EFFECT OF INTRAOPERATIVE LUNG PROTECTIVE VENTILATION ON CEREBRAL BLOOD FLOW, CEREBRAL OXYGENATION, AND INTRACRANIAL PRESSURE IN NEUROSURGICAL PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY

Dr. SARATH SURENDRAN

DM NEUROANAESTHESIA THESIS

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A THESIS SUBMITTED BY

Dr. SARATH SURENDRAN

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE AWARD OF

DM NEUROANAESTHESIA

JULY 2023

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. Sarath Surendran hereby certify that I had personally carried out the work depicted in the thesis titled 'Effect of intraoperative lung protective ventilation on cerebral blood flow, cerebral oxygenation, and intracranial pressure in neurosurgical patients: a prospective observational study' under the capable supervision and guidance of Dr. Manikandan S, Professor and Head, Division of Neuroanaesthesia and Neurocritical Care, Department of Anaesthesiology, the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram. No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

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This is to certify that this thesis titled 'Effect of intraoperative lung protective ventilation on cerebral blood flow, cerebral oxygenation, and intracranial pressure in neurosurgical patients: a prospective observational study' is a bonafide work of Dr. Sarath Surendran, Senior Resident, Division of Neuroanaesthesia and Neurocritical Care of this institute. This work was done under the keen supervision of his guide, Dr. Manikandan S, and he has shown keen interest and hard work in this thesis.

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APPROVAL OF THE THESIS

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	ALI	Acute Lung Injury
2	ARDS	Acute Respiratory Distress Syndrome
3	ASA	American Society of Anaesthesiologists
4	BMI	Body Mass Index
5	CBF	Cerebral Blood Flow
6	CO_2	Carbon Dioxide
7	COPD	Chronic Obstructive Pulmonary Disease
8	CPP	Cerebral Perfusion Pressure
9	CV	Conventional Ventilation
10	CVP	Cerebral Venous Pressure
11	DBP	Diastolic Blood Pressure
12	ECG	Electrocardiogram
13	$ETCO_2$	End Tidal Carbon Dioxide
14	FiO2	Fraction of inspired oxygen
15	FV	Flow Velocity
16	GCS	Glasgow Coma Scale
17	HR	Heart Rate
18	IBW	Ideal Body Weight
19	ICP	Intracranial Pressure
20	ICSOL	Intracranial Space Occupying Lesion
21	ICU	Intensive Care Unit
22	LPV	Lung Protective Ventilation
23	MAP	Mean Arterial Pressure
24	MCA	Middle Cerebral Artery
25	MHz	Mega Hertz
26	NIBP	Non-Invasive Blood Pressure
27	NIRS	Near Infra-Red Spectroscopy
28	NPE	Neurogenic Pulmonary Edema
29	PBW	Predicted Body Weight
30	PCO2	Partial Pressure of Carbon Dioxide
31	PCV	Pressure Control Ventilation
32	PI	Pulsatility Index
33	POPC	Postoperative Pulmonary Complications
34	PRx	Pressure Reactivity index
35	RR	Respiratory Rate
36	rSO_2	Regional cerebral oxygen saturation
37	SBP	Systolic Blood Pressure
38	SD	Standard Deviation
39	TBI	Traumatic Brain Injury
40	TCD	Transcranial Doppler
41	VAP	Ventilator Associated Pneumonia

42	VCV	Volume Control Ventilation
43	VILI	Ventilator Induced Lung Injury
44	Vt	Tidal Volume
45	WHO	World Health Organization

SYNOPSIS

Title: Effect of intraoperative lung protective ventilation on cerebral blood flow, cerebral oxygenation, and intracranial pressure in neurosurgical patients: a prospective observational study

Background

Mechanical ventilation with lung-protective ventilation (LPV) using low tidal volumes (Vt of 6-8 ml/kg) has been shown to clinical benefit critically ill patients. We hypothesize that cerebral hemodynamics will change significantly during LPV in neurosurgical patients as compared to conventional ventilation (CV) (with Vt-10 ml/kg) in the intraoperative period.

Objectives

To study the effect of LPV on cerebral hemodynamics, respiratory parameters, dynamic ventilatory parameters and systemic hemodynamics.

Methods

A prospective observational cross over study was conducted in elective cranial & spine surgery patients. After induction of general anesthesia, the patients were ventilated initially with CV (Vt-10ml/kg predicted body weight (PBW), PEEP-5, respiratory rate (RR) adjusted to a $EtCO_2$ of 32-36 mm of Hg). After steady state of 10 minutes, data on systemic and cerebral hemodynamics, respiratory variables were collected. The patients were switched over to LPV (Vt-6ml/kg PBW, PEEP-5, RR adjusted for $EtCO_2$ of 32-36 mm of Hg). The study parameters were repeated. Data were recorded at baseline (T0), during CV (T1) and during LPV (T2). Intracranial pressure (ICP) was

measured using subdural cannula in the cranial surgery using CV and LPV before dural opening. The primary outcomes studied were changes in cerebral oxygenation (rSO_2) using Near-infrared spectroscopy, transcranial doppler (TCD) flow velocity and ICP.

Results

Among 40 analysed patients, the TCD indices and rSO2 in both sides were comparable at T1 and T2 in both surgery groups. The mean ICP was lower during LPV than CV (14.1±4.2 Vs 14.7±4.7; p=0.019). There was significant improvement in PaO_2, $PaCO_2$-$ETCO_2$ gradient, alveolar- arterial O_2 gradient and PaO_2/FiO_2 ratio during LPV. Airway pressures including driving pressure were also significantly reduced at T2 in both groups with similar systemic hemodynamic variables.

Conclusion

Cerebral hemodynamics were comparable and ICP was lower in LPV Vs CV. LPV is superior in terms of respiratory parameters which indirectly benefits neurosurgical patients.

1. INTRODUCTION

1. INTRODUCTION

Optimizing the perioperative ventilation strategy in patients with brain diseases especially in the setting of acute brain injury, intracranial pressure, etc. is very challenging for the neuroanaesthesiologist. The conflicts between potential or actual lung and brain injury in terms of the pathogenesis and management is a matter of debate for many years. Mechanical ventilation is an essential part of severe brain injury management especially in patients with refractory intracranial pressure. Damage to the lungs, like ventilator associated pneumonia (VAP), acute respiratory distress syndrome (ARDS) and neurogenic pulmonary oedema may occur as a result of acute brain injury. Occurrence of these complications and subsequent mechanical ventilation for lung support can worsen the secondary brain injury, increase the morbidity and mortality, neurological outcome and increase intensive care unit and hospital length of stay.(1) In addition to the above issues, patients undergoing various neurosurgical procedures necessitates general anaesthesia with mechanical ventilation.

The primary aim of the mechanical ventilation during the neurosurgical procedures is to maintain the oxygenation, control the CO_2 elimination at the lowest intrathoracic pressures. The secondary objectives are to maintain the cerebral and systemic hemodynamics, adequate cerebral oxygenation, brain relaxation and control of ICP, prevention of secondary brain injury and avoidance of postoperative pulmonary complications (POPC).(2) The anaesthetic management of resection of intracranial space occupying lesions (ICSOL) targets maintenance of cerebral perfusion pressure (CPP), cerebral oxygenation and avoidance of rise in intracranial pressure (ICP) and brain swelling. Hyperventilation is usually performed to reduce

intraoperative brain oedema. To fulfil these objectives, conventional mechanical ventilation with a tidal volume of 10-12 ml/kg, aimed to provide mild hyperventilation ($PaCO_2$ 32-35 mm Hg) is commonly employed during neurosurgical procedures.

Inappropriate mechanical ventilation even for shorter periods of time can lead to lung damage. Occurrence of the Ventilator-induced lung injury (VILI) is a major concern in conventional mechanical ventilation strategies. The important mechanisms by which the VILI occurs include alveolar overdistention (volutrauma), barotrauma, atelectotrauma, and inflammation (biotrauma).(3) Bickenbach, et. al, in porcine model found that high Vt (12ml/kg) ventilation could increase the inflammatory response and impair cerebral oxygenation and metabolism compared to low Vt.(4) Therefore, lung protective ventilation strategy (LPV) is now more frequently applied in various surgical procedures.

The LPV strategies are used to prevent injury from alveolar overdistention by using lower Vt and lower inspiratory pressures (volume and pressure-limited ventilation) or injury from ventilation with atelectasis and alveolar flooding at the end of expiration by using positive end expiratory pressure (PEEP) application.(5) According to ARDSNet criteria, components of LPV are low Vt (6-8ml/kg predicted body weight), low positive end expiratory pressure (PEEP) and often include permissive hypercapnia.(6) The 'Multicentre Local ASsessment of VEntilatory management during General Anaesthesia for Surgery' (LAS VEGAS) study results showed that low Vt and PEEP were not associated with increase in POPCs. (7)

It is well known that the respiratory physiological parameters influence the cerebral blood flow (CBF) predominantly arterial partial pressure of carbon dioxide ($PaCO_2$)

and oxygen (PaO_2), intracranial pressure and cerebral venous return by the effects of airway and intrathoracic pressure. It is noted that in various studies on protective intraoperative ventilation neurosurgical patients were usually excluded because of the theoretical knowledge that use of low Vt during LPV might result in hypercapnia with detrimental effects on cerebrovascular physiology. Effect of variable PEEP and dynamic ventilatory parameters like plateau pressure (Pplat) and peak airway pressure on ICP and cerebral hemodynamics is still debated in various trials.(8)

Multimodal monitoring has been gaining traction in neurosurgical patients both intraoperatively and in critical care. Near-infrared spectroscopy (NIRS) is a non-invasive technique to measure regional cerebral oxygenation (rSO_2) with advantage of continuous monitoring. Transcranial doppler (TCD) measures cerebral blood flow velocity which can be used as a surrogate of CBF. Combination of NIRS, TCD and ICP monitoring are helpful in the maintenance of CPP and providing individualized patient care.

In the recent publication on the recommendations of the European Society of Intensive Care Medicine consensus, with regards to the role of mechanical ventilation in patients with acute brain injury, the authors were unable to provide a suitable recommendation on LPV in patients with acute brain injury who have clinically significant ICP elevation. Moreover, the guidelines did not mention on the role of LPV in brain injured without raised ICP features.(9) Hence it is important to study the effects of LPV in patients on cerebral physiology with various brain diseases to come to meaningful conclusion.

Lulu jiang et al found that intraoperative administration of small Vt and PEEP is beneficial to traumatic brain injury (TBI) patients in terms of improved oxygenation and respiratory mechanics parameters, decreased incidence of PPCs, and smaller elevation in serum levels of biomarkers.(10) However, the fact that no study till date exist which assesses the effects of LPV Vs conventional ventilation on cerebral hemodynamics during neurosurgery. We planned a study to understand the effects of LPV on cerebral hemodynamic changes.

1.1 Hypothesis:

Conventional mechanical ventilation is routinely employed during neurosurgical procedures, whereas lung protective ventilation is yet to attain the acceptance during neurosurgery.

Null hypothesis: We hypothesize that cerebral blood flow velocity, cerebral oxygenation and intracranial pressure will be different during lung protective ventilation as compared to conventional mechanical ventilation in the intraoperative period in patients undergoing elective neurosurgical procedures.

Alternate hypothesis: We hypothesize that no significant differences will occur in the cerebral blood flow velocity, cerebral oxygenation and intracranial pressure during lung protective ventilation as compared to conventional mechanical ventilation in the intraoperative period in patients undergoing elective neurosurgical procedures.

1.2 Aims and Objectives:

Primary aim:

The primary aim of the study is to compare changes in cerebral blood flow, cerebral oxygenation and intracranial pressure during lung protective ventilation Vs conventional mechanical ventilation in patients undergoing various elective neurosurgical procedures.

1. To assess the changes in cerebral blood flow velocity in lung protective ventilation.

2. To assess the changes in cerebral oxygenation with lung protective ventilation.

3. To compare changes in subdural intracranial pressure in lung protective ventilation before opening the duramater.

Secondary aim:

1. To assess the effects of lung protective ventilation on pulmonary oxygenation compared to conventional ventilation in elective neurosurgery

2. To assess the effects of lung protective ventilation on dynamic ventilatory parameters compared to conventional ventilation in elective neurosurgery

3. To assess the changes in systemic hemodynamics in lung protective ventilation compared to conventional ventilation in elective neurosurgery

2.LITERATURE REVIEW

2. LITERATURE REVIEW

Mechanical ventilation is an integral part of general anaesthesia. Intraoperative mechanical ventilation in elective neurosurgical procedures is commonly done by either volume control (VC) or pressure control (PC) mode. Limited literature exists on the preferred mode in intraoperative neurosurgical procedures.

The main components of VCV mode of mechanical ventilation include fraction of inspired oxygen (FiO_2), tidal volume (Vt), respiratory rate (RR), inspiratory – expiratory ratio (I:E ratio) and positive end expiratory pressure (PEEP). During VCV, airway pressure may increase in response to low compliance, increased resistance or active exhalation which can increase the risk of VALI. In contrast, PCV limits the delivered airway pressure to the lung, but may result in variable tidal volume.(11) The positive pressure ventilation during anaesthesia will cause mismatch between the ventilation (going preferentially to the non-dependent lung regions) and perfusion (going preferentially to the dependent lung regions). This shunting depends on the fraction of cardiac output undergoing gas exchange in the pulmonary capillary bed. Meta-analysis show that volume guaranteed PCV provides lower Peak and plateau pressure, better lung compliance and PaO_2/FiO_2 ratio compared to VCV in elective surgery.(12) Similar results are shown in spine surgery done in prone position, but intraoperative hemodynamic variables were similar between the two modes.(13)

VALI can occur as a complication of non-physiological mechanical ventilation.(14) It includes volutrauma (alveolar overdistension), barotrauma (alveolar rupture and

pneumothorax), atelectrauma (repeated opening and closure of alveoli) and biotrauma (release of inflammatory mediators). Atelectasis develops in around 90% of patients undergoing general anaesthesia due to collapse of small airways, compression of alveoli, impairment of lung surfactant function and absorption of intra-alveolar gas content.(15)

The benefits of either VC or PC mode in acute lung injury is a matter of debate. In a Cocharane review, Binila Chacko et al. noted that the evidence with ventilation with either mode in reducing mortality and barotrauma was insufficient.(16)

High tidal volume, application of appropriate PEEP and recruitment manoeuvres have shown to prevent atelectasis during intraoperative period.(17) Recent literature supports use of the lung protective ventilation (LPV) approach in areas such as multiple transfusions, trauma, sepsis, and high-risk cardiac surgeries. Limited data exists about the role of intraoperative LPV in elective neurosurgical procedures.(18)

2.1 Effects of Mechanical Ventilation on Brain

It is important to understand the effects of mechanical ventilation on the cerebral hemodynamics and the interaction with brain injury. Acute brain injury patients presenting with concomitant lung injury are associated with high morbidity and mortality.(19) It is well known that there is a complex crosstalk of the brain with organs like heart and lung. Neurogenic pulmonary edema and acute lung injury occurring as complications of acute and chronic cerebral pathologies due to excessive sympathetic discharge and release of inflammatory mediators point towards the importance of stabilizing both end organs.(20) Literature on management of these patients is well known. In contrast to acute brain injury, in patients presenting with

gradual onset, slow growing brain pathology like tumors limited knowledge exists on the lung involvement. Neurosurgical procedures can result in acute brain injury, initiate stress and systemic inflammatory response that can affect other organ functions.

The use of the ventilator affects the ICP, cerebral blood flow and oxygenation of brain-injured patients in multiple ways. Although strategies that emphasize maximum oxygen support with high FiO_2 have been proposed, studies are limited about benefit of prophylactic use of high FiO_2 in brain injured patients. Moreover, it can result in oxygen induced lung injury in the form of absorption atelectasis especially in patients with pulmonary compromise. So, high FiO_2 is not needed as long as peripheral oxygen saturation is adequate.(21) Recent development of neuromonitoring modalities like NIRS, jugular venous oximetry and intraparenchymal brain sensors will help in assessment of cerebral oxygenation.

Historically, mechanical ventilation of the lungs in the operating room or intensive care unit (ICU) utilizes relatively large tidal volumes. (10-12 ml/kg) High Vt or maintaining a positive pressure of 20 cm H_2O to 25 cm H_2O is advocated to increase end expiratory tidal volume which in turn results in reduction of intraoperative atelectasis. Bendixen et al. did a study including 18 healthy people requiring general anaesthesia. One group of participants received 1% halothane while the other group received nitrous oxide. PCV mode of ventilation with pressure between 15-20 cm H_2O was applied in both groups at a rate between 20 breaths per minute and 25 breaths per minute. PaO_2, $PaCO_2$ and compliance were measured every 10-30 minutes starting after 10 seconds of hyperinflation at 20-25 cm H_2O. The authors found that there was

15% decrease in compliance and 22% decrease in PaO_2 over time. There was a linear relationship between decrease in PaO_2 and increase in $PaCO_2$ over time. They concluded that hyperinflation which resulted from larger tidal volume was protective against atelectasis and intrapulmonary shunt, whereas smaller tidal volume would facilitate them.(22) So, since the 1960s, supraphysiologic tidal volume was more demanded. Recently, in a 5-year observational study, in which 45,575 patients were recruited, 16–18 % of patients continued to receive a Vt more than 10 ml/kg without application of PEEP. The presence of obesity and a less height were the main risk factors for receiving a large Vt during prolonged general anaesthesia.(23)

Hyperventilation to reduce $PaCO_2$ allows dramatic reduction in ICP in neurosurgical patients. This method is often employed in ventilating patients to achieve higher minute ventilation through increases in the Vt or RR. The hypocapnia induced alkalosis results in vasoconstriction and CBF is decreased, which causes lowering of ICP. It is mediated by mechanisms involved in the perivascular space of the small arterioles of cerebral parenchyma. This result in temporary right shift of autoregulatory curve, resulting in lower CBF and ICP at higher mean arterial pressure (MAP). But the effect of hypocapnia on ICP will remain only for 6–12 hours after initiation. The Brain Trauma Foundation (BTF) guidelines advocate hyperventilation to reduce refractory increase in ICP in severe TBI patients with advanced neuromonitoring methods like jugular venous oximetry and brain tissue oxygen saturation ($PbtO_2$).

2.2 Lung protective ventilation strategies

2.2.1 Evolution of lung protective ventilation

LPV uses low tidal volume (Vt) , and avoids high plateau pressures (Pplat) along with use of appropriate positive end expiratory pressure (PEEP).(24) The famous Acute Respiratory Syndrome Network (ARDSnet) trial compared lower tidal volume ventilation (6ml/kg with maximum plateau pressure of 30 cmH_2O) with traditional tidal volume ventilation (12ml/kg with maximum plateau pressure of 50 cm H_2O) for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The results showed that mortality was lower in the group treated with lower Vt than in the group treated with traditional Vt (31% vs 39.8%, P=0.007), and the number of ventilator free days during the first 28 days after randomization was higher in this group (mean ± SD, 12±11 vs. 10±11; P=0.007).(25) Thereafter LPV is considered as a standard of care in ARDS patients by minimizing alveolar overdistension and barotrauma, titration of oxygen to avoid severe hyperoxia.(26) According to ARDSnet ventilation strategy predicted body weight (PBW) in kg was used to calculate Vt. PBW in males is computed by 50 + 0.91(cm of height- 152.4) and 45.5 + 0.91(cm of height- 152.4) in females.(27) Although this trial was prematurely terminated after enrolment of 861 participants, many subsequent trials and meta-analysis confirmed the advantage of LPV in both patients with diseased lung and normal lung.(28) The plateau pressure may be misleading in some conditions as spontaneously breathing patients shows lower Pplat, but the lung overdistension and transalveolar pressure may still be high because of large pleural pressures. Likewise, patients with reduced chest wall

compliance (obesity, increased intra-abdominal pressure) may have high Pplat without pulmonary overdistension.

2.2.2 Lung protective ventilation in patients with lung injury

Patients with a diseased lung like ARDS have impaired endogenous surfactant system independent of the cause and increase in surface tension will result in atelectasis of alveoli, pulmonary oedema, enlargement of the functional right-to-left shunt, impaired gas exchange and further hypoxemia. These patients require proper mechanical ventilation to reduce their work of breathing to decrease the life-threatening hypoxemia and respiratory acidosis. But ARDS lung requires higher airway pressure to achieve targeted tidal volume due to lower distensibility compared to healthy lung. Sponge lung concept explains the non-homogeneity of alveoli and the superimposed pressure causing closure of dependent lung regions. The use of appropriate PEEP opposes these counteracting pressures.

The use of LPV in animal studies has shown that it reduces diffuse alveolar damage with pulmonary oedema, activation and recruitment of inflammatory cells, local production of inflammatory mediators such as cytokines and leakage of these mediators in to the systemic circulation.(29) Amato et al. studied the effect of protective ventilation strategy in ARDS. They compared conventional ventilation (Vt of 12 ml/kg with lowest PEEP for acceptable oxygenation and normal $PaCO_2$) and protective ventilation (less than 6 ml/kg, driving pressures of less than 20 cmH2O above PEEP and permissive hypercapnia). The results showed that 11 of 29 patients (38%) in the lung protective group had died, as compared with 17 of 24 (71%) in the conventional ventilation group ($P<0.001$) at 28 days. The authors also found

significant reduction in barotrauma and faster weaning from the ventilator in the protective ventilation group.(30)

The European Society of Intensive Care Medicine (ESICM), Society of Critical Care Medicine and American Thoracic Society clinical practice guidelines recommend strong evidence for mechanical ventilation with low Vt (4-8 ml/kg PBW) and lower inspiratory pressures (Pplat <30 cm H_2O) (moderate confidence in effect estimates) in ARDS patients.(31) In a retrospective study, Gajic et al reported 3,261 mechanically ventilated patients who did not have ARDS at the onset in which 205 (6.2%) patients developed ARDS 48 hours or more after the initiation of mechanical ventilation. The main risk factors associated with lung injury were large tidal volume, high PEEP and high peak pressure at initial ventilator setting, acidaemia, history of restrictive lung disease and transfusion of blood products.(32) The main aim of LPV is to decrease regional end inspiratory stretch, thereby reduce alveolar damage as well as alveolar decompartmentalization or inflammation.

2.2.3 Lung protective ventilation in patients without lung injury

Recent studies have shown that mechanical ventilation with traditional Vt initiates and exacerbates an inflammatory response, when compared with low Vt ventilation with appropriate PEEP, not only in injured lungs but in healthy lungs as well. Subsequently, anaesthesiologists have started using the ‘low Vt’ concept with the assumption that healthy patients also need ‘lung protection’ from the deleterious effects of high Vts.

Wan-Jie Gu et al. had done a meta-analysis of 19 randomized control trials (RCTs) to evaluate the effect of this unique ventilation strategy on postoperative outcomes. The results showed that patients in LPV group had a reduced risk of acute lung injury (RR 0.36, 95% CI 0.17 to 0.78; I^2 = 0%) and lung infection (RR 0.46, 95% CI 0.26 to 0.83; I^2 = 8). No statistically significant differences were observed between both groups in occurrence of complications such as atelectasis, length of hospital stay, length of intensive care unit stay, mortality and the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (P/F ratio).(18) The multicentre Intraoperative Protective Lung Ventilation (IMPROVE) trail enrolled 400 adult patients undergoing major abdominal surgeries to study the benefit of LPV. The results showed that 5% of patients who underwent LPV required non-invasive ventilation or intubation in the postoperative period as compared to 17.0% assigned to nonprotective ventilation method (RR, 0.29; 95% CI, 0.14 to 0.61; P = 0.001). The hospital length of stay was also lower in patients receiving protective lung ventilation than control group (mean difference, −2.45 days; 95% CI, 4.17 to −0.72; P = 0.006).(33)

Frederico Longini et al conducted a single-centre, pilot RCT at the University Hospital “Maggiore della Carità” (Novara, Italy) to evaluate feasibility of LPV in patients undergoing major neurosurgical interventions. They recruited 60 patients, randomized in to spinal and cerebral neurosurgical interventions. No significant difference was found between groups in the rate of composited and separated intraoperative complications. The brain relaxation score assessed by the surgeon was comparable in both groups (grade 2 score-42.9%(n=9) in control group vs 43.5% (n=10) in LPV) (8). This study concluded that LPV is feasible in neurosurgical population in spite of the

controversial effect of hypercarbia resulting from low Vt and its effect on cerebrovascular physiology.

In another RCT, Dharshi et al. studied the effect of intraoperative low Vt (6ml/kg PBW) vs conventional Vt (10 ml/kg PBW) on POPCs in patients undergoing major surgery. All 1236 patients received PEEP of 5 cm H_2O. The POPCs was not statistically significant between low Vt (38%) and high Vt (39%) group within first 7 postoperative days. But, participants in low Vt group had significantly lower airway peak pressures (mean difference, −2.4 cmH_2O [95% CI, −3.1 to −1.7 cm H_2O]; $P < .001$).(34)

Type of surgery	Author	Number of patients	Tidal Volume (ml/kg) Case/ control	PEEP (cmH2O) Case/ control	Recruitment Case/control	Outcome
Cardiac	Reis et al.(35)	69	4-6/6-8	10/5	Yes/ No	Lower postoperative hypoxemia and better FRC
	Zupancich et al.(36)	40	8/10-12	10/2-3	No/No	Reduced pulmonary and systemic inflammatory markers
	Wrigge et al.(37)	44	6/12	9/7	No/No	Lower pulmonary inflammatory markers, similar systemic inflammatory markers
	Sundar et al.(38)	149	6/10	5/5	No/No	Time to extubation was similar, lower reintubation rate

Thoracic	Schilling et al.(39)	32	5/10	0/0	No/No	Reduced pulmonary IL-8, IL-10, TNF-α
	Michelet et al.(40)	52	5/9	5/0	No/No	Reduced systemic IL-6&8, IL-1 B, better oxygenation
	Yang et al.(41)	100	6/10	5/0	No/No	Better oxygenation, lower POPC
Abdominal	Weingarten et al.(42)	40	6/10	12/0	Yes/No	Better intraoperative PaO2 & lung mechanics
	Treschan et al.(43)	101	6/12	5/5	No/No	Similar postoperative dynamic spirometry
	Severgnini et al.(44)	56	7/9	10/0	Yes/No	Lower clinical pulmonary infection score, better postoperative respiratory function
	Futier et al.(45)	400	6-8/10-12	6-8/0	Yes/No	Lower pulmonary and extrapulmonary complications, shorter hospital stays

Table 2.1. Randomized controlled trials comparing LPV VS CV during general anaesthesia. POPC, Postoperative pulmonary complications, FRC, functional residual capacity.

2.2.4 Effect of low tidal volume with PEEP

Although several studies of low Vt have consistently shown improvement in pulmonary function and reduction of PPCs, the optimal level of PEEP remains a matter of debate. However, the use of a low Vt without adequate PEEP may increase the risk of atelectrauma as a result of cyclic lung de-recruitment (fig 2.1). This is shown by a

large retrospective study by Levin et al. including 29,343 participants who underwent general anaesthesia with mechanical ventilation between 2008 and 2011. The authors found that low Vt (6–8 ml/kg PBW) with minimal PEEP was associated with a significant increase in 30-day mortality compared to conventional Vt (8–10 ml/kg IBW) with hazard ratio (HR) of 1.6 [95% confidence interval (CI) [1.25-2.08]; P=0.0002].(46)

The effects of zero end expiratory pressure (ZEEP) include a major reduction in end-expiratory lung volume (EELV) after anaesthesia induction and also an increase in the regions of atelectasis. This loss of EELV and atelectasis contribute to decreased respiratory system compliance in de-recruited areas and increased risk for overinflation of aerated lung tissue. The level of PEEP should be chosen according to the individual characteristics like the type of surgical approach and positioning. Thus, individual titration of PEEP depends on oxygenation, dead space or EELV, mechanical properties of the respiratory system and distribution of ventilation. Clinical studies have shown that adequate PEEP is required to improve lung compliance without increasing dead space and maintain EELV during general anaesthesia (GA) in both obese and non-obese individuals. So, allowing airway/alveolar pressure to achieve ZEEP is not recommended and optimal PEEP increases oxygenation; and improves dependent lung ventilation and postoperative pulmonary function.

However, one large international multicentre RCT, protective ventilation during GA for open abdominal surgery: high versus low positive end-expiratory pressure (PROVHILO) revealed no significant difference in the development of postoperative pulmonary complications (POPCs) with low Vt and either high or low levels of PEEP

(≤2 cm H_2O vs 12 cm H_2O). The results also showed that patients in the higher PEEP group developed more intraoperative hypotension and need for more vasoactive drugs compared to low PEEP group.(47)

Low Vt + Low PEEP	Higher atelectasis + minimal overinflation
High Vt + Low PEEP	Less atelectasis + overinflation at end-inspiration + higher collapse and reopening of alveoli during breathing cycling
Low Vt + High PEEP	Less atelectasis + overinflation at end inspiration and expiration + minimal collapse and reopening of alveoli during breathing cycling

Table 2.2. showing effect of high and low tidal volume and variable PEEP during general anaesthesia.

PEEP is most effective if proceeded by a recruitment manoeuvre to open up the collapsed alveoli for improving the oxygenation. Different methods for employing recruitment include “bag squeezing method” by partial closure of airway pressure limiting valve, stepwise increment of tidal volume or gradual increase of PEEP. This method decreases intrapulmonary shunt and improve the lung compliance. The disadvantages of recruitment manoeuvre are overdistension of alveoli, injury to pulmonary epithelium and increase in the intra-thoracic pressure which compromises hemodynamic parameters because of reduction in venous return and

cardiac output for a smaller duration. So, the optimal method of recruitment that gives the best balance of benefit and risk and the effects on long term clinical outcome are still under debate, and more evidence is needed. (48)

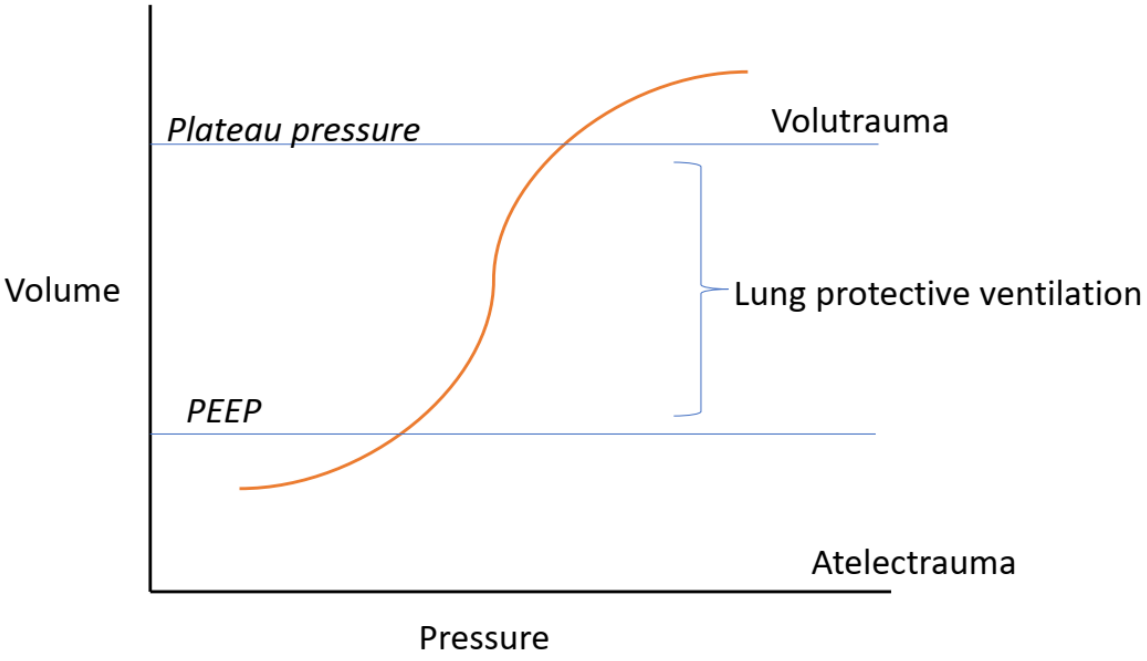

Fig. 2.1 showing action of lung protective ventilation on volume- pressure inspiratory curve.

2.3 Consequences of lung injury and mechanical ventilation on brain function

Lung injuries or pathologies that affect oxygenation can cause changes at neuronal level of both peripheral and central nervous system. These alterations result in memory problems, cognitive problems, disorientation and language alterations.(49)

The alveolar stretch causes recruitment of macrophages and monocytes in the lungs which increases neuroinflammatory mediators that can directly reach the CNS through the humoral route. The afferents of the vagal pathway connect the brain and the nucleus of the solitary tract and alteration in vagal signalling implicated as cognitive impairment. Also release of tumour necrosis factor (TNF) in the lungs stimulates the release of monocyte chemoattractant protein-1 at the brain level, which promotes the recruitment of activated monocytes both at the level of peripheral nervous system and CNS.(50)

The triggering factors initiated in the lung in the form of alveolar damage, micro thrombosis, capillary leak, impaired gas exchange, lung oedema and impaired mechanics can lead to increase in transpulmonary and trans vascular pressures. These pathophysiological changes can signal higher brain centres which in turn lead to flow desynchrony and higher respiratory drive. The biochemical input (acidosis, dead space, shunt), mechanical input (from lung mechanoceptors) and suprapontine input (anxiety, discomfort, pain) along with neurotropism and neuroinflammation are the major CNS triggers for elevated respiratory drive. It can cause diaphragm and lung injury if unrecognised. Therefore, we should optimise the ventilatory settings with the importance of peak inspiratory flow relative to individual requirement.(51)

Bickenbatch et al. evaluated the neurological outcome after experimental lung injury and hypoxia in pigs. They randomised study subjects into hypoxia only group and acute lung injury (ALI) group. After the study, neurocognitive performance had worsened, and the neurologic deficit score (NDS) elevated in the ALI group. But histopathology examination revealed no significant differences. Oxygenation was

comparable between groups, but inspiratory pressures was significantly higher after ALI. The inflammatory mediators like cytokines showed higher levels in ALI group. The authors concluded that the neurocognitive compromise after ALI seems to be due to an increased inflammatory response and deleterious mechanical ventilation.(4)

2.4 Effect of brain injury on pulmonary function

Lung is one of the main organs which gets affected as an extracranial manifestation of brain injury especially in acute scenario line TBI. The most important conditions passed from brain to lung include neurogenic pulmonary edema (NPE), ARDS and ventilator associated pneumonia (NPE). As a primary response after trauma, there will be catecholamine storm which can result in increase in pulmonary hydrostatic pressure and capillary permeability. In addition, cerebral and systemic inflammatory response will be triggered which causes pulmonary chemotactic hyperactivity, alveolar phagocytic action and massive destruction of type 2 pneumocytes. These changes impart severe oedema, alveolar inflammation and the end point is acute lung injury.(49) The increased sympathetic activity after brain trauma is due to cerebral hypoxia and intracranial hypertension. Also elevated systemic arterial blood pressure and increased left atrial and lung hydrostatic pressure, culminating in pulmonary oedema, are attributed to rise in sympathetic response, mainly α-adrenergic, provoked by lesions of the hypothalamus or spinal cord.(52)

The general risk factors for the development of ARDS after brain injury and mechanical ventilation (MV) are found to be young age, male sex, ethnicity, history of chronic arterial hypertension, diabetes, chronic obstructive pulmonary disease

(COPD), development of sepsis, involvement of cardiovascular, renal, and haematological dysfunctions.(53) The distribution of ARDS has a bimodal involvement, consisting of an early peak on the second or third day after the initiation of MV and a later peak on the eighth or ninth day after ventilation, usually related to pneumonia.

2.5 Effect of lung protective ventilation on cerebral homeostasis

The balance between cerebral blood inflow and outflow is critical to maintain normal ICP and CPP. Cerebral metabolic rate (CMR) predominantly depends on the utilization of glucose and oxygen in the brain. Among the total energy produced in the brain, 60% is consumed to maintain neuronal integrity and 40% utilized for cellular homeostasis. Recent evidence from Monro-Kellie 2.0 doctrine establishes the importance of extracranial venous system for the maintenance of cerebral homeostasis. According to this hypothesis any cause of increased intrathoracic pressure like chest infection, mechanical ventilation or ARDS cause extracranial venous hypertension through increasing the resistance within the thorax.(54) This can be mitigated by providing low tidal volume, and by avoiding high PEEP and unnecessary recruitment manoeuvres.

A systemic review of respiratory mechanics in brain injury by Antonia et al. concluded that brain damaged individuals without ALI exhibit variations of respiratory system mechanics, most importantly increased pulmonary elastance and airway resistance, and hypoxemia. Optimal ventilatory management of such patients should target at optimizing neurologic protection, but at the same time avoiding further deterioration

of pulmonary dysfunction. According to the authors, the ventilator parameters probably associated with better prognosis include low Vt and moderate levels of PEEP.(55)

2.5.1 Lung protective ventilation in brain-injured patients

Ventilation strategies in brain injured patients a major challenge to anaesthesiologists since the fragile brain- lung balance should be preserved. Prevention of secondary brain injury is most important by avoiding hypoxia and hypercarbia. A multicentre cross-sectional study and survey of LPV in brain injured patients was done in China including 47 ICUs. They enrolled mechanically ventilated patients (>18 years) with brain injury including TBI, stroke, post-surgery with intracranial lesion, hypoxic-ischemic encephalopathy (HIE), cerebral infection, and idiopathic seizure. The median Vt was 8 ml/kg (interquartile range [IQR], 7.0–8.9 ml/kg) of the PBW; 50 (48.1%) patients received LPV. The median PEEP was set to 5 cmH2O (IQR, 5–6 cmH2O).(56)

Another study by Mascia et al. assessed the role of extracranial predisposing factors, including hemodynamic and ventilatory management, as predictors of ALI in brain injured patients. The results found that in addition to a reduced PaO_2/FiO_2 (odds ratio (OR) 0.98, 95% confidence interval (CI) 0.98-0.99), ventilation with high Vt (OR 5.4, 95% CI1.54-19.24) and relatively increased RR (OR 1.8, 95% CI 1.13-2.86) were independent predictors of ALI ($p < 0.01$).(57)

2.5.2 Effect of lung protective ventilation on Cerebral blood flow

Major determinants of cerebral blood flow are cerebral metabolic rate of oxygen ($CMRO_2$), myogenic regulation, carbon dioxide (CO_2) reactivity, oxygen (O_2)

reactivity, blood viscosity, temperature, and autonomic influences. CBF-metabolism coupling is described as the proportional change in global or regional cerebral perfusion in response to neuronal activation or stimulation.(58) Low tidal volume can result in harmful hypercapnic acidosis if RR is not adjusted to maintain minute ventilation which may be deleterious in brain injured patients. L Schlunzen et al. studied regional CBF responses to hyperventilation during anaesthesia with sevoflurane using positron emission tomography (PET). They found that mean $PaCO_2$ decreased from 5.5 ± 0.7 to 3.8 ± 0.9 kPa during hyperventilation and total CBF decreased during the hypocapnic state by 44% and it is more pronounced in subcortical grey matter.(59)

Cerebral autoregulation refers to the ability of cerebral vasculature to maintain CBF relatively constant between 50 and 150 mm Hg mean arterial pressure (MAP). CBF begins to decrease below the lower limit of autoregulation (LLA) curve, and it increases above the upper limit of autoregulation (ULA). Maximum vasodilation of the vasculature occurs at ULA and vasoconstriction is at its peak at LLA, after which CBF becomes pressure passive. Ludwig et al. studied the effect of airway pressure (Paw) changes on ICP and CBF velocity changes in MCA in severe TBI patients. They collected information from central venous pressure (CVP), ICP, MAP, CPP, MCA flow velocity and airway pressure, and were analysed on the basis of variations between the maximum (during inspiration) and minimum Paw values (during expiration). The results found that increase in Paw of 20 to 35 cm H_2O resulted in changes of the mean ICP from 4.1 to 6.0 mmHg ($r = 0.9$, $p < 0.05$). A correlation was obtained for the variations of systolic blood pressure and mean CPP due to Paw changes which ranged from 4.5 to 11.6 mmHg ($r = 0.99$, $p < 0.05$). The TCD CBF

velocity of the MCA showed a positive correlation to Paw with a $r = 0.99$, $p < 0.05$. The authors concluded that increase in venous outflow resistance and a transient increase in cardiac output have to be regarded as mechanisms for transmission of transthoracic pressure changes to intracranial pressure changes and the variations in elastance can be derived from intermittent airway pressure changes.(60)

2.5.3 Effect of lung protective ventilation on Cerebral oxygenation

Cerebral oxygen saturation monitoring has become a key indicator of cerebral perfusion in neurosurgical patients in the perioperative period. It helps for the early diagnosis and management of cerebral hypoxia and ischemia. Monitoring of cerebral oxygenation helps to avoid secondary brain injury caused by anoxia and ischemia. The effect of low tidal volume ventilation on cerebral oxygenation is less studied in clinical practice. Recently, Alberto et al. did a prospective observational study on the effect of PEEP increase (from 5 to 15 cm H_2O) on cerebral hemodynamics in patients with acute brain injury. PEEP increase from 5 to 15 cm H_2O did not lead to impaired autoregulation (PRx, from 0.17 (-0.003-0.28) to 0.18 (0.01-0.24), p=0.83). Even though ICP and CPP varied significantly (ICP from 11.11 (6.73-15.63) to 13.43 (6.8-16.87) mmHg, p=0.003, and CPP from 72.94 (59.19-84) to 66.22 (58.91-78.41) mmHg, p=0.004), these values did not reach clinically important levels. There were no significant changes in cerebral oxygenation measured by NIRS in the study. (61)

The cerebral hypoxia is described as 20 % decrease in rSO_2 value from the baseline or less than 50% of the absolute value. The interventions to improve rSO_2 include providing higher FiO_2, increasing the cardiac output and infusion of packed red cell to improve oxygen carrying capacity. Yuma Sato et al reported the usefulness of NIRS

monitoring during one lung ventilation (OLV) in idiopathic pulmonary fibrosis. In that case, although the SpO_2 value reduced to 80% (hypoxaemia), NIRS derived rSO_2 values remained higher than 60% (98.3% of baseline value). The authors concluded that estimating peripheral oxygenation with pulse oximeter alone would have resulted in targeting a higher FiO_2. But, NIRS monitoring allowed them to avoid a higher intraoperative FiO_2.(62)

In another study, Ishiyama et al studied effect of hyperventilation on cerebral oxygen saturation in sevoflurane and propofol based anaesthesia. They measured rSO_2, arterial carbon dioxide partial pressure ($PaCO_2$) and arterial oxygen saturation after induction of anaesthesia and 5minute and 15 minutes of hyperventilation to a $PaCO_2$ of 30mm Hg. The results showed that the rSO2 changes during hyperventilation were -10 ± 8% (left) and -9 ± 7% (right) in the sevoflurane group and -10 ± 7% (left) and -11 ± 8% (right) in the propofol group. They concluded that change in rSO_2 was well correlated with ventilation changes and the effects of hyperventilation on calculated rSO_2 were similar with sevoflurane and propofol anaesthesia.(63)

Cerebral desaturation during intraoperative period can result in postoperative cognitive dysfunction. The important role of LPV in preventing postoperative delirium (POD) in elderly patients undergoing spine surgery was studied by Wang J et al. They randomized 71 patients aged ≥65 years to receive LPV (Vt-6ml/kg PBW, PEEP-5 cm H_2O, RR-15/min and recruitment manoeuvre every 30 minute) or CV (Vt-8ml/kg PBW, RR-12/min). Arterial blood gas (ABG) analysis details and rSO_2 were recorded at different time intervals (induction (T_0), 10 min (T_1) and 60 min (T_2) after prone positioning, immediately after surgery (T_3), and 15 min after extubation (T_4). The

results found that compared with the CV group, pH was lower and $PaCO_2$ higher in the LPV group at T_2. The PaO_2, PaO_2/FiO_2 and SaO_2 were higher at T_1, and T_4, and rSO_2 was higher at T_3, and T_4 in the LPV group than in the CV ($P<0.05$ each). In addition, postoperative inflammatory markers such as serum GFAP and IL-6 were lower and IL-10 higher in the LPV group. The incidences of cerebral desaturation and POD were significantly lower in the LPV than CV($P<0.05$).(64)

2.5.4 Effect of lung protective ventilation on intracranial pressure

The classical LPV method used in ARDS lung consisted of a combination of low tidal volume, high PEEP and plateau pressure along with permissive hypercapnia. The increase in intrathoracic pressure associated with mechanical ventilation can result in increase in ICP and decrease in CPP. Transient hyperventilation is commonly employed to decrease refractory increase in ICP in neurosurgical practice. Hyperventilation induced hypocapnia decreases the $PaCO_2$, which induces vasoconstriction in the cerebral resistance arterioles. This constriction decreases CBF, which reduces cerebral blood volume (CBV) and, finally, reduces the patient's ICP. The effects of this therapeutic hyperventilation are temporary, but the risks associated with the changes in cerebral and systemic physiology must be carefully considered before the management can be deemed advisable.(65)

Data is limited whether the application of PEEP during mechanical ventilation adversely affects intracranial pressure (ICP) and cerebral perfusion pressure (CPP). The actions of PEEP on ICP are multifactorial. The application of high PEEP or high Vt causes increased intrathoracic pressure which is directly transmitted to intracranial compartment. Subsequent rise in jugular venous pressure also causes cerebral venous

congestion. This is coupled with reduced venous return and cardiac output. These overall effect leads to impairment of CPP.(66) But patients with normal ventricular and pulmonary compliance may have ability to buffer against variations in ICP in response to changes in venous outflow and vascular pressure. Myles et al. retrospectively studied the effect of PEEP on ICP in patients with severe acute brain injury. In the analysis, a statistically significant relationship between PEEP and CPP and between PEEP and ICP was detected only in observations found during periods of severe lung injury. For every cm of H_2O increase in PEEP, there was a 0.31 mmHg rise in ICP (p = 0.04; 95 % CI [0.07, 0.54]) and a 0.85 mmHg decrease in CPP (p = 0.02; 95 % CI [−1.48, −0.22]). These results suggest that PEEP can be safely applied in patients with acute brain injury because it does not have a clinically significant impact on ICP or CPP.(8) In other words, an optimal PEEP and low tidal volume strategy is preferred to maintain cerebral hemodynamics with improvement in oxygenation.(67)

3. MATERIAL AND METHODS

3.MATERIAL AND METHODS

We planned the current prospective observational study to compare the effect of intraoperative lung protective ventilation Vs conventional ventilation on ventilatory parameters, arterial blood gases and their effects on cerebral hemodynamics (cerebral blood flow assessment using transcranial doppler, cerebral oxygenation by NIRS and ICP measurement using subdural catheter) in patients undergoing elective neurosurgical procedures in the Neuro-Surgical Operation Theatre (NSOT) of Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, which is a specialized tertiary referral center. We also intend to compare the above parameters with those who had intracranial pathology with no intracranial pathology, namely the spine diseases undergoing surgical procedures.

Institutional Ethics Committee Approval: Institutional Ethics Committee approved our study. (IEC approval number: SCT/IEC/1845/FEBRUARY/2022).

CTRI Number: CTRI/2022/09/045844

Study Period: The study was conducted from March 2022 to April 2023.

Study Design: Prospective cross over randomized controlled study.

Patient enrolment: Patients for the study were recruited from the elective neurosurgical operation theatre list after fulfilling the inclusion and exclusion criteria enumerated below.

Inclusion criteria:

- Consenting adult patients undergoing craniotomy for supratentorial surgery in supine position or spinal surgery.
- Age 18-60 years.
- ASA (American Society of Anaesthesiologists) class 1 and 2
- Glasgow coma scale 15

Exclusion criteria:

- Patient refusal
- Craniotomies other than supine position
- Recent respiratory infection
- Patients with chronic lung disease or pulmonary infections 1 month before surgery
- Acute respiratory failure (pneumonia, acute lung injury, ARDS)
- Emergency surgery
- Patients with clinical signs (headache, vomiting, confusion, papilledema, pupillary asymmetry) or radiological signs (midline shift > 1cm, presence of hydrocephalus) of raised intracranial pressure preoperatively.
- Long standing uncontrolled diabetes mellitus, systemic hypertension, cardiovascular disease, COPD
- Patients with previous history of stroke, transient ischemic attacks
- Obesity, smoking

- ASA class 3,4,5 patients
- Patients with subarachnoid haemorrhage, vasospasm
- Pregnant and lactating mothers
- Any difficulty in TCD insonation and NIRS application

Study protocol

Informed written consent was obtained from the from the patients fulfilling the criteria for recruitment.

The selected patients were divided into the following groups:

- Group A: Those who had supratentorial tumours undergoing craniotomy for tumour excision.
- Group B: Those who are undergoing spine surgery for spinal cord disease.

For all the recruited patients, baseline demographics and predicted body weight was calculated. Predicted body weight (PBW) was calculated as 50$\pm$2.3 (height in inches – 60) in males and 45.5$\pm$2.3 (height in inches – 60) in females. PBW was used to calculate the tidal volumes. For conventional ventilation a Vt of 10ml/kg PBW and for LPV, a Vt of 6ml/kg of PBW was calculated for employing in the intraoperative period.

Preoperative fasting period was nil per oral of 6 hours for solid foods, 4 hours for liquids and 2 hours for clear fluids. No opioid/ sedative premedication was given. Patients were administered their routine medications like antiepileptics, steroids and

anti-aspiration prophylaxis in the form of pantoprazole 1mg/kg orally as per our institute protocol.

Patients were shifted to the operation room (OR) after completing WHO (World Health Organisation) surgical safety checklist. In the OR, for ASA standard monitoring consisting of ECG (Electrocardiography), peripheral oxygen saturation using pulse oximeter, non-invasive blood pressure monitoring (NIBP), bi-spectral index sensor for monitoring depth of anaesthesia and for regional cerebral oxygenation (rSO2) using NIRS with bilateral sensors on forehead (Masimo Root O3, California, USA) were initiated (figure 1).

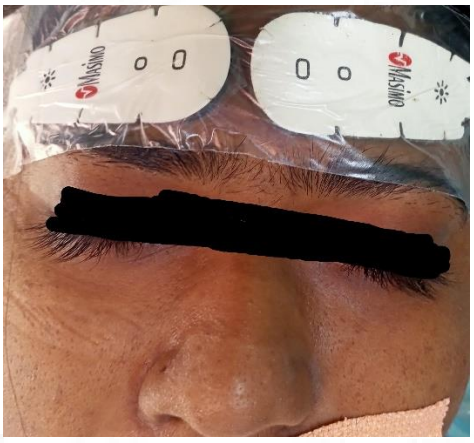

Figure 3.1 shows NIRS electrode position on the forehead.

Baseline (T0) hemodynamic parameters including heart rate, blood pressure (systolic, diastolic and mean arterial pressure (MAP), SpO_2 and BIS value, rSO_2 were recorded.

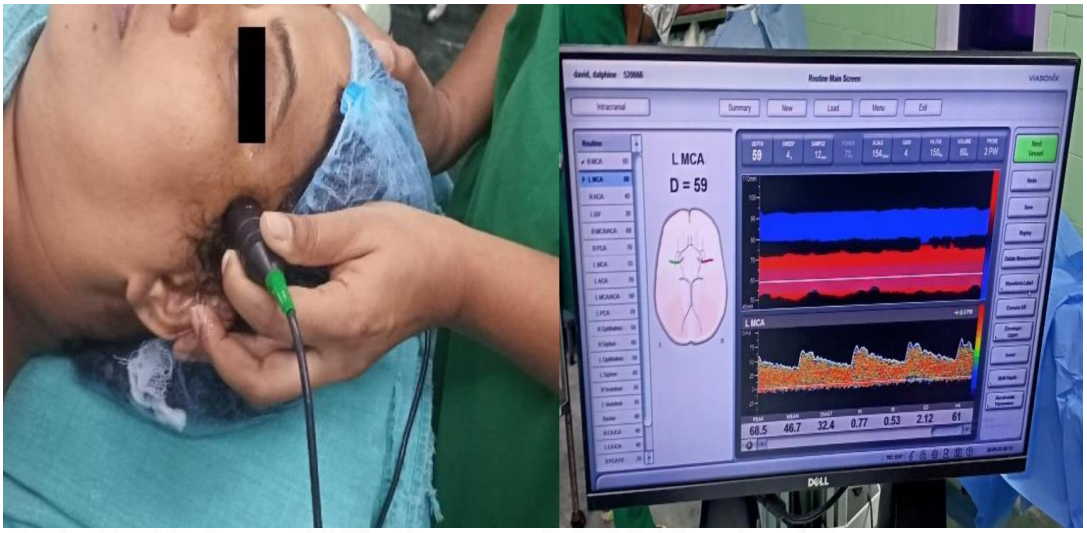

Figure 3.2. Trans-temporal insonation of TCD probe and the monitor showing TCD waveform and CBF velocities.

Baseline TCD examination of bilateral middle cerebral artery (MCA) was done before inducing anaesthesia as described below.

Technique for MCA flow velocity assessment by TCD

The patients were placed in supine position with head positioned in neutral position and with a head support of height 15 cm. The 2 MHz TCD probe (Dolphin Viasonix) was placed in front of the tragus of ear above an imaginary line joining outer canthus of the eye to the tragus on the same side (figure 2). The depth in the TCD monitor was pre-set to 40-60 mm with power setting of 50% and gain of 8. The MCA flow was identified in the M-mode window showing red colour. The TCD flow velocities including peak systolic flow velocity (PSV), mean flow velocity, end diastolic velocity (EDV) and the pulsatility index (PI) were recorded bilaterally from the dedicated window for the same.

After recording the baseline data, a wide bore intravenous cannula (16G) was inserted in the peripheral vein. All the recruited patients were preoxygenated for 3 minutes with FiO2 of 1.0 at a flow rate of 10L/min. General anaesthesia was induced with fentanyl 2 mcg/kg and propofol 2 mg/kg and vecuronium 0.2 mg/kg was given after confirming mask ventilation and proceeded with endotracheal intubation. The patients were ventilated in the volume control mode, initially using the conventional ventilation (CV) method with the settings of; tidal volume of 10ml/kg of predicted body weight, an inspiratory-expiratory ratio (I: E) of 1:2, Oxygen/Air mixture of 50:50, and positive end expiratory pressure (PEEP) -5cm H_2O. The respiratory rate was adjusted targeting a $ETCO_2$ value of 32-36mm of Hg. Assuming a $PaCO_2$-$EtCO_2$ gradient of 4 mm Hg, we anticipated that this $PaCO_2$ will be normocarbia range. Anaesthesia was maintained using TIVA with propofol 100-150 microgram/kg/min and fentanyl 2microgram/kg/min. BIS value was maintained between 50 and 60. Invasive arterial line via, radial artery cannulation was done.

After 10 minutes of steady state of ventilation and hemodynamics, arterial blood gas sample, bilateral rSO_2 values and TCD parameters of bilateral MCA such as peak systolic velocity (PSV), mean flow velocity, end diastolic velocity (EDV) and pulsatility index (PI) were noted and recorded as T1.

Once the recording at CV was completed, lung protective ventilation (LPV) was initiated by reducing the tidal volume to 6 ml/kg predicted body weight and PEEP-5. Respiratory rate was readjusted to $ETCO_2$ value of 32-36mm of Hg by ensuring adequate minute ventilation (figure 3).

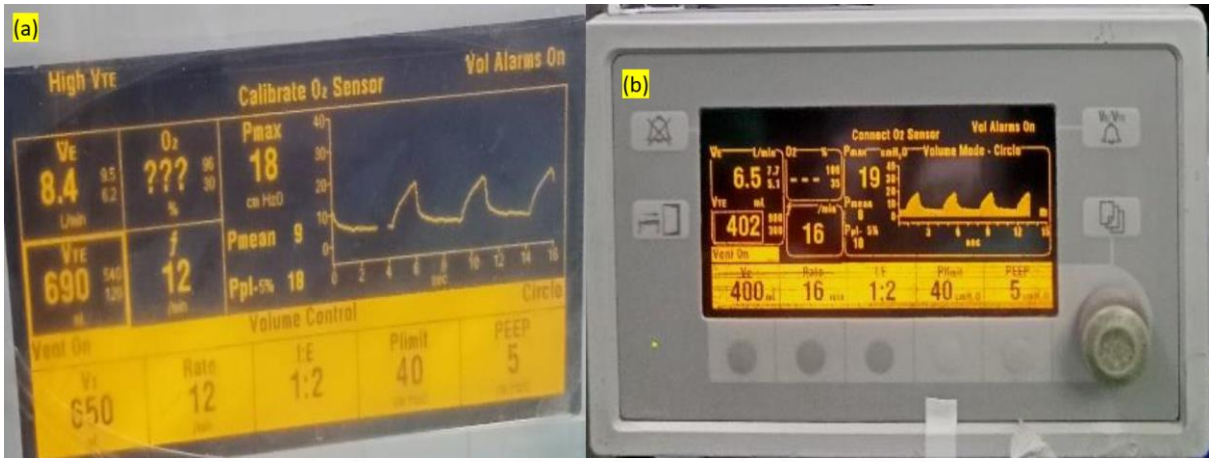

Figure 3.3. Ventilator settings and dynamic ventilatory parameters during (a) conventional ventilation and (b) lung protective ventilation.

After 10 minutes of steady state of ventilation and hemodynamics, arterial blood gas sample, bilateral rSO_2 values and TCD parameters of bilateral MCA such as peak systolic velocity (PSV), mean flow velocity, end diastolic velocity (EDV) and pulsatility index (PI) were noted and recorded as T2 (figure 4 & 5).

Figure 3.4.: showing NIRS values recorded at T0, T1 and T2 time points.

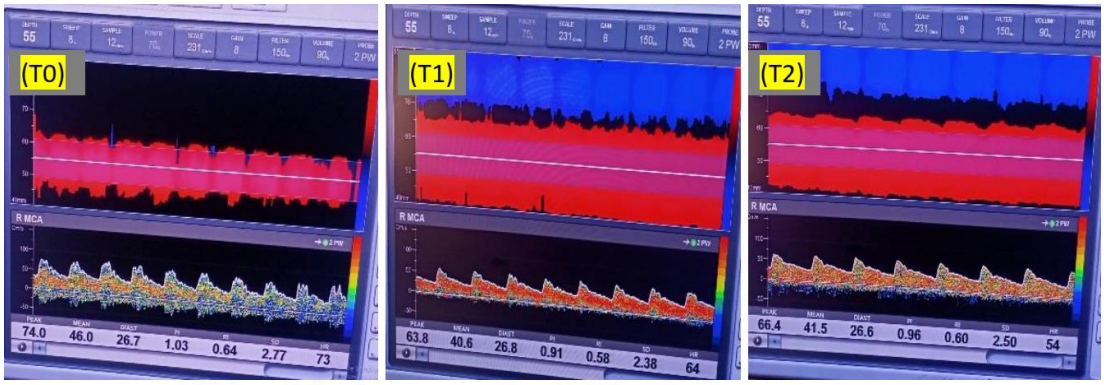

Figure 3.5. showing TCD indices recorded at T0, T1 and T2 time points.

After the T2 period, the ventilation was changed to the settings of conventional ventilation and the surgery performed.

In Group B patients, after the T2 recordings, the study was completed and the before the patient to prone position. However, in Group A patients, further assessment of ICP monitoring and brain relaxation assessment was done.

In those undergoing craniotomy with the patients on conventional ventilation, after initial burr hole was made, measurement of ICP was done using 22-gauge intravenous cannula inserted by the operating surgeon (figure 6). The other end of the cannula was connected to the transducer through a pressure monitoring line under aseptic precautions. The zero hydrostatic reference point for ICP was chosen at external auditory meatus corresponding to the foramen of Monro. By this method ICP was estimated during conventional tidal volume ventilation and after 10 minutes of lung protective mechanical ventilation. When the measurement was over, conventional tidal volume ventilation was resumed. If the surgeon finds the brain was found to be “tense” after craniotomy, moderate hyperventilation ($EtCO_2$ 28-30 mm Hg) was given till dura

was open or external ventricular drain was inserted. However, our study was completed and the hyperventilation if needed has not interfered in the study results. Then, the ventilation was adjusted back to conventional tidal volume after ICP recording.

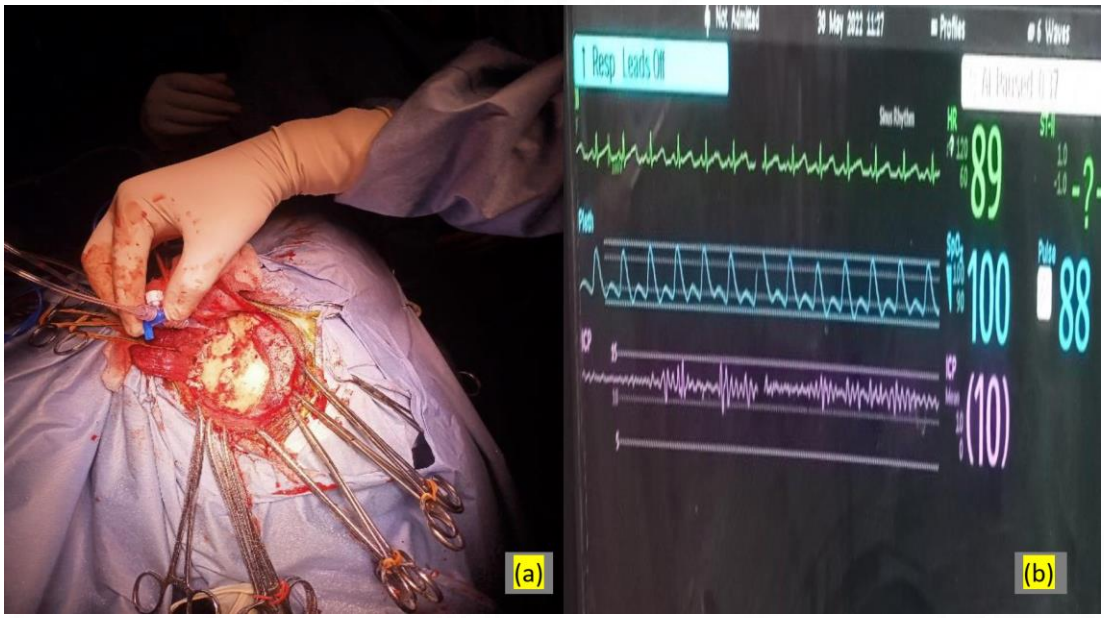

Figure 3.6. (a) ICP monitoring method using subdural cannula inserting after first burr hole and (b) the monitor showing ICP value.

MAP was maintained within 20% of the baseline values throughout the procedure using boluses of intravenous fluids ± intravenous Inj. Mephenteramine as per institute protocols.

Data Collection:

Systemic hemodynamic parameters, respiratory parameters and cerebral hemodynamic variables were assessed and recorded at 3 time periods.

1) Baseline (before induction of anaesthesia)

2) After 10 minutes of Conventional Ventilation (CV)

3) After 10 minutes of Lung Protective Ventilation (LPV)

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and peripheral oxygen saturation were noted from the anaesthesia monitor. End tidal carbon dioxide ($EtCO_2$) and dynamic ventilatory parameters like peak, plateau pressure and mean airway pressure, ventilator driving pressure were recorded/calculated from the anaesthesia workstation. Arterial blood sampling was done at these time periods and the values of arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were noted.

An anaesthesiologist who is not a part of the study noted the values of TCD, NIRS and ICP after the two methods of ventilation strategies. Similar anaesthesia machines were used in all study subjects. Anaesthesia protocol was standardized for all the patients included in the study.

3.b Statistical analysis

3.b.1 Sample Size Calculation

We calculated the sample size through the website sample size tables for clinical studies. The values of cerebral blood flow velocity using variable PEEP mechanical ventilation was 53 and 52 in the study group and control group respectively with standard deviation of 2, $\alpha = 0.05$, $\beta = 0.20$. Based on this, the calculated sample size for this study was 17 patients in each of Group A and Group B. Considering the dropouts due to poor TCD window, a total of 48 patients were recruited with 24 patients in each group.

3.b.2 Statistical Methods

Statistical analyses were done using a statistical software package SPSS, version 20.0. Categorical and quantitative variables were expressed as frequency (percentage) and mean ± SD respectively. Independent t test was used to compare quantitative parameters between groups. Chi-square test was used to find independence of categorical variables between groups. Paired t test was used to compare quantitative parameters between two time intervals in each group and Wilcoxon Signed Rank Test was carried out to compare ordinal variables between two intervals of time before and after intervention Comparison of quantitative parameters at three different time intervals were carried out using Repeated measure ANOVA. For all statistical interpretations, $p < 0.05$ was considered the threshold for statistical significance. Statistical analyses were performed by using a statistical software package SPSS, version 20.0.

4. RESULTS

4.RESULTS

We have assessed 68 patients for the eligibility and recruited 48 eligible patients for the study who were then allocated in to two groups representing craniotomy (Group A) and spine surgery (Group B). Three patients from the Group A and four patients from group B were excluded in view of inadequate TCD window. One patient was excluded from group A due to technical inconvenience for ICP monitoring. The details of the recruitment and analysis of the study is depicted in the CONSORT flow diagram (Fig 1).

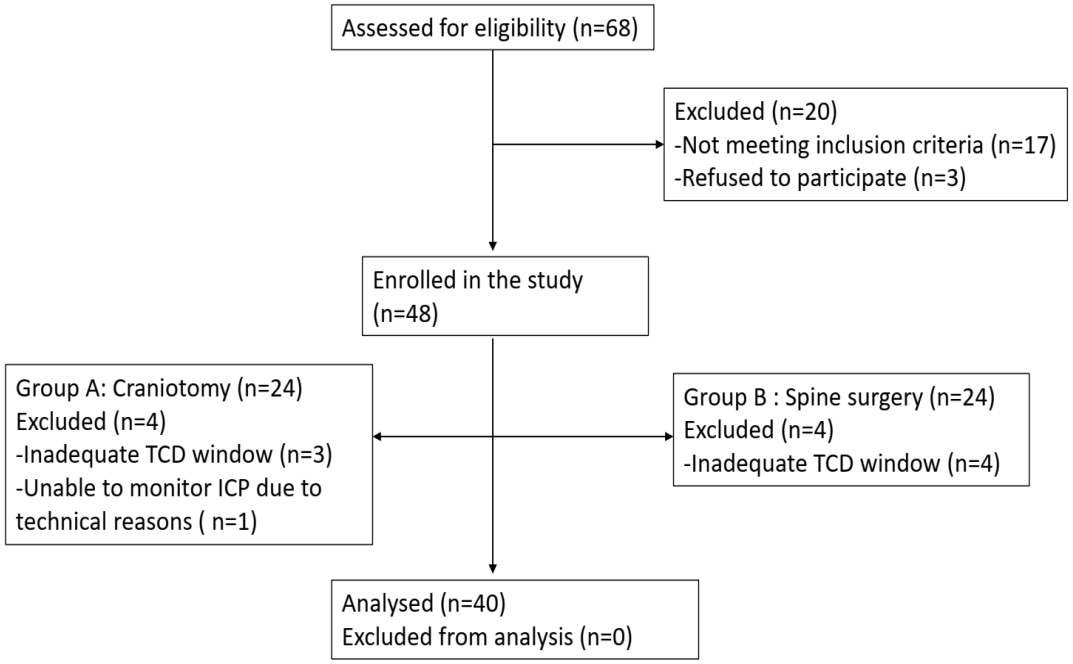

Fig 4.1. CONSORT flow diagram of the enrolment, methodology, and analysis of the study

4.1 Demographic characteristics

Table 4.1 shows the comparison of demographic data between cranial and spine surgery groups

Parameters		Group A (N=20) Mean ± SD	Group B (N=20) Mean ± SD	p-value
Age (years)		42.3 ± 10.8	42.2 ± 11.2	0.989
Weight (kg)		69.9 ± 6.7	70.3 ± 9.3	0.877
Height (cm)		168.5 ± 7.8	169 ± 5.7	0.818
BMI (kg/m2)		24.6 ± 3.3	24.5 ± 2.5	0.940
Gender n (%)	Male	12 (60)	8 (40)	0.206
	Female	8 (40)	12 (60)	
ASA physical status (I:II:III:1V) Number (%)		4:16:0:0 (20:80:0:0)	4:16:0:0 (20:80:0:0)	1.000#

Group A - Cranial Surgery, Group B – Spine Surgery

# $p<0.05$ considered significant by unpaired t-test or chi-square test.

The mean age of the patients was similar between group A and group B (Mean± SD:42.2 ± 11.2 vs 42.3 ± 10.8) and was not statistically significant. The demographic variables like weight, height, and body mass index (BMI) were comparable between the groups. Female patients predominated in the spine surgery group (n=12, 60%), whereas we noted that 60% (n=12) were males in cranial surgery group. Majority of the patients belonged to ASA physical status 2 (80%) in both the groups (Table 4.1).

4.2 Intraoperative Characteristics

Table 4.2 shows the comparison of intraoperative characteristics between cranial and spine surgery groups.

Parameters	Group A (N=20)	Group B (N=20)	p-value
	Mean ± SD	Mean ± SD	
Duration of anaesthesia (min)	396 ± 89	376 ± 108	0.526
Duration of surgery (min)	364 ± 83	346 ± 107	0.557
Total fluid intake (ml)	3477 ± 655.5	2783 ± 938.3	0.010**
Intra operative urine output (ml)	1510 ± 278.9	1230 ± 388.1	0.010**
Baseline hemoglobin (Hb) g/dL	12.6 ± 1.5	13 ± 1.4	0.430

Group A - Cranial Surgery, Group B – Spine Surgery, $p<0.05$ considered significant by unpaired t-test, **: - Significant at 0.01 level.

The mean duration of anaesthesia and surgery was higher in cranial surgery than spine surgery group. Total intravenous fluid intake including blood products was higher in cranial surgery (3477 ± 655.5) as compared to spine surgery (2783 ± 938.3) and it was statistically significant (p=0.010). The mean intraoperative urine output was also significantly higher in cranial surgery group (1230 ± 388.1) as compared to spine surgery (1510 ± 278.9), p=0.013 (Table 4.2). There was no significant difference in baseline haemoglobin level between group A and B.

4.3 Comparison of the systemic hemodynamic parameters

Table 4.3 shows the comparison of heart rate (HR) at different time periods in surgery groups.

Surgery group	Heart rate (beats/min)			p-value^
	Baseline (T0)	During CV (T1)	During LPV (T2)	
	Mean ± SD	Mean ±SD	Mean ± SD	
Group A (N=20)	69.0 ± 13.9	66.2±13.6	63.4±11.7	0.275
Group B (N=20)	66.2 ± 13.6	77.8±14.9	75.8±15.2	0.015
p-value*	0.003	0.014	0.007	

Group A - Cranial Surgery, Group B – Spine Surgery, p-value^: p values comparing the two ventilations (Pair wise comparison with Bonferroni Correction) using repeated

measures ANOVA, p-value*: p values comparing HR between two surgery groups using unpaired t test, p-value <0.05 is significant.

Heart rate showed decreasing trend from baseline value (69.0 ± 13.9) to during CV (66.2±13.6) and during LPV (63.4±11.7) in cranial surgery group. But there was no significant difference in HR when comparing between two ventilation strategies in this group (p=0.275). The mean heart rate was significantly higher during CV (77.8 ± 14.9) as compared to LPV in spinal surgery (75.8± 15.2) (p=0.015). The intergroup comparison between surgery groups showed significant difference in HR during CV (p=0.014) and LPV (p=0.007) (Table 4.3).

Table 4.4 shows the comparison of blood pressure at different time periods in surgery groups.

Surgery group	SBP (mmHg)			
	Baseline	During CV	During LPV	p-value^
	Mean ± SD	Mean ± SD	Mean ± SD	
Group A (N=20)	125.1±13.6	116.0±11.2	114.6±12.0	1.000
Group B (N=20)	124.2±5.6	116.6±12.0	115.0±10.1	1.000
p-value*	0.786	0.882	0.910	
	DBP (mmHg)			

Group A (N=20)	70.8±9.1	67.8±12.0	65.2±11.2	0.440
Group B (N=20)	77.1±8.3	68.5±9.4	70.1±9.1	0.990
p-value*	0.028	0.839	0.134	
	MAP (mmHg)			
Group A (N=20)	84.9±11.6	82.1±11.0	79.1±9.5	0.176
Group B (N=20)	90.8±7.1	82.3±10.7	84.2±8.8	0.621
p-value*	0.058	0.942	0.083	

Group A - Cranial Surgery, Group B – Spine Surgery, p-value^: p values comparing the two ventilations (Pair wise comparison with Bonferroni Correction) using repeated measures ANOVA, p-value*: p values comparing SBP between two surgery groups using unpaired t test, p-value <0.05 is significant.

The mean SBP was 125.1±13.6 mmHg at baseline and 116.0±11.2 mmHg during CV in group A. It further reduced to 114.6±12.0 mmHg during LPV. The baseline SBP in group B was 124.2±5.6 mmHg and it was comparable during CV and LPV (116.6±12.0 vs 115.0±10.1 mmHg). However, the change was insignificant when comparing LPV and CV in cranial surgery and spine surgery patients. Comparing the

SBP between surgery groups also showed no statistically significant results in all three time points (Table 4.4).

There was no statistically significant change in mean DBP between CV and LPV in cranial surgery (67.8±12.0 vs 65.2±11.2 mmHg; p=0.440) and spine surgery group (68.5±9.4 vs 70.1±9.1 mmHg; p=0.990). The comparison between group A and B also showed no significant difference in mean DBP at T1 (p=0.839) and T2 (p=0.134).

Patients in cranial surgery group had a mean MAP of 82.1 ± 11 mmHg in CV and 79.1 ± 9.5 mmHg in LPV as compared to baseline value of 84.9 ± 11.6 mmHg. The mean MAP noted in patients undergoing spine surgery was 82.3 ± 10.7 mmHg in CV and 84.2±8.8 mmHg in LPV as compared to baseline value of 90.8 ± 7.1 mmHg. But there was no significant change comparing the mean value of MAP between CV and LPV in group A (p=0.176) and group B (p=0.621). The comparison among surgery groups also showed no difference in MAP during CV (p=0.942) and LPV (p=0.083) (Fig 4.2)

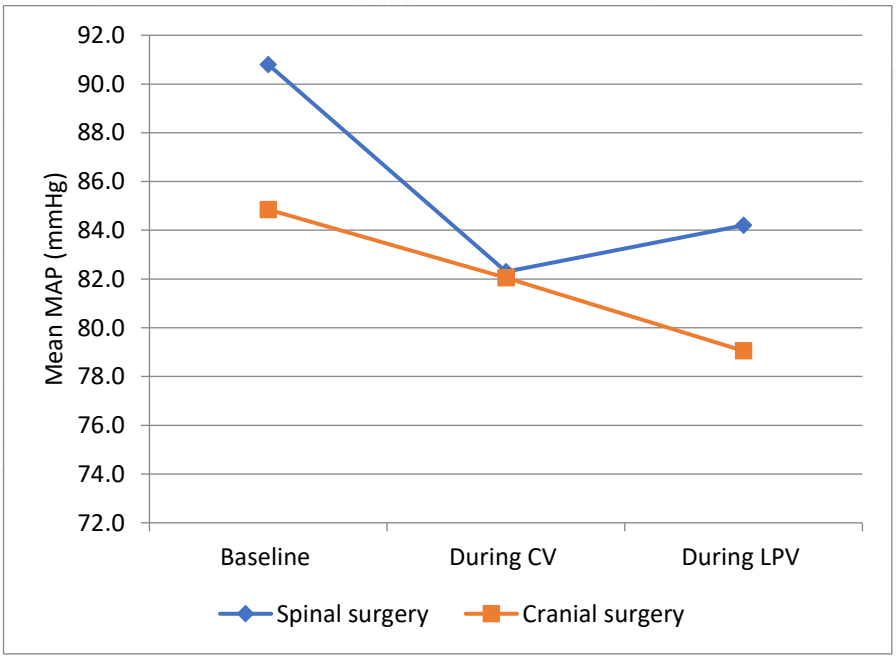

Fig. 4.2. Comparison of MAP in two surgery groups at different time points

4.4 Comparison of respiratory parameters

Table 4.5 shows the comparison of $EtCO_2$, $PaCO_2$ and $PaCO_2$-$EtCO_2$ gradient during CV and LPV in surgery groups

Surgery group	During CV	During LPV	p-value^
	Mean ± SD	Mean ± SD	
$EtCO_2$ (mmHg)			
Group A (N=20)	34.0±2.0	34.1±2.2	0.895
Group B (N=20)	35.0±1.9	34.6±1.4	0.154
p-value*	0.113	0.394	
$PaCO_2$ (mmHg)			
Group A (N=20)	37.8±1.8	36.3±1.6	0.003
Group B (N=20)	38.1±1.6	36.6±1.6	0.002
p-value*	0.575	0.603	
$PaCO_2$-$EtCO_2$ gradient (mmHg)			

Group A (N=20)	3.7±2.2	2.5±1.7	0.019
Group B (N=20)	3.2±1.6	2.2±1.5	0.008
p-value*	0.434	0.490	

Group A - Cranial Surgery, Group B – Spine Surgery, p-value^: p values comparing the two ventilations using paired t test, p-value*: p values comparing $ETCO_2$ between two surgery groups using unpaired t test, p-value <0.05 is significant.

The mean $EtCO_2$ measurement was comparable between CV and LPV in cranial surgery (34 ± 2 vs 34.1 ± 2.2 mmHg, p=0.895) and spine surgery (35 ± 1.9 vs 34.6 ± 1.4 mmHg, p=0.154) patients. Similarly, there was no significant difference in mean $EtCO_2$ during intergroup comparison at T1 (p=0.113) and T2 (p=0.394).

The mean $PaCO_2$ was 37.8±1.8 mmHg during CV in group A and it significantly reduced to 36.3±1.6 mmHg during LPV (p=0.003). Similar reduction in $PaCO_2$ during LPV was also observed in group B (38.1±1.6 vs 36.6±1.6 mmHg; p=0.002). However, the mean $PaCO_2$ was comparable between two surgery groups in two ventilation strategies.

Patients who underwent LPV had better mean $PaCO_2$- $EtCO_2$ gradient than CV in group A (2.5 ± 1.7 vs 3.7 ± 2.2 mmHg; p=0.019) and group B (2.2 ± 1.5 vs 3.2 ± 1.6 mmHg; p=0.008). The comparison among surgery groups showed no significant change in mean $PaCO_2$- $EtCO_2$ gradient at T1 (0.434) and T2 (0.490) (Table 4.5).

Table 4.6 shows the comparison of PaO_2, Alveolar- arterial gradient (A-a gradient) and PaO_2/FiO_2 ratio during CV and LPV in surgery groups.

Surgery group	PaO_2 (mmHg)		
	During CV	During LPV	
	Mean ± SD	Mean ± SD	p-value^
Group A (N=20)	235.8±45.4	265.4±30.7	0.002
Group B (N=20)	251.8±30.3	268.1±31.2	0.01
p-value*	0.197	0.788	
A-a gradient (mmHg)			
Group A (N=20)	75.3±45.8	43.3±30.0	0.01
Group B (N=20)	58.3±30.2	42.9±31.3	0.01
p-value*	0.174	0.970	
PaO_2/FiO_2 ratio			
Group A (N=20)	471.5±90.8	527.4±60.0	0.002
Group B (N=20)	493.6±77.3	536.1±62.5	0.004

p-value*	0.412	0.656	

Group A - Cranial Surgery, Group B – Spine Surgery, p-value^: p values comparing the two ventilations using paired t test, p-value*: p values comparing PaO_2 between two surgery groups using unpaired t test, p-value <0.05 is significant.

There was a hike in mean PaO_2 level in LPV compared to CV in both craniotomy (265.4±30.7 vs 235.8±45.4 mmHg; p=0.002) and spine surgery (268.1±31.2 vs 251.8±30.3 mmHg; p=0.01) cases. But there was no significant change in PaO_2 between surgery groups during CV (p=0.197) and LPV (p=0.788).

The obtained mean alveolar- arterial gradient in cranial surgery patients during CV and during LPV was 75.3±45.8 mmHg and 43.3±30.0 mmHg respectively. In spine surgery patients, this gradient was found to be 58.3±30.2 mm Hg and 42.9±31.3 mm Hg during CV and LPV. When comparing the two modes of ventilation, there was statistically significant difference in mean alveolar- arterial gradient in both surgery groups (p<0.01). But it was insignificant while comparing the mean alveolar- arterial gradient at T1 (p=0.174) and T2 n(p=0.970) between surgery groups.

We kept 50% FiO_2 after induction in all cases. So, the calculated mean PaO_2/FiO_2 ratio was higher in LPV than CV in group A (527.4±60 vs 471.5±90.8; p=0.002) and group B (536.1 ±62.5 vs 493.6 ± 77.3. p=0.004). The comparison among surgery groups revealed no significant difference in mean PaO_2/FiO_2 ratio at T1 (0.412) and T2 (0.656) (Table 4.6).

4.5 Comparison of dynamic ventilatory parameters

Table 4.7 shows the comparison of Peak airway pressure, Plateau pressure, mean airway pressure (Pmean) and dynamic compliance (Cdyn)during CV and LPV in surgery groups.

Surgery group	Peak airway pressure (cm H_2O)		
	During CV	During LPV	
	Mean ± SD	Mean ± SD	p-value^
Group A (N=20)	20.1±3.2	17.6±3.1	p<0.01
Group B (N=20)	19.7±2.6	16.8±2.2	p<0.01
p-value*	0.629	0.347	
Plateau pressure (cm H_2O)			
Group A (N=20)	18.5±2.9	15.9±3.0	p<0.01
Group B (N=20)	17.9±2.7	15.8±2.1	p<0.01
p-value*	0.469	0.903	
Pmean (cm H_2O)			
Group A			

(N=20)	9.3±1.0	8.6±1.0	p<0.01
Group B (N=20)	9.8±1.7	8.9±1.3	p<0.01
p-value*	0.269	0.425	
Cdyn (ml/cmH_2O)			
Group A (N=20)	48.7±13.9	38.4±11.0	0.002
Group B (N=20)	49.4±12.1	36.3±6.9	p<0.01
p-value*	0.865	0.471	
Driving pressure (cmH_2O)			
Group A (N=20)	13.50 ± 2.91	11.40 ± 2.14	0.032
Group B (N=20)	12.85 ± 2.70	11.50 ± 2.21	0.001
p-value*	0.468	0.091	

Group A - Cranial Surgery, Group B – Spine Surgery, p-value^: p values comparing the two ventilations using paired t test, p-value*: p values comparing Peak airway pressure between two surgery groups using unpaired t test, p-value <0.05 is significant.

Among the dynamic ventilatory parameters, the mean peak airway pressure was expectedly lower in LPV as compared to CV in group A (16.8±2.2 vs 19.7±2.6 cmH_2O; p=0.01) and group B (17.6±3.1 vs 20.1 ±3.2 cmH_2O; p=0.01). The intergroup comparison revealed no significant difference in mean peak airway pressure during CV (p=0.629) and LPV (p=0.347) (Fig 4.3).

Similarly mean plateau pressure in patients of group A was found to be 18.5±2.9 cmH_2O during CV and 15.9±3.0 cmH_2O during LPV (p<0.01). Participants of group B also showed significant reduction in mean plateau pressure during LPV (15.8±2.1 cmH_2O) than CV (17.9±2.7 cmH_2O), (p=0.01). But the results are comparable between the surgery groups at T1 (p=0.469) and T2 (p=0.903) (Table 4.7).

There was statistically significant reduction in mean airway pressure during LPV than CV in group A (8.6±1 vs 9.3±1 cmH_2O; p<0.01) and group B (8.9±1.3 vs 9.8±1.7 cmH_2O; p=0.01). However, the difference was insignificant on comparing between surgery groups on two methods of ventilation (p=0.269 and p=0,425 during CV and LPV respectively).

We calculated the dynamic compliance using online calculator (MEDCalc) using the parameters such as tidal volume, peak airway pressure and PEEP. Since the tidal volume used in CV was higher, the mean Cdyn was found to be increased during CV than LPV in both spine surgery (49.4±12.1 vs 36.3 ±6.9 ml/cmH_2O; p<0.01) and cranial surgery (48.7±13.9 vs 38.4±11 ml/cmH_2O; p=0.002) patients. There was no significant difference in dynamic compliance while comparing between group A and B at T1 (p=0.865) and T2 (p=0.471) (Table 4.7).

The calculated driving pressure (plateau pressure – PEEP) was 11.40 ± 2.14 cmH_2O during LPV and 13.50 ± 2.91 during CV (p=0.032) in craniotomy patients. Similarly, there was significant reduction in driving pressure during LPV than CV in spine cases (11.50 ± 2.21 vs 12.85 ± 2.70; p=0.001) (Table 4.7).

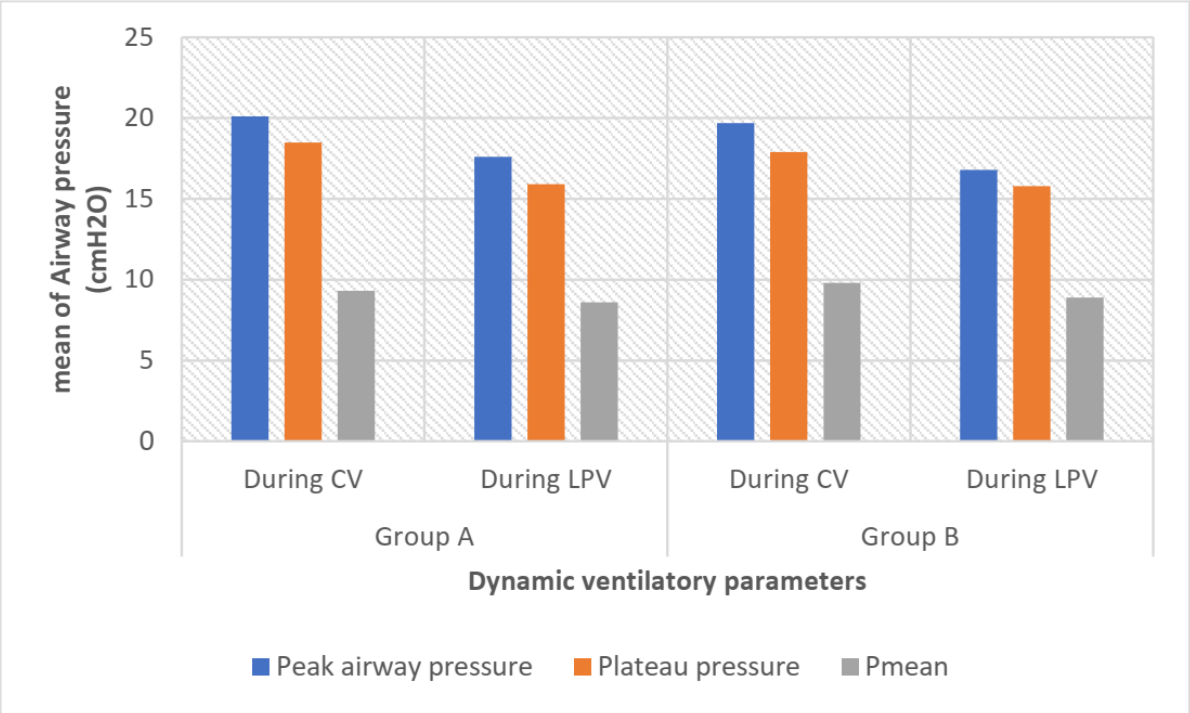

Fig. 4.3. Comparison of dynamic ventilatory parameters in two surgery groups at different time points

4.6 Comparison of cerebral hemodynamics

Table 4.8 shows the comparison of rSO_2 at different time periods in surgery groups.

Surgery group	rSO_2 on Right side (%)			
	Baseline	During CV	During LPV	
	Mean ± SD	Mean ± SD	Mean ± SD	p-value^
Group A (N=20)	70.5±6.8	71.6±7.1	72.2±7.3	1.000
Group B (N=20)	69.3±6.1	71.0±6.3	70.5±6.1	1.000
p-value*	0.543	0.779	0.446	
rSO_2 on Left side (%)				
Group A (N=20)	70.9±5.3	73.2±5.5	73.6±5.4	1.000
Group B (N=20)	69.2±3.1	71.1±5.5	71.2±6.1	1.000
p-value*	0.237	0.228	0.196	

Group A - Cranial Surgery, Group B – Spine Surgery, p-value^: p values comparing the two ventilations (Pair wise comparison with Bonferroni Correction) using repeated measures ANOVA, p-value*: p values comparing rSO_2 on Right side between two surgery groups using unpaired t test, p-value <0.05 is significant.

The baseline mean rSO_2 on right side was 70.5±6.8% in group A and 69.3±6.1% in group B. It was 71.6±7.1% at T1 and 72.2±7.3% at T2 in group A. Similarly, the mean rSO_2 was 71.0±6.3% at T1 and 70.5±6.1% at T2 in group B. The values are comparable during CV and during LPV in both cranial surgery (p=1.00) and spine surgery (p=1.00) patients (Fig 4.4). But there was no significant difference in rSO_2 between the surgery groups at different time intervals (Table 4.8).

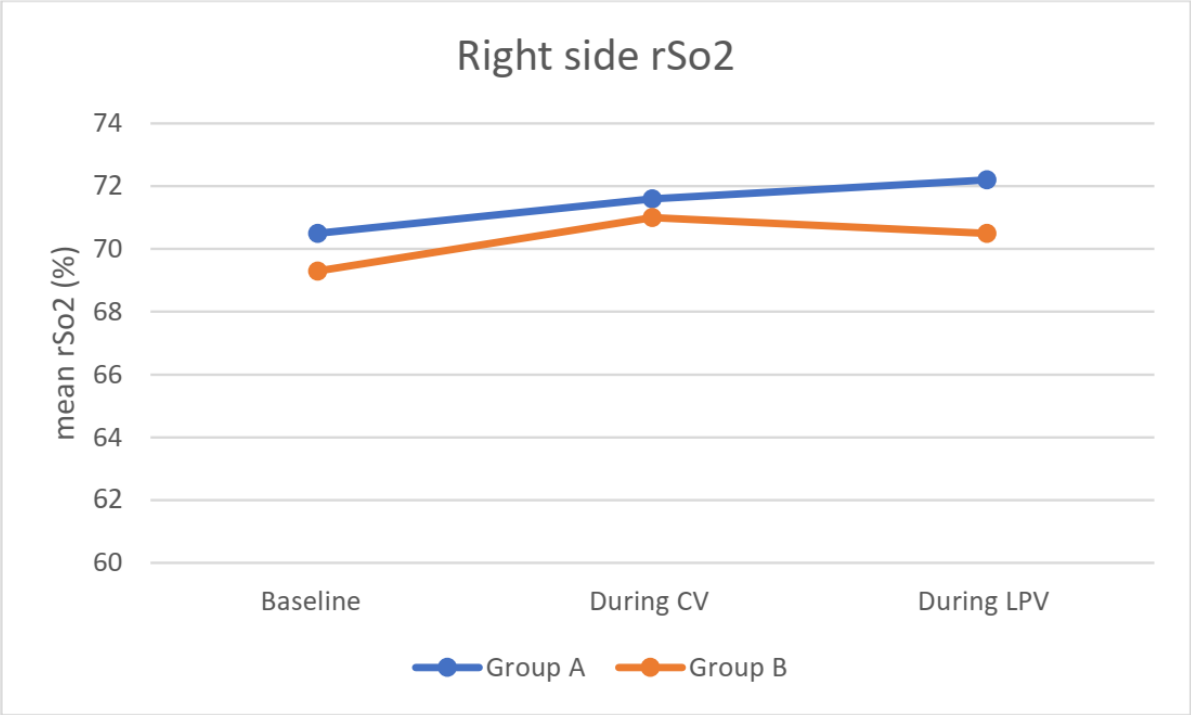

Fig. 4.4. Comparison of rSO_2 on right side in two surgery groups at different time points

The baseline rSO_2 on the left side was 70.9±5.3% in group A and 69.2±3.1% in group B. Like right side, left frontal region also showed comparable mean rSO_2 values between LPV and CV in cranial surgery (73.6±5.4 vs 73.2±5.5%; p=1.00) and spine surgery (71.2±6.1 vs 71.1±5.5%; p=1.00). However, the difference was insignificant

while comparing among surgery groups at T0 (p=0.237), T1 (p=0.228) and T2 (p=0.196) ((Table 4.8, Fig 4.5).

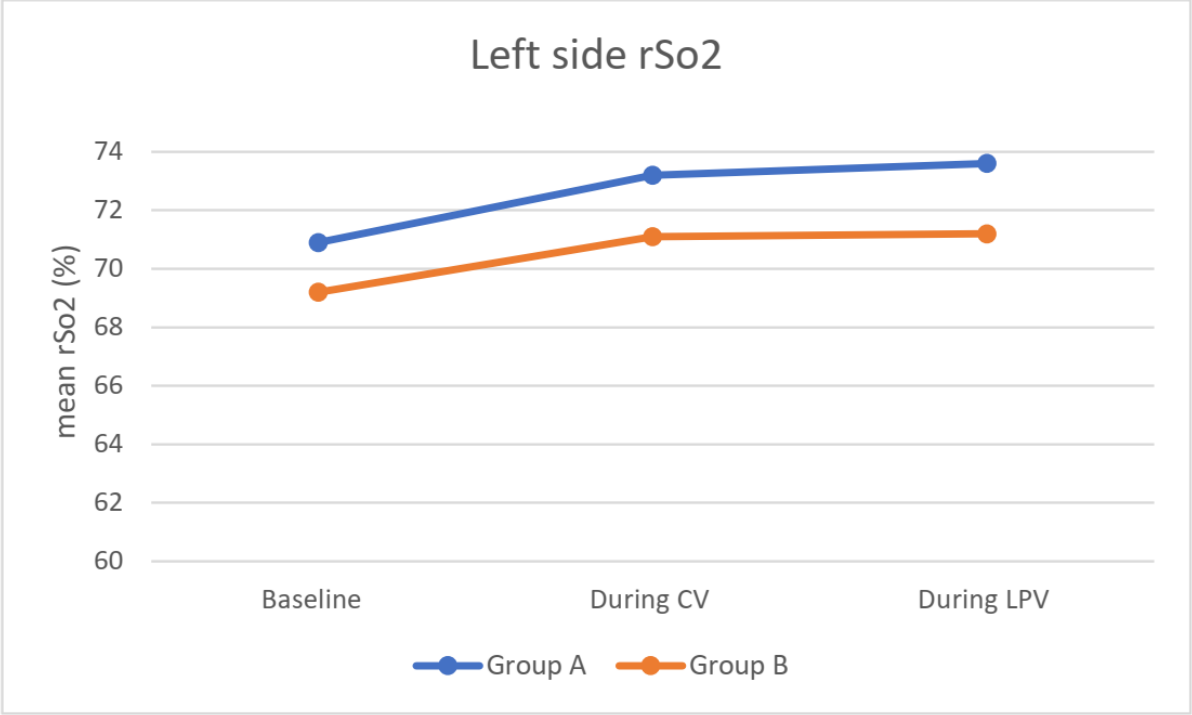

Fig. 4.5. Comparison of rSo2 on left side in two surgery groups at different time points

Table 4.9 shows the comparison of ICP and CPP (MAP-ICP) during CV and during LPV in cranial surgery group.

Group A (N=20)	During CV	During LPV	p-value
Parameter	Mean ± SD	Mean ± SD	
ICP (mmHg)	14.7±4.7	14.1±4.2	0.019$
CPP (mmHg)	67.4±13.0	65.0±11.4	0.184#

$: Paired t test. #: Wilcoxon Signed Rank Test. P<0.05 is Significant

The mean ICP which was measured by subdural cannula was 14.7±4.7 mmHg during CV and 14.1±4.2 mmHg during LPV (p=0.019) ((Table 4.9, Fig 4.6). Even though it was statistically significant, clinically it was insignificant. The calculated mean CPP value showed no significant difference between CV and LPV (67.4±13 vs 65±11.4 mmHg; p=0.184) ((Table 4.9, Fig 4.7).

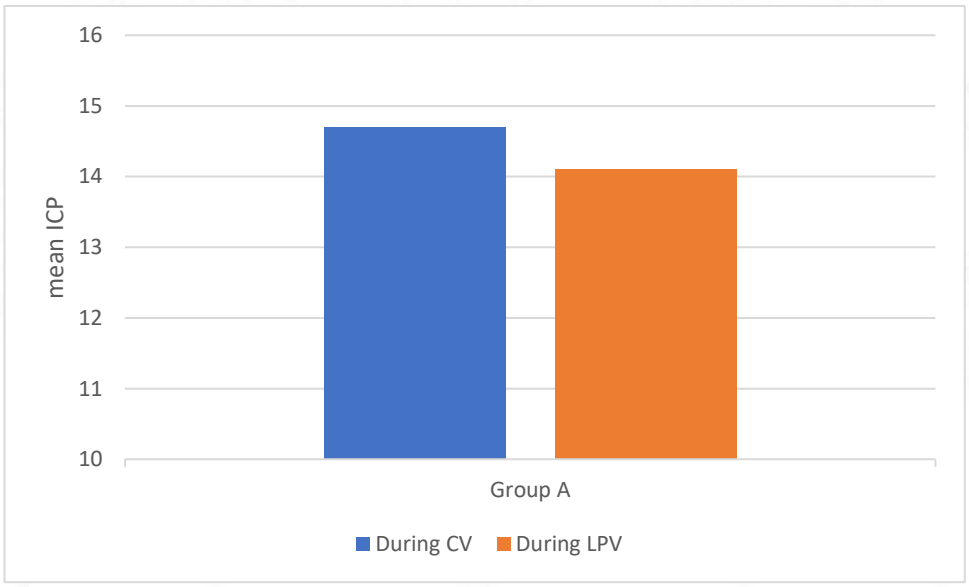

Fig. 4.6. Comparison of ICP in group A during CV and LPV

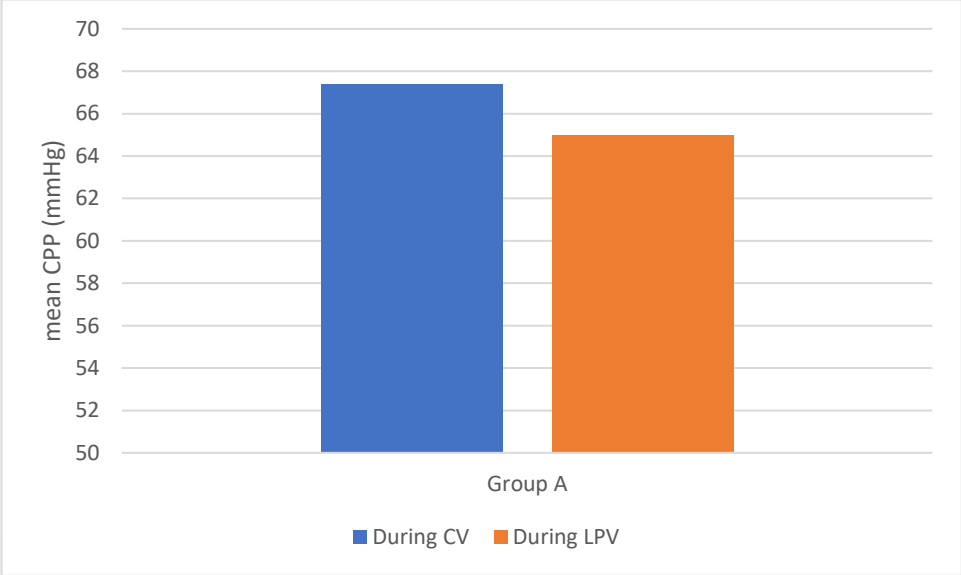

Fig. 4.7. Comparison of CPP in group A during CV and LPV

Table 4.10 shows the comparison of TCD indices on right side at different time periods in surgery groups.

Surgery group	MCA-Right side PSV (cm/sec)			
	Baseline	During CV	During LPV	p-value^
	Mean ± SD	Mean ± SD	Mean ± SD	
Group A (N=20)	57.9±16.6	58.0±12.3	53.2±13.3	0.663
Group B (N=20)	66.0±17.7	58.3±13.2	60.5±10.5	1.000
p-value*	0.144	0.942	0.063	
	MCA-Right side EDV (cm/sec)			

Group A (N=20)	22.0±8.0	25.7±8.8	24.7±12.0	1.000
Group B (N=20)	30.3±9.9	24.8±7.2	27.6±8.0	0.356
p-value*	0.006	0.716	0.369	
	MCA-Right side Mean velocity (cm/sec)			
Group A (N=20)	36.5±9.7	39.1±10.5	35.4±8.3	0.726
Group B (N=20)	44.3±12.8	37.6±9.0	40.0±9.3	0.767
p-value*	0.038	0.630	0.109	
Surgery group	MCA-Right side PI			p-value^
	Baseline	During CV	During LPV	
	Mean ± SD	Mean ± SD	Mean ± SD	
Group A (N=20)	0.99±0.29	0.87±0.25	0.85±0.19	1.000
Group B (N=20)	0.84±0.24	0.90±0.21	0.88±0.22	1.000
p-value*	0.084	0.643	0.708	

Group A - Cranial Surgery, Group B – Spine Surgery, p-value^: p values comparing the two ventilations (Pair wise comparison with Bonferroni Correction) using repeated

measures ANOVA, p-value*: p values comparing MCA-Right side PSV between two surgery groups using unpaired t test, p-value <0.05 is significant.

The TCD mean MCA PSV on the right temporal window in cranial surgery group was 57.9±16.6 cm/sec at baseline, 58±12.3 cm/sec during CV and 53.2±13.3 cm/sec during LPV. In spine surgery patients the mean MCA PSV was 66.0±17.7 cm/sec at T0, 58.3±13.2 cm/sec at T1 and 60.5±10.5 cm/sec at T2. We compared the flow velocities between T1 and T2 and it was comparable among CV and LPV in cranial surgery (p=0.663) and spine surgery (p=1.000) patients. The intergroup comparison also revealed no significant difference in PSV at T0 (p=0.144), T1 (p=0.942) and T2 (p=0.063) (Table 4.10).

The mean MCA EDV on right side at the baseline was 22.0±8.0 in group A. In cranial surgery group, this flow velocity was 25.7±8.8 cm/sec at T1 and it was 24.7±12 cm/sec at T2. The baseline mean MCA EDV obtained in group B was 30.3±9.9 and it changed to 24.8±7.2 cm/sec during CV and 27.6±8.0 cm/sec during LPV. When comparing between LPV and CV there was no statistically significant difference in group A (p=1.00) and group B (p=0.356). The evaluation of mean MCA EDV on right side between surgery groups also showed comparable results at T1 (0.716) and T2 (0.369) (Table 4.10).

The mean MCA velocity mean value on right side was also stable at baseline (36.5±9.7 cm/sec), during CV (39.1±10.5 cm/sec) and during LPV (35.4±8.3 cm/sec) in cranial surgery patients. In spine cases it was 44.3±12.8 cm/sec during baseline, 37.6±9.0 cm/sec during CV and 40.0±9.3 cm/sec during LPV. There was no significant difference between CV and LPV between group A (p=0.726) and group B (p=0.767).

The assessment of MCA mean velocity on right side between surgery groups also revealed comparable results at T1 (p=0.630) and T2 (0.109) (Fig 4.8).

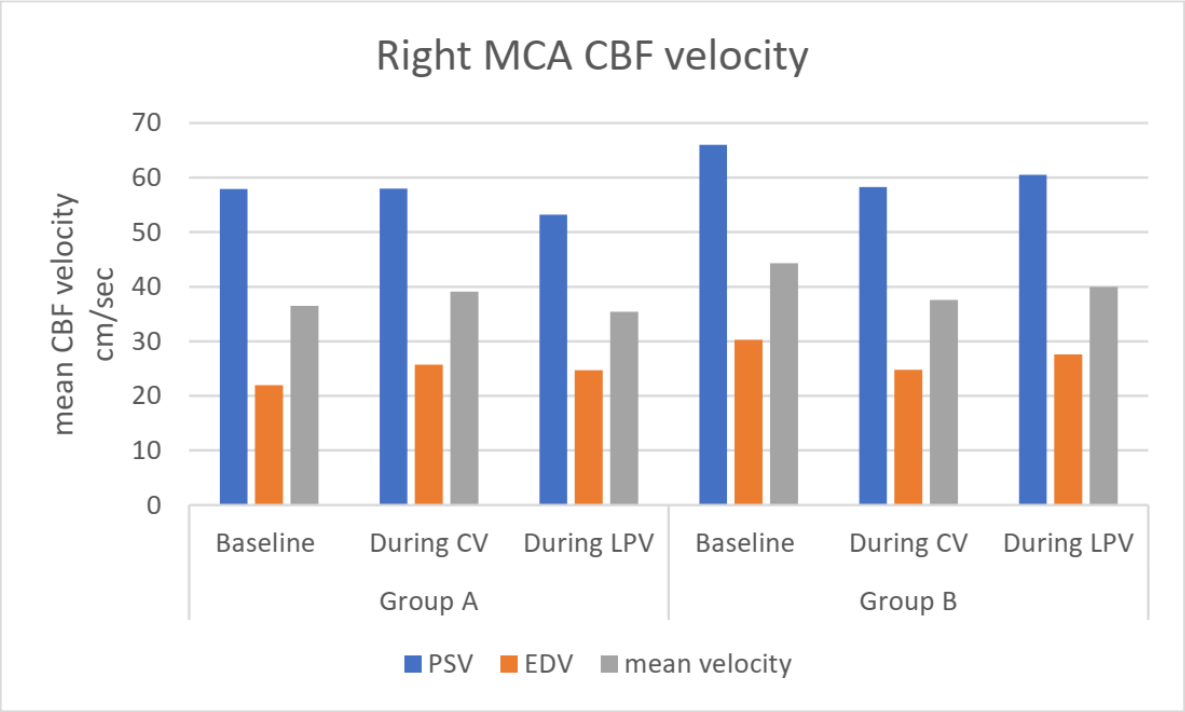

Fig. 4.8. Comparison of MCA CBF velocity on right side in two surgery groups at different time points

The baseline mean PI of right MCA was 0.99±0.29 at baseline, 0.87±0.25 during CV and 0.85±0.19 during LPV in cranial surgery group (p=0.084). Similarly, the mean PI of right MCA was 0.84±0.24 at baseline, 0.90±0.21 during CV and 0.88±0.22 during ventilation with LPV in spine group (p=0.569). Both ventilation modes showed no significant difference in the right-side PI in both groups (p=1.00). The comparison between surgery groups also showed comparable results at T1 (0.643) and T2 (0.708) (Fig 4.9).

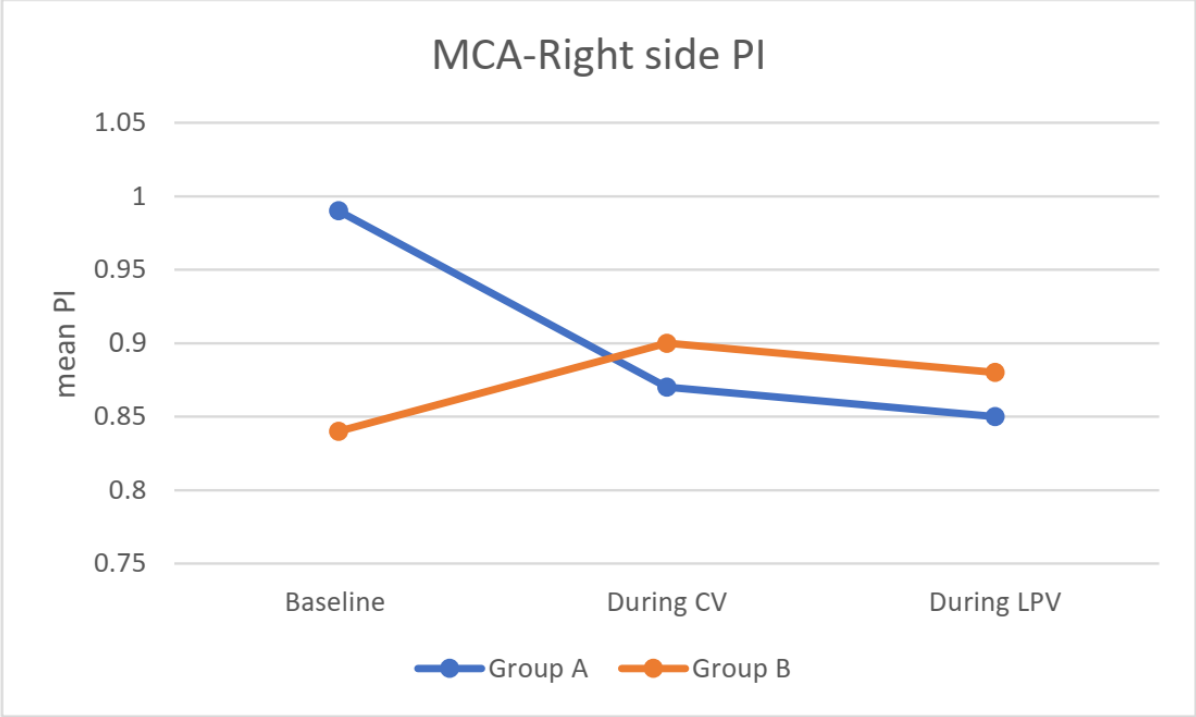

Fig 4.9. Comparison of TCD PI of right-side MCA in two surgery groups at different time points

Table 4.11 shows the comparison of TCD indices on left side at different time periods in surgery groups.

Surgery group	MCA-Left side PSV (cm/sec)			
	Baseline	During CV	During LPV	p-value^
	Mean ± SD	Mean ± SD	Mean ± SD	
Group A (N=20)	59.7±19.0	53.5±15.4	51.7±10.1	1.000
Group B (N=20)	70.5±22.8	59.9±20.4	59.3±12.6	1.000
			0.040	

p-value*	0.113	0.274		
MCA- Left side EDV (cm/sec)				
Group A (N=20)	24.8±9.9	22.8±7.0	23.0±6.3	1.000
Group B (N=20)	31.8±10.3	24.7±8.6	25.9±7.3	1.000
p-value*	0.036	0.450	0.184	
MCA- Left side Mean velocity (cm/sec)				
Group A (N=20)	38.9±13.1	34.9±9.5	35.1±7.5	1.000
Group B (N=20)	46.6±14.9	38.7±12.6	40.0±7.8	1.000
p-value*	0.089	0.289	0.050	
Surgery group	MCA- Left side PI			p-value^
	Baseline	During CV	During LPV	
	Mean ± SD	Mean ± SD	Mean ± SD	
Group A (N=20)	0.89±0.21	0.89±0.13	0.84±0.20	1.000
Group B (N=20)	0.86±0.19	0.93±0.18	0.89±0.21	1.000
			0.453	

p-value*	0.695	0.427		

Group A - Cranial Surgery, Group B – Spine Surgery, p-value^: p values comparing the two ventilations (Pair wise comparison with Bonferroni Correction) using repeated measures ANOVA, p-value*: p values comparing MCA-Left side PSV between two surgery groups using unpaired t test, p-value <0.05 is significant.

The mean MCA PSV on the left side was 59.7±19.0 cm/sec at baseline, 53.5±15.4 cm/sec during CV and 51.7±10.1 cm/sec during LPV in cranial surgery. This parameter in spine surgery group was 70.5±22.8 cm/sec at baseline, 59.9±20.4 cm/sec during CV and 59.3±12.6 cm/sec during LPV. The comparison between the two modes of ventilation also showed no significant difference in mean PSV of left side MCA (p=1.000). The intergroup comparison resulted in similar values at T1 (p=0.274) and statistically significant increase in mean MCA PSV at T2 (0.040).

Results of the mean EDV of left MCA showed a flow velocity of 24.8±9.9 cm/sec at baseline, 22.8±7 cm/sec during CV and 23±6.3 cm/sec during LPV in group A. In group B, this velocity was 31.8±10.3 cm/sec at baseline, 24.7±8.6 cm/sec during CV and 25.9±7.3 cm/sec during LPV. There was no significant difference in mean EDV of left MCA between CV and LPV in cranial and spine surgery (p=1.000). Even though there was significant change in EDV of left MCA at baseline (p=0.036) between surgery groups, it was comparable at T1 (0.450) and T2 (0.184).

The mean MCA velocity on the left side recorded a mean value of 38.9±13.1 cm/sec at baseline in group A. After ventilating with CV, it became 34.9±9.5 cm/sec and then 35.1±7.5 cm/sec during LPV. The mean of MCA mean velocity on left side in spine surgery group was 46.6±14.9 cm/sec, 38.7±12.6 cm/sec and 40.0±7.8 cm/sec

respectively at baseline, during CV and LPV. However, there was no significant difference in mean value of MCA mean velocity on left side between the two ventilation strategies in group A and B (p=1.00) (Fig 4.10). The comparison among surgery groups also indicated insignificant change at T0 (0.089), T1(0.289) and T2 (0.050) (Table 4.11).

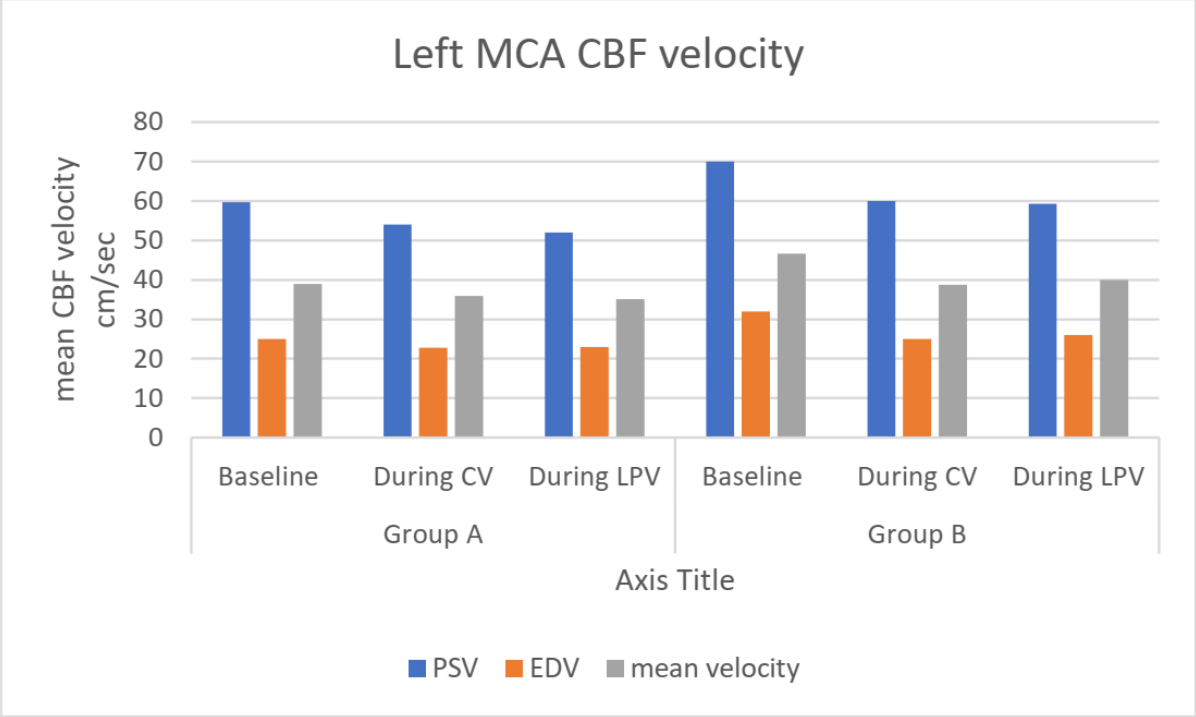

Fig. 4.10. Comparison of MCA CBF velocity on left side in two surgery groups at different time points

The mean PI of left MCA was 0.86±0.19 at baseline, 0.89±0.13 during CV and 0.84±0.20 during LPV in cranial surgery group. In spine group also PI on left side was comparable between baseline, during CV and during LPV (0.86±0.19 vs 0.93±0.18 vs 0.89±0.21) (Fig 4.11). The comparison of PI between two ventilation modes also showed no significant difference between group A and B(p=1.00). The intergroup

evaluation of mean PI of left MCA was also comparable during CV (0.427) and LPV (0.453).

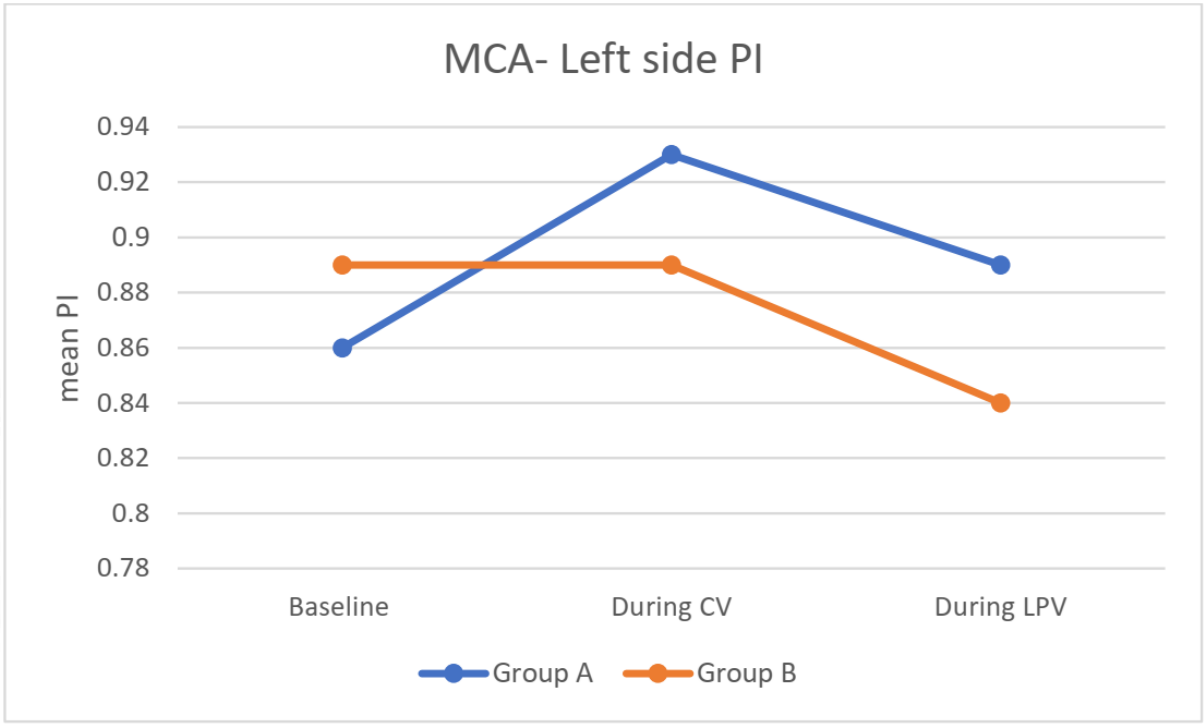

Fig. 4.11. Comparison of TCD PI of left side MCA in two surgery groups at different time points

4.6.1 Comparison of cerebral hemodynamic parameters on the lesion side and opposite side of the lesion.

Table 4.12 shows the comparison of cerebral hemodynamic parameters on the side of the lesion and opposite side at different time periods in cranial surgery group.

Group A (N=20)		Baseline	During CV	During LPV	p-value^
Parameter		Mean ± SD	Mean ± SD	Mean ± SD	
rSO_2 (%)	Ipsilateral	70.3±5.6	72.0±5.5	72.7±5.5	1.000
	Contralateral	71.1±6.5	72.8±7.2	73.1±7.3	1.000
MCA PSV (cm/sec)	Ipsilateral	61.0±17.1	55.7±13.7	52.4±7.6	0.952
	Contralateral	56.6±18.2	55.8±14.6	52.4±14.9	1.000
MCA EDV (cm/sec)	Ipsilateral	25.7±8.6	24.3±6.7	23.7±6.4	1.000
	Contralateral	21.1±9.0	24.3±9.2	24.0±12.0	1.000
MCA mean FV (cm/sec)	Ipsilateral	39.6±11.3	36.9±8.8	36.2±6.5	1.000
	Contralateral	35.9±11.5	37.1±11.5	34.3±9.0	1.000
	Ipsilateral				

MCA PI		0.85±0.22	0.86±0.21	0.83±0.22	1.000
	Contralateral	1.03±0.27	0.89±0.19	0.86±0.16	1.000

p-value^: p values comparing the two ventilations (Pair wise comparison with Bonferroni Correction) using repeated measures ANOVA. P<0.05 is Significant.

We analysed the regional cerebral oxygenation and CBF velocity on the side of the lesion and the opposite side (non-operating side) in group A. The comparison of mean rSO_2 between CV and LPV showed no significant difference on the lesion side (72±5.5 vs 72.7±5.5%; p=1.00) as well as on opposite side (72.8±7.2 vs 73.1±7.3%; p=1.00). The mean PSV of MCA at the side of lesion was comparable between CV and LPV and there was no significant difference between them (55.7±13.7 vs 52.4±7.6 cm/sec; p=0.952). Similarly, the mean PSV of MCA on the contralateral side of the lesion during CV was 55.8±14.6 and during LPV was 52.4±14.9 cm/sec (p=1.00). The mean EDV of MCA at the side of the lesion and other side were comparable between the ventilation modes (p=1.00). There was no significant difference in mean of MCA mean velocity during CV and LPV) on the ipsilateral side (36.9±8.8 vs 36.2±6.5 cm/sec; p=1.00) and normal side (37.1±11.5 vs 34.3±9 cm/sec; p=1.00). The comparison of PI on the lesion side showed no significant difference while ventilating the patient with CV and LPV (0.86±0.21 vs 0.83±0.22; p=1.00). There was no significant difference in mean PI between CV and LPV on the contralateral side of the lesion (0.89±0.19 vs 0.86±0.16; p=1.00) (Table 4.12).

5. DISCUSSION

5.DISCUSSION

Our study's primary aim was to assess the effects of intraoperative LPV on the cerebral hemodynamics such as cerebral blood flow, cerebral oxygenation, and intracranial pressure compared to the conventional ventilation strategy routinely followed in neurosurgery. The currently available studies comparing the LPV with CV were done to evaluate the pulmonary complications, lung dynamics and outcomes in perioperative period or intensive care unit in different group of patients. The patient population in these studies are also varied ranging from acute brain injury to acute lung injury where comparisons can be difficult due to different type of pathologies. Our study was a cross over study, designed to compare the two modes of ventilation in intraoperative period with same patients to avoid the confounding factors.

The main findings of our study include the cerebral blood flow velocity and regional cerebral oxygen saturation were comparable during both LPV and CV in patients with intracranial pathology as well as spine diseases. In patients undergoing craniotomy, the intracranial pressure was slightly lower in LPV compared to CV whereas the CPP remained unchanged. The systemic hemodynamic parameters also were comparable between two ventilation strategies. We also noted that major advantage of LPV is on the pulmonary mechanics as shown by significant improvement in PaO_2/FiO_2 ratio, lower $PaCO_2 – EtCO_2$ gradient and A-a gradient along with reduction in dynamic ventilatory parameters such as peak airway pressure, mean airway pressure and plateau pressure.

In our study, the mean age of patients between the groups were similar; however, in group A 60% of them were males while in group B, females (60%) predominated.

Patients with severe comorbidities were excluded as 80% of study subjects included in ASA physical status I. Cranial surgery cases had significantly longer duration of surgery higher intraoperative fluid intake and urine output compared to spine surgery. Hemodynamics also were found to be within the baseline in both the groups at T0, T1 and T2 time periods.

5.1 Effects of LPV and CV on Cerebral Blood Flow Velocity (CBFV)

Maintenance of cerebral blood flow is an important goal in neurosurgery. Measurement of CBFV using TCD is a surrogate marker for CBF. Changes in CBF could be due to local factors affecting the brain or systemic factors like mean arterial pressure, blood gas changes, ventilatory parameters, etc. In our study, we maintained a steady state of anesthesia, minute ventilation targeted to a constant $EtCO_2$ value and the hemodynamics to mitigate the effects of these local factors, hemodynamics on CBFV. Hence if any changes in CBFV were noted, it can be attributable to effects of ventilation and indirectly by the lung mechanics, systemic oxygenation, and $PaCO_2$ levels.

5.2 Effect of LPV on Systemic hemodynamics

In our study, there was no significant changes in mean MAP between CV and LPV in both spinal and cranial surgery. Patients in cranial surgery group had a mean MAP of 82.1 ± 11 mmHg at T1 and 79.1 ± 9.5 mmHg at T2 as compared to baseline value of 84.9 ± 11.6 mmHg. These findings ensuring the maintenance of cerebral perfusion in a normal ICP scenario. The mean SBP and DBP were also comparable between CV and LPV in both surgery groups. Even though the mean heart rate was

lower in LPV than CV (75.8 ± 15.2 vs 77.8 ± 14.9; p=0.015) in spine surgery group, it was clinically not significant. However, mean heart rate changes were similar between both modes of ventilation in cranial surgery (p=0.275). Previous evidence pointed out that mechanical ventilation can produce hemodynamic changes by altering systemic venous return to the right ventricle (RV) (RV preload), pulmonary arterial pressure (RV afterload), ventricular interdependence (Left ventricular (LV) preload), or transmural LV ejection pressure (LV afterload). These interactions are higher when the changes in lung volume and intrathoracic pressure are increased which can be negated by providing LPV.(68)

5.3 Effect of LPV on Blood gas, Ventilation and Respiratory Mechanics

An important observation in our study is, that despite the constant mean $EtCO_2$ levels in either of the ventilation strategies, mean $PaCO_2$ was significantly less in LPV compared to CV. This change was reflected on improvement in mean $PaCO_2$-$EtCO_2$ gradient during LPV as compared to CV in both groups (spine group 2.2 ± 1.5 vs 3.2 ± 1.6; p=0.008 and cranial group 2.5 ± 1.7 vs 3.7 ± 2.2; p=0.019). Similarly, there was significant improvement in mean PaO_2, PaO_2/FiO_2 ratio and alveolor-arterial gradient (A-a gradient) in the LPV mode. Better $PaCO_2$-$EtCO_2$ gradient, PaO_2/FiO_2, and A-a gradient indicates a better ventilation-perfusion maintenance in LPV as compared to CV.

Jing Liu et al. evaluated the effect of intraoperative LPV in patients undergoing laparoscopic gastrectomy. A total of 120 patients were randomly divided into CV with a TV of 10 mL/kg without PEEP, and LPV with 7 mL/kg TV and personal level of

PEEP with regular recruitment manoeuvre every 30 min. This study concluded that LPV improved the lung oxygenation index (PaO_2/FiO_2), reduced the A-a gradient and improved dynamic compliance compared to CV.(69) Our results also found similar improvement in lung oxygenation parameters during LPV. In our study the only difference between the two modes was the even though the dynamic compliance was higher in CV mode which attributed to the higher lung volumes used during CV and use of similar PEEP in both modes in our study.

Lulu Jiang et al. studied the effects of intraoperative LPV on postoperative pulmonary complications (POPC) and intraoperative respiratory mechanics in patients with TBI. In the study, ninety patients were randomly allocated to three groups such as Vt 10 mL/kg only (Group A), Vt 8 mL/kg + PEEP 5 cmH_2O (Group B) and Vt 8 mL/kg + PEEP 5 cmH_2O + recruitment manoeuvres (Group C). The intraoperative PaO_2 and dynamic lung compliance of Groups B and C were higher than those of Group A ($P = 0.028$; $P = 0.005$), while peak airway pressure and plateau pressure were lower than those of group A ($P = 0.004$; $P = 0.005$). The authors concluded that intraoperative administration of small Vt + PEEP is beneficial to TBI patients, manifesting as improved oxygenation and respiratory mechanics, decreased incidences of POPCs, and mild increase in posttraumatic serum levels of brain injury markers.

The lower tidal volume strategy used in the present study significantly lowered the dynamic ventilatory parameters like peak, plateau, and mean airway pressures compared to CV. Thus, use of LPV helps to reduce the lung stress and alveolar damage, improved the ventilation- perfusion ratio, which indirectly improved systemic oxygenation and CO_2 elimination. All these changes are expected to provide a

favourable cerebral hemodynamics. The lower driving pressure (DP) shown to have outcome benefit during mechanical ventilation due to resultant lowering of cyclic lung inflation/stretching and reduction in lung stress.(70) In a study including acute brain injury patients without lung injury, the authors found that DP was lower during low Vt compared to CV in both high PEEP (8 ± 2 vs 10± 2 cmH_2O) and low PEEP (7±2 vs 9±2 cmH_2O). Similarly, our study also revealed significant reduction in DP during LPV as compared to CV in cranial surgery (11.40 ± 2.14 vs 12.85 ± 2.70; p=0.032) and spine surgery patients.(71)

5.4 Effect of LPV on Cerebral blood flow Velocity (CBFV)

To date no prospective clinical trials are available to compare the effect of low tidal volume ventilation with maintenance of normocarbia on CBF velocity using TCD in neurosurgery population. Based on our study results, we noted that CBFV remained stable irrespective of change in ventilation from CV to LPV.

Weizhi zhang *et al*, studied the effects of low minute ventilation with different targeted $EtCO_2$ on cerebral hemodynamics in infants undergoing ventricular septal defect repair. They adjusted the Vt and RR to obtain variable $EtCO_2$ levels such as 30 mmHg (T1), 35 mmHg (T2), 40 mmHg (T3), or 45 mmHg (T4). The results showed that CBF velocity (PSV, EDV, and mean flow velocity) increased linearly and PI and resistance index decreased linearly from T1 (PSV, 84 ± 19 cm/second; EDV, 14 ± 4 cm/sec; mean flow velocity, 36 ± 10 cm/sec; PI, 2.13 ± 0.59; resistance index, 0.84 ± 0.12) to T4 (PSV, 113 ± 22 cm/sec; EDV, 31 ± 6 cm/sec; mean flow velocity, 58 ± 11 cm/sec; PI, 1.44 ± 0.34; resistance index, 0.72 ± 0.07) ($p < 0.001$). The cerebral oxygenation measured using NIRS also indicated an increasing trend. They concluded

that low minute ventilation strategy increases cerebral blood flow by cerebral vasodilation, improves cerebral oxygenation and brain perfusion in infants.(72)

In our study, the effect of carbon dioxide on CBF velocity was nullified by providing same minute ventilation in both modes of ventilation. Our results showed MCA mean FV of 39.1±10.5 cm/sec on right side in cranial surgery patients during CV and it changes to 35.4±8.3 cm/sec during LPV which was not significant. In the left side also, we got comparable results such as 34.9±9.5 cm/sec and 35.1±7.5 cm/sec during CV and LPV respectively. Recently, Carr et al reported that ventilation per se does not affect the cerebrovascular reactivity. The cerebrovascular reactivity to CO_2 changes is heterogenous and protective in response to changes to systemic acid-base status.(73)

The mean PI of right MCA in our study was 0.90±0.21 during CV and 0.88±0.22 during LPV in cranial surgery patients. Likewise, left side PI was 0.93±0.18 and 0.89±0.21 during CV and LPV. Similar comparable results were also obtained in patients undergoing spine surgery. These findings indicated intactness of the cerebrovascular flow resistance during LPV.

In another study, Axel Nyberg et al studied effect of LPV on cerebral metabolism and non- inflammatory brain injury in porcine experimental sepsis. The study concluded that protective ventilation did not affect inflammatory cytokines. The low Vt group (6ml/kg) had increased CBF, cerebral oxygen delivery and cerebral metabolism together with increased levels of brain injury biomarkers compared with medium-high tidal volume (10ml/kg) ventilation.(74) However, in our study there was

no significant change in CBF velocity on changing to LPV which imparts on the maintenance of autoregulation and insignificant effect on this unique ventilation.

5.5 Effect of LPV on Cerebral Oxygenation

Fewer studies addressed the effects of ventilation on cerebral oxygenation. We measured regional cerebral oxygen saturation (rSO_2) using NIRS measured bilaterally and found to be comparable on either side of the cerebral hemisphere during CV and LPV in both cranial and spinal surgery patients. In the present study the baseline mean Rso_2 on right frontal region was 70.5±6.8% in craniotomy patients which became 71.6±7.1% during CV and 72.2±7.3% during LPV. Similar to right side, left hemisphere also showed comparable mean rSO2 values between LPV and CV in cranial surgery (73.6±5.4 vs 73.2±5.5%; p=1.00). In spine surgery patients also stable rSO_2 values were observed during all time points in both sides. These observations indicated the maintenance of cerebral oxygenation and perfusion during protective lung ventilation.

Tamas Vegh et al. performed a crossover study to compare the influences of low vs. high TV on systemic and cerebral oxygenation during one lung ventilation in patients scheduled for thoracic surgery. During OLV patients were alternately ventilated with high Vt (10 ml/kg with ZEEP for 30 min) and low Vt (5 ml/kg with 5 cmH_2O PEEP for 30 min). Respiratory rate was adjusted in order to maintain $PaCO_2$ between normal limits. Patients ventilated with low Vt showed a higher rSO_2 (high 70±10 vs low 74±11%, P=0.006). Vt related changes in $PaCO_2$ and rSO_2 were significantly correlated (Pearson's correlation, r=0.34, p<0.001) and patients' rSO_2-derived CO_2 reactivity was not homogeneous. The authors opined that

increased rSO2 appears to result from CO2-mediated cerebral blood flow augmentation. The magnitude of the Vt effect is related to the extent of patient rSO_2-derived CO_2 reactivity.(75) However, in the 'brain vent study' by Beqiri, et al. the rSO_2 showed no significant change at Vt 9ml/kg +5 cm H_2O PEEP Vs 6ml/kg + 5 cm H_2O PEEP. However, they noted that low Vt (6ml/kg + 10 cm H_2O PEEP) was associated with low rSO_2.(71)

5.6 Effect of LPV on Intracranial pressure

A positive pressure mechanical ventilation may affect ICP by different mechanisms like changes in PaCO2, by transmitting increased intrapulmonary pressure caused by mechanical ventilation to the intracranial compartment through the venous system and by impairment of systemic hemodynamics. The venous pressure transmitting to the intracranial space decreases the venous blood and CSF outflow from the brain.(76)

Recently Longhini et al. did a single-centre randomized control trial to determine whether LPV strategies would be feasible compared with a control group in adult patients undergoing cranial or spinal surgery. They randomized patients in to either LPV (Vt = 6 ml/kg of PBW, RR =16 breaths/min, PEEP at 5 cmH2O and application of a recruitment manoeuvre (RM) immediately after intubation and at every disconnection from the ventilator) or control treatment (Vt = 10 ml/kg of PBW, RR= 6–8 breaths/min, no PEEP, and no RM). The results showed that the cerebral tension assessed by brain relaxation score were similar between control and LPV strategies. No difference in the rate of intraoperative adverse events was found among both groups. The rate of postoperative pulmonary and extrapulmonary complications and major clinical outcomes were similar between groups.(77)

Brain trauma foundation guidelines recommend a target of 22 mm Hg for raised ICP management in TBI patients. Our study results revealed a mean ICP of 14.1±4.2 mmHg in LPV and 14.7±4.7 mmHg during CV which denotes that protective ventilation strategies have no deleterious effect on ICP. Moreover, it could be seen that LPV had lowered ICP and maintained the CPP within normal limits.

In 2023 Erta Beqiri, et al. assessed neurological and respiratory effect of LPV in acute brain injury patients (Brain Vent study). This prospective crossover study included 30 patients who were randomly assigned to receive low Vt [6 ml/kg/PBW) at either low (5 cmH_2O) or high PEEP (12 cmH_2O). Like our study they kept the PCO_2 in the range 34-36 mmHg by adjusting the respiratory rate, hence, variations in carbon dioxide were not associated with the increase in ICP. The results indicated the ICP increased significantly from baseline to "low Vt/low PEEP" and "low Vt/high PEEP" by 2.2 mmHg and 2.3 mmHg respectively and was considered clinically irrelevant by investigators. None of the interventions affected cerebral oxygenation or autoregulation significantly.

In another study, Francesco et al. evaluated the feasibility of protective ventilation on elective supratentorial neurosurgery. This randomized double-blind cross over study alternatively ventilated the patients with Vt 9 mL/kg—PEEP 0 mm Hg and Vt 7 mL/kg—PEEP 5 mm Hg. Respiratory rate was adjusted to maintain normocarbia. ICP was measured through a subdural catheter inserted before dural opening. They found that ICP did not differ between traditional and protective ventilation (11.28± 5.37, 11 [7 to 14.5] vs. 11.90 ± 5.86, 11 [8 to 15] mm Hg; P= 0.541) and dural tension was

"acceptable for surgery" in all cases. The authors concluded that protective ventilation is a feasible alternative to traditional mode of ventilation in elective neurosurgery.(76)

Newer multimodality neuromonitoring techniques aimed to achieve optimal CPP for individualized care. BTF guidelines recommend avoiding CPP of more than 70 mmHg to reduce pulmonary complications. In the current study CPP was 67.4±13.0 mmHg on CV and 65.0±11.4 mmHg during LPV which was not significant. So, the protective ventilation strategies maintain the cerebral perfusion compared to conventional mode of ventilation. We did not measure the autoregulatory indices.

5.7 Changes in cerebral hemodynamics at side of the lesion compared to non-operated side during LPV.

A systemic review of cerebral and tumoral blood flow (TBF) in adult supratentorial gliomas using magnetic resonance imaging demonstrated that mass effect from brain tumours impairs blood flow in the surrounding brain parenchyma that can improve with surgery. The authors concluded that pre-operative TBF and peritumoral flow increased with increasing tumour grade and was accompanied by a corresponding decrease in CBF.(78) We compared the CBF velocity and cerebral oxygenation at the side of the tumour with opposite side in both ventilation strategies. The results showed that there was no significant difference in TCD indices and rSO_2 of lesion side and non-operating side during CV and LPV. The mean rSO_2 on the lesion side was similar during CV (72.0±5.5%) and LPV (72.7±5.5%) and it was not statistically significant. Similarly, rSO_2 in the normal side also was comparable between CV and LPV (72.8±7.2% vs 73.1±7.3%; p=1.00).

Limitations

Our study has the following limitations;

1. The study is done in a single centre and small numbers. Hence, a multi-center trial with higher sample size may be beneficial to make recommendations.
2. TCD technique is prone to technical errors as it is operator dependent and causing inter observer variability. We tried to reduce the errors by taking the mean values of three readings. Moreover, a well-trained neuroanesthesiologists had evaluated all the parameters. The TCD assessment was done by the PI and Co-PI in all cases.
3. TCD acoustic window is deficient in 10-15% of patients. We have excluded those patients with poor TCD window in the preoperative examination.
4. We have not estimated the actual CBF but measured the CBF velocity as a surrogate of CBF due to unavailability of other methods for intraoperative use. Hence, we deemed TCD the best choice considering its reproducibility and non-invasiveness.
5. NIRS measures only regional cerebral oxygenation changes in frontal area; hence any change in the oxygenation in other brain areas was not quantified.
6. The NIRS, TCD and ICP details were recorded 10 minutes after altering the ventilation modes. Though this time has been established to be enough for hemodynamic and respiratory equilibrium to occur, it would have been more

useful if recordings were done after ventilating the patient for longer periods. This was not practical in intraoperative period in neurosurgical procedures.

7. We have not evaluated the autoregulation status of the patients so that we can also evaluate the effect of LPV in patients with impaired autoregulation.
8. We have not evaluated the effects of LPV Vs CV throughout the surgery as well as postoperative pulmonary outcomes.
9. Patients with features of acute raised ICP were excluded. The feasibility of LPV on patients with raised ICP and cerebral herniation features are to be further studied.
10. We excluded patients with prior lung diseases and obesity in whom the benefit of LPV over CV is already established. Future studies regarding the effects of ventilation strategy on the cerebral hemodynamics involving these specific population, needs to be conducted to extend the benefits of LPV.

7.SUMMARY AND CONCLUSION

SUMMARY

Mechanical ventilation poses distinctive challenges in patients undergoing neurosurgical procedures due to the effects of ventilation, cardiopulmonary interactions and the resultant changes in blood gases which affects the brain homeostasis. Ventilator strategies needs to be optimized to minimize the impact of the ventilation on ICP, cerebral blood flow and brain oxygenation that in turn affects the brain relaxation, bleeding, recovery, etc. LPV being widely used in management of critically ill patients has not been evaluated fully in the intraoperative neurosurgical theaters. This study was conducted primarily to evaluate the role of lung protective ventilation on cerebral hemodynamics such as cerebral blood flow velocity (measured using TCD), cerebral oxygenation (using NIRS) and ICP (using subdural cannula). We also assessed the effect of LPV on systemic hemodynamics, pulmonary oxygenation and lung mechanics compared to CV.

This prospective observational crossover study enrolled 48 patients undergoing cranial and spine surgery in 1:1 ratio and finally analysed 20 patients in each surgery groups (total 40). We included ASA 1 and 2 patients, aged 18-60 years without any features of raised ICP and lung injury. This study found that TCD CBF velocity and rSO_2 were comparable on both sides during both ventilation strategies. There was statistically significant reduction in ICP during LPV as compared to CV (14.1±4.2 Vs 14.7±4.7; p=0.019). Similarly, CPP was also similar between two modes of ventilation. We also found that pulmonary oxygenation will be better during LPV in the form of lower $PaCO_2$- $ETCO_2$ gradient and alveolar- arterial gradient, high PaO_2 and PaO_2/FiO_2 ratio

along with reduction in dynamic ventilatory parameters like Ppeak, Pplat and Pmean. The systemic hemodynamic variables such as heart rate, SBP, DBP and MAP were comparable in both modes of ventilation.

This study found that LPV is a better alternative to CV in elective neurosurgical patients by maintaining the cerebral blood flow, oxygenation and reducing ICP. We also found that LPV is superior to CV in terms of respiratory parameters to provide better ventilation- perfusion matching and low airway pressures.

CONCLUSION

Intraoperative ventilation using lung protective strategy with a low tidal volume of 6 ml/kg with PEEP of 5 cm H_2O as compared to conventional ventilation was found associated with lower airway pressures, better gas exchange and similar systemic hemodynamic profile. Cerebral blood flow velocity, regional cerebral oxygenation was similar between the CV and LPV whereas the ICP was lower in LPV group.

Considering the results of our study, we conclude that application of lung protective ventilation is advantageous in better systemic oxygenation and pulmonary mechanics in neurosurgical patients, especially in situations where high airway pressure or impaired oxygenation is a major perioperative concern during conventional tidal volume ventilation. Further studies are warranted to assess the effects of LPV in patients with suspected poor brain compliance and as well as in patients with lung diseases.

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ANNEXURES

Study Proforma

Title

Effect of intraoperative lung protective ventilation on cerebral hemodynamics (cerebral blood flow assessment using transcranial doppler, cerebral oxygenation by NIRS and ICP measurement using subdural catheter) in neurosurgical patients: a prospective observational study

Serial number:

Group (cranial /spinal) : Group A / Group B

Age:

Sex:

Weight:

Height:

BMI:

Diagnosis:

Procedure:

GCS:

ASA grade:

Comorbidities:

Intraoperative use of osmotherapy:

Intraoperative fluid therapy: crystalloids: colloids: blood products:

Duration of surgery:

	Baseline Values (T0)	T 1 (Conventional ventilation)	T2 (Lung protective ventilation)
HEMODYNAMIC PARAMETERS			
Heart rate			
Systolic blood pressure			
Diastolic blood pressure			
Mean arterial pressure			
RESPIRATORY PARAMETERS			
SpO2 (%)			
EtCO2 mm Hg			
PaCO2 mmHg			
PaO2 mm hg			
VENTILATORY PARAMETERS			
Tidal volume (ml)			
Respiratory rate (/min)			
PEEP (cm H2O)			
P peak (cm H2O)			
P plat (cm H2O)			
Mean Pressure (cm H2O)			
TCD PARAMETERS (MCA)			
Peak velocity (cm/sec)			
Mean velocity(cm/sec)			
Diastolic velocity(cm/sec)			
PI			
NIRS VALUES (rSO_2)			
Right side			
Left side			
INTRACRANIAL PRESSURE (mm Hg)			

CONSENT FORM

Title: Effect of intraoperative lung protective ventilation on cerebral hemodynamics (cerebral blood flow assessment using transcranial doppler, cerebral oxygenation by NIRS and ICP measurement using subdural catheter) in neurosurgical patients: a prospective observational study

Participant's name: Age (in years):

I_____, son/daughter of _____

Declare that (Please tick boxes)

- I have read the above information provided to me regarding the study "Effect of intraoperative lung protective ventilation on cerebral hemodynamics in neurosurgical patients" ( )
- I have clarified any doubts that I had. [ ]
- I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
- I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]
- I understand that my identity will not be revealed in any information released to third parties or published [ ]
- I voluntarily agree to take part in this study [ ]
- I have been provided with the contact numbers of the principle investigator, in case I want to know more about the study and participants rights [ ].
- I received a copy of this signed consent form [ ]

Name:

Signature:

Date:

Name of witness:

Relation to participant:

Signature:

Person Obtaining Consent

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Name:

Signature: Date:

സമ്മതപത്രം

പഠനശീർഷകം

ന്യൂറോസർജിക്കൽ രോഗികളിലെ ശസ്ത്രക്രിയാ സമയത്തെ ശ്വാസകോശം സംരക്ഷിക്കുന്ന വിധത്തിലുള്ള കൃത്രിമ ശ്വസനംമൂലം തലച്ചോറിലെ രക്തചംക്രമണത്തിലുണ്ടാക്കുന്ന പ്രഭാവം (തലച്ചോറിലെ രക്തപ്രവാഹം ട്രാൻക്രേനിയൽ ഡോപ്ലർ ഉപയോഗിച്ച് വിലയിരുത്തും, തലച്ചോറിലെ പ്രണവായുവിന്റെ പ്രവാഹം എൻഐആർഎസ്ഉം ഐസിപി അളവുകൾ സബ്ഡ്യൂറൽ കത്തിറ്ററുമുപയോഗിച്ച് എടുക്കുക): ഒരു ഭാവികാലപ്രാപ്യമായ നിരീക്ഷണ പഠനം

പങ്കെടുക്കുന്നയാളുടെ പേര്: വയസ്സ് (വർഷത്തിൽ)

ഞാൻ..... മകൻ/മകൾ.....

പ്രഖ്യാപിക്കുന്നതെന്തെന്നാൽ (കോളങ്ങൾ അടയാളപ്പെടുത്തുക)

പ്രഖ്യാപിക്കുന്നതെന്തെന്നാൽ (കോളങ്ങൾ അടയാളപ്പെടുത്തുക)

ന്യൂറോസർജിക്കൽ രോഗികളിലെ ശസ്ത്രക്രിയാ സമയത്തെ ശ്വാസകോശം സംരക്ഷിക്കുന്ന വിധത്തിലുള്ള കൃത്രിമ ശ്വസനംമൂലം തലച്ചോറിലെ രക്തചംക്രമണത്തിലുണ്ടാക്കുന്ന പ്രഭാവം (തലച്ചോറിലെ രക്തപ്രവാഹം ട്രാൻക്രേനിയൽ ഡോപ്ലർ ഉപയോഗിച്ച് വിലയിരുത്തും, തലച്ചോറിലെ പ്രണവായുവിന്റെ പ്രവാഹം എൻഐആർഎസ്ഉം ഐസിപി അളവുകൾ സബ്ഡ്യൂറൽ കത്തിറ്ററുമുപയോഗിച്ച് എടുക്കുക): ഒരു ഭാവികാലപ്രാപ്യമായ നിരീക്ഷണ പഠനം എന്ന പഠനത്തിൽ, പങ്കെടുക്കുന്നവർക്കുള്ള കാര്യവിവരണപത്രത്തിൽ വിശദീകരിക്കുന്നവ ഞാൻ വായിച്ചു	[ ]
എനിക്കുണ്ടായ സംശയങ്ങൾ പരിഹരിച്ചു	[ ]
എന്റെ പങ്കാളിത്തം സ്വമേധയായാണെന്നും, കാരണമൊന്നും നൽകാതെയും എന്റെ/എന്റെ കുട്ടിയുടെ നിയമപരമായ അവകാശങ്ങളെയും വൈദ്യപരിചരണത്തെയും ബാധിക്കാതെയും ഏതു സമയത്തും എനിക്ക് പിൻമാറാൻ സ്വാതന്ത്ര്യമുണ്ടെന്നും മനസ്സിലാക്കുന്നു.	[ ]
ഞാൻ പഠനത്തിൽ നിന്നും പിൻമാറിയാലും പഠന സംഘാംഗങ്ങൾക്കും ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മിറ്റി അംഗങ്ങൾക്കും എന്റെ ആരോഗ്യരേഖകൾ പരിശോധിക്കാൻ എന്റെ സമ്മതം ആവശ്യമില്ലെന്ന് ഞാൻ മനസ്സിലാകകുന്നു. അതിന് ഞാൻ സമ്മതം നൽകുന്നു.	[ ]
പഠനഫലമായി ശേഖരിച്ച വിവരങ്ങൾ പ്രസിദ്ധീകരിക്കുമ്പോഴോ മൂന്നാം കക്ഷികൾക്ക് നൽകുമ്പോഴോ എന്നെ തിരിച്ചറിയാനിടയാകുന്നതൊന്നും വെളിപ്പെടുത്തുകയില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു.	[ ]
സ്വമേധയാ പഠനത്തിൽ പങ്കെടുകാകൻ ഞാൻ സമ്മതിക്കുന്നു.	[ ]
ഒപ്പിട്ട സമ്മതപത്രവും കിട്ടിയതായി ഞാൻ അറിയിക്കുന്നു.	[ ]

പേര്

ഒപ്പ്

തീയതി

സാക്ഷിയുടെ പേര്

പങ്കെടുക്കുന്നയാളുമായുള്ള ബന്ധം

ഒപ്പ്

(സമ്മതം വാങ്ങുന്നയാൾ)

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനു വേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണപദ്ധതിയെപ്പറ്റി സാങ്കേതികേതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകടസാധ്യതകളും പാർശ്വഫലങ്ങളും വിശദീകരിക്കുകയും ചെയ്തു. പങ്കാളിയെ ചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

സമ്മതം വാങ്ങുന്നയാളുടെ പേരു ഒപ്പും.....

PATIENT INFORMATION FORM

TITLE: Effect of intraoperative lung protective ventilation on cerebral hemodynamics (cerebral blood flow assessment using transcranial doppler, cerebral oxygenation by NIRS and ICP measurement using subdural catheter) in neurosurgical patients: a prospective observational study

Name of the Investigators:

Dr. Sarath Surendran (PI), Dr. Manikandan S (Guide and CO-PI), Dr.Ranganatha Praveen C S. (Co guide and CO-PI), Dr Easwer HV(CO-PI)

You are being requested to participate in the above titled study which is being conducted to evaluate the effects of two methods of ventilation strategy (conventional high tidal volume and lung protective ventilation) used to ventilate patients under needing mechanical ventilation. Your neurosurgical procedure will require general anesthesia which mandates mechanical ventilation. The study is conducted to see the effects of the two types of ventilatory methods on changes in brain blood flow, brain oxygenation and the pressure changes inside the skull. After giving general anaesthesia, your cerebral hemodynamics parameters (cerebral blood flow assessment using transcranial doppler, cerebral oxygenation using near infrared spectroscopy (NIRS) and intracranial pressure measurement using subdural catheter) will be measured during conventional high tidal volume and lung protective ventilation.

We recruit two groups of patients namely cranial surgery Group (Group A) and spinal surgery (Group B). As per your surgery planned you will be assigned either Group A or Group B. The main difference between the two groups in the study is in group B, no intracranial pressure monitoring during surgery will be performed.

What is Conventional and lung protective ventilation?

Mechanical ventilation is needed for giving general anaesthesia and to perform surgery on you. Conventionally patients in the operating room are ventilated with high tidal volume of 10 ml /kg but may cause lung injury. To prevent lung injury, Lung protective ventilation is the current standard of care for mechanical ventilation especially in an ICU setup. It involves low tidal volume (6ml/kg predicted bodyweight) ventilation, and it reduces ventilator associated lung injury. However, during neurosurgery conventional mode of ventilation is still practised. In this study we try to assess the benefits of Lung protective ventilation over conventional ventilation method.

What is NIRS?

Near infrared spectroscopy (NIRS) is a non-invasive technology that continuously monitors regional tissue oxygenation using sensors placed in the forehead which is totally pain free. Cerebral NIRS is an indirect indicator of perfusion adequacy. So, it allows continuous information on oxygen supply-versus-demand balance in the brain.

What is transcranial doppler?

Transcranial doppler (TCD) is a non-invasive study of brain blood flow velocity quantification. It is a painless procedure. It uses ultrasound doppler principle where a non-invasive probe will be placed over the scalp above the ears and the machine will detect the blood flow wave form which will be computed for quantification by the machine.

What is intracranial pressure monitoring?

ICP monitoring is done only in Group A patients where brain surgery is performed. The ICP is the pressure inside the covering of brain namely dura mater. The disease for which you are undergoing brain surgery by increase in intracranial volume causes increase in ICP which is known to cause adverse effects. In the operation theatre the surgeon puts a catheter/cannula below the covering to monitor the pressure. If the intracranial pressure measured is high, then treatment needs to be initiated to bring the pressure down till surgeon reaches the pathological area. The monitoring and treatment of ICP is a practise followed in neurosurgery.

If you take part, what will you have to do?

Preoperatively, the PI will explain the procedures that happen in operation theatre and will obtain informed written consent about the study. All the monitoring and evaluation will be done after giving general anaesthesia only. Baseline hemodynamic parameters will be noted after attaching monitors and then proceeding with endotracheal intubation. TCD, NIRS and ICP measurements will be done after ventilating with normal tidal volume ventilation and lung protective ventilation.

Does TCD or NIRS monitoring have any side effects?

These two procedures are non-invasive and routinely used to monitor patients. They do not carry any risk. Adverse events from doing these procedures are nil.

Does ICP monitoring cause any side effects?

Intraoperatively ICP measurement is done inserting a small gauge (22G) subdural cannula which is placed below the dura mater after burr hole is placed by the surgeon as a part of the neurosurgical procedure. It is only a minimally invasive

procedure, and it doesn't cause any harm. Moreover, dura will be opened widely by the surgeon intraoperatively. Intraoperative intracranial pressure can also be detected by this method and treatment can be initiated if pressure is high.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way. In addition, if you experience any side effects, the study will be stopped, and you will be given treatment for the side effects.

Will you have to pay for the cost of using the test?

The tests employed are used as a part of anaesthesia procedure for surgery. So, no additional cost will be charged for it.

Will your personal details be kept confidential?

The results of this study will be used for thesis submission as a part of academic research and will be submitted to a medical journal for publication, but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask DR. SARATH SURENDRAN (Principal investigator) mobile number: 9400943357. Email: sarat@sctimst.ac.in

If you have any questions, concerns or complaints about the research please contact:
Dr. SRINIVAS G, member secretary, Institutional Ethics Committee,
Sree Chitra Tirunal Institute for Medical Sciences and Technology
Tel: 0471-2524689, Email:iec.mem.sec@sctimst.ac.in

രോഗികൾക്കുള്ള കാര്യവിവരണ പത്രം

പഠനശീർഷകം

ന്യൂറോസർജിക്കൽ രോഗികളിലെ ശസ്ത്രക്രിയാ സമയത്തെ ശ്വാസകോശം സംരക്ഷിക്കുന്ന വിധത്തിലുള്ള കൃത്രിമ ശ്വസനംമൂലം തലച്ചോറിലെ രക്തചംക്രമണത്തിലുണ്ടാക്കുന്ന പ്രഭാവം (തലച്ചോറിലെ രക്തപ്രവാഹം ട്രാൻക്രേനിയൽ ഡോപ്ലർ ഉപയോഗിച്ച് വിലയിരുത്തും, തലച്ചോറിലെ പ്രണവായുവിന്റെ പ്രവാഹം എൻഐആർഎസ്ഉം ഐസിപി അളവുകൾ സബ്ഡ്യൂറൽ കത്തിറ്ററുമുപയോഗിച്ച് എടുക്കുക): ഒരു ഭാവികാലപ്രാപ്യമായ നിരീക്ഷണ പഠനം

ഗവേഷകരുടെ പേര്

ഡോ. ശരത് സുരേന്ദ്രൻ (പ്രധാന ഗവേഷകൻ), ഡോ. മണികണ്ഠൻ എസ്, (ഗൈഡും സഹ ഗവേഷകനും), ഡോ. രംഗനാഥ പ്രവീൺ സി. എസ് (സഹ ഗൈഡും സഹ ഗവേഷകനും, ഡോ. ഈശ്വർ എച്. വി (സഹ പ്രധാന ഗവേഷകൻ)

ശ്രീ/ശ്രീമതി,

യാന്ത്രിക ശ്വസനസഹായം വേണ്ടിവരുന്ന രോഗികളിൽ ഉപയോഗിക്കുന്ന രണ്ട് വിധത്തിലുള്ള കൃത്രിമ ശ്വസനത്തിന്റെ (സാനമ്പ്രദായികമായ ഉയർന്ന അളവിലുള്ളതും ശ്വാസകോശത്തെ സംരക്ഷിക്കുന്ന വിധത്തിലുള്ളതുമായ) പ്രഭാവം വിലയിരുത്തുന്ന പഠനത്തിൽ പങ്കെടുക്കുവാൻ താങ്കളെ ഞങ്ങൾ ക്ഷണിക്കുന്നു. താങ്കളുടെ ന്യൂറോ ശസ്ത്രക്രിയയ്ക്ക് പൊതുവിലുള്ള മയക്കലും അതിന് യാന്ത്രിക ശ്വസനസഹായിയും ആവശ്യമാണ്. തലച്ചോറിലെ രക്തപ്രവാഹം, പ്രാണവായുവിന്റെ ലഭ്യത, തലയോട്ടിക്കുള്ള ിലെ സമ്മർദ്ദ വ്യതിയാനങ്ങൾ എന്നിവയിൽ രണ്ട് തരത്തിലുള്ള ശ്വസന സമ്പ്രദായമുണ്ടാക്കുന്ന പ്രഭാവം മനസ്സിലാക്കാനാണ് ഈ പഠനം. പൊതുവായ മയക്കൽ നടത്തിയശേഷം താങ്കളുടെ തലച്ചോറിലെ രക്തചംക്രമണ ഘടകങ്ങളും (ട്രാൻസ് ക്രേനിയൽ ഡോപ്ളർ ഉപയോഗിച്ച് തലച്ചോറിലെ രക്തപ്രവാഹം വിലയിരുത്തും, തലച്ചോറിലെ പ്രാണവായുവിന്റെ ലഭ്യത നീയർ ഇൻഫ്രാ റെഡ് സ്പെക്ട്രോസ്ക്കോപ്പി ഉപയോഗിച്ചും തലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദം സബ്ഡ്യൂറൽ കത്തിറ്റർ ഉപയോഗിച്ചും അളക്കും) സാമ്പ്രദായികമായ ശ്വസനരീതിയിലും ശ്വാസകോശത്തെ സംരക്ഷിച്ചുകൊണ്ടുള്ള ശ്വസനരീതിയിലും അളക്കും.

ഞങ്ങൾ രോഗികളുടെ രണ്ട് സംഘത്തെ തിരഞ്ഞെടുക്കും, ക്രേനിയൽ ശസ്ത്രക്രിയ നടത്തുന്ന സംഘവും (എ ഗ്രൂപ്പ്), സ്പൈനൽ ശസ്ത്രക്രിയ നടത്തുന്ന സംഘവും (ബി ഗ്രൂപ്പ്). ശസ്ത്രക്രിയ നടത്താൻ തീരുമാനിക്കുന്ന മുറയ്ക്ക് താങ്കളെ എഗ്രൂപ്പിലേയ്ക്കോ ബി ഗ്രൂപ്പിലേയ്ക്കോ നിശ്ചയിക്കും. രണ്ട് സംഘങ്ങളും തമ്മിലുള്ല പ്രധാന വ്യത്യാസം, ബി ഗ്രൂപ്പിൽ തലച്ചോറിനുള്ളിലെ സമ്മർദ്ദം ശസ്ത്രക്രിയാസമയത്ത് നിരീക്ഷിക്കില്ല എന്നതുമാത്രമാണ്.

എന്താണ് സാമ്പ്രദായിക കൃത്രിമശ്വസനവും, ശ്വാസകോശം സംരക്ഷിച്ചുകൊണ്ടുള്ള കൃത്രിമശ്വസനവും.

താങ്കൾക്ക് ശസ്ത്രക്കിയ നടത്തുവാൻ പൊതുവായി മയക്കേണ്ടതുണ്ട് അതിന് യാന്ത്രിക ശ്വസനം വേണ്ടിവരും. സാമ്പ്രദായികമായി ശസ്ത്രക്രിയാ മുറിയിൽ രോഗിക്ക് ഉയർന്ന അളവിൽ 10 മില്ലി/കെജി എന്ന യളവിൽ പ്രാണവായു നൽകും ഇത് ശ്വാസകോശത്തിന് മുറിവുണ്ടാക്കിയേക്കാം. ശ്വാസകോശത്തിന് മുറിവുണ്ടാകാതിരിക്കാൻ, ഇപ്പോഴത്തെ അംഗീകൃത പരിചരണ രീതിയായി ശ്വാസകോശം സംരക്ഷിച്ചുകൊണ്ടുള്ള കൃത്രിമശ്വസനമാണ്, പ്രത്യേകിച്ചും തീവ്രപരിചരണ സംവിധാനത്തിൽ ചെയ്യുന്നത്. ഇതിൽ കുറഞ്ഞ അളവിലുള്ള (6മില്ലി/കെജി, പ്രതീക്ഷിക്കുന്ന ശരീരഭാരത്തിനനുസരിച്ച്)കൃത്രിമശ്വാസം നൽകുന്നത് അതുമായി ബന്ധപ്പെട്ട ശ്വാസകോശത്തിന്റെ പരുക്ക് കുറയ്ക്കും. എന്നിരുന്നാലും, ന്യൂറോ ശസ്ത്രക്രിയാസമയത്ത് സാമ്പ്രദായികമായ ശ്വസനരീതിയാണ് ഉപയോഗിക്കുന്നത്. ഈ പഠനത്തിൽ സാമ്പ്രദായിക ശ്വസനത്തിൻമേൽ ശ്വാസകോശം സംരക്ഷിച്ചുകൊണ്ടുള്ള രീതിയുടെ നേട്ടം വിലയിരുത്താൻ ഞങ്ങൾ ശ്രമിക്കുകയാണ്.

എന്താണ് എൻഐആർഎസ്?

നീയർ ഇൻഫ്രാറെഡ് സ്പെക്ട്രോസ്കോപ്പി (എൻഐആർഎസ്) പ്രാദേശിക കലകളിലെ പ്രാണവായു ലഭ്യത നെറ്റിയിൽ ഘടിപ്പിക്കുന്ന സെൻസറുകൾ വഴി ശരീരത്തിൽ പ്രവേശിക്കാതെ തുടർച്ചയായി നടത്തുന്ന പൂർണ്ണമായും വേദനാരഹിതമായ നിരീക്ഷണ സംവിധാനമാണ്. തലച്ചോറിലെ എൻഐആർഎസ് വേണ്ടും വിധത്തിൽ പ്രാണവായു ലഭ്യമാണെന്നതിന്റെ സൂചനയാണ്. ആകയാൽ തലച്ചോറിലെ പ്രാണവായുവിന്റെ ആവശ്യത്തെപ്പറ്റിയും തുടർച്ചയായ വിവരം നൽകും.

എന്താണ് ട്രാൻസ്ക്രോനിയൽ ഡോപ്ലർ?

ട്രാൻസ്ക്രോനിയൽ ഡോപ്ലർ (റ്റിസിഡി) തലച്ചോറിലെ രക്തപ്രവാഹത്തിന്റെ വേഗത കണക്കാക്കുന്ന ശരീരത്തിൽ പ്രവേശിക്കാതെയുള്ള ഒരു പഠനമാണ്. ഇത് വേദനാരഹിതമാണ്. ചെവിക്കുമുകളിൽ ഒരു പ്രോബ് ശരീരത്തിൽ പ്രവേശിക്കാതെ വച്ച അൾട്രാസൗണ്ട് ഡോപ്ലർ നിയമങ്ങൾ ഉപയോഗിച്ച് രക്തപ്രവാഹം യന്ത്രം തിരിച്ചറിഞ്ഞ് അളവ് കണക്കാക്കും.അത്

എന്താണ് തലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദ നിരീക്ഷണം?

തലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദ നിരീക്ഷണം ഗ്രൂപ്പ് എ രോഗികളിൽ തലച്ചോറ് ശസ്ത്രക്രിയ നടത്തുമ്പോൾ ചെയ്യും. ഡ്യൂറാമാറ്ററെന്ന പേരിലുള്ള തലച്ചോറിന്റെ കവചത്തിനുള്ളിലെ സമ്മർദ്ദമാണ് ഐസിപി. താങ്കൾ തലച്ചോറിന്റെ ശ്സ്ത്ര്കരിയയ്ക്ക് വിധേയമാകുമ്പോൾ തലയോട്ടിക്കുള്ള ിലെ സമ്മർദ്ദം വർദ്ധിക്കുന്നു ഇത് പ്രതികൂല ഫലങ്ങളുണ്ടാക്കും. ശസ്ത്ര്ക്രിയാമുറിയിൽ സ്രാജൻ ഒരു കത്തിറ്റർ/കുഴൽ കവചത്തിനടിൽ സമ്മർദ്ദം നിരീക്ഷിക്കാൻ വെയ്ക്കും. തലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദം വലുതാണെങ്കിൽ, സർജൻ ശസ്ത്രക്രിയ നടത്തേണ്ടുന്ന പ്രദേശത്ത് എത്തുന്നതുവരെയും സമ്മർദ്ദം കുറയാക്കാനാവശ്യമായ ചികിത്സ നടത്തും. ന്യൂറോ ശസത്രക്രിയയ്ക്ക് ഐസിപി നിരിക്ഷണവും ചികിത്സയും ഒരു നടപടിക്രമമാണ്.

താങ്കൾ പങ്കെടുക്കുകയാണെങ്കിൽ എന്ത് ചെയ്യണം?

ശസ്ത്രക്രിയയ്ക്കുമുമ്പ് പ്രധാനഗവേഷകൻ ശസ്ത്രക്രിയാമുറിയിൽ നടക്കുന്ന നടപടികൾ വിശദീകരിക്കുകയും പഠനത്തിനായി രേഖാമൂലമുള്ള സമ്മതം വാങ്ങുകയും ചെയ്യും. പൊതുവായ മയക്കൽ നൽകിയശേഷമാണ് എല്ലാ നിരീക്ഷണങ്ങളും വിലയിരുത്തലുകളും നടത്തുക. നിരീക്ഷണ സംവിധാനങ്ങൾ ബ്ധിപ്പിച്ചശേഷം അടിസ്ഥാന രക്തചംക്രമണ ഘടകങ്ങൾ രേഖപ്പെടുത്തും എന്നിട്ട് എൻഡോട്രാക്കിയയിൽ കുഴൽ കടത്തും. സാധാരണ അളവിലുള്ള കൃത്രിമശ്വസനവും, ശ്വാസകോശം സംരക്ഷിച്ചുകൊണ്ടുള്ള ശ്വസനവും നൽകിയശേഷം നൽകിയശേഷം റ്റിസിഡി, എൻഐആർഎസ്, ഐസിപി അളവുകൾ എടുക്കും.

റ്റിസിഡിക്കോ എൻഐആർഎസിനോ പാർശ്വഫലങ്ങളുണ്ടോ?

ഈ രണ്ട് നടപടികളും പതിവായുള്ലതും ശരീരത്തിൽ പ്രവേശിക്കാതെ രോഗികളെ നിരീക്ഷിക്കുന്നതുമാണ്. അവയ്ക്ക് അപായങ്ങളൊന്നുമില്ല. ഈ നടപടികൾചെയ്യുന്നതിൽനിന്നും ദോഷകരമായ സംഭവങ്ങളൊന്നുമില്ല.

ഐസിപി നിരീക്ഷണത്തിൽ പാർശ്വഫലങ്ങളുണ്ടോ?

ന്യൂറോ ശസ്ത്രക്രിയയുടെ ഭാഗമായ സുഷിരം ഉണ്ടാക്കിയശേഷം ന്യൂറോ സർജൻ ,ശസ്ത്രക്രിയാസമയത്ത് ഒരു ചെറിയ വലുപ്പത്തിലുള്ള (22ജി) സബ്ഡ്യൂറൽ കുഴൽ ഡൂറാമാറ്ററിനടിയിൽ സ്ഥാപിക്കും. ഇത് വളരെ കുറവ് ശരീരത്തിൽ പ്രവേശിക്കുന്ന തും അപായമൊന്നും ഉണ്ടാക്കാത്തതുമാണ്. തലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദവും ഈ രീതിയിലുടെ കണ്ടെത്തുകയും സമ്മർദ്ദം വലുതാണെങ്കിൽ ചികിത്സ ആരംഭിക്കുകയും ചെയ്യും.

താങ്കൾക്ക് പഠനമാരംഭിച്ചശേഷം പിൻമാറാനാകുമോ?

താങ്കളുടെ പങ്കാളിത്തം പൂർണ്ണമായും സ്വമേധയായാണ്, ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതിൽ നിന്നും പിൻമാറാനും താങ്കൾക്ക് സ്വാതന്ത്ര്യമുണ്ട്. താങ്കളങ്ങനെ ചെയ്യുന്നതുകൊണ്ട് ഈ ആശുപത്രിയിലെ താങ്കളുടെ ചികിത്സയെ ഒരു വിധത്തിലും ബാധിക്കില്ല.. കൂടാതെ താങ്കൾക്കെന്തെങ്കിലും പാർശ്വഫലങ്ങളുണ്ടായാൽ പഠനം നിർത്തുകയും പാർശ്വഫലത്തിനുള്ള ചികിത്സ നൽകുകയും ചെയ്യും.

പരിശേധനയുടെ ചിലവ് താങ്കൾ വഹിക്കണോ?

ശസ്ത്രക്രിയയ്ക്ക് വേണ്ടിയുടെ മയക്കൽ നടപടികളുടെ ഭാഗമാണ് ഈ പരിശോധനകൾ. പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് അധിക ചിലവുകൾ ഒന്നും ഉണ്ടാകില്ല.

താങ്കളുടെ വ്യക്തിപരമായ വിശദാംശങ്ങൾ രഹസ്യമായിരിക്കുമോ?

ഈ പഠനത്തിന്റെ ഫലങ്ങൾ ഒരു അക്കാഡമിക് ഗവേഷണത്തിന്റെ ഭാഗമായി സമർപ്പിക്കുകയും ഒരു വൈദ്യശാസ്ത്ര ജേർമലിൽ പ്രസിദ്ധീകരിക്കുകയും ചെയ്യും, പക്ഷേ താങ്കളെ പേരുകൊണ്ട് ഒരു പ്രസിദ്ധികരണത്തിലോ പ്രദർശനത്തിലോ തിരിച്ചറിയാനാകില്ല. എന്നിരുനനാലും, താങ്കൾ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിക്കുകയാണെങ്കിൽ താങ്കളുടെ ചികിത്സാരേഖകൾ പഠനവുമായി ബന്ധപ്പെട്ടവർ താങ്കളുടെ അധികമായ സമ്മതമില്ലതെ അവലോകനം ചെയ്തേക്കാം.

താങ്കൾ ഈ വിവരങ്ങൾ വയിക്കുമ്പോൾ താങ്കളെ ചികിത്സിക്കുന്ന ഡോക്ടർ താങ്കൾക്കുണ്ടാകുന് ഏത് ചോദ്യത്തിനും ഉത്തരം നൽകാൻ സന്നിഹിതമായിരിക്കും. താങ്കൾക്ക് ചോദ്യങ്ങളുണ്ടെങ്കിൽ ബന്ധപ്പെടുക

ഡോ. ശരത് സുരേന്ദ്രൻ
സീനിയർ റസിഡന്റ്, ന്യൂറോഅനസ്തിഷ്യോളജി വിഭാഗം, അനസ്തീഷ്യോളജി ഡിപ്പാർട്ട്മെന്റ്

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി,
തിരുവനന്തപുരം, ഫോൺ: 94009433577ഇമെയിൽ: sarat@sctimst.ac.in

ഗവേഷണത്തെപ്പറ്റി ചോദ്യങ്ങളോ, ഉത്കണ്ഠകളോ, പരാതികളോ ഉണ്ടെങ്കിൽ ജയവായി ബന്ധപ്പെടുക

ഡോ. ശ്രീനിവാസ് ജി

മെമ്പർ സെക്രട്ടറി

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1845/FEBRUARY/2022 17.03.2022

Dr. Sarath Surendran
Resident
Department of Anaesthesiology
SCTIMST, Thiruvananthapuram

Dear Dr. Sarath Surendran,

The Institutional Ethics Committee held on 19th February, 2022, reviewed and discussed your application to conduct the study titled "**EFFECT OF INTRAOPERATIVE LUNG PROTECTIVE VENTILATION ON CEREBRAL HEMODYNAMICS (CEREBRAL BLOOD FLOW ASSESSMENT USING TRANSCRANIAL DOPPLER, CEREBRAL OXYGENATION BY NIRS AND ICP MEASUREMENT USING SUBDURAL CATHETER) IN NEUROSURGICAL PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY**" (IEC/1845).

The following members of the Ethics Committee were present at the meeting held on 19th February, 2022

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
8.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
9.	Dr. Harikrishna Varma PR	Ph.D (Materials Science)	Male	Medical Technology	Yes
10.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
11.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 29.12.2021*
2. *IEC Application form*
3. *Project Proposal*
4. *Declaration form*
5. *Patient Information Sheet in English and Malayalam*
6. *Consent Form in English and Malayalam*
7. *CV of PI and Co-PIs*
8. *Study Proforma*
9. *Checklist Form*
10. *SRC Recommendation Letter*

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

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MASTER CHART

Pt No	Age	Sex	Weight	Height	BMI	ASA grade	Baseline Hb	Fluid intake	Urine output	Anaesthesia duration	Surgery duration	HR			SBP			DBP
Group A												T0	T1	T2	T0	T1	T2	T0
1	46	1	80	174	26.4	1	13.1	2800	1200	324	300	59	53	54	104	102	104	56
2	62	1	70	172	23.7	1	12.3	2200	1400	390	360	88	86	86	126	114	108	80
3	45	1	75	174	24.8	2	13.2	4750	1400	540	510	56	58	58	102	128	124	73
4	36	1	66	169	23.1	1	15.4	3000	1500	390	360	64	66	52	118	108	104	60
5	36	2	65	172	22	1	13.3	2500	1300	330	300	74	64	60	126	138	148	62
6	47	2	76	171	25.9	1	11.2	4350	2000	432	390	64	76	68	124	106	116	66
7	27	2	80	161	30.9	1	13.4	4060	2200	510	480	74	78	76	122	126	124	80
8	42	2	74	160	28.9	2	10	3040	1800	432	390	66	66	80	124	126	130	74
9	37	1	70	170	24.2	1	11.9	4330	1700	432	390	76	56	54	118	104	108	65
10	37	2	80	174	26.4	2	12.8	3320	1200	378	360	68	63	63	147	132	130	65
11	40	1	59	176	19	1	10.6	3100	1400	330	300	57	58	58	118	104	104	62
12	47	2	69	156	28.2	1	12.1	3300	1200	360	330	68	60	58	122	116	110	66
13	37	2	69	148	31.3	1	11.1	3000	1200	330	300	58	52	60	110	100	116	69
14	42	1	74	178	23.4	1	15.1	3530	1600	450	420	54	56	56	126	112	118	67
15	22	1	70	176	22.6	1	11.8	4050	1600	552	510	60	61	58	128	118	100	65
16	42	2	64	166	20.7	1	11.5	3800	1400	372	330	54	56	53	127	104	110	73
17	27	1	72	178	22.7	1	12.5	4050	1800	540	480	65	60	58	138	115	106	86
18	57	1	67	165	24.6	2	15.1	3500	1600	330	300	72	60	49	163	115	117	90
19	59	1	58	164	21.6	1	13.8	3600	1300	240	220	104	98	83	130	128	113	74
20	57	1	60	166	21.8	1	11.4	3260	1400	270	250	98	96	84	128	124	101	82
Group B																		
1	64	2	66	166	24	1	13.6	2500	900	330	300	82	67	70	126	123	102	76
2	51	2	85	176	27.4	2	12.4	2800	1200	390	360	86	78	74	120	106	110	76
3	37	1	60	174	19.8	1	16	2000	700	330	300	76	74	74	121	118	116	75
4	24	1	68	170	23.5	1	10.7	4250	1800	480	450	88	60	58	130	122	116	72
5	32	2	67	159	26.5	1	14.1	2500	700	450	420	68	66	58	128	102	105	64
6	42	2	72	170	24.9	2	13.6	2800	1200	510	480	106	104	100	130	128	127	94
7	45	2	68	162	25.9	1	12	1400	800	186	150	78	80	74	120	102	106	78
8	52	1	70	170	24.2	1	12.4	1200	1000	270	240	70	76	78	130	134	125	74
9	47	1	59	162	22.5	1	14.3	1500	800	204	180	88	72	68	123	102	108	70
10	33	2	55	160	21.4	1	11.8	2000	1000	330	300	102	108	106	128	132	122	80
11	35	2	58	162	22.1	2	13.5	1800	1100	300	270	68	58	56	115	110	108	71
12	42	2	72	175	23.5	1	12.2	3000	1400	450	420	89	82	83	122	132	130	74
13	60	1	60	170	20.8	1	10	3630	1600	510	480	74	78	74	126	120	122	68
14	45	1	66	168	23.4	1	11.8	3500	1800	510	480	58	60	56	130	126	128	67
15	28	1	78	176	25.2	1	13.2	3500	1700	480	450	67	66	68	129	125	129	76
16	26	2	88	178	27.8	1	15	2500	1200	270	240	98	100	98	130	128	123	90
17	52	2	78	170	26.9	2	13	3500	1300	300	270	78	66	64	118	102	104	76
18	43	2	76	174	25.1	1	14.4	4000	1800	480	430	102	100	100	114	116	99	84
19	53	1	80	168	28.3	1	12.8	4280	1700	480	450	82	78	78	115	101	107	94
20	33	2	80	170	27.6	1	12.2	3000	900	270	250	88	83	78	128	102	112	82

		MAP			ETCO2		PaCO2		PaCO2-ETCO2 gradient		PaO2		P/F		A-a gradient		Ppeak		Pplat
T1	T2	T0	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1
52	58	66	68	68	35	36	40.5	37.4	5.5	1.4	284	306	568	612	27.3	3.8	14	16	14
78	68	90	84	82	36	36	41.6	37	5.6	1	306	288	612	576	5	22.3	19	17	17
100	94	81	106	100	33	33	36.2	36	3.9	3	202	280	404	560	109.3	31.5	18	15	16
48	52	72	68	65	36	35	36.2	35.4	0.2	0.4	231	244	462	488	80.6	69.5	17	15	15
76	82	62	96	82	37	36	38.8	37.8	1.8	1.8	270	299	540	598	38	10.3	20	17	18
58	62	76	74	75	35	30	37.9	35.6	2.9	5.6	120	188	240	376	189.1	124	24	21	22
66	64	94	74	84	33	34	40.3	36.2	7.3	2.2	244	278	488	556	65	30.8	22	18	20
78	86	92	96	100	33	33	34.3	33.9	1.3	0.9	234	223	468	446	79.6	91.1	17	18	15
57	57	83	74	76	36	36	37.9	36.4	1.9	0.4	299	276	598	552	10.1	35	27	26	25
67	58	92	89	82	36	35	38.4	35.8	2.4	0.8	157	259	314	518	157.1	52.8	24	22	22
54	54	72	66	65	36	37	37.8	39.7	1.8	2.7	205	293	410	518	104.3	13.9	16	15	15
62	61	84	82	80	34	38	36.8	39	2.8	3	232	273	464	546	78.5	34.8	24	20	22
66	56	79	72	77	33	33	35.3	34.4	2.3	1.4	243	306	486	612	69.4	7.5	20	19	19
67	68	87	82	79	31	31	36.8	33.9	1.8	2.9	228	276	456	552	85.8	38.1	21	13	19
68	60	80	79	66	36	35	39.6	36.3	3.6	1.3	282	266	564	532	27.8	45.1	16	14	16
60	64	91	75	79	30	32	38.4	34.4	8.4	5.4	260	276	520	552	53.9	37.5	21	18	19
67	68	103	83	79	32	32	37.8	34.8	5.8	2.8	205	233	410	466	109.5	80	22	17	20
78	54	106	90	75	32	32	37.2	36.4	5.2	4.4	218	224	436	448	92	39	20	15	17
74	63	90	88	83	34	35	36.8	38.5	2.8	3.5	264	272	528	544	46.5	36.4	21	19	20
80	74	97	95	84	32	32	38.2	37.4	6.2	5.4	231	248	462	496	77.8	61.8	19	16	19
70	53	86	65	69	33	34	36.2	34.6	3.2	1.6	228	280	456	560	83.3	31.3	21	19	20
55	58	87	71	74	33	35	36.4	37.9	3.4	2.9	282	296	564	592	29	13.1	21	18	19
74	74	90	88	87	31	32	38.4	39.2	7.4	7.2	258	270	516	540	56.8	44	17	15	15
64	66	81	83	79	36	34	38.7	35.1	2.7	1.1	302	308	604	616	6.1	4.6	15	13	13
54	61	84	63	79	34	32	40.3	34	6.3	2	231	215	462	430	80.8	99	21	18	19
62	69	102	84	88	35	35	38.4	36	3.4	1	198	208	396	416	110.5	103.5	20	19	18
64	62	82	76	79	35	36	40	37	5	1	250	288	500	576	56.5	22.3	24	19	22
70	68	93	91	87	37	34	38.6	36.9	1.6	2.9	278	303	556	606	32.4	5.3	22	19	20
56	62	88	71	73	38	36	41.2	37.1	3.2	1.1	198	206	396	412	110	102.9	18	13	16
79	72	96	96	84	33	33	36.1	34.8	3.1	1.8	246	265	492	530	65.4	48	17	14	15
68	66	80	72	71	37	35	39.4	36.9	2.4	1.9	244	288	488	576	66.4	25	17	18	15
69	70	90	90	90	34	34	36.9	34.2	2.9	1.8	229	268	458	536	84.8	42.4	15	14	13
80	76	87	93	91	37	37	39.7	37	2.7	0	264	259	528	518	42.9	51.3	19	16	17
65	77	88	85	94	34	33	35.2	34.5	1.2	1.5	290	303	580	606	23.4	9.5	19	15	17
75	82	94	92	98	38	36	38.9	37.5	1.9	1.5	245	268	290	536	62.9	41.6	20	17	18
79	91	104	95	102	36	36	37.1	39	1.1	3	298	304	596	608	13.5	7.5	19	15	18
73	73	90	82	83	35	36	36.8	37.2	1.8	1.2	241	252	482	504	69.5	58	21	17	19
84	79	94	95	87	36	35	39.2	38.6	3.2	3.6	288	281	576	562	19.5	27.3	23	19	21
77	79	103	86	89	35	35	38.7	38.1	3.7	3.1	234	248	468	496	74.1	60.9	21	18	20
52	64	97	68	80	33	33	36.7	36.1	3.7	3.1	232	251	464	502	78.6	60.4	23	19	22

	Pmean		Driving pressure		Cdyn		NIRS-right			NIRS -left			ICP		PSV R MCA			EDV R MCA	
T2	T1	T2	T1	T2	T1	T2	T0	T1	T2	T0	T1	T2	T1	T2	T0	T1	T2	T0	T1
17	9	7	9	12	85.7	41.7	69	70	70	64	66	67	22	20	50.2	62	54.9	26.5	23.4
16	8	8	12	11	54.2	37.5	72	74	74	70	68	70	17	16	30.9	74.1	42.6	11.2	17.3
16	9	8	11	11	54.5	50	77	83	79	70	84	75	13	12	58.5	63.3	52	28.6	31.9
15	8	8	10	10	62.5	50	68	69	78	68	74	80	12	11	61.5	74.5	52.3	26.6	32.2
17	8	8	13	12	46.2	37.5	67	66	68	66	66	71	13	13	53.9	54.5	34	17.9	24.2
19	9	8	17	14	38.2	28.6	80	82	82	72	78	77	10	9	44.6	34	36	14.9	13.1
19	10	10	15	14	36.7	31.8	69	68	64	70	76	70	14	14	64.1	68.7	88	28.3	31
18	12	11	10	13	65	36.4	57	61	62	62	70	68	11	9	57.5	50.5	47.9	15.3	16.4
22	10	9	20	17	30	19.7	75	70	72	78	73	74	15	14	50.9	53.8	57	11	24.1
19	9	9	17	14	35.3	25	75	72	75	72	75	75	6	6	58.8	65.9	61	23.8	28.5
15	10	8	10	10	66.7	46.9	71	72	70	66	68	68	25	22	101	50.7	54.3	36.5	23.6
21	9	9	17	16	35.3	28.8	61	62	63	71	71	78	15	17	42.5	80.9	27.3	15.6	51.8
20	9	9	14	15	46.2	33.3	65	69	68	70	73	74	11	11	45.8	45.9	44.2	30.4	33
17	11	10	14	12	42.9	66.7	71	69	70	73	73	74	10	11	52.1	54	60.5	23.9	27.1
16	9	9	11	11	63.9	53.6	80	84	87	80	80	82	11	10	46.6	40.1	61.6	13.3	17.6
18	9	8	14	13	42.9	36.4	78	78	74	74	73	72	20	19	87.1	60.2	59.2	27.5	30.2
15	10	9	15	10	43.3	40	62	64	64	64	65	64	17	17	41.7	43.1	47.3	8.16	13.5
17	8	7	12	12	44.6	40	75	76	81	72	75	76	20	18	74	63.8	66.4	26.7	26.8
19	9	8	15	14	40	28.6	77	80	80	83	85	86	14	14	59.7	51.8	52.2	22	19.8
17	10	9	14	12	40	36.4	61	62	62	72	71	70	18	18	76.4	68.1	65.2	31.2	29.4
19	11	10	15	14	40	31.3	71	67	70	69	63	65	NA	NA	72.7	41.4	52.1	29.5	14.2
19	8	8	14	14	46.4	30.8	80	71	67	75	68	64	NA	NA	36.1	62.5	58	15.7	19.1
15	8	7	10	10	60	41.7	76	82	82	74	80	82	NA	NA	58.1	65.5	60.7	32.8	32.1
13	9	8	8	8	75	46.9	73	71	64	70	69	66	NA	NA	62.4	65.1	63.4	26.8	24.9
17	12	9	14	12	39.3	29.2	70	74	72	68	76	72	NA	NA	63.9	73.4	43.3	24.3	25.3
16	10	10	13	11	38.5	29.2	62	64	64	64	70	68	NA	NA	50.6	58.4	53.4	19.9	21.8
20	10	9	17	15	35.3	33.3	54	54	55	68	70	70	NA	NA	71.2	50.2	50.6	18.4	24.7
18	13	12	15	13	43.3	30.8	63	78	78	65	69	70	NA	NA	54.6	42.4	40.2	25.5	23.9
16	8	8	11	11	50	50	78	80	78	72	87	90	NA	NA	60.4	40.7	71	26.8	17.8
13	12	10	10	8	50	41.3	73	77	75	72	75	72	NA	NA	102	46.5	64.8	55.6	16.4
14	9	8	10	9	60	29.2	65	75	75	71	77	78	NA	NA	41.6	54.4	63.1	17.5	25.8
14	8	8	8	9	81.3	43.8	70	75	75	68	69	70	NA	NA	65.2	54.1	60.2	30.1	20.6
15	12	10	12	10	54.2	41.7	68	70	70	67	67	68	NA	NA	76.2	70.3	70	34.7	29.2
14	12	11	12	9	54.2	44.4	66	65	70	66	67	70	NA	NA	60.2	61.8	66.3	26.1	25.2
16	9	9	13	11	50	40	68	69	68	65	66	70	NA	NA	47.8	56.2	51.2	28.5	30.1
17	9	8	13	12	46.4	40	72	70	74	70	70	72	NA	NA	98.4	75.8	80.2	40.1	34.4
19	9	8	14	14	44.6	33.3	64	66	66	68	69	69	NA	NA	98.7	89.2	80.4	45.1	43.1
19	11	10	16	14	39.1	30.4	66	68	65	70	68	66	NA	NA	68.1	60.8	58.4	38.4	31.4
18	8	7	15	13	40	30.8	72	71	72	68	68	68	NA	NA	64.8	59.7	62.7	29.4	21.8
18	8	8	17	13	40.6	28.6	74	72	70	74	73	73	NA	NA	66.4	37.4	59.2	40.2	14.5

	MEAN FV R MCA			PI R MCA			PSV L MCA			EDV L MCA			MEAN FV L MCA			PI L MCA	
T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1
23.3	37.5	39	36.4	0.63	0.99	0.87	77.8	54.7	58.8	36.4	23.5	26.4	55.2	0.75	39.7	0.75	0.86
15.3	20.3	40.7	25.7	0.97	1.4	1.06	31	36	43.2	12.5	14.4	15.3	18.6	0.99	26.4	0.99	0.88
31.2	40.8	51.7	41.9	0.73	0.61	0.5	52	47.4	47.8	22.7	24.6	23.7	41	0.72	33.1	0.72	0.62
16	41.9	47.9	29.9	0.83	0.88	1.22	46.9	69.3	56.5	15.9	23.7	20.1	29.1	1.07	32.1	1.07	1.2
16.4	35.7	36	24.4	1.01	0.84	0.72	52	55.8	38.5	19.7	22.4	20.6	34.8	0.93	30.4	0.93	0.86
14.3	28	22.7	21.2	1.06	0.92	0.92	70.8	30.7	47.6	14.5	13.1	17.6	38.5	1.46	30.7	1.46	0.82
69	43.3	49.5	51.6	0.88	0.76	0.53	93.4	45.7	57	22.1	24.6	14	50.4	0.97	39.9	0.97	0.61
22.6	28.9	28.9	34.2	1.46	1.18	0.74	89.7	61.2	61	43.2	27.8	32.3	62.8	0.74	45.3	0.74	0.84
24.6	28.1	35.8	35.3	1.42	0.83	0.92	40	63.9	40.6	17.7	26.2	18.7	25.9	0.86	26.4	0.86	0.92
19.3	37.2	42.4	39.9	0.94	0.88	1.05	31.8	39.4	39.8	11.5	18.4	18.1	20.5	0.99	26.3	0.99	0.8
29.6	59.1	33.9	37.7	1.1	0.8	0.65	64.9	52.8	53.7	26.6	21.8	21.7	36.5	1.05	29.9	1.05	1.03
9.9	27.6	67.6	18.2	0.98	0.36	1	41.3	21.8	44.9	17.9	8.8	19.6	20.8	0.88	31	0.88	0.9
24.1	36.7	39.7	33.6	0.42	0.32	0.6	59.9	57.4	37.7	34.4	22.6	16.9	49	0.52	23.5	0.52	0.95
29.6	35.6	37	40.8	0.79	0.73	0.76	68.5	79.4	58.5	32.4	36.7	24.1	46.7	0.77	39.4	0.77	0.78
21.9	29.4	25.4	42.1	1.13	0.89	0.94	35.8	66	54.5	15.3	30	33.9	24.3	0.84	46.3	0.84	0.83
30.5	48.6	44.6	44.4	1.22	0.88	0.84	69.4	57.6	47.2	38.2	25.5	23.8	50.2	0.62	35.9	0.62	0.94
23.1	21	25.1	37.7	1.6	1.18	0.82	73.6	40.6	58.4	27	14.9	33.1	44	1.06	45.2	1.06	0.97
26.6	46	40.6	41.5	1.03	0.91	0.96	67.7	65.7	55.8	37.3	28.7	30.6	50.6	0.6	40.8	0.6	0.9
19.7	38.3	30.7	31.2	0.63	1.04	1.04	45.3	44.8	51.1	16.8	16.2	18.5	28.6	0.99	31.2	0.99	1.03
26.8	46.8	42.2	40.3	0.96	0.91	0.95	82.1	80.3	80.4	34.2	32.8	31.4	50.3	0.95	48.3	0.95	0.97
23.9	49.4	24.5	35.6	0.88	1.11	0.79	40.2	42.1	41.8	18.1	15.4	7.48	27.7	25.1	23.5	0.8	1.06
19.4	23.2	32.2	31.2	0.88	1.35	1.24	124	116	60.4	51.8	47.8	23	77.6	72.8	34.5	0.92	0.94
30.8	44.8	43.6	42.3	0.56	0.77	0.7	46	59.4	57.3	22.4	32.2	29.9	31.3	42.7	39.3	0.75	0.63
18.9	38.6	39.4	32.8	0.98	1.02	1.36	59.3	67.4	60.1	17.3	21.2	22	30.3	35.3	37.1	1.38	1.31
13.7	40.1	39.4	23.6	0.99	1.22	1.25	47.4	48.5	47.3	25.3	16.4	17.5	34.5	31	36.4	0.64	1.04
19.9	35.3	34.1	33	0.57	1.07	1.01	78.3	80.8	77	26.3	31.8	30.7	51.8	49.1	48.9	1.01	1
25.7	33.2	35.7	36.6	1.59	0.72	0.68	93.2	42.1	51.8	45.1	19.8	24.7	64.9	28.6	36.6	0.74	0.78
18.4	39	32.8	27	0.75	0.56	0.8	45.5	27.8	48.6	23.2	13.3	17.3	32.3	20.1	31.8	0.69	0.72
29	44	26.6	42.9	1.02	0.86	0.98	54.6	56.1	48.9	22.9	20.2	20.2	36.1	34.2	37.2	0.96	0.87
24.9	77.4	26.5	40.6	0.61	1.13	0.98	109	43.3	59.7	51.3	14.4	20.6	75	22.5	35.2	0.77	1.28
36	28.6	38.6	49.4	0.84	0.74	0.55	73.3	50	67.6	34.8	19.3	38.2	54.9	30.4	51.9	0.7	1.01
27.3	41.2	33.7	44.2	0.8	0.73	0.78	72.1	55.2	59.2	30.1	27.1	34.8	44.1	39.3	42.3	0.93	0.84
36.9	44.7	44.4	42.7	0.65	0.79	0.82	56.8	54.7	50.2	33.1	30	30.8	40.1	42.9	44.2	0.89	0.8
37.2	40	44.3	44.8	0.94	0.92	1.1	58.1	53.2	57.3	26.9	22.7	30.9	36.3	42.3	44.3	1.2	0.99
19.7	33.7	41.2	29.2	0.89	0.75	0.87	70.4	60.7	60.3	36.4	24.8	33.3	45.2	42.1	42.8	0.95	0.94
38.5	61.2	54.8	58.7	1.06	0.88	0.65	102	96	94.2	41.2	37.2	28.9	61.3	60.4	58.2	0.71	0.67
43.4	66.2	58.4	59.1	0.84	0.59	0.76	84.2	80.4	78.8	39.4	33.4	34.1	60.2	49	48.2	0.74	0.95
30.1	51.2	41.2	40.2	0.58	0.71	0.7	74.4	56.7	55.8	39.2	24.8	25.4	50.8	35.3	36.2	0.69	0.9
28.2	41.2	34.7	40.8	0.85	1.09	0.84	68.2	62.1	63.8	26.4	23.9	24.8	40.8	37.4	38.2	1.04	1.02
30.4	52.1	25.2	45.1	0.5	0.99	0.72	52	44.9	46.2	23.9	18.9	24.2	37.4	34	33.4	0.75	0.76

	CPP		NIRS - IPSILATERAL			NIRS: CONTRALATERAL			PSV IPSILATERAL			EDV IPSILATERAL			MEAN FV IPSILATERAL		
T2	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2
0.82	46	48	64	66	67	69	70	70	77.8	54.7	58.8	36.4	23.5	26.4	55.2	36.1	39.7
1.06	67	66	72	74	74	70	68	70	30.9	74.1	42.6	11.2	17.3	15.3	20.3	40.7	25.7
0.73	93	88	77	83	79	70	84	75	58.5	63.3	52	28.6	31.9	31.2	40.8	51.7	41.9
1.14	56	54	68	69	78	68	74	80	61.5	74.5	52.3	26.6	32.2	16	41.9	47.9	29.9
0.59	83	69	66	66	71	67	66	68	52	55.8	38.5	19.7	22.4	20.6	34.8	38.7	30.4
0.98	64	66	72	78	77	80	82	82	70.8	30.7	47.6	14.5	13.1	17.6	38.5	21.3	30.7
1.08	60	70	70	76	70	69	68	64	93.45	45.7	57	22.1	24.6	14	50.4	34.4	39.9
0.63	85	91	62	70	68	57	61	62	89.7	61.2	61	43.2	27.8	32.3	62.8	40	45.3
0.83	59	62	78	73	74	75	70	72	40	63.9	40.6	17.7	26.2	18.7	25.9	41.1	26.4
0.83	83	76	75	72	75	72	75	75	58.8	65.9	61	23.8	28.5	19.3	37.2	42.4	39.9
1.07	41	43	66	68	68	71	72	70	64.9	52.8	53.7	26.6	21.8	21.7	36.5	30.2	29.9
0.82	67	63	71	71	78	61	62	63	41.3	21.8	44.9	17.9	8.8	19.6	20.8	14.4	31
0.88	61	66	65	69	68	70	73	74	45.8	45.9	44.2	30.4	33	24.1	36.7	39.7	33.6
0.67	72	68	71	69	70	73	73	74	52.1	54	60.5	23.9	27.1	29.6	35.6	37	40.8
0.44	68	56	80	80	82	80	84	87	35.8	66	54.5	15.3	30	33.9	24.3	43.4	46.3
0.95	55	60	74	73	72	78	78	74	69.4	57.6	47.2	38.2	25.5	23.8	50.2	38.2	35.9
0.65	66	62	64	65	64	62	64	64	73.6	40.6	58.4	27	14.9	33.1	44	26.6	45.2
0.62	70	57	72	75	76	75	76	81	67.7	65.7	55.8	37.3	28.7	30.6	50.6	41.1	40.8
1.05	74	69	77	80	80	83	85	86	59.7	51.8	52.2	22	19.8	19.7	38.3	30.7	31.2
1.01	77	66	61	62	62	72	71	70	76.4	68.1	65.2	31.2	29.4	26.8	46.8	42.2	40.3
1.46	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1.08	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1.03	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.82	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.95	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.74	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.98	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.99	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1.11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.57	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.76	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.68	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.88	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.95	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.61	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.92	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.83	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1.02	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.74	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

PI IPSILATERAL			PSV CONTRALATERAL			EDV CONTRALATER			MEAN FV CONTRALATER			PI CONTRALATERAL		
T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2
0.75	0.86	0.82	50.2	62	54.9	26.5	23.4	23.3	37.5	39	36.4	0.63	0.99	0.87
0.97	1.4	1.06	31	36	43.2	12.5	14.4	15.3	18.6	24.5	26.4	0.99	0.88	1.06
0.73	0.61	0.5	52	47.4	47.8	22.7	24.6	23.7	41	36.5	33.1	0.72	0.62	0.73
0.83	0.88	1.22	46.9	69.3	56.5	15.9	23.7	20.1	29.1	38.1	32.1	1.07	1.2	1.14
0.93	0.86	0.59	53.9	54.5	34	17.9	24.2	16.4	35.7	36	24.4	1.01	0.84	0.72
1.46	0.82	0.98	44.6	34	36	14.9	13.1	14.3	28	22.7	21.2	1.06	0.92	0.92
0.97	0.61	1.08	64.1	68.7	88	28.3	31	69	43.3	49.5	51.6	0.88	0.76	0.53
0.74	0.84	0.63	57.5	50.5	47.9	15.3	16.4	22.6	28.9	28.9	34.2	1.46	1.18	0.74
0.86	0.92	0.83	50.9	53.8	57	11	24.1	24.6	28.1	35.8	35.3	1.42	0.83	0.92
0.94	0.88	1.05	31.8	39.4	39.8	11.5	18.4	18.1	20.5	26.1	26.3	0.99	0.8	0.83
1.05	1.03	1.07	101	50.7	54.3	36.5	23.6	29.6	59.1	33.9	37.7	1.1	0.8	0.65
0.88	0.9	0.82	42.5	80.9	27.3	15.6	51.8	9.9	27.6	67.6	18.2	0.98	0.36	1
0.42	0.32	0.6	59.9	57.4	37.7	34.4	22.6	16.9	49	36.8	23.5	0.52	0.95	0.88
0.79	0.73	0.76	68.5	79.4	58.5	32.4	36.7	24.1	46.7	54.5	39.4	0.77	0.78	0.67
0.84	0.83	0.44	46.6	40.1	61.6	13.3	17.6	21.9	29.4	25.4	42.1	1.13	0.89	0.94
0.62	0.94	0.95	87.1	60.2	59.2	27.5	30.2	30.5	48.6	44.6	44.4	1.22	0.88	0.84
1.06	0.97	0.65	41.7	43.1	47.3	8.16	13.5	23.1	21	25.1	37.7	1.6	1.18	0.82
0.6	0.9	0.62	74	63.8	66.4	26.7	26.8	26.6	46	40.6	41.5	1.03	0.91	0.96
0.63	1.04	1.04	45.3	44.8	51.1	16.8	16.2	18.5	28.6	27.8	31.2	0.99	1.03	1.05
0.96	0.91	0.95	82.1	80.3	80.4	34.2	32.8	31.4	50.3	48.8	48.3	0.95	0.97	1.01
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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