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Effect of positive end-expiratory pressure on intracranial pressure in post cranial surgery using ultrasonic imaging measurement the optic nerve sheath diameter

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ABSTRACT:

Background: While positive end-expiratory pressure (PEEP) is beneficial for oxygenation, it may potentially increase intracranial pressure (ICP): especially in post-cranial surgical patients. The optic nerve sheath diameter (ONSD) is the non-invasive method of ICP measurement. Our study focuses on the association between PEEP and intracranial pressure (ICP) in post-cranial surgery patients using optic nerve sheath diameter (ONSD) as a surrogate marker.

Method: A prospective non-randomized interventional study was conducted on post-cranial surgical patients who required mechanical ventilation with ages 16-80 years, initial PEEP at 5 mmH_2O were included in this study. Patients with intracranial hypertension (defined as ICP ≥22 mmHg), a history of traumatic brain injury, or cardiopulmonary disease at enrollment were excluded from the study. ONSD measurement was performed at varying PEEP levels from 5 to 20 cmH_2O.

Result: In adult (18-60 years) patients who had post-cranial surgery within 72 hours and required a mechanical ventilator, ONSD corresponding to ICP significantly increased when PEEP exceeded 13 cmH_2O. PEEP more than 15 cmH_2O resulted in a significant increase in ONSD exceeding 5.5 mm (corresponding to ICP > 22 mmHg); Mean arterial pressure (MAP) significantly decreased with an increase in PEEP value ($p < 0.001$). PEEP 20 cmH_2O reduced MAP to below 65 mmHg.

Conclusion: PEEP less than 15 cmH_2O can be safely applied to post-cranial surgical patients, whereas PEEP more than 20 cmH_2O may be harmful due to both ICP elevation and MAP decrement for these patients.
Keyword: Positive end-expiratory pressure, intracranial pressure, Optic nerve sheath diameter, post cranial surgery

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INTRODUCTION

Surgery in the cranial cavity through craniotomy is the most common procedure in neurosurgery. The other procedures are craniectomy or endoscopic surgery. [1, 2] The average number of craniotomies performed is 475 cases per year in a single hospital in the United States. [3] Bhumibol Adulyadej Hospital performs an average of 600 surgeries each year, including procedures for brain injuries from accidents, intracranial bleeding, tumors, and brain infections [4]. All pathologies within the cranial cavity can potentially elevate the risk of increased intracranial pressure (ICP), particularly in cases of traumatic brain injury, where the mortality rate rises from 17% to 47%.[5]

Monitoring ICP is essential for patient safety and effective treatment, and there are various methods of ICP monitoring that can be used, however, no single method has proven to be the best. [6] Currently, the most widely used is the direct ICP measurement technique, by inserting a pressure monitoring catheter directly into the cranial cavity for continuous pressure measurement. While the direct ICP is the most effective, it does have the significant limitations and complications associated with invasive monitoring, such as bleeding and infection. [7]

The measurement of ICP by using ultrasound to assess the optic nerve sheath diameter (ONSD) has become a prominent method over the past decade, with a diagnostic sensitivity of 94%, specificity of 98%, and AUC of 0.97. [8] Even though there are some limitations, such as operator dependence or baseline optic nerve size, this technique is non-invasive, cost-effective, and can be performed feasibly in any patient care units. [9]

Respiratory complications are common in patients with brain injuries, affecting approximately 20% of patients following brain trauma and post-cranial surgery. These include acute respiratory distress syndrome (ARDS), ventilator-associated pneumonia, and neurogenic pulmonary edema. [10] Patients experiencing these issues result in worse prognoses compared to those without such complications. Proper positive end-expiratory pressure (PEEP) must be provided to guarantee effective gas exchange in the lungs. [11]

Elevating PEEP may result in a negative impact on intracranial pressure. Research on patients with severe head injuries, particularly those with a Glasgow Coma Score (GCS) below 8, reveals a troubling trend. When PEEP exceeds 10 cmH_2O, ICP may exceed 20 mmHg. [12] This alarming increase in ICP not only results in prolonged hospital stays but is also associated with increasing mortality. [13]

Cranial surgeries involving craniotomy, craniectomy, or even an endoscopic approach are all at risk of elevated ICP, influenced by both the brain disease conditions and the diverse complications of surgical procedures. Several studies clearly demonstrate a significant link between increased ICP and PEEP level in patients with head injuries [12]. A significant knowledge gap remains in those undergoing craniotomies without brain injuries. The differing pathophysiological conditions in these patient groups suggest that PEEP may have varying effects on ICP, particularly in cases such as intracerebral hemorrhage. So, it's crucial to determine the specific level of PEEP required to elevate ICP above the critical threshold of 20 to 22 mmHg [14] in post-cranial surgical patients.

Research on PEEP level is essential for patients with pulmonary complications. It is critical to guarantee effective gas exchange of oxygen and carbon dioxide after cranial surgery. The findings of this study could be pivotal in establishing safe PEEP levels, ultimately safeguarding the outcomes of post-cranial surgical patients. Understanding how to balance respiratory support with neurological safety can enhance patient care and significantly reduce the risk of adverse effects after surgery.

KEY MESSAGES:

- PEEP can enhance oxygenation but may increase ICP in patients following cranial surgery. The relationship between PEEP and ICP can be assessed using the ONSD to determine safe PEEP levels.
- ONSD measurement is significantly correlated with PEEP increments.
- PEEP less than 15 cmH2O can be safely used in patients following cranial surgery.
- A safe PEEP is crucial for balancing cerebral oxygen delivery, venous return, and cardiac preload. Prioritizing respiratory support and neurological safety enhances patient care and minimizes postoperative complications.

MATERIALS AND METHODS

This study is a non-randomized prospective intervention study being conducted at Bhumibol Adulyadej Hospital. Patients underwent screening and were recruited between January and March 2025 in our neurosurgical ICU. The inclusion and exclusion are specified and prescribed with the sentence bellow.

Inclusion criteria

1. Adult intensive care patients aged 18 to 60 years
2. Required mechanical ventilation
3. Within 72 hours after postcranial surgery

Exclusion criteria

1. History of traumatic brain injury or post-cranial surgery or eye globe within 3 months
2. Pregnancy: Non-pregnancy confirmed by patient having a negative urine or plasma hCG or being postmenopausal, defined as females at 60 years old or beyond or at the investigator's discretion.
3. Known increased intracranial pressure: Defined by direct ICP monitoring exceeding 22 mmHg or non-invasive measurement ultrasound ONSD exceeding 5.5 mm.
4. The underlying condition is increased eye globe pressure, especially glaucoma or a suspected abnormality in the anatomy and function of the eye.

5. Respiratory failure is defined as having an SpO_2 level of less than 94% with an FiO_2 greater than 0.4, or an $EtCO_2$ level greater than 45 mmHg.
6. Cardiovascular instability is defined as mean arterial pressure below 65 mmHg or heart rate below 50 BPM or exceeding 120 BPM.
7. Allergic reaction to midazolam
8. Already receiving PEEP more than 15 cm H_2O
9. Abnormalities of the cranial vault ,e.g., congenital skull disease, post-operative craniectomy
10. Previously included in another trial
11. Informed consent cannot be obtained from patients where the treating physician or investigator was unable to obtain the necessary consent.

The researcher is responsible for providing comprehensive explanations of the research procedures, apprising patients and/or their relatives of potential side effects and how to safely treat all of the complications, and obtaining informed consent before the cranial operation will perform.

Sample size and calculation

Based on the review of literature [13] and research related to the "correlation of positive end-expiratory pressure and intracranial pressure using ultrasonographic-guided measurement of optic nerve sheath diameter in traumatic brain injury patients", the study found that the size of the optic nerve sheath and intracranial pressure significantly increased when the positive end-expiratory pressure was elevated in patients with severe head injuries at a level of 15 cmH_2O. The sample size was determined using power analysis through G*power 3 (Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A., 2007), with a test power set at 30, a confidence level of 0.05, and an effect size of 0.80, referring to a confidence level of 0.05 and a test power of 0.80.

The power of the test is determined from a sample size of 30 samples based on the reviewed research above. A minimum sample size of 29 is required, so the researcher increased the sample size by 5%, resulting in a total sample size of 30.

After recruiting 60 patients, cranial surgery was performed. The 33 patients were excluded because they could not initiate the intervention within 72 hours postoperatively, as Figure 1 shows. Then 27 patients were in the study protocol.

Intervention protocol

Enrolled patients received the incremental PEEP from a mechanical ventilator used in neurosurgery intensive care units. The mechanical ventilator (Event Inspiration LS® model) was set in volume control mode, tidal volume was 6-8 cmH_2O per kilogram of predicted body weight, oxygen concentration (FiO_2) was between 0.3 and 0.4, respiratory rate was 14 to 16 breaths per minute, and PEEP was as specified in the research methodology. The setting of a mechanical ventilator depends on oxygen saturation (SpO_2) more than 95% and end-tidal carbon dioxide ($EtCO_2$) between 30 and 45 mmHg. The intervention must begin within 72 hours postoperatively.

Protocol for PEEP adjustment, ONSD measurement and data collection

After sedation with intravenous midazolam to keep the Richmond Agitation Assessment Score (RAAS) at 0 to -1, the initial PEEP setting was at 5 cmH_2O for 2 minutes, and ONSD was measured by a 7.5-MHz linear-array probe ultrasound machine (Venue GO GE®). Then stepwise PEEP titration every 2 minutes to be 8, 10, 13, 15, 18, and 20 cmH_2O. The timing of intervention and measurement was about 15 minutes. It is crucial to wait for 2 minutes after each PEEP adjustment before performing the ONSD measurement in order to allow the effects of the positive pressure from the mechanical ventilator to stabilize (Figure 2).

All ultrasound measurements were performed by a single operator, who was experienced and trained in ONSD measurement for 1 year. A training session for the operator, who is the researcher, will be conducted to measure patients in the intensive care unit at Bhumibol Adulyadej Hospital. A total of 50 patients will be measured during the period of May to August 2024. The validity of measurement

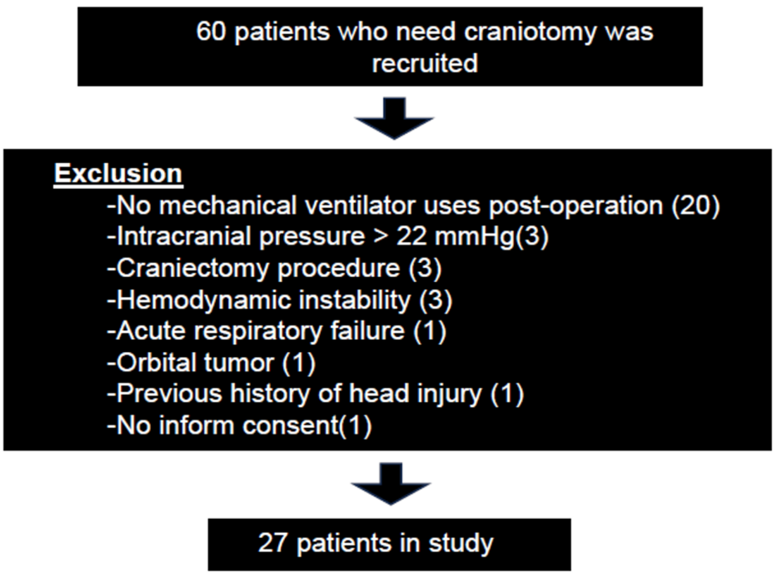


Figure 1. Screening and eligible patients' protocol.

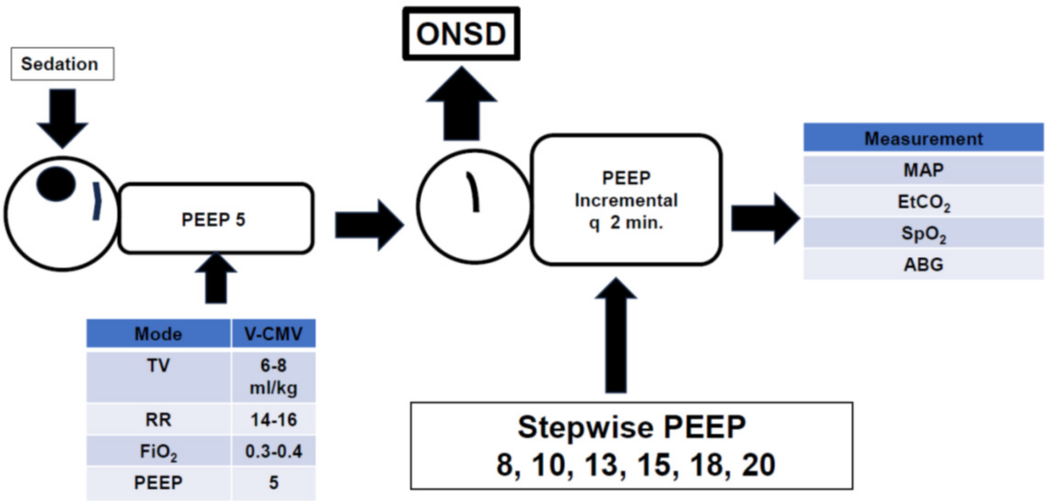


Figure 2. Study protocol.

is 0.85, as indicated by the coefficient of consistency, which is compared to one experienced neuro-intensivist. This is to assess whether the measurement results obtained from the training are consistent with the established repetitive and precise measurement ONSD protocol.

Measurement protocol

The patient lies in a supine position without an elevated head of bed (0-degree angle). Their right eyes are covered with Tegaderm® dressings. The probe is positioned at the lower inner corner of the right eye. It is then moved upward and outward from the inside of the orbit until an axial cross-sectional view of the orbit is obtained, then turned 90 degrees to change the axial view to a longitudinal view of ONSD (Figure 3). The probe is adjusted to visualize the starting point of the optic nerve from the posterior margin of the eyeball at a depth of 4-5 centimeters. The ONSD view protocol has image brightness (gain) adjusted to create a hypoechoic posterior chamber, with a well-defined black vitreous humor and a white lens of the eyeball (Figure 3). The ONSD must be measured perpendicularly from 3 mm from the posterior edge of the eye globe (Figure 4).

Complication prevention and management from the PEEP incremental procedure

The investigator collected demographic data from all participants. These include gender, age, neurological disorders, past medical history, brain function in Glasgow Coma Score (GCS), respiratory system, cardiovascular system, vital signs, SpO_2, $EtCO_2$, arterial gas analysis results, etc. Vital signs, SpO_2, $EtCO_2$, direct ICP monitoring, and ONSD measurements were continuously monitored and recorded during each PEEP level. The measurement was performed when hemodynamic, gas exchange, and ventilation parameters were most stable.

The values obtained from the ONSD are recorded in millimeters (mm) with one decimal place. A measured diameter less than 5.0 mm indicates intracranial pressure below 20 mmHg, while an optic nerve sheath diameter greater than 5.5 mm indicates intracranial pressure below

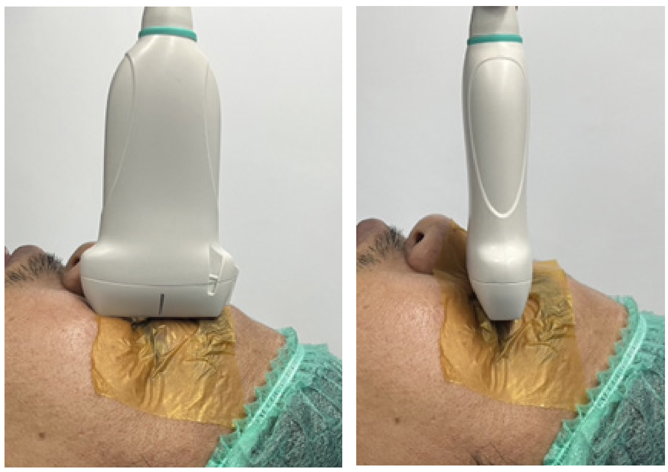


Figure 3. ONSD Measurement by using Reproducible ultrasound measurement protocol.

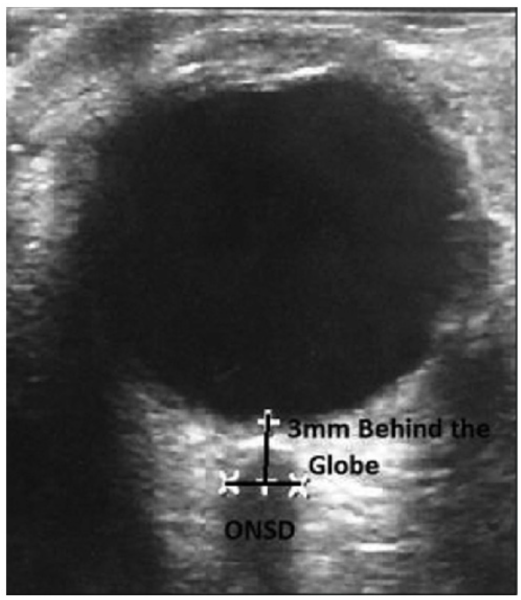


Figure 4. The ONSD view protocol shows the lens, eye globe, and methods of the ONSD measurement.

22 mmHg. Whereas an optic nerve sheath diameter of 6.0 mm indicates intracranial pressure of 25 mmHg, and an optic nerve sheath diameter of 7.0 mm indicates intracranial pressure of 30 mmHg [15]. So, if a participant's ONSD is greater than 5.5 mm at the baseline or greater than 7.0 mm during intervention, all interventions must be terminated.

If the ONSD does not increase above 7 mm or ICP does not exceed 30 mmHg, and vital signs and gas exchange results remain stable over a testing period of approximately 2 minutes per PEEP level, close continuous monitoring must take place for 6 hours after the test is completed. If potential complications such as increased intracranial pressure, hemodynamic instability, or abnormal gas exchange occur for more than 5 minutes, participants will have their PEEP discontinued, a standardized ICP management protocol will apply, and they will receive an emergency computed tomography (CT) brain scan followed by a neurosurgical consultation.

In the event of severe complications resulting from the research, such as cardiopulmonary failure (defined with exclusion criteria), participants must receive treatment according to standards and may be withdrawn from the study. Participants are allowed to withdraw from the research at any time. If a participant is unable to express their wish to withdraw due to severe complications, the researchers will request that the participant immediately leave the experiment. Patients were continuously observed in the ICU for a minimum of 72 hours. Pre-specified or any serious adverse events were reported to the Bhumibol Adulyadej Hospital Ethics Committee of Human Research. All data and variables, including all patients' outcomes, were recorded into an electronic case report using Microsoft Excel 2021 for further analysis.

Statistical analysis

Statistical analyses were conducted using STATA version 17 (Stata Corp LLC, College Station, TX, USA). The primary analysis included all relevant data. The threshold for statistical significance was set at 0.05, and all tests were conducted as one-sided.

Categorical variables, such as gender, underlying medical conditions, and the specific conditions treated during surgery, were summarized as frequencies and percentages. Continuous variables were presented as means and standard deviations.

The primary outcome was the relationship between PEEP and ONSD measurements, controlling for MAP, analyzed using partial correlation coefficients.

Secondary outcomes included the relationships between increased PEEP and SpO_2, $EtCO_2$, heart rate, and blood pressure, which were assessed using Pearson's correlation coefficient.

Comparisons between two groups were performed using independent two-tailed t-tests. For comparisons involving more than two groups, one-way analysis of variance (ANOVA) was employed. A p-value < 0.05 was considered statistically significant.

Ethics approval

The Bhumibol Adulyadej Hospital Ethics Committee and Human Research approved this study on February 10, 2025. The Institutional Review Board number is IRB4/68 and the registration with Thai Clinical Trial Registry number is TCTR20250404002.

RESULTS

The baseline demographic profile, including age, gender, BMI, level of consciousness, and respiratory function, was presented with means and standard deviations in the samples. The open surgery group: craniotomy accounted for 74.1%, while the endoscopic surgery group constituted 23%.

The cut-off point for lesion size is set at 30 mL due to the critical harm associated with increased intracranial pressure and the difficulties in surgical operation related to the size of the lesion. [16] 59% of patients enrolled are in these categories. Finally, the main type of lesion in our sample is brain tumors, comprising 75% of cases; the others are spontaneous intracerebral hematomas (Table 1).

The baseline respiratory evaluations (CXR and ABG) of all enrollments were normal.

Effect of PEEP to ONSD

A significant positive correlation was found between the ONSD and PEEP. Pearson's correlation coefficient is 0.790, statistically significant (Figure 5).

We indicated that PEEP level 13 shows a stronger positive correlation than those below PEEP level 13 cmH_2O (Figure 6).

A significant positive strong correlation between PEEP levels and ONSD, with Pearson's correlation coefficient of 0.790 ($p<0.001$), MAP should be included as a covariate in the analysis, as it may vary with PEEP and also influence ONSD-related ICP. The graphic below shows the correlation of PEEP and ONSD with MAP controlled; the correlation coefficient is 0.781, still statistically significant (Figure 7).

The cut-off points of ONSD at 5.0 mm (which indicated ICP of 20 mmHg) and 5.5 mm (which indicated ICP of 22 mmHg) were calculated. ONSD at 5.0 mm is correlated to PEEP levels between 10 and 13 cmH_2O. Whereas ONSD at 5.5 mm is correlated to PEEP level 13-15 cmH_2O (Table 2).

Comparing each subgroup of patients with larger brain lesions (≥30mL) and smaller brain lesions (<30 mL), ONSD at any PEEP level is not different between these two subgroups (Table 3 and Figure 8).

For enrolled patients with different GCS at baseline, there is no difference in ONSD at any PEEP level when compared between each subgroup of different GCS (Table 3 and Figure 8).

The results related to the cardiovascular-derived parameters, based on heart rate and mean arterial blood pressure, did not have an impact on the size of the lesions or the baseline level of consciousness. Also, the results of gas

Table 1. Demographic data.

Characteristics	Mean ± SD. or n (%)	Median [min - max]
Demographi data		
Age	40.74 ± 13.73	41 [18 - 70]
Gender		
Female	12 (44.4%)	
Male	15 (55.6%)	
BMI (Kg/m^2)	22.07 ± 2.24	22.77 [16 - 25.39]
Underlying		
Hypertension	8(29.6%)	
Diabetes	2(7.4%)	
Dyslipidemia	2(7.4%)	
Others	3(11.1%)	
Ventilator parameters and baseline gas exchange		
TV (ML/KG)	6.57 ± 0.41	6.5 [6 - 7]
$EtCO_2$	37.37 ± 1.98	38 [35 - 40]
SpO_2	95.96 ± 1.63	96 [94 - 99]
Baseline GCS (except verbal score due to intubation)		
	5 (18.5%)	
	5 (18.5%)	
	8 (29.6%)	
	9 (33.3%)	
After sedation with RAAS = O	27(100%)	
Midazolam (mg)		
2	1(3.7%)	
3	4(14.8%)	
5	22(81.5%)	
Operation and brain pathology		
Lesion size (ml)	28.59 ± 9.83	30 [10 - 45]
<30	11 (40.7%)	
30-45	16 (59.3%)	
Operation		
Craniotomy	20(74.1%)	
Endoscopic surgery	7(25.9%)	
Operative time (hours)	3.87 ± 1.85	3 [2 - 8]
Post operative timing to ONSD (min)	220.37 ± 183.07	145 [30-600]
Pathology		
Chronic subdural hematoma right hemisphere	3 (11.1%)	
Intracerebral hematoma left hemisphere	2 (7.4%)	
Cerebellar hematoma	1 (3.7%)	
Intracerebral hematoma right hemisphere	4 (14.8%)	
Brain stem tumor	1 (3.7%)	
Left hemispheric tumor	1 (3.7%)	
Pituitary gland tumor	6 (22.2%)	
Cerebellar tumor	2 (7.4%)	
Right hemispheric tumor	7 (25.9%)	

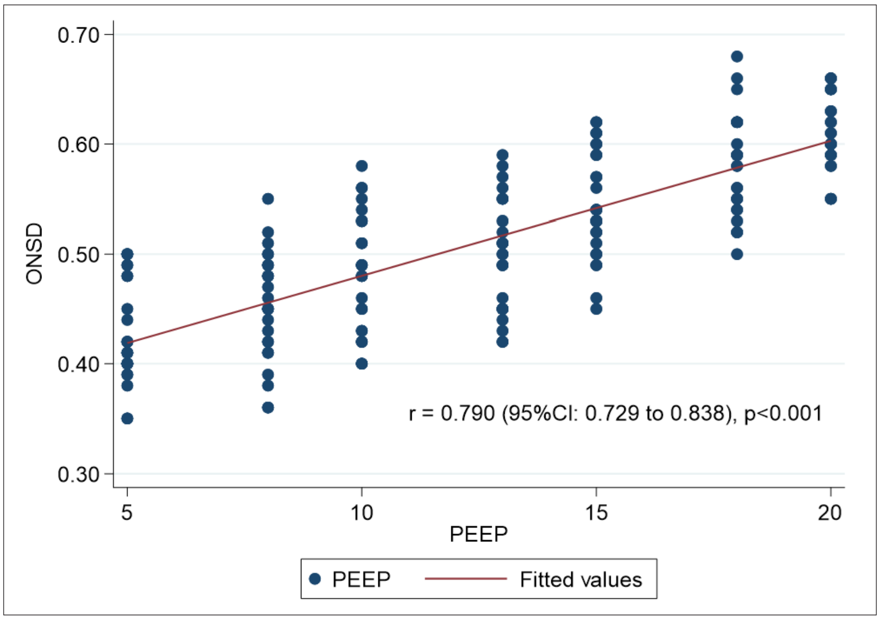


Figure 5. Correlation of the PEEP and ONSD without MAP controlling.

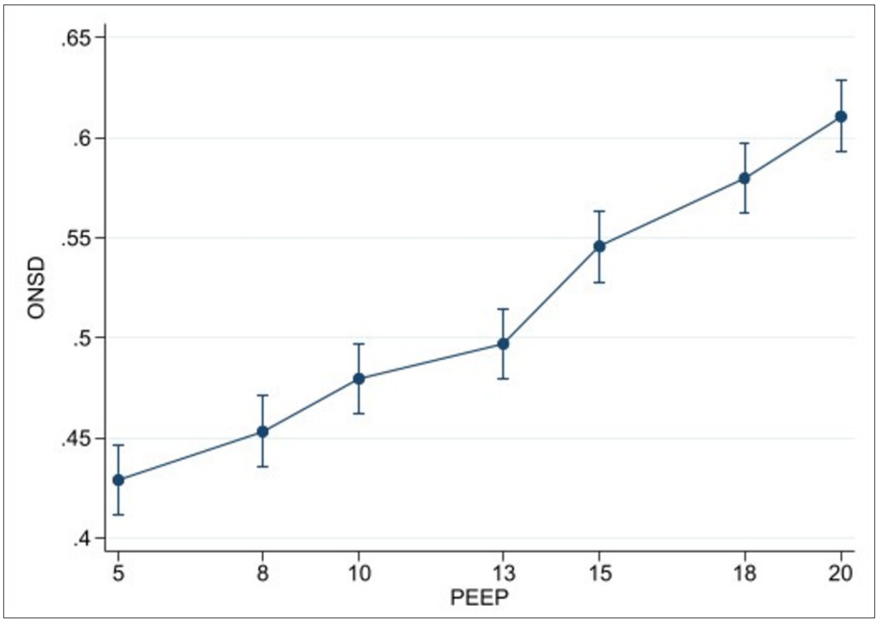


Figure 6. ONSD changes within PEEP intervals.

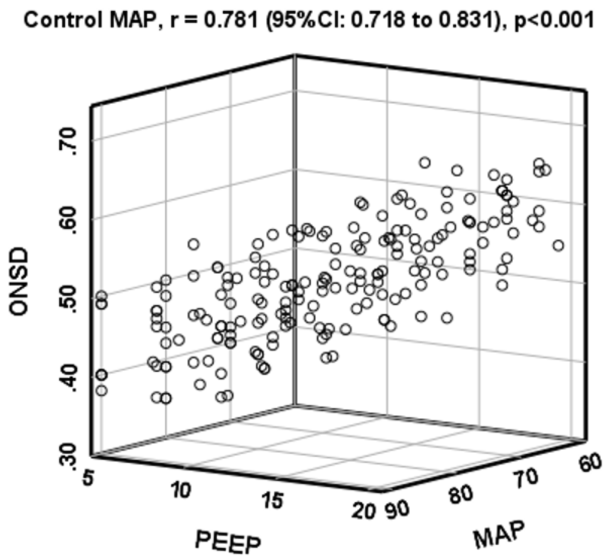


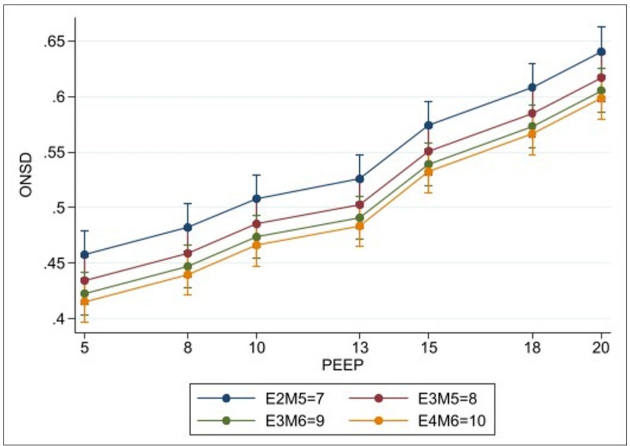
Figure 7. Correlation of the PEEP and ONSD with/without MAP controlling.

Table 2. ONSD cut point value for ONSD 5.0 and 5.5 mm with each PEEP level.

PEEP level (cmH_2O)	ONSD ≥ 5.0 mm		ONSD ≥ 5.5mm	
	n	%	n	%
PEEP 5	4	14.8%	0	0%
PEEP 8	5	18.5%	1	3.7%
PEEP 10	9	33.3%	4	14.8%
PEEP 13	14	51.9%	7	25.9%
PEEP 15	23	85.2%	11	40.7%
PEEP 18	27	100%	20	74.1%
PEEP 20	26	96.3%	26	96.3%

Table 3. Correlation of PEEP with ONSD in the subgroup of the level of consciousness and size of lesions.

PEEP (cmH_2O)	ONSD (cm)	GCS					Lesion		
		E2M5 (n=5)	E3M5 (n=5)	E3M6 (n=8)	E4M6 (n=9)	p-value	Lesion <30 (n=11)	Lesion 30-45 (n=16)	p-value
5	0.43 ± 0.05	0.46 ± 0.04	0.44 ± 0.04	0.42 ± 0.05	0.42 ± 0.05	0.428	0.42 ± 0.05	0.43 ± 0.05	0.528
8	0.45 ± 0.05	0.48 ± 0.03	0.46 ± 0.05	0.44 ± 0.06	0.45 ± 0.05	0.657	0.46 ± 0.05	0.45 ± 0.05	0.855
10	0.48 ± 0.05	0.5 ± 0.06	0.48 ± 0.05	0.48 ± 0.07	0.47 ± 0.05	0.793	0.49 ± 0.06	0.48 ± 0.05	0.601
13	0.5 ± 0.05	0.53 ± 0.06	0.5 ± 0.04	0.49 ± 0.06	0.48 ± 0.04	0.311	0.5 ± 0.06	0.5 ± 0.05	0.866
15	0.55 ± 0.05	0.58 ± 0.05	0.55 ± 0.05	0.54 ± 0.05	0.53 ± 0.04	0.336	0.55 ± 0.05	0.54 ± 0.05	0.820
18	0.58 ± 0.05	0.61 ± 0.04	0.59 ± 0.04	0.57 ± 0.05	0.56 ± 0.04	0.200	0.58 ± 0.05	0.58 ± 0.04	0.719
20	0.61 ± 0.03	0.63 ± 0.03	0.62 ± 0.02	0.61 ± 0.04	0.6 ± 0.03	0.273	0.61 ± 0.04	0.61 ± 0.03	0.751



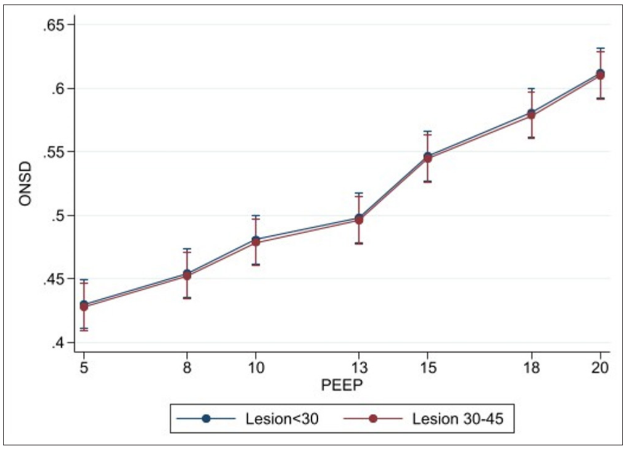


Figure 8. Effect of the baseline GCS and lesion size to ONSD.

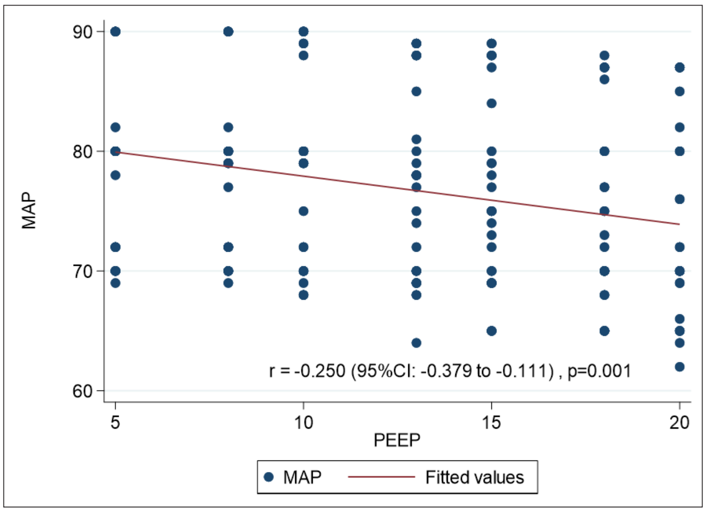


Figure 9. Correlation of the PEEP and MAP.

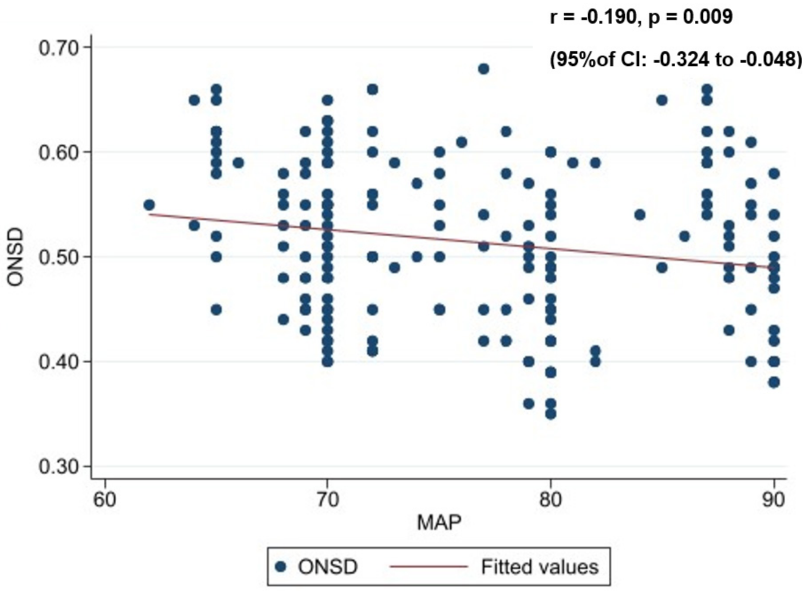


Figure 10. Correlation of the MAP and ONSD.

Table 4. Correlation of PEEP with MAP below 65 mmHg.

PEEP (cmH_2O)	MAP <65 mmHg	
	n	%
5	0	0%
8	0	0%
10	0	0%
13	0	0%
15	0	0%
18	0	0%
20	2	7.4%

exchange showed constant $EtCO_2$ (37.50 ± 1.94) and SpO_2 (95.95 ± 1.63) during the varying PEEP levels.

Additionally, figure 9 shows a significant negative mild correlation between PEEP levels and mean arterial pressure (MAP), with Pearson's correlation coefficient of 0.250 ($p<0.001$).

Finally, a significant negative correlation was observed between MAP values and ONSD with Pearson's correlation coefficient of 0.190, $p<0.001$ (Figure 10).

Regarding the MAP values, however, the MAP dropped below 65 mmHg at a PEEP level of 20 cmH_2O (Table 4). But it is insignificant, with the p-value being 0.136. This suggests that there is a critical point at which PEEP affects cardiovascular function in patients following cranial surgery in the study, albeit insignificantly.

DISCUSSION

PEEP and ICP

The study aims to determine the level of PEEP that affects ICP, which can worsen cerebral perfusion pressure. The previous reference of increased ICP greater than 20 mmHg correlated to ONSD more than 5 mm. However, the current guidelines for managing patients with brain injuries agreed on a new threshold of ICP that intervenes with cerebral perfusion pressure (CPP): the value is greater than 22 mm Hg, which correlates to ONSD more than 5.5 mm. [9, 14] This is the reason we established two cut-off points for ONSD at 5.0 and 5.5 mm.

Interpretation of results

This research shows the safety margin of the PEEP values that can be set for patients after brain surgery is below 10 cmH_2O if the goal is to keep ONSD not exceeding 5 mm (corresponding to an ICP less than 20 mmHg, according to previous ICP recommendations). Alternatively, for the current recommendation of ICP 20 mmHg as the value that interferes with cerebral perfusion pressure, the cut-off point is set at an ONSD of 5.5 mm; this correlates with a set PEEP level at 15 cmH_2O.

According to the ICP limitation at 20 mmHg, PEEP can be safely set up to 10 cmH_2O, in the other hand, if the limitation of ICP is 22 mmHg, PEEP can be safely set up to 13 cmH_2O.

Although the ICP level of 22 mmHg results in a significant impact on clinical outcomes, according to recent data from Riparbelli, et al. [17,21]. However, other studies against an ICP level of 20 or 22 mmHg do not result in a significantly different impact on clinical outcomes [15]. It appears that evaluating ICP alone may be insufficient when considering patient outcomes, as treatment approaches tend to focus on the goal of maintaining CPP. Additionally, the use of the MAP challenge test helps assess whether a patient's vasoreactivity remains intact [18].

There is a statistically significant relationship showing that a decrease in MAP correlates with an increase in the size of the ONSD. The findings indicate that the MAP in the studied group exceeded 75 mmHg when PEEP was set between 5 and 15 mmHg, following the principles of heart-lung interaction. As intrathoracic pressure increases, blood pressure tends to decrease [17]. In a study involving postcranial patients, it was evident that MAP dropped significantly below 65 mmHg when PEEP exceeded 20. The reduction in blood pressure due to heart-lung interaction, when intrathoracic pressure increases, leads to a decrease in cerebral perfusion pressure as a result of decreased mean arterial pressure. This, in turn, can cause further brain ischemia, causing an increase in ICP. Our study also indicated that MAP decrement correlates to enlargement of ONSD (or ICP increment), which is consistent with previous studies [12,16].

Comparison with literature

Although no previous studies have defined the optimal PEEP in post-cranial surgical patients, there are many studies about the safety limit. Our study showed the PEEP value of 13 cmH_2O slightly increased ICP and was clinically safe for adult post-cranial surgery patients. Several previous studies in traumatic brain injury (TBI) demonstrate various cut points of PEEP levels between 5 and 15 cmH_2O can lead to ICP increments. However, most recommendations from the meta-analysis are limited to PEEP settings below or equal to 12 cmH_2O due to a greater number of participants and the quality of studies. [15,17,18,20]

The safety limit of PEEP is below 13 cmH_2O. May from the difference in the pathophysiology of the brain injury resulting from severe TBI compared to other non-traumatic post-cranial surgery, especially since all of our participants mostly underwent elective surgery such as brain tumor surgery (75%) and did not have any postoperative brain complications that required reoperation or ICP-reducing protocols, so we extrapolate that the brain injury and cytotoxic injury may be less than in the severe TBI case. Cerebral compliance due to surgical trauma may be a higher chance of increased ICP or decreased CPP compared to our study participants. Therefore, the safety limit for PEEP in our study is higher.

The influence of PEEP on ICP may depend on baseline characteristics of patients such as obesity, from Chen H, et al. [23]. Our study showed no significant difference in ONSD compared to baseline characteristics, as the demographic data and pathology of the patients, who mostly had brain tumors, were relatively similar. As well as baseline GCS, subgroups show no significant difference in ONSD measurements according to any PEEP levels. This result may be due to the inclusion of all patients with a baseline ONSD of less than 5 mm and the small number of participants; therefore, it may not be possible to identify risk factors for ICP increments following changes in PEEP in this study.

These findings underscore the importance of cautious PEEP titration in neurosurgical patients. While PEEP is crucial for oxygenation, particularly in cases of lung injury or atelectasis. On the contrary, it's the high PEEP potential to cause barotrauma in the normal lung compliance, which may lead to hypercarbia and hypoxemia, especially risky post cranial surgery when cerebral compliance is impaired. Carbon dioxide can also affect cerebral blood flow by the vasoreactivity response to acid-base balance. But our results show stable values of the $EtCO_2$ and SpO_2. Assuming that our PEEP setting may be short-time to affect the gas exchange and carbon dioxide level was controlled by the protocol ($EtCO_2$ exceeding 45 mmHg and/or SpO_2 less than 95% will be rejected).

In comparison with prior studies, Zhang XY, et al. reported in 2011 that PEEP titration from 0 to 21 cmH_2O during recruitment maneuver in TBI patients with low partial oxygenation/FiO_2 ratio, did not interfere with MAP but had a moderate negative correlation with CPP. [24] Gupta, et al. reported in 2001 that they showed a negative correlation between PEEP and MAP as well, especially when PEEP was increased from 10 to 15 cmH_2O. [12] Whereas Giogiadis D, et al. report in 2001 that PEEP titration from 0 to 12 cmH_2O results in worsening CPP by interfering with MAP but not ICP increment [25].

Hemodynamic effects of PEEP

In our study, we also found a negative correlation between MAP (MAP decrement) and increasing PEEP. Especially when the PEEP level was at 20 mmHg, 20% of patients' MAP decreased to be lower than 65 mmHg. Compared to previous studies, our result revealed significant MAP interference (MAP <65 mmHg) at higher PEEP levels. This difference may be due to our participants being more hemodynamically stable.

On the other hand, MAP reduction from elevated PEEP may lead to increased ONSD (corresponding to increased ICP), impairing CPP, which, in combination with elevated ICP and lowering MAP, significantly raises the risk of secondary brain injury. Managing these competing demands, oxygenation via PEEP and cerebral perfusion via MAP control is essential.

During the testing at PEEP levels of 18 and 20 cmH_2O, the ONSD values were 5.8 and 6.1 mm, respectively. Both ONSD values exceeding 5.5 mm indicate the increased ICP (greater than 22 mmHg and must persist more than 5 minutes); it could lead to pathological changes in cerebral compliance. In our experiment, we maintained each PEEP level for 2 minutes. PEEP levels of 18 and 20 cmH_2O are lower than 5 minutes, which may be too short a time to increase ICP as defined. Significant changes in the ONSD were obviously corresponding to elevated ICP. All participants were prevented from complications according to the methodology. There were no clinical complications related to increased ICP, including hemodynamic or respiratory system.

The clinical implications

We firmly recommend that PEEP levels below 13 cmH_2O are safe for patients recovering from cranial surgery, as they do not adversely affect ICP. Moreover, maintaining PEEP levels below 20 cmH_2O can significantly minimize hemodynamic interference. However, our study selected participants who did not have cardiopulmonary disease; high PEEP may cause harm. Real-time non-invasive monitoring using ONSD offers a practical tool for bedside assessment, aiding clinicians in optimizing respiratory support without compromising cerebral perfusion.

We can use our results to guarantee effective ICP, gas exchange, and hemodynamics after cranial surgery with safe PEEP. The safe PEEP balances cerebral oxygen delivery and cerebral venous return, including cardiac preload. Balancing respiratory support with neurological safety can enhance patient care and significantly reduce the risk of adverse effects after surgery.

ONSD as a monitoring tool

The ONSD measurement related to ICP has a significant correlation with PEEP increment. PEEP increment directly increases intrathoracic pressure, thus decreasing venous return from the brain, resulting in ICP increment. Accurate measurement of ONSD can reflect changes in intracranial pressure, with a sensitivity of 94%, specificity of 98%, and an AUC of 0.97[15]. In this study, we measured with the following protocol and a single operator who trained and studied ONSD measurement and used it in clinical practice for 1 year before participating in the research. We found the ONSD measurement is a non-invasive, cost-effective procedure that can be performed continuously and can serve as an alternative to direct ICP measurement when direct ICP monitoring is not possible due to unavailability or contraindications. Similar to our experimental results, all of the study participants did not receive direct ICP monitoring because both the healthcare providers and the participants did not want to undergo an invasive procedure.

In 2021, Gupta N, et al[12] demonstrated that ONSD measurements on either eye are well correlated, so we decided to select right-eye ONSD measurements for our study.

Study limitations

Limitations in this study. Firstly, our participants had a baseline ICP less than 22 mmHg and were hemodynamically stable without any gas exchange pathologies. Although our results are useful, further research is needed to confirm the exact PEEP cut points for those patients, such as patients with severe pneumonia, ARDS, increased ICP, and shock.

Secondly, the ICP assessment in this study is not considered the gold standard like the invasive ICP measurements. However, ONSD is a good alternative to invasive ICP measurement as it's easy to perform and repeatable without any harmful risks. Thus, ONSD measurement is operator-dependent, but our operator was experienced and calibrated ONSD readings to another operator before the initiation of this study.

Thirdly, we selected only participants with relatively normal ICP (ONSD < 5 mmHg). Therefore, our result may not apply to those post-cranial surgeries with increased ICP. Fourthly, the PEEP effect after 2 minutes in this study may be different from the longer duration of PEEP usage in such patients with ARDS.

Finally, our study has a small sample size and relies on single-center data. The limited number of participants was due to the unpredictability of ventilator need, hemodynamic instability, and increased ICP before recruiting to our experiment. This constraint may lead to limitations in generalizability, as the results may not accurately reflect all patients undergoing postcranial surgery, particularly in emergencies such as hemorrhagic stroke and brain edema. Future research to provide better insights into clinical outcomes should focus on larger sample sizes to emphasize statistical power, more extended duration of studies, and multicenter trials to explore these findings.

CONCLUSION

In post-cranial surgical patients who require mechanical ventilation and are hemodynamically stable without gas exchange abnormalities, PEEP settings below 13 cmH_2O can be safely used without clinically significant increases in ICP as measured by ONSD.

Whereas PEEP ≥ 20 cmH_2O is considered harmful hemodynamic interference. Further research should be performed in post-cranial surgical patients with severe gas exchange abnormalities or those who are hemodynamically unstable.

There are many gaps in our knowledge of the relationship between PEEP, ICP, and clinical outcomes. From our findings, further multicenter studies including realist evaluation of mortality, functional status, and length of ICU/hospital stay are essential to validate these findings and guide safe ventilatory strategies in patients with more complex neurocritical profiles.

CONFIDENTIALITY

I confirm that this manuscript is original and has not been shared beyond the intended submission process. I acknowledge and adhere to the journal's confidentiality policies, ensuring that all unpublished content, including participant data, remains secure and is handled in accordance with ethical and regulatory guidelines. This study has obtained ethical approval from the institutional review board, and informed consent was obtained from all human participants, ensuring compliance with ethical standards for research.

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AUTHORS' CONTRIBUTIONS

N.L. conceived, designed the study, collected and analyzed the data. J.P. contributed to the interpretation of results. A.C. drafted the manuscript. And all authors reviewed and approved the final version.

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