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Comparative Analysis of 5 cmH_2O Versus 10 cmH_2O PEEP on Cerebral Oxygen Saturation in Brain Tumor Surgery: A Randomized Controlled Clinical Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The main concern regarding lung-protective ventilation strategies during neurosurgery is the reduction in venous return and increase in cerebral blood flow when using high positive end-expiratory pressure (PEEP). This study aimed to evaluate and compare the changes in regional cerebral oxygen saturations (rSO_2) during the use of 5 cmH_2O and 10 cmH_2O PEEP in patients undergoing craniotomy for tumor resection.

Material/Methods: The study was designed as a prospective, single-blind randomized controlled study. Patients aged between 18 and 70 years, scheduled for an elective craniotomy for tumor resection, were divided into 2 groups: 5 cmH_2O PEEP (Group Low PEEP) and 10 cmH_2O PEEP (Group High PEEP). The PEEP was applied during general anesthesia, for controlled mechanical ventilation. The main outcome was the measurement of rSO_2 before dura opening. Changes in rSO_2, hemodynamic parameters, and peripheral oxygen saturation (SpO_2) during different periods of surgery were compared between the groups.

Results: Sixty-four patients were included. There were no significant differences between the 2 groups regarding demographic data. Mean arterial blood pressure and changes in SpO_2 were statistically similar in all periods between the groups (P=0.141 and P=0.081). When compared with the baseline value, SpO_2 increased significantly at all measurement times (P<0.05). No difference was observed in rSO_2 values compared with baseline rSO_2 values between the groups (P=0.218).

Conclusions: PEEP at the level of 10 cmH_2O can be safely applied during craniotomy without altering hemodynamics, and without causing a decrease in rSO_2.

Keywords: **Craniotomy • Spectroscopy, Near-Infrared • Oxygen Saturation**

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Introduction

Postoperative pulmonary complications (PPCs) are the most important causes of morbidity and mortality after major surgeries [1,2]. PPCs are seen in approximately 25% of patients undergoing general anesthesia [3]. The incidence of PPCs in patients with neurosurgery lasting for longer than 300 min is 28.4% (20.2-37.9%) [4]. General anesthesia has a reducing effect on functional residual capacity that can lead to atelectasis [5,6]. The strategy of lung-protective ventilation (LPV), defined as the combination of low tidal volume, positive end-expiratory pressure (PEEP), and recruitment, is used for preventing atelectasis and alveolar over-expansion [7,8].

LPV strategy is not only recommended for neurocritical care patients [9] but also for controlled mechanical ventilation during general anesthesia [10]. The main concern about using high PEEP during neurosurgery is the reduction in venous return and increase in cerebral blood flow (CBF) [11,12]. Intrathoracic pressure and pulmonary vascular resistance increase during PEEP application [13]. Thus, jugular venous pressure and intracranial pressure (ICP) may increase while cerebral perfusion pressure (CPP) decreases [14]. Vasodilatation occurs due to cerebral autoregulation, which restores the CPP. However, the effect of vasodilatation is an increase in CBF [15]. The CBF can be monitored by near-infrared spectroscopy (NIRS) [16]. Values achieved from NIRS reflect a balance between oxygen consumption and delivery [17]. So, cerebral ischemia and hypoxia can be easily detected.

Various studies have compared the effect of different PEEP levels on regional cerebral oxygen saturation (rSO2) in different types of surgeries [18,19]. However, there are limited studies about the use of PEEP in neurosurgery. Therefore, this study aimed to evaluate and compare the effect of 5 cmH_2O and 10 cmH_2O of PEEP on rSO_2 in patients undergoing elective craniotomy for intracranial tumor resection.

Material and Methods

Ethical Statement

Approval was obtained from the Ethics Committee of University of Health Sciences Izmir Bozyaka Training and Research Hospital (Approval number: 2023/14), and the study was registered in the American National Institutes of Health registration protocol system (NCT05961917). Written and verbal consent were obtained from patients after they were informed about the research.

Study Design

The study was planned as a single-center, prospective, single-blind randomized controlled study. The study included patients who were aged 18-70 years, were scheduled for an elective craniotomy of tumor resection, between February 2023 and January 2024, and had American Society of Anesthesiologists (ASA) I-II physical condition scores. We did not include patients in the study who had a hemoglobin concentration of less than 9 mg/dL, intracranial masses greater than 3 cm, pulmonary edema, congestive heart failure, severe chronic obstructive lung disease, a history of carotid surgery or stenosis of the carotid artery, uncontrolled hypertension, unstable hemodynamics, cerebrovascular disease, intracranial masses greater than 3 cm, skin reaction to the NIRS sensor, or emergency surgery.

Age, sex, weight (kg), height (cm), body mass index (BMI) (kg/m^2), comorbidities, and surgical site were recorded as demographic data. Patients were divided into 2 groups by a computer-based randomization technique. These 2 groups were the 5 cmH_2O PEEP (Group Low PEEP) and 10 cmH_2O PEEP (Group High PEEP). PEEP was applied during general anesthesia, for controlled mechanical ventilation.

The primary outcome was the measurement of rSO_2 before opening the dura. The secondary outcomes were the measurements of mean arterial pressure (MAP) and peripheral oxygen saturation (SpO_2) changes during the surgery.

Collecting patient data, anesthetic management, and follow-up throughout surgery were carried out by an anesthesiologist who was not involved in the study, for objective collection and interpretation of data.

Anesthesia Protocol

Premedication was not used. Standard monitoring, including electrocardiogram, pulse oximetry, and non-invasive blood pressure measurement was used for all patients in the operating room. A NIRS sensor was placed on the frontotemporal area of the patient and regional cerebral oxygen saturation was monitored (INVOS™ 5100C Cerebral/Somatic Oximeter, USA). A bispectral index (BIS) sensor (Bispectral Index™ Monitoring System, Covidien, USA) was also placed to monitor the depth of anesthesia. The infusion of remifentanil at a dose of 0.25 mcg/kg/min was initiated 2 minutes prior to the induction of anesthesia. Following a period of preoxygenation involving the administration of 6 L/min of oxygen for a duration of 5 minutes, the induction of anesthesia was conducted in both groups via the intravenous administration of 2 mg/kg of propofol. The induction of muscle relaxation was facilitated by the administration of rocuronium bromide at a dose of 0.6 mg/kg. Subsequently, the patient was intubated via the endotracheal route. The utilization of controlled mechanical ventilation was to be employed during the surgical procedure. All patients were ventilated with the same anesthetic machine (S/5 Avance anesthetic machine; GE Healthcare, Madison, WI).

Central venous and radial arterial lines were placed for hemodynamic monitoring and fluid administration in both groups. Fluid management was planned according to urine output and pulse pressure variation (PPV). The urine output was targeted to be 0.5-1 mL/kg/h urine output and PPV below 12%.

In the low PEEP group, the patients' ventilation settings were as follows: a tidal volume of 6-8 mL/kg, an inspired oxygen fraction (FiO_2) of 0.4, and PEEP of 5 cmH_2O. The frequency of ventilation was adjusted according to the end-tidal carbon dioxide pressure ($ETCO_2$), with settings set to 30-32 mmHg.

Conversely, in the high PEEP group, the ventilation settings were set at a tidal volume of 6-8 mL/kg, an inspired oxygen fraction (FiO_2) of 0.4, and a PEEP of 10 cmH_2O. The frequency was adjusted based on the $ETCO_2$, with the target range being 30-32 mmHg.

Remifentanil was administered at a dose of 0.05-2 mcg kg/min, and propofol was administered at a dose of 50-200 mcg/kg/min. These anesthetics were infused for the maintenance of general anesthesia, with BIS monitoring. In both groups, the BIS score was maintained between 40 and 50. The dosage of remifentanil infusion was modified in accordance with the arterial blood pressure. In instances where the mean arterial blood pressure and/or heart rate decreased by 20% of the baseline mean arterial blood pressure and heart rate, the infusion dose was reduced. In instances where the decrease in heart rate exceeded 25%, the administration of intravenous atropine 0.5 mg was initiated. Furthermore, in instances in which the mean arterial blood pressure was found to be less than 55 mmHg, the administration of intravenous 5 mg ephedrine was initiated. In cases where the mean arterial blood pressure continued to decrease, the PEEP was also reduced. Conversely, if the peripheral oxygen saturation was found to be less than 92%, the inspired oxygen fraction or PEEP were increased. In the event of these conditions being met, the patient was excluded from the study.

In all patients, 1 g of paracetamol was administered intravenously for postoperative pain. Sugammadex was used with a dose of 4 mg/kg for extubation.

After extubation, patients were transferred to the post-anesthesia care unit (PACU) and monitored for 1 hour postoperatively. Afterwards, all patients were transferred to computed tomography (CT) imagining. The first 24-hour follow-up visit was held in the neurosurgery intensive care unit (ICU).

Evaluation of Regional Cerebral Oxygen Saturation

Regional cerebral oxygen saturation (rSO_2) was monitored with a Covidien Invos 5100c cerebral/somatic oximeter and recorded 9 times during the study; pre-induction (period 1), post-induction (period 2), skull pinning (period 3), before dura opening (period 4), after dura opening (period 5), surgical resection of the mass (period 6), dura closure (period 7), end of the surgery (period 8), and end of anesthesia (period 9).

In these periods, MAP, heart rate, and SpO_2 were also recorded in addition to NIRS rSO_2 values.

Exclusion Criteria

Elevated ICP or swelling of brain tissue due to PEEP during the surgery, persistent hypotension and circulatory instability, anesthesia lasting less than 2 hours or longer than 4 hours, reintubation or a second surgery within 24 hours after the surgery, and failed extubation after the surgery were determined as criteria for the participants to be excluded from the study.

Statistical Analysis

All data were analyzed with SPSS software version 18.0 (IBM Corp., Armonk, NY, USA). There were no similar publications in the literature that could be referenced to calculate sample size. So, sample size calculation was based on our prior study with 10 patients in each group. The primary outcome variable was the value of rSO_2 before dura opening. A change of 25% compared with baseline was considered statistically significant. For an αvalue of 0.05 and a power of 95%, 58 subjects were required. Thus, 64 subjects were included to cope with an expected loss of 10%.

Normal distributions of data were assessed using the Kolmogorov-Smirnov test. Descriptive statistics are shown as mean±SD, and nominal variables are shown as the number of cases and percentages (%). Mann-Whitney U test and *t* test were used to verify the statistical significance of the differences between groups for continuous variables. Nominal variables were analyzed using the Pearson's chi-square test and Fisher's exact test. In all tests, $P<0.05$ was considered to be statistically significant.

Results

The present study included 64 patients. No patient was withdrawn from the study after induction of anesthesia. Data analysis was performed on the 2 groups.

The median age of patients in Group I was 61 (11) and the median age in Group II was 60 (35) (P=0.400). Female patients comprised the majority in both groups, with 61.3% in Group I and 54.5% in Group II. There were no significant differences between groups regarding weight and height (P=0.120, P=0.588,

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Table 1. Demographic and clinical characteristics of patients.

Parameter	Group I (n=31)	Group II (n=33)	*P* value
Age (years)	61 (11)	60 (35)	0.400
Sex (M/F)	12 (19.7)/19 (61.3)	15 (45.5)/18 (54.5)	0.314
Height (cm)	167 (5)	168 (12)	0.588
Weight (kg)	70 (12)	79 (21)	0.120
Comorbidities (n)			0.169
None	9 (29)	16 (48.5)	
HT	16 (51.6)	14 (42.3)	
DM	3 (9.7)	3 (9.1)	
CAD	3 (9.7)	0	
ASA (n)			0.103
I	3 (9.7)	10 (30.3)	
II	12 (38.7)	8 (24.2)	
III	16 (51.6)	15 (45.5)	
Smoking (yes/no)	16 (51.6)/15 (48.4)	9 (27.3)/24 (72.7)	0.072
Preoperative Hg (mg/dL)	13.02±2.21	13.16±1.85	0.793
Preoperative Htc (%)	38 (3.4)	39.7 (3.8)	0.861

Data are presented as median (IQR) and n (%). F – Female; M – Male; ASA – American Society of Anesthesiologists Physical Status Classification System; BMI – body mass index; HT – hypertension; DM – diabetes mellitus; CAD – coronary artery disease; Hg – hemoglobin; Htc – hematocrit.

respectively). Hypertension was the most common comorbidity, followed by diabetes mellitus and coronary artery disease. Most patients were classified as ASA III in both groups. No significant difference was found in terms of comorbidities, smoking status, ASA scores, preoperative hemoglobin, and hematocrit values between the 2 groups (*P*=0.169, *P*=0.072, *P*=0.103, *P*=0.793, *P*=0.861, respectively) (**Table 1**).

None of the patients received blood transfusion or inotropic drug infusion during the surgery.

The measurements of MAP were statistically similar in all periods between the groups (*P*=0.192). Changes in MAP are seen in **Figure 1**.

The changes in SpO_2 were statistically similar between the groups (*P*=0.081). When compared with the baseline value; SpO_2 increased significantly at all measurement times (*P*<0.05).

No difference was observed in rSO_2 values, compared with baseline rSO_2 values, between the patients in the 2 groups and in all measurement periods (**Figure 2**).

Discussion

No difference was found between 5 cmH_2O and 10 cmH_2O PEEP in terms of effect on rSO_2 in patients with increased ICP. The measurements of MAP remained similar between the groups. SpO_2 increased significantly when compared with baseline values, but changes in SpO_2 were also similar in Group I and Group II. This study presented safe application of up to 10 cmH_2O PEEP without a clinically important increase in ICP and decrease in CPP.

LPV strategies are used to ventilate patients both in intensive care units and during surgery. It is recommended that patients with acute brain injury (ABI) who have clinically significant ICP elevation should be mechanically ventilated with the same level of PEEP as patients without ABI [20]. High tidal volumes are no longer used due to ventilator-associated lung injury (VALI) [21,22]. PEEP, as a part of LPV strategies, improves pulmonary functions and reduces pulmonary complications [23]. Studies investigating the effects of increased PEEP levels on ICP have yielded different results. According to various previous studies, ICP can increase [24-26], not change [27,28], or decrease [23].

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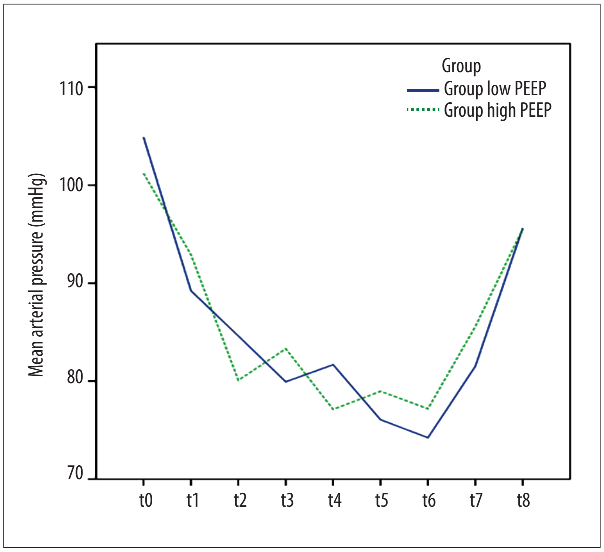

Figure 1. Mean arterial blood pressure measurements in Group I and Group II. Measurement periods: t0 – pre-induction; t1 – post-induction; t2 – skull pinning; t3 – before dura opening; t4 – after dura opening; t5 – surgical resection; t6 – dura closure; t7 – end of surgery; t8 – end of anesthesia. PEEP – positive end-expiratory pressure. *Created with SPSS software version 18.0 (IBM Corp., Armonk, NY, USA).*

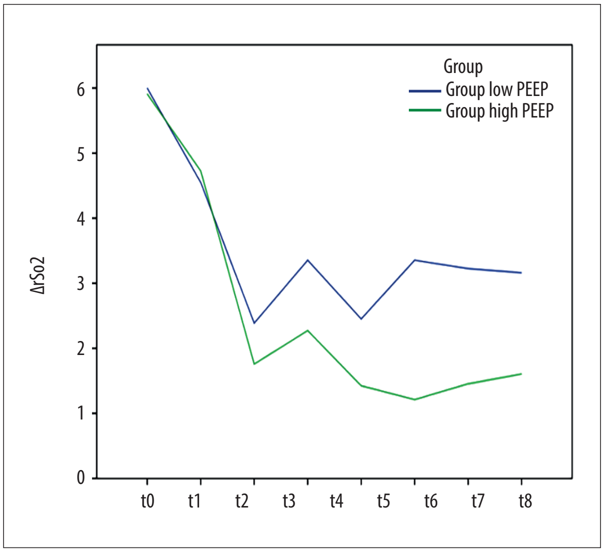

Figure 2. Differences in regional cerebral oxygen saturation (rSO_2) values compared with pre-induction value (t0) in Group I and Group II. Measurement periods: t0 – pre-induction; t1 – post-induction; t2 – skull pinning; t3 – before dura opening; t4 – after dura opening; t5 – surgical resection; t6 – dura closure; t7 – end of surgery; t8 – end of anesthesia. PEEP – positive end-expiratory pressure. *Created with SPSS software version 18.0 (IBM Corp., Armonk, NY, USA).*

Haring et al reported a significant increase in the mean CBF rate following 12 cmH_2O continuous positive airway pressure (CPAP) [29]. McGuire et al applied 5, 10, and 15 cmH_2O PEEP in neurosurgical patients and CPP was unchanged throughout the groups [24]. Schranc et al studied different levels of PEEP and found that PEEP above 10 cmH_2O had no impact on ICP [30]. In another study, administration of different levels of PEEP in laparoscopic surgery did not affect cerebral oxygenation or rSO_2 [31]. It has been shown that PEEP can be used at up to 10 cmH_2O without a clinically important increase in ICP and a decrease in CPP [32]. The results of the present study are similar to these studies, as changes in rSO_2 did not differ between 5 and 10 cmH_2O PEEP.

PEEP increases intrathoracic pressure, which increases central venous pressure and reduces cardiac filling pressure. This causes a reduction in cardiac output. Insufficient circulatory compensation results in a decrease in blood pressure and a reduction of CPP [33,34]. This effect is more evident in volume-depleted patients [35]. Chen at al demonstrated that ICP could be elevated by increasing PEEP in animals with normal blood volume; and that increasing PEEP resulted in decreased ICP in volume-depleted animals. They concluded that, from the results of their experimental study, both volume status and respiratory mechanics determine the impact of PEEP on ICP and cerebral oxygenation [36].

It has been shown that vessels in the brain can maintain a constant CBF by regulating the vascular tone throughout a wide range of MAP or CPP, with intact cerebral autoregulation in animals [37,38]. As in patients with an intact CBF autoregulation response, MAP reduction can be also be tolerated without development of cerebral ischemia. MAP and CPP are thought to be indirect markers for cerebral perfusion [39]. In the present study, MAP was an important factor to provide sufficient CBF and oxygenation due to elevated ICP. Volume status was evaluated by observing the balance between the infusions and urine output, as well as PPV. All patients received adequate intravenous fluids and patients requiring blood transfusion were excluded from the study. The difference between $rSO_{2,}$ as an indicator of ICP, at different periods of surgery was not statistically significant; it was considered a result of normal blood volume.

Another factor effecting rSO_2 is FiO_2. The constant FiO_2 and PEEP provided higher sPO_2 when compared with the baseline value, including the values of all periods.

There were some limitations to the present study. Firstly, this was a small study with 64 patients, with ages ranging between 18 and 70 years. We conducted the study in a single center with a single surgeon. The number of the patients should be increased and age groups should be divided to achieve better results. Secondly, although tumors larger than 3 cm were not

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included in the study, the location of the tumor was not the same in every patient. Another limitation was the lack of invasive ICP monitoring. NIRS is a non-invasive method that calculates oxygen saturation of hemoglobin and correlates with the change in regional tissue blood flow. The effect of PEEP on cardiac output, which reflects the sufficiency of circulatory compensation, was not monitored. Evaluation of cardiac output gives an objective measurement of cerebral perfusion pressure. Although arterial cannulation and a central venous catheter were used, central venous pressure and CPP were not followed. These are also important indicators.

Conclusions

PEEP at the level of 10 cmH_2O, can be safely applied during craniotomy without altering hemodynamics, and without causing a decrease in rSO_2 in normovolemic patients with stable MAP. Application of adequate PEEP should be applied under monitoring of MAP, ICP, and CPP.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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