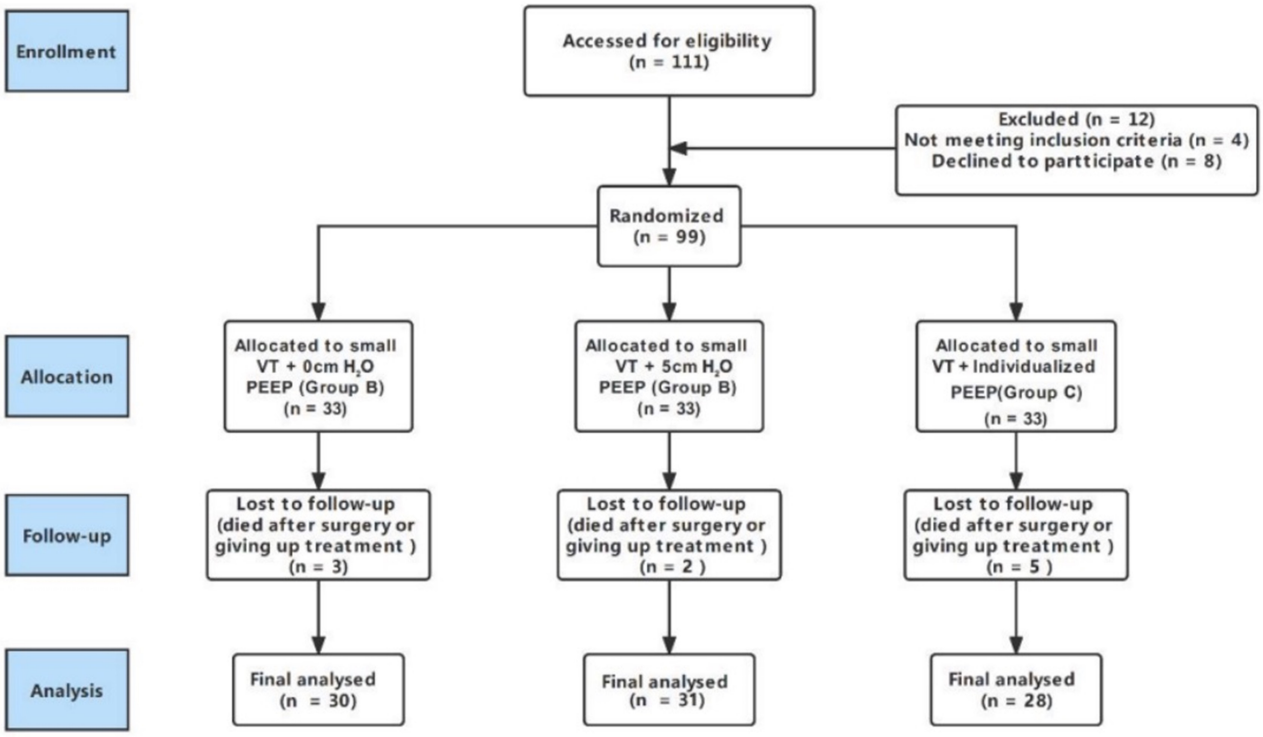

Fig. 1. Study flow diagram. VT, tidal volume.

of both eyes 3 mm posterior to the optic disc. It is essential to avoid putting too much pressure on the eye during the procedure. The optimal probe angle was determined when the ultrasound showed the best contrast between the retrobulbar fatty tissue and the vertical hypoechoic band. ONSD was measured before anesthesia induction (T1), immediately after PEEP titration (T2), which corresponded to 10 minutes of ventilation in groups A and B, and at the end of the operation (T4) [27].

Neuron-specific enolase (NSE) protein expression in plasma samples: Plasma samples were collected upon admission to the operating room and on postoperative days 1 and 3. NSE protein expression was quantified using a commercially available NSE enzyme, linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions (E, EL, H1047c, Elabscience, Beijing, China).

High mobility group box 1 protein (HMGB1) expression in plasma samples:Plasma samples were collected upon admission to the operating room and on postoperative days 1 and 3. HMGB1 expression was quantified using a commercially available HMGB1 ELISA kit according to the manufacturer's instructions (Amphoterin, SEKH-0409-96T, Solarbio, Beijing, China).

Secondary Endpoints

Admission to operating room (T0), before anesthesia induction (T1), immediately after PEEP titration (T2), 60 minutes after the start of surgery (T3), and at the end of surgery (T4), 1 mL of arterial blood was taken for blood gas analysis to record PaO_2 and arterial carbon dioxide partial pressure ($PaCO_2$). Dynamic lung compliance (Cdyn) and mean arterial pressure (MAP) were also recorded at this time. The Clinical Pulmonary Infection Score (CPIS) and postoperative pulmonary complications were recorded at 1, 3, and 7 days postoperatively (postoperative day 1 (T5), postoperative day 3 (T6), and postoperative day 7 (T7)).

Statistical Analysis

The sample size was calculated using PASS 15 software (Version 15, NCSS; LLC; Kaysville, UT, USA) based on an expected clinically significant difference in primary outcomes. A power of 0.9 and an alpha level of 0.05 were used to detect these differences, leading to the required sample size of 111 patients, allowing for a 20% dropout rate.

A linear mixed-effect model was used to compare the changes in LUS, ONSD, serological indicators, hemodynamic variables, respiratory variables, CPIS, and NSE and HMGB1 expression levels within and between groups. The data was described as least square mean values (95% confidence interval (CI)). Baseline data was assessed for data distribution using the Kolmogorov, Smirnov analysis. Data were described as median (Interquartile range) due to non-normal distribution. The Kruskal-Wallis (K-W) test was used for comparing unrelated samples across the three groups. The Chi-squared test was used to compare two or more ratios (PPCs). Furthermore, Two-way Analysis of Variance (ANOVA) was conducted to evaluate the effects of group, time, and interaction variables on LUS, res-

Table 1. Demographic data in the 0 cmH_2O PEEP, 5 cmH_2O PEEP, and individualized PEEP groups during surgery in patients with traumatic brain injury.

	A (n = 30)	B (n = 31)	C (n = 28)	H/χ^2	*p*
Gender, % (Male)	12 (40.0)	12 (38.7)	15 (53.6)	1.588	0.452
Age (years)	58.5 (34.0, 74.0)	60.0 (49.0, 71.0)	54.5 (50.0, 74.0)	3.1	0.216
ASA, %					
III	11 (36.7)	9 (29.0)	9 (32.1)	0.408	0.816
IV	19 (63.3)	22 (71.0)	19 (67.9)		
BMI (kg/m^2)	24.0 (20.3, 26.8)	24.3 (20.9, 33.0)	24.6(19.6, 35.0)	0.68	0.709
Intraoperative bleeding (mL)	310.0 (200, 550)	300.0 (200, 450)	310.0 (210, 479.5)	0.99	0.579
Intraoperative fluid amount (mL)	2500 (1879.0, 3100.0)	2600 (1926.0, 3150.0)	2500 (1900, 3000.0)	0.89	0.642
Duration of anesthesia (min)	235.2 (195, 291.7)	245.0 (205, 284.0)	240.8 (200.6, 276.4)	1.61	0.448
Duration of operation (min)	185.5 (165.0, 230.5)	193.0 (174.8 251.5)	191.3 (169.4, 242.6)	0.84	0.538

Group A: zero end-expiratory pressure with low tidal volume ventilation; Group B: 5 cmH_2O PEEP with low tidal volume ventilation; Group C: individualized PEEP guided by driving pressure with low tidal volume ventilation. PEEP, positive end-expiratory pressure; ASA, American Society of Anesthesiologists; BMI, Body mass index.

Table 2. Lung ultrasound scores in the 0 cmH_2O PEEP, 5 cmH_2O PEEP, and individualized PEEP groups during surgery in patients with traumatic brain injury.

	A (n = 30)	B (n = 31)	C (n = 28)	H	*p*
T1	3.95 (2.80, 5.10)	4.65 (3.50, 5.80)	4.65 (3.50, 5.80)	0.354	0.838
T2	4.45 (3.30, 5.60)	4.25 (3.10, 5.40)	3.95 (2.80, 5.10)^{c}	7.560	0.005
T4	5.25 (4.10, 6.40)^{a}	3.75 (2.60, 4.90)^{b}	2.50 (1.35, 3.65)^{cA}	18.450	<0.001

Compared to the T1 group: $^{a; b; c}$ $p < 0.05$; Compared to Group A: ^{A} $p < 0.05$. T1: before induction of anesthesia; T2: immediately after PEEP titration; T4: at the end of surgery. Group A: zero end-expiratory pressure with low tidal volume ventilation; Group B: 5 cmH_2O PEEP with low tidal volume ventilation; Group C: individualized PEEP guided by driving pressure with low tidal volume ventilation.

piratory mechanics, and hemodynamics. All analyses were conducted in R (version 4.2.1, MSN, Redmond, WA, USA).

Results

Patient Enrollment and Demographics

A total of 111 patients were initially enrolled in the study. Eight patients refused to participate, and four were excluded due to preoperative findings of pulmonary lesions such as pleural effusion. The remaining 99 patients were randomly assigned to three groups. However, 10 patients either died due to injuries within one week or were discharged after surgery and abandoned further treatment, resulting in 89 patients completing the final analysis. The participant selection protocol was illustrated in Fig. 1. There was no statistically difference between groups in these demographic data (Table 1).

Lung Ultrasound Score (LUS) Changes during Surgery

LUS increased during surgery in Group A but decreased in Groups B and C. At T1, the LUS was significantly lower in Group A (3.95 [2.80, 5.10]) than at T4 (5.25 [4.10, 6.40]) ($p < 0.05$). However, Groups B and C showed significantly lower LUS at T4 than at T1 ($p < 0.05$). Notably, Group C had a significantly lower LUS at T4 (2.50 [1.35, 3.65]) compared to Group A (5.25 [4.10, 6.40]) ($p < 0.05$). No significant differences were observed between Groups B and A at T4 ($p > 0.05$) (Table 2).

Intraoperative Hemodynamic Indices and Respiratory Parameters

Compared to T1, PaO_2, $PaCO_2$, Cdyn, and MAP showed significant differences among Groups A, B, and C at T3 and T4 ($p < 0.05$). No significant differences among Groups A, B, and C were observed at T1 ($p > 0.05$). PaO_2 and Cdyn increased during surgery across all groups. However, Group C had significantly higher PaO_2 at T3 and T4 compared to Groups A and B. Cdyn was also significantly higher in Group C than in Group A at T4 ($p < 0.05$) (Table 3).

Postoperative Pulmonary Complications and Clinical Pulmonary Infection Score (CPIS)

Group C exhibited a significantly lower incidence of postoperative pulmonary atelectasis compared to Groups A and B ($p < 0.05$). No significant differences were found in the infection, hydrothorax, or emphysema among the groups ($p > 0.05$) (Table 4).

CPIS decreased significantly on postoperative days 3 and 7 compared to postoperative day 1 in all groups ($p < 0.05$). At T6, Group C had a significantly lower CPIS (1.45 [0.955,

Table 3. Oxygenation index and hemodynamic indexes in the 0 cmH_2O PEEP, 5 cmH_2O PEEP, and individualized PEEP groups during surgery in patients with traumatic brain injury.

		A (n = 30)	B (n = 31)	C (n = 28)	H	*p*
PaO_2	T1	219 (193, 246)	254 (228, 280)	257 (231, 283)	5.427	0.085
	T3	302 (276, 329) [a]	333 (307, 360) [b]	365 (339, 391) [cAB]	9.424	0.005
	T4	355 (329, 381) [a]	398 (371, 424) [bA]	421 (395, 447) [cAB]	12.631	0.002
$PaCO_2$	T1	42.8 (41.1, 44.5)	43.8 (42.2, 45.5)	44.5 (42.8, 46.2)	2.199	0.36
	T3	40.4 (38.7, 42.1) [a]	39.1 (37.4, 40.8) [b]	37.8 (36.1, 39.5) [c]	0.978	0.542
	T4	37.8 (36.1, 39.5) [a]	37.1 (35.4, 38.8) [b]	36.0 (34.3, 37.7) [c]	2.155	0.316
Cdyn	T1	37.6 (36.7, 38.4)	38.0 (37.1, 38.8)	37.5 (36.6, 38.3)	0.127	0.706
	T3	40.7 (39.8, 41.5) [a]	41.9 (41.0, 42.8) [b]	42.1 (41.2, 43.0) [ABc]	6.781	0.049
	T4	41.8 (40.9, 42.7) [a]	43.1 (42.2, 44.0) [bA]	44.0 (43.1, 44.8) [ABc]	12.657	0.004
MAP	T1	105.4 (100.0, 110.8)	109.3 (103.8, 114.7)	104.5 (99.1, 109.9)	1.225	0.434
	T3	85.7 (80.3, 91.2) [a]	80.5 (75.1, 85.9) [b]	82.4 (76.9, 87.8) [c]	1.667	0.395
	T4	89.3 (83.9, 94.7) [a]	83.1 (77.7, 88.5) [b]	83.6 (78.1, 89.0) [c]	3.099	0.211

Compared to the T1 group: [a; b; c] $p < 0.05$; Compared to the Group A: [A] $p < 0.05$; Compared to the Group B: [B] $p < 0.05$; T1: before induction of anesthesia; T3: 60 minutes after the start of surgery; T4: at the end of surgery. Group A: zero end-expiratory pressure with low tidal volume ventilation; Group B: 5 cmH_2O PEEP with low tidal volume ventilation; Group C: individualized PEEP guided by driving pressure with low tidal volume ventilation. PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure; Cdyn, dynamic lung compliance; MAP, mean arterial pressure.

Table 4. Pulmonary complications in the 0 cmH_2O PEEP, 5 cmH_2O PEEP, and individualized PEEP groups after surgery in patients with traumatic brain injury [n (%)].

		A (n = 30)	B (n = 31)	C (n = 28)	χ^2	*p*
Infection	Yes	12 (40.0%)	11 (35.5%)	7 (25.0%)	1.525	0.466
	No	18 (60.0%)	20 (64.5%)	21 (75.0%)		
Hydrothorax	Yes	19 (63.3%)	20 (64.5%)	15 (53.6%)	0.873	0.646
	No	11 (36.7%)	11 (35.5%)	13 (46.4%)		
Atelectasis	Yes	14 (46.7%)	3 (9.7%)	1 (3.6%)[AB]	19.951	<0.001
	No	16 (53.3%)	28 (90.3%)	27 (96.4%)		
Emphysema	Yes	3 (10.0%)	6 (19.4%)	2 (7.1%)	2.258	0.323
	No	27 (90.0%)	25 (80.6%)	26 (92.9%)		

[A] $p < 0.05$ when compared to the Group A; [B] $p < 0.05$ when compared to the Group B; Group A: zero end-expiratory pressure with low tidal volume ventilation; Group B: 5 cmH_2O PEEP with low tidal volume ventilation; Group C: individualized PEEP guided by driving pressure with low tidal volume ventilation.

1.95]) compared to Group A (2.80 [2.305, 3.30]) ($p < 0.05$), but no significant difference was observed between Group B and Group A ($p > 0.05$). At T7, CPIS was significantly lower in both Groups B (1.55 [1.055, 2.05]) and C (1.10 [0.605, 1.60]) compared to Group A (2.40 [1.905, 2.90]) ($p < 0.05$) (Table 5).

Intraoperative Optic Nerve Sheath Diameter (ONSD) Analysis

Significant differences in ONSD were observed among Groups A, B, and C before anesthesia induction (T1) and at the end of surgery (T4) ($p < 0.05$). In Group A, the ONSD increased from 4.92 [4.74, 5.10] before induction to 5.02 [4.84, 5.20] after PEEP titration (T2), whereas no significant changes were observed in Groups B and C ($p > 0.05$) (Table 6).

Variations in Serum Nerve Damage Indicators

Compared to the T0, HMGB1 and NSE expression levels decreased significantly at T5 and T6 in all three groups ($p < 0.05$) (Tables 7,8). Compared to group A, HMGB1 serum levels in group B and C decreased significantly at T5 and T6 ($p < 0.05$). Compared to group B, HMGB1 serum levels in group C decreased significantly at T5 and T6 ($p < 0.05$) (Table 7). Group C showed a more significant reduction in NSE on the first (4.40 [3.89, 4.41]) and third (2.79 [2.28, 3.30]) postoperative days ($p < 0.05$). Compared to Group A and Group B, NSE serum levels in Group C decreased significantly at T5 and T6 ($p < 0.05$) (Table 8).

Table 5. Clinical pulmonary infection score in the 0 cmH_2O PEEP, 5 cmH_2O PEEP, and individualized PEEP groups after surgery in patients with traumatic brain injury.

	A (n = 30)	B (n = 31)	C (n = 28)	H	*p*
T5	3.45 (2.955, 3.95)	3.40 (2.905, 3.90)	3.00 (2.505, 3.50)	1.509	0.47
T6	2.80 (2.305, 3.30) [a]	2.15 (1.655, 2.65) [b]	1.45 (0.955, 1.95) [cA]	18.34	<0.001
T7	2.40 (1.905, 2.90) [a]	1.55 (1.055, 2.05) [bA]	1.10 (0.605, 1.60) [cA]	20.49	<0.001

Compared to the T5 group: [a; b; c] $p < 0.05$; Compared to the Group A: [A] $p < 0.05$. T5: postoperative day 1; T6: postoperative day 3; T7: postoperative day 7. Group A: zero end-expiratory pressure with low tidal volume ventilation; Group B: 5 cmH_2O PEEP with low tidal volume ventilation; Group C: individualized PEEP guided by driving pressure with low tidal volume ventilation.

Table 6. Optic nerve sheath diameter (mm) in the 0 cmH_2O PEEP, 5 cmH_2O PEEP, and individualized PEEP groups during surgery in patients with traumatic brain injury.

	A (n = 30)	B (n = 31)	C (n = 28)	H	*p*
T1	4.92 (4.74, 5.10)	4.99 (4.81, 5.17)	5.02 (4.83, 5.20)	0.593	0.743
T2	5.02 (4.84, 5.20)	4.99 (4.81, 5.17)	5.02 (4.83, 5.20)	0.086	0.958
T4	5.16 (4.97, 5.34) [a]	5.10 (4.92, 5.28) [b]	5.09 (4.90, 5.27) [c]	1.02	0.6
p	<0.001	<0.001	0.002		

Compared to the T1 group: [a; b; c] $p < 0.05$. T1: before induction of anesthesia; T2: immediately after PEEP titration; T4: at the end of surgery. Group A: zero end-expiratory pressure with low tidal volume ventilation; Group B: 5 cmH_2O PEEP with low tidal volume ventilation; Group C: individualized PEEP guided by driving pressure with low tidal volume ventilation.

Discussion

In this randomized controlled study, the individualized PEEP guidance group exhibited a notable reduction in LUS readings post, surgery, specifically displaying a significant decrease in LUS at T4. A comprehensive analysis of intraoperative respiratory parameters and hemodynamic indicators revealed that Group C demonstrated elevated PaO_2 and Cdyn values compared to Group A at T3 and T4. Moreover, Group C exhibited a significantly higher Cdyn than Group A at T4. Subsequently, we conducted a thorough examination of postoperative patient data. Remarkably, Group C exhibited a substantially lower incidence of postoperative lung atelectasis than the other two groups, coupled with a gradual decrease in postoperative CPIS values. Concurrently, intraoperative ONSD monitoring revealed higher ONSD readings at T4 than at T1 across all three groups. Lastly, we observed a prominent reduction in the serum expression level of NSE at T5 and T6 for Group C. Additionally, Group C showcased a remarkable decline in the serum expression level of HMGB1 at T5.

In clinical outcomes associated with lung-protective ventilation strategies, driving pressure has emerged as a pivotal determinant, owing to its profound reflection of overall lung compliance [28, 29]. Notably, meticulously guided by minimal driving pressure, individualized PEEP has demonstrated significant efficacy in mitigating postoperative atelectasis after open upper abdominal surgery. This approach not only enhances oxygenation but also effectively diminishes the incidence of PPC [30]. However, in contrast to studies of open lung approaches, it is clear that while open lung approaches (titrated PEEP based on maximal respiratory compliance) have the potential to reduce airway driving pressures, there is also significant potential for harm. In a well, known ARDS trial, an aggressive open lung strategy increased 28-day all-cause mortality compared with conventional protective ventilation due to pneumatic pressure injuries and increased hemodynamic instability. In contrast, we hypothesized that postoperative pulmonary complications were reduced in the driven pressure group because patients were ventilated according to their "functional lung size". "Functional lung size" is the volume of the inflated lung that can be used for tidal ventilation. Both are more detrimental than the functional size of overinflated (pneumoconiosis) or underventilated (atelectasis) lungs. Respiratory system static compliance (CRS) is highest when the lung is ventilated according to its functional lung size. Driving pressure is defined as VT/CRS. Therefore, ventilation at the lowest driving pressure is the best way to ventilate a patient according to the patient's "functional lung size" while avoiding underinflation or overinflation. LUS is effective in assessing pulmonary resuscitation endpoints and optimal PEEP during mechanical ventilation in patients with ARDS, with results comparable to those obtained using chest CT, and has been identified as an accurate and repeatable assessment of patient lung ventilation in recent study [31]. Furthermore, lung ultrasonography has been used to successfully titrate PEEP in laparoscopic obese patients, enhancing patient oxygenation and pulmonary compliance and decreasing the occurrence of postoperative pulmonary atelectasis and hypoxia

Table 7. HMGB1 in the 0 cmH_2O PEEP, 5 cmH_2O PEEP, and individualized PEEP groups of patients with traumatic brain injury.

	A (n = 30)	B (n = 31)	C (n = 28)	H	*p*
T0	643 (614, 672)	638 (609, 667)	662 (633, 691)	1.12	0.546
T5	443 (414, 472) [a]	362 (333, 391) [bA]	229 (200, 258) [cAB]	16.35	<0.001
T6	335 (306, 364) [a]	260 (231, 289) [bA]	166 (137, 195) [cAB]	18.21	<0.001
p	<0.001	<0.001	<0.001		

Compared to the T0 group: [a; b; c] $p < 0.05$; Compared to the Group A: [A] $p < 0.05$; Compared to the Group B: [B] $p < 0.05$; T0: admission to operating room; T5: postoperative day 1; T6: postoperative day 3. Group A: zero end-expiratory pressure with low tidal volume ventilation; Group B: 5 cmH_2O PEEP with low tidal volume ventilation; Group C: individualized PEEP guided by driving pressure with low tidal volume ventilation. HMGB1, High mobility group box 1 protein.

Table 8. NSE levels in the 0 cmH_2O PEEP, 5 cmH_2O PEEP, and individualized PEEP groups after surgery in patients with traumatic brain injury.

	A (n = 30)	B (n = 31)	C (n = 28)	H	*p*
T0	11.27 (10.76, 11.78)	10.79 (10.28, 11.30)	10.95 (10.44, 11.46)	1.209	0.489
T5	5.79 (5.28, 6.30) [a]	5.75 (5.24, 6.26) [b]	4.40 (3.89, 4.41) [cAB]	16.48	<0.001
T6	3.57 (3.06, 4.08) [a]	3.35 (2.84, 3.86) [b]	2.79 (2.28, 3.30) [cAB]	18.92	<0.001
p	<0.001	<0.001	<0.001		

Compared to the T0 group: [a; b; c] $p < 0.05$; Compared to the Group A: [A] $p < 0.05$; Compared to the Group B: [B] $p < 0.05$; T0: admission to operating room; T5: postoperative day 1; T6: postoperative day 3. Group A: zero end-expiratory pressure with low tidal volume ventilation; Group B: 5 cmH_2O PEEP with low tidal volume ventilation; Group C: individualized PEEP guided by driving pressure with low tidal volume ventilation. NSE, neuron-specific enolase.

[32]. Therefore, we used bedside lung ultrasonography to guide driving pressure and determine the appropriate PEEP.

Compared to group A, wherein LUS notably decreased by the conclusion of the surgery, group C exhibited a continuous reduction in LUS throughout the entire surgical procedure. These observations imply that individualized PEEP can effectively enhance intraoperative lung ventilation. This enhancement is further underscored by the analysis of respiratory parameters, with group C displaying significantly elevated intraoperative PaO_2 and Cdyn values compared to group A at both T3 and T4. Furthermore, the Cdyn at T4 significantly increased compared to group A. Remarkably, the incidence of postoperative atelectasis was markedly lower in group C than in the remaining two groups, consistent with findings from prior research endeavors. Notably, a study focusing on elderly patients undergoing laparoscopic surgery unveiled that the LUS score in the PEEP, adjusted group significantly surpassed that of both the fixed PEEP and conventional ventilation groups. This improvement in LUS scores translated to enhanced respiratory mechanics and a reduced prevalence of postoperative atelectasis [33]. Consequently, our clinical findings offer robust support for utilizing individualized PEEP guided by driving pressure within lung-protective ventilation strategies.

On the other hand, secondary lung injury in TBI can exacerbate neurological damage through hypoxia and intracranial hypertension, establishing a detrimental cycle [34]. This intricacy presents a formidable challenge in the anesthesia management of TBI. The utilization of PEEP for pulmonary protective ventilation during cranial surgery remains contentious due to its potential to elevate intrathoracic pressure and hinder central venous return, thereby exacerbating ICP elevation. Consequently, study has recommended maintaining PEEP at minimal or low levels ($\leq$5 cmH_2O) when managing mechanically ventilated patients with brain injuries [35]. Previous investigations infrequently employed protective pulmonary ventilation in neurosurgery due to concerns regarding increased intracranial pressure stemming from low TV and PEEP application [36]. However, a recent small randomized clinical trial in patients undergoing elective neurosurgery demonstrated no significant difference in ICP between the traditional and protective ventilation groups. Moreover, all patients in the protective ventilation group could undergo surgery for dura mater tension [37]. Our findings align with this study, as we identified no substantial variance in intracranial pressure among the three groups. These results thus robustly support the secure implementation of driving pressure, targeted PEEP in neurosurgical procedures.

The measurement of ONSD allows for real, time and noninvasive ICP monitoring [38, 39]. Gupta *et al*. [40] explored the correlation between PEEP and ICP in TBI patients using ONSD and discovered that increasing PEEP from 0 to

10 cmH_2O did not lead to a significant rise in either ONSD or ICP; in contrast, Balakrishnan's study indicated a notable increase in ONSD with an elevation of PEEP from 5 to 10 cmH_2O [41]. Our mixed, effects model analysis revealed a slight upward trend in ONSD across all three groups over time, yet no significant differences were observed simultaneously. As such, PEEP appears to have no direct correlation with ICP within a specific range. This outcome could be attributed to several factors: (1) PEEP only influences ICP when it induces a significant increase in $PaCO_2$ [42]; However, in our study, the employed PEEP levels did not lead to elevated perioperative $PaCO_2$ levels. (2) Given that nearly all TBI patients necessitate urgent surgery, the duration of maintained PEEP during breathing is insufficient to prompt changes in ONSD. Additionally, Gupta *et al*. [40] observed a marked increase in ONSD and ICP when PEEP was raised from 10 to 15 cmH_2O. Furthermore, Nemer *et al*. [43] investigated the impact of high PEEP levels on ICP and cerebral perfusion pressure (CPP) in TBI patients, concluding that a PEEP of 10 cmH_2O was safe and did not result in a significant ICP elevation. Therefore, our study set the maximum titrated PEEP at 10 cmH_2O.

NSE is a glycolytic enolase isoenzyme primarily localized within neuronal cytoplasm and neuroendocrine cells [44]. It serves as a recognized biomarker for nerve injury, with its levels correlating with injury severity [45]. At the studies' commencement, NSE levels in the three TBI patient groups were within the concentration range reported in the literature [46, 47]. The elevation in NSE within the bloodstream following nerve injury, coupled with reperfusion injury, induced positive feedback and an exacerbating inflammatory immune response on compromised neurons, may contribute to this observation. Additionally, the NSE expression progressively declined over time. Comparatively, the reduction in NSE expression levels was more pronounced in the individualized PEEP group on the first postoperative day and the third day as opposed to the control group. This effect can be attributed to the intraoperative LPVS, which sustained alveolar oxygen partial pressure and curtailed potential neurological harm from hypoxia, induced pulmonary, brain syndrome. Consequently, a driven pressure, guided, individualized PEEP approach holds promise in safeguarding the brain among TBI patients.

HMGB1, a nuclear DNA, binding protein, is pivotal in DNA transcription stimulation and ribosome structure maintenance [48]. Its recognition as a potent pro, inflammatory mediator in sepsis patients dates back to its initial identification [49]. The release of HMGB, 1 into the bloodstream has been demonstrated to manifest shortly after trauma, peaking as early as 2–6 hours post, injury. Our findings align with these outcomes, as HMGB1 expression peaked upon admission, marking the early post, trauma period, across all three TBI patient groups. Over time, a gradual decline in HMGB1 expression level becomes evident [50]. Employing personalized PEEP, HMGB1 expression levels displayed a more pronounced downward trajectory on the first postoperative day and the third day, contrasting with the control group. Using anti, HMGB1 antibodies in trauma animal models has exhibited the ability to diminish pro, inflammatory cytokine levels and attenuate post, injury organ dysfunction, including acute lung injury stemming from hemorrhagic shock [51, 52]. In parallel, Ogawa *et al*. [53] demonstrated in a rabbit model of mechanical ventilation, induced lung injury that obstructing endogenous HMGB1 resulted in enhanced oxygenation, reduced microvascular permeability, and limited inflow of neutrophil granulocytes into the alveolar lumen. Consequently, our hypothesis postulated that individualized PEEP guided by driving pressure could elevate perioperative pulmonary oxygenation, curtail cranial injury severity, and reduce plasma HMGB1 expression levels, lowering postoperative pulmonary complications. Further research is thus warranted to validate the underlying mechanisms.

Nonetheless, our study encompasses several limitations. Primarily, the utilized sample size necessitates expansion, warranting a follow, up multicenter investigation surrounding a larger cohort to substantiate the obtained results. Secondly, the spacing of measurement time points in our study was closely situated, effectively capturing short, term changes, while the postoperative intensive care unit phase implemented varied ventilation methods. Consequently, the findings might inadequately encompass the comprehensive and scientific impact of intraoperative lung protective ventilation (LPV) strategies on brain and lung function in TBI patients. Thus, subsequent studies should strive to standardize ventilation techniques and augment monitoring time points. Lastly, while our current research monitored serological indicators around the perioperative period of TBI patients, the monitored indicators were limited to a solitary aspect. Notably, HMGB1 typically exhibits heightened activity only in tandem with pro-inflammatory factors. Hence, forthcoming investigations should encompass monitoring pro-inflammatory factors (cytokines) in conjunction with HMGB1 to offer a more comprehensive perspective.

Nonetheless, our study has several limitations. Firstly, the sample size used in this study requires expansion. A follow-up multicenter investigation with a larger cohort is needed to validate the results. Secondly, the time intervals for measurement in our study were closely spaced, which effectively captured short-term changes. However, during the postoperative intensive care unit phase, various ventilation methods were employed. As a result, the findings may not fully reflect the broader and more scientific impact of intraoperative LPVS on both brain and lung function in patients with TBI. Therefore, future studies should aim to standardize ventilation techniques and extend the monitoring periods. Additionally, this study involved multiple comparisons across different outcomes. Although no formal adjustments for multiple comparisons were made, we acknowledge the possibility of inflating Type I error rates.

The primary endpoints were predefined, and we concentrated on clinically significant outcomes to minimize the risk of false-positive findings. Nevertheless, the secondary outcomes should be interpreted with caution, as there remains a risk of Type I errors. Lastly, while we monitored serological markers during the perioperative period in TBI patients, these markers were limited to a single category. Notably, HMGB1 tends to show significant activity only in the presence of pro-inflammatory factors. Therefore, future research should include the monitoring of pro-inflammatory cytokines alongside HMGB1 to provide a more comprehensive understanding.

In summary, our study focuses on a drive pressure-guided individualized PEEP strategy tailored to optimize lung protection and neurological outcomes in TBI patients. Continuous monitoring and dynamic adjustments based on real, time clinical parameters are central to this approach. The primary and secondary endpoints provide a robust framework for evaluating the efficacy and safety of the intervention.

Conclusions

Individualized PEEP with drive pressure-guided titration is practical for patients with TBI who are scheduled to undergo emergency surgery. This approach could improve the patient's perioperative pulmonary oxygenation function and the occurrence of postoperative pulmonary complications to some extent. Moreover, the patients showed no significant ICP elevation intraoperatively, and the postoperative serological index suggested that this strategy was more conducive to recovery from postoperative neurological injury. The mechanism may be related to reduced inflammatory response.

Availability of Data and Materials

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

Author Contributions

XPC, ZW and JG designed the research study. XPC and JG performed the research. YLG and LQY provided help and advice on the ELISA experiments. ZW analyzed the data. XPC drafted this manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Written informed consent was obtained from patients with TBI undergoing emergency craniocerebral surgery after receiving approval from the Northern Jiangsu People's Hospital, (2019-KY180-1). If the patient was unconscious, written consent was obtained from the patient's relatives according to local regulations. The study is in accordance with The Declaration of Helsinki. The study adhered to the guidelines outlined in the Consolidated Standards of Reporting Trials (CONSORT).

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Conflict of Interest

The authors declare no conflict of interest.

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