EFFECT OF SODIUM NITROPRUSSIDE (SNP) INFUSION ON CEREBRAL BLOOD FLOW VELOCITY AND INTRACRANIAL PRESSURE USING TRANSCRANIAL DOPPLER SONOGRAPHY AND OPTIC NERVE SHEATH DIAMETER IN POSTOPERATIVE PATIENTS UNDERGOING POSTERIOR FOSSA SURGERIES – A PROSPECTIVE OBSERVATIONAL STUDY

Dr Revikrishnan S

DM THESIS

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SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

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Effect of sodium nitroprusside(SNP) infusion on cerebral blood flow velocity and intracranial pressure using Transcranial doppler sonography and Optic nerve sheath diameter in postoperative patients undergoing posterior fossa surgeries – a prospective observational study

A THESIS SUBMITTED BY

DR Revikrishnan S

TO

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

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM NEUROANAESTHESIA

2023

DECLARATION BY THE STUDENT

CERTIFICATE

I, Revikrishnan S hereby certify that I had personally carried out the work depicted in the thesis titled, “**Effect of sodium nitroprusside(SNP) infusion on cerebral blood flow velocity and intracranial pressure using Transcranial doppler sonography and Optic nerve sheath diameter in postoperative patients undergoing posterior fossa surgeries – a prospective observational study**”

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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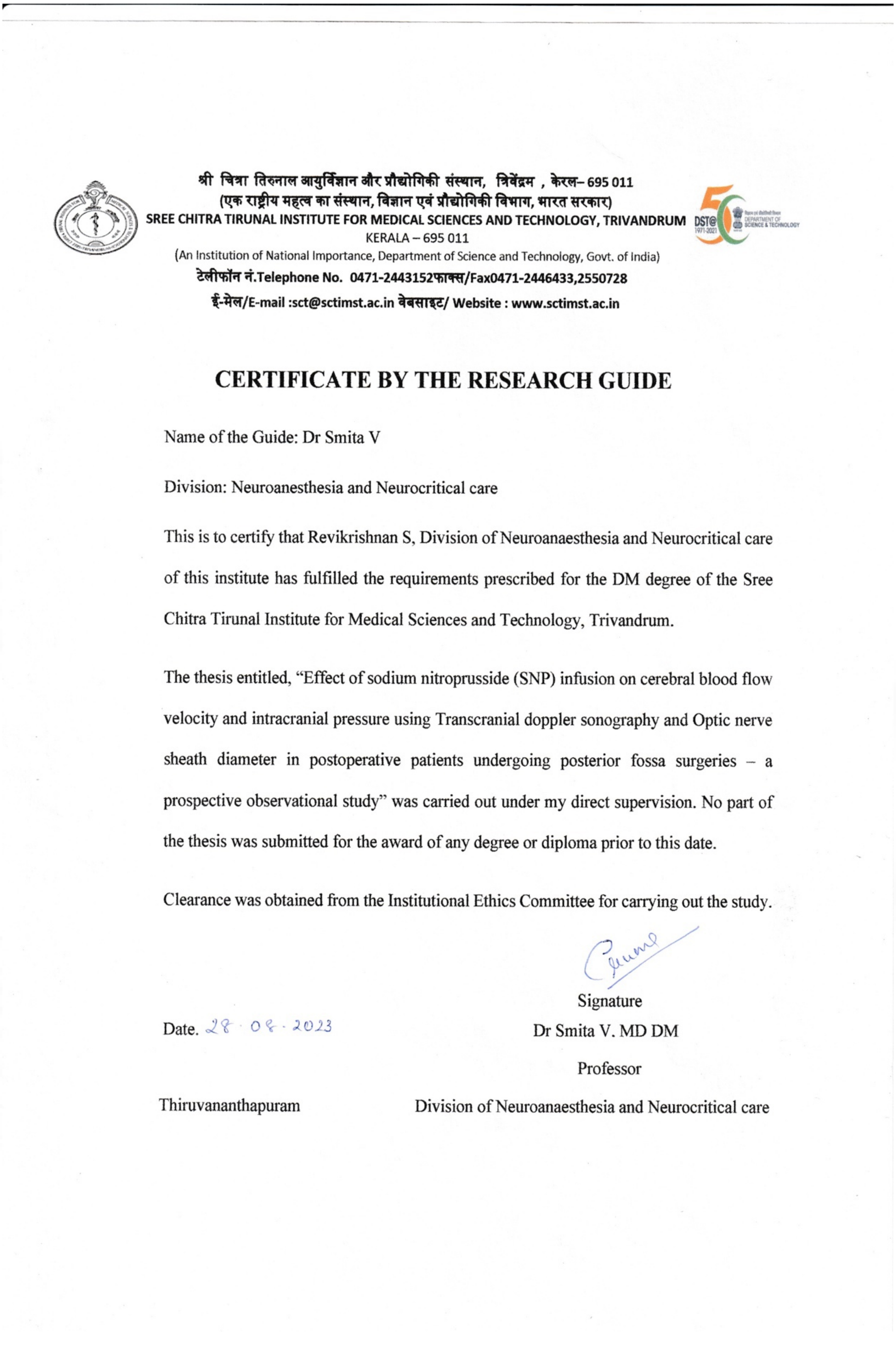
Date. *Name of the Candidate*



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APPROVAL OF THE THESIS

The thesis entitled

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Submitted by

Dr Revikrishnan S

or the degree of

DM Neuroanaesthesia

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

is evaluated and approved

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(Name & Signature of the Guide) (Name & Signature of thesis examiner)

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	ACA	Anterior Cerebral Artery
2	ANOVA	Analysis of variance
3	ASA	American Society of Anesthesiology
4	CA	Cerebral Autoregulation
5	CBF	Cerebral blood flow
6	CBFV	Cerebral blood flow velocity
7	CBV	Cerebral Blood Volume
8	CMR	Cerebral Metabolic Rate
9	CMRO2	Cerebral Metabolic Rate of Oxygen
10	CPP	Cerebral perfusion presure
11	CO2	Carbon dioxide
12	CT	Computed Tomography
13	CVR	Cerebro-vascular resistance
14	DA	Dynamic Autoregulation
15	DBP	Diastolic Blood Pressure
16	EDV	End-diastolic velocity
17	$ETCO_2$	End-tidal carbon dioxide
18	FV	Flow velocity
10	HR	Heart rate

11	ICA	Internal Carotid Artery
12	ICP	Intracranial pressure
13	ICU	Intensive care unit
14	MAP	Mean arterial pressure
15	MCA	Middle cerebral artery
16	MFV	Mean flow velocity
17	MHZ	Mega heartz
18	NO	Nitric oxide
19	ONSD	Optic nerve sheath diameter
20	$PaCO_2$	Partial pressure of carbon dioxide
21	PaO2	Partial pressure of oxygen
22	PCA	Posterior cerebral artery
23	PI	Pulsatility index
24	PSV	Peak systolic velocity
25	PWD	Pulse wave doppler
26	rCBF	Regional cerebral blood flow
27	RBC	Red blood cell
28	RI	Resistivity Index
29	RR	Respiratory rate
30	SA	Static autoregulation
31	SaO_2	Saturation of arterial oxygen
32	SD	Standard deviation
33	SNP	Sodium nitroprusside

34	SpO2	Saturation of peripheral oxygen
35	SPSS	Statisctical package for social sciences
36	SV	Stroke volume
37	SVR	Systemic vascular resistance
38	TCD	Transcranial doppler
39	THRR	Transient hyperaemic response ratio
40	USG	Ultrasonography

SYNOPSIS

Title : Effect of sodium nitroprusside(SNP) infusion on cerebral blood flow velocity and intracranial pressure using Transcranial doppler sonography and Optic nerve sheath diameter in postoperative patients undergoing posterior fossa surgeries – a prospective observational study

Background : Systemic hypertension contributes to intracranial haemorrhage and cerebral oedema following craniotomy. Sodium nitroprusside being a vasodilator can increase intracranial pressure and hence was not preferred as an antihypertensive in neurosurgical patients. SNP has been found to have no direct effect on cerebral vasculature during cardiopulmonary bypass and preserves cerebral autoregulation. Since we could not find any recent study evaluating the effect of sodium nitroprusside on cerebral haemodynamics in neurosurgical patients, we have planned to do the same in our study.

Methodology : After IEC clearance 35 ASA I and II adult patients undergoing elective posterior fossa surgeries were recruited. Prior to surgery Transcranial doppler (TCD) of middle cerebral artery (MCA) was performed and baseline peak systolic velocity (PSV), end diastolic Velocity (EDV) ,mean flow velocity (MFV), pulsatility index (PI), resistivity index (RI), transient hyperaemic response ratio (THRR) were recorded. Baseline Optic Nerve sheath diameter (ONSD) was also measured in all subjects . Subsequent recordings were done prior to the start of SNP infusion for post operative blood pressure control (T1) as well as after reduction of systolic blood pressure within 20% of baseline (T2) and after 12 hours of initiation of SNP infusion or point of termination of infusion (T3). The data was analysed using descriptive statistics for categorical variables and the mean & S.D were used for continuous variables. For repeated measurements of TCD values and ONSD, repeated measures ANOVA with Bonferroni correction was applied parametric data and Friedman's two way analysis of variance by ranks for non-parametric data. P value of < 0.05 is considered as statistically significant. . Cerebral autoregulation was assessed by linear regression of percentage changes in cerebral vascular reactivity index (CVRi) in responses to percentage changes in mean arterial pressure (MAP). A linear regression slope of ≈ 0 for ΔCVRi% or ΔCVR% was taken as impaired autoregulation, whereas a slope of ≈ 1.0 indicated intact autoregulation.

Results: Baseline ONSD values were < 5.5mm and THRR were >1.1 in all patients. SNP infusion reduced the systolic blood pressures to 20% of baseline. The PSV showed significant reduction from T1 to T2 ($p < 0.01$). The MFV and EDV were also reduced from T1 to T2 but were not significant ($p > 0.05$) . There was no significant change in PI, Intracranial pressure, RI and ONSD following SNP infusion ($p > 0.05$). Cerebral vascular resistance index (CVRi) and transient hyperaemic response ratio after SNP injection showed no significant difference ($p > 0.05$). Linear regression analysis to examine the relationship between changes in CVRi

and arterial pressure at different time points revealed significant linear relationships between T1 and T2 (slope=0.82, adjusted R square=0.77, $p<0.05$) and between T1 and

T3 (slope=0.75, adjusted R square=0.88, $p<0.05$). Linear regression analysis was performed to analyse the relationship between changes in MCA MFV and arterial pressure at different time points, revealing a linear regression slope of 0.22 and an adjusted R square of 0.16 with a p-value of 0.06 between T2 and T1, and a linear regression slope of 0.21, an adjusted R square of 0.29, and a p-value of 0.055 between T3 and T1 for % Δ MFV to % Δ MAP.

Conclusion: The use of SNP as a treatment for acute post-operative hypertension in patients who have undergone elective posterior fossa surgery does not significantly affect cerebral blood flow velocities and maintain cerebral autoregulation without increasing intracranial pressure, potentially due to the reduced influence of nitic oxide on mechano-regulation and increased sympathetic activity in these patients which may counteract the direct vasodilator properties of SNP.

INTRODUCTION

1. INTRODUCTION

Hemodynamic control is an integral part of the perioperative management of patients undergoing neurosurgical or neurovascular procedures. Systemic hypertension associated with emergence from anaesthesia has long been believed to contribute to intracranial haemorrhage and cerebral oedema following craniotomy. This can be extremely deleterious in posterior fossa surgeries. Lewelt et al demonstrated that elevated postoperative blood pressure correlates with intracerebral bleeding after craniotomy.(1) Forster et al observed that in anesthetized animals, sudden substantial increases in arterial pressure can result in a breach of the blood-brain barrier.(2). Basali et al report an incidence of 57% for post-craniotomy hypertension.(3)

The ideal agent for blood pressure reduction should have a rapid but smooth onset of action and a short duration of action to allow careful adjustment of the dosage and easy termination of effect. In addition, the agent should have minimal effects on heart rate, cardiac function, myocardial oxygen demand, cerebral hemodynamics and have an otherwise benign adverse-effect profile. No agent meets this profile; the choice of drug therapy depends on the clinical presentation, patient characteristics, the environment of care, the properties of the drug, and the clinician's experience.

The most commonly used agents in the post-operative period are labetalol, nicardipine, hydralazine, esmolol, nitroglycerine and sodium nitroprusside (SNP) among which our neurosurgical ICU uses sodium nitroprusside and labetalol. Compared to labetalol, nitroprusside is a very potent agent, with an onset of action of seconds, a duration of action of 1 to 2 minutes, and a plasma half-life of 3 to 4 minutes.(4) The onset of action of labetalol occurs within 2 to 5 minutes after its IV administration, reaching a peak at 5 to 15 minutes following administration, and lasting for about 2 to 4 hours.(5) This variability makes labetalol extremely difficult to titrate as a continuous infusion. Moreover patients who have undergone posterior fossa surgeries are more likely to have bradycardia which limits the use of labetalol in such patients. However the literature regarding the cerebrovascular effects of SNP is contentious. Studies conducted by various researchers such as Griffiths et al., Bunemann et al., and Pinaud et al. did not demonstrate any significant augmentation in cerebral blood flow (CBF). (6–8) On the other hand, investigations carried out by Brown et al., Henriksen et al., and et al. revealed a decline in CBF(9–11), while those conducted by Larsen et al., Butterworth et al., and Vajkoczy et al. reported an increase in CBF.(12–14) The potential explanation for the contradictory outcomes could be attributed to the variance in the autoregulatory state and the influence of variables such as anesthetic agents and carbon dioxide levels. Furthermore, the discrepancies in the rate of administration and quantity of SNP administered may have also contributed to the conflicting findings across various investigations.

There is a lack of research in literature examining the impact of SNP on intracranial pressure and cerebral autoregulation through TCD sonography in postoperative neurosurgical patients. As there also appears to be a lack of current literature examining the impact of sodium nitroprusside on cerebral haemodynamics in the immediate postoperative period, the present study has been designed to address this gap. The measurement of optic nerve sheath diameter (ONSD) serves as an indirect indicator of intracranial pressure (ICP). SNP is believed to dilate cerebral blood vessels and decreases cerebral vascular resistance resulting in an increase in cerebral blood volume and intracranial pressure. Cottrell et al, Guillermo et al, and Turner et al conducted studies on intracranial pressure changes induced by SNP in patients with intracranial mass lesion and found that it should not be used in patients with raised ICP unless previous measures have been taken to improve intracranial compliance, that intracranial pressure rose proportionately to the nitroprusside dose during infusion, and that a statistically significant increase in intracranial pressure occurred during the early stages of the infusion of nitroprusside in patients. undergoing neurosurgery. However these studies were done under anaesthesia and in patients with an already compromised intracranial compliance Meanwhile Immink et al. who evaluated the effects of SNP in malignant hypertensive patients concluded that the effect of SNP on peripheral vascular resistance is significantly higher than on cerebrovascular resistance. Moreover an intact sympathetic system as well as a renin angiotensin system is believed to counter the vasodilatory effects of SNP in the brain. Through the serial monitoring of ONSD, trends in ICP levels during sodium nitroprusside infusion can be assessed. Thus this study intends to evaluate the safety of SNP in postoperative patients in whom the tumour has been removed and the effects of tumour and anaesthetic agents on intracranial pressure is eliminated. If no significant changes in cerebral haemodynamics and intracranial pressure are detected, the current perspective on the use of sodium nitroprusside in neurosurgical patients may be modified.

Aim

To study the effects of sodium nitroprusside (SNP) on cerebral blood flow, cerebrovascular reactivity and intracranial pressure when used for control of acute post-operative hypertension in patients who underwent posterior fossa surgeries

Hypotheses

Sodium nitroprusside infusion results in decrease in cerebral vascular resistance and an increase in cerebral blood flow thereby can increase the intracranial pressure

Objectives

1. To assess the effect of sodium nitroprusside on cerebral blood flow velocities, cerebrovascular resistance and cerebral autoregulation during management of acute post-operative hypertension in patients who underwent posterior fossa surgery
2. To assess the effect of SNP on ICP when used for management of acute post-operative hypertension in patients who underwent elective posterior fossa surgeries

LITERATURE REVIEW

2 LITERATURE REVIEW

2.1 Postoperative Hypertension in Neurosurgical patients

Acute postoperative hypertension (APH) is a condition that refers to a significant increase in blood pressure (BP) in the immediate postoperative period.(15) This condition can lead to severe neurologic, cardiovascular, or surgical-site complications, which may require imperative management. Despite the widespread recognition of APH, there is currently no standardized definition for this disorder. However, Marik et al. considered an increase in systolic blood pressure (SBP) by more than 20% or an increase in diastolic blood pressure (DBP) to above 110 mm/Hg as indicative of APH.(15) Acute postoperative hypertension typically develops within two hours of surgery and resolves within a few hours. Complications associated with APH include myocardial ischemia, myocardial infarction (MI), cardiac arrhythmia, congestive heart failure with pulmonary oedema, as well as haemorrhagic stroke, cerebral ischemia, and encephalopathy. APH poses a significant threat to surgical outcomes, as it can exacerbate bleeding at the surgical site and compromise vascular anastomoses. This condition is known to occur following major surgeries, with a higher incidence among individuals undergoing cardiothoracic, vascular, head and neck, and neurosurgical procedures.

This phenomenon may be attributed to the activation of the sympathetic and renin-angiotensin systems, as evidenced by elevated plasma levels of norepinephrine, epinephrine and renin during the emergence phase.(16,17) Even with the advancements in anaesthetic techniques, such as total intravenous anaesthesia, the incidence of APH following craniotomy remains high at approximately 50%.(18,19) The occurrence of hypertension subsequent to posterior cranial fossa surgical procedures is much greater than that following supratentorial procedures. Previous studies by Jannetta et al., Geiger et al., and Sindou et al. have identified the rostral ventrolateral medulla (VLM) and root entry zone (REZ) of IX–X cranial nerves as the locations for neurogenic hypertension.(20–22) In addition to direct medullary compression caused by posterior fossa tumors, systemic hypertension can also be induced by posterior fossa crowding, elevated intracranial pressure, and tumors containing vasoactive neuropeptides.(23,24) The onset of new hypertension in the immediate postoperative period following posterior fossa surgery, which resolved over a period of 24–36 hours, has also been reported by some authors, who attributed the occurrence to probable postoperative edema.(25,26) Moreover, in patients who are intubated and mechanically ventilated, plasma norepinephrine levels remain elevated, along with an increased oxygen consumption.(27) Anaesthesiologists and surgeons are very much concerned with the potential complications of intracranial hypertension, which include bleeding and brain oedema. During the immediate post-operative period, hypertension poses a heightened risk for haemorrhage in the resection cavity due to disruption of haemostatic platelet plugs, impaired cerebrovascular autoregulation, and the disrupted blood-brain barrier in the surgical site. (28) Almost 20% of patients experience early intracranial hypertension following elective craniotomy, with a significant portion of this incidence attributed to intracranial hemorrhage (ICH). ICH is a severe complication of surgery, with a prevalence ranging from 0.9% to 3.5% among cranial surgery patients.(29,30). Basali et al. discovered that the occurrence of ICH postoperatively had a median time of 21 hours and hence blood pressure control is crucial in the first 24 hours.(3) The study demonstrated that patients with systolic blood pressure (SBP) greater than 160 mm Hg had an odds ratio of 4.6 for postoperative hemorrhage.(3) Consequently, it is recommended that the SBP goal for the first post-operative day be within the range of 100 to 160 mm Hg or, alternatively, a more conservative approach of 100 to 140 mm Hg may be taken.(31) In certain cases, such as patients with coronary artery disease or congestive heart failure, lower levels of SBP may be necessary.(31) Schubert et al. advocates for the general management of blood pressure to be maintained within the systolic range of 120-150 mm Hg, which may help to mitigate potential complications and improve patient outcomes.(32)

Vascular complications, specifically hematoma, are a grave concern following posterior fossa surgery.(33) The posterior fossa is a confined area with little room for space-occupying lesions and brainstem compression, and obstructive hydrocephalus can progress rapidly, leading to life-threatening situations.(34) Unfortunately, the literature on the incidence, management, and outcomes for vascular complications of posterior fossa surgery is scarce. Symptomatic postoperative hemorrhage rates are highest within the cerebellopontine angle cisternal space, and mortality rates range from 25% to 100%.(35–37)

APH may lead to cerebral oedema as a result of increased microvascular pressures. The occurrence of vasomotor paralysis with persistent vasodilation that lasts well beyond the duration of pressure increase is a characteristic feature of acute severe hypertension. Severe hypertension can also produce structural changes in the cerebral vasculature, including vessel damage and necrosis, which lead to increased vascular permeability and cerebral oedema.(38) As a consequence of progressive cerebral oedema, there is a decrease in CBF and subsequent brain injury. Although the mechanism for the sustained, maximal vasodilation and cerebral oedema is not entirely clear, it may involve a forced vasodilation phenomena.(39)

The production of oxygen radicals mediates hypertension-associated vascular and parenchymal injury, at least in part.(40–42) Regardless of the mechanism, acute hypertension impairs vascular reactivity to physiologic stimuli. Response to vasoconstrictor stimuli, such as hypocapnia, and to vasodilators, such as hypercapnia or exogenous acetylcholine application.(43) The impairment of vascular reactivity in acute hypertension may have important clinical implications. .Consequently, controlling postoperative blood pressure is critical in preventing these avoidable complications.

2.1.2 Antihypertensives and cerebral haemodynamics

The ideal antihypertensive agent should have a rapid but smooth onset of action and a short duration of action to allow careful adjustment of the dosage and easy termination of effect with minimal effect on cerebral hemodynamics. However no agent till date fits the profile. Labetalol may not be the optimal agent in certain circumstances due to its low potency, sluggish onset of peak effect, and unpredictability in dosage requirements. Similarly, esmolol is only mildly effective and can trigger bradycardia and conduction defects. Nicardipine is more effective in controlling peri-extubation hypertension than both labetalol and esmolol. However, calcium channel blockers have been linked to dose-dependent cerebral vasodilation, inhibition of autoregulation, and hypotension. Experience with hydralazine has been discouraging since it significantly raises intracranial pressure. SNP serves as a titratable agent that exhibits an exceptional degree of controllability, thereby enabling precise regulation of blood pressure on a minute-by-minute basis. However the findings regarding the impact of SNP on cerebral hemodynamics have been rather ambiguous.

Table 1. Table showinh the effects of different antihypertensives on cerebral hemodynamics

Drug	Type	CBF	CBFV	CMRO$_2$	Other effects
Labetalol	Mixed alpha and beta adrenergic blocker	0(44)	0	0	CBF reduction when used for emergence hypertension(45)
Esmolol	beta adrenergic blocker	0(46)		0	No effect assuming CPP is maintained; esmolol reduces cerebral hyperaemia on emergence from craniotomy.

Dexmedetomidine	Alpha-adrenergic agonist	-(47)		0	CBF decrease persists beyond 30 minutes after agent discontinuation
Nicardipine (3$_e$5 mg/h)	Calcium channel blocker	++(48)			
Nitroprusside	Direct vasodilator	+/0(49)		0(50) 31/08/23 10:05:00 PM	
Nitro glycerine	Direct vasodilator	+++(51)	0		Nitro-glycerine dilates larger cerebral vessels, but global CBF is largely unaffected.
Hydralazine	Direct vasodilator	+++(52)			

2.1.3 Sodium Nitroprusside and Cerebral Haemodynamics

SNP is an organic nitrate vasodilator that is nonselective in nature and causes the relaxation of arterial and venous smooth muscle. Upon intravascular administration, the nitrate reacts with sulfhydryl groups present in both red blood cells and the vessel wall, thereby generating cyanide and nitric oxide, which is an endothelium-dependent relaxing factor. Nitric oxide induces dilation by activating the guanylate cyclase-cyclic guanosine monophosphate signalling pathway in the vascular smooth muscle**.**

Intracranial hypertension impairs cerebral blood flow and metabolism, and it is associated with poor clinical outcomes and high mortality rates. The results from previous studies suggest that intracranial pressure increases with the use of SNP and hence it should not be used in neurosurgical patients. Because of the ability of SNP to dilate cerebral blood vessels and decrease cerebral vascular resistance, it can result in an increase in cerebral blood volume and can subsequently rise intracranial pressure. Cottrell et al. studied the intracranial pressure changes induced by SNP in patients with intracranial mass lesions. They suggested that SNP should not be used in patients with raised ICP unless previous measures have been taken to improve intracranial compliance.(53) Candia et al. found out that intracranial pressure rose proportionately to the nitroprusside dose during the infusion.(54) Turner et al measured intracranial pressure in 45 patients undergoing neurosurgery during the induction of deliberate hypotension using either sodium nitroprusside or trimetaphan.(55) A statistically significant increase in intracranial pressure (ICP) occurred during the early stages of the infusion of nitroprusside in normocapnic patients. The mechanism of the increase in ICP with nitroprusside was thought to be expansion of the intracranial blood volume as a result of cerebral vasodilatation.(55)

However Larsen et al. studied the effects of nitroprusside-induced hypotension on cerebral blood flow and cerebral oxygen consumption were investigated in nine patients scheduled for cerebral arterial aneurysm surgery and demonstrated that SNP produced hypotension but did not significantly alter cerebral blood flow which remained virtually at pre-infusion values upon cessation of infusion.(13) Cerebral oxygen uptake also did not change significantly during hypotension.(13). Henriksen et al investigated the effect on cerebral haemodynamics of arterial hypotension induced by SNP infusion in nine patients at the end of operations for intracranial aneurysms under N2O-O2-halothane anaesthesia and concluded that sodium nitroprusside has only a minor influence on cerebral haemodynamics in the anaesthetized state.(56) The study by Joshi et al. showed that SNP reduces SVR, but when infused directly in the carotid artery, it does not modify cerebrovascular resistance in healthy subjects.(49) Lavi et al. demonstrated that in normotensive subjects a reduction in MAP by SNP does not affect MCA Mean flow velocity (MFV) suggesting that when BP is reduced pharmacologically, MCA MFV is secured by autoregulation-mediated cerebral vasodilatation as opposed to a direct SNP-induced pharmacological effect on the cerebral vasculature.(57)

Clearly, an important research gap exists in the literature with respect to the impact of SNP on autoregulation and intracranial pressure (ICP) in postoperative neurosurgical population. Despite an extensive search, we found no published studies on the effects of SNP in patients with posterior fossa lesions. Furthermore, to our knowledge, there are no studies that have evaluated the association of SNP with ICP utilizing optic nerve sheath diameter as a measure.

2.2 Trasncranial Doppler

Transcranial doppler (TCD) is a non-invasive, bed side, real time monitoring and diagnostic tool of measuring blood flow velocity (FV) and other derived parameters in various intracranial arteries. A phased array probe with frequency of 1–2 MHz is used to insonate the intracranial arteries . The use of TCD has expanded drastically over the last three decades and has emerged as cost-effective tool for evaluating cerebral hemodynamics, detecting stenosis, collateral flow. (58). Transcranial Doppler ultrasonography (TCD) was introduced in 1982 by Aaslid and colleagues as a non-invasive technique for monitoring blood flow velocity (FV) in the basal cerebral arteries.(59)

TCD employs a range-gated, pulsed-Doppler ultrasonic beam with a frequency shift of 2 MHz. The TCD probe consists of a piezoelectrical crystal that generates sound waves directed towards basal arteries through TCD 'acoustic windows' by positioning the probe appropriately. These acoustic windows serve as the entry point of the ultrasonic beam, allowing for an accurate and focused assessment of the cerebral blood flow. The ultrasonic wave traverses the cranial bones by way of these acoustic windows and returns after bouncing off the mobile red blood cells present in its trajectory, which are subsequently received back by the TCD probe.(59,60). A positive deflection of the waveform indicates that the direction of blood flow in the vessel is towards the probe whereas, a negative deflection of the waveform suggests that the flow is away from the probe.

The variation in frequency between the signal transmitted and the signal received is referred to as the Doppler shift. It is calculated using the formula:

$$\textbf{Doppler frequency shift} = 2 \cdot V \cdot Ft \cdot \cos\theta / C$$

where V is the velocity of the reflector (red blood cells); Ft is frequency of the transmitted signal , C is the velocity of ultrasonic wave in soft tissue, and cosθ is the correction factor based on the angle of insonation (θ).

The parameters of Ft (2 MHz) and C (1540 m/s) are constant during TCD examination constant, which in turn, results in the frequency shift being heavily reliant on the blood flow velocity and the angle of insonation of the TCD probe. It is worth noting that TCD is a measure of blood FV and not cerebral blood flow (CBF). Nonetheless, under specific circumstances, FV can serve as a proxy marker for vessel diameter or CBF

2.2.1 Technique

TCD examination is done by using a 2 MHZ ultrasound and a sweep speed of 3-5 seconds. The few areas of the skull bone are relatively thinner allows penetration of ultrasound waves to visualise the underlying cerebral blood vessels. The four commonly employed accoustic windows are temporal, orbital, sub occipital, and submandibular windows. (figure). The examination of the terminal internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), and communicating arteries can be facilitated through the utilization of the transtemporal window.

Fig 1: Acoustic windows used for Transcranial Doppler - transorbital (A), transtemporal (B), submandibular (C) and suboccipital (D) windows.

Transtemporal TCD procedure : The temporal window is defined as an area delineated by a line drawn from the tragus to the lateral canthus of the eye, and the area 2 cm above this. Moving the probe slowly and systematically over the whole area, the examiner searches for a signal, initially starting at a depth of 50 mm. The toward- and away- flow signals are from the MCA and ACA, respectively.

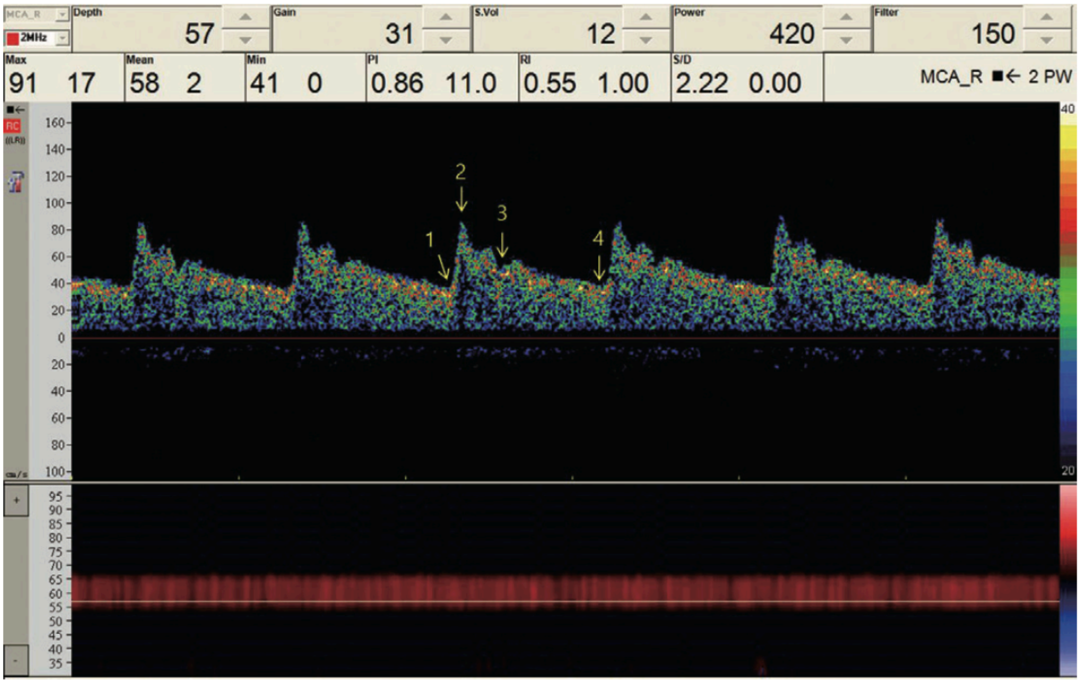
Once a band of frequency shifts is seen at any depth, the appropriate sample gate is selected by moving the gate selection line to the appropriate depth, and the doppler waveform is then visualized. Ideally, the doppler waveform should be a mix of colours with blue colour (smaller number of RBCs) being near the spectral envelop and yellows/red colour occupying the main body of the wave. A readjustment of probe position is needed if all colors are blue, indicating that the artery is not being insonated properly.

2.2.2 Analysis of TCD waveform

The movement of erythrocytes within a vessel differs in velocity, which results in a combination of various frequency components in the Doppler signal obtained from blood flow. Transcranial Doppler machines employ spectral analysis and display three-dimensional Doppler data in a two-dimensional format, with time being depicted on the horizontal scale, frequency shift (velocity) on the vertical scale, and signal intensity as the relative brightness or color. To calculate flow velocity, a spectral envelope is generated that corresponds to the maximum FV during the cardiac cycle. Subsequently, different parameters are measured from the spectral envelope.

The normal spectral waveform shows a sharp systolic upstroke and stepwise deceleration with positive end diastolic flow.

Fig. 2. Normal transcranial Doppler spectral waveform of the middle cerebral artery. The interval from phase 1 to phase 2 is referred to as systolic acceleration and reflects the resistance from the heart to the artery of interest. The interval from phase 3 to phase 4 is the diastolic phase and reflects the resistance from the artery of interest to the periphery.



MCA_R 2MHz
Depth 57
Gain 31
S.Vol 12
Power 420
Filter 150
Max 91 17
Mean 58 2
Min 41 0
PI 0.86 11.0
RI 0.55 1.00
S/D 2.22 0.00
MCA_R ■← 2 PW

Peak systolic velocity (PSV) is the first peak on the on a TCD waveform from each cardiac cycle. The end diastolic velocity (EDV) lies between 20 to 50% of the peak systolic velocity indicating the low resistance pattern of intracranial arteries. Mean flow velocity (cm/sec) is derived from PSV and EDV. MCA has the highest MFV. The mean flow velocity is the commonly used parameter in TCD studies, given by the formula:

$$\mathbf{MFV = EDV+1/3(PSV-EDV)}$$

In our study we mainly used Mean flow velocity (MFV) parameter, since mean flow velocity waveform shows least variation in TCD. The standard range for mean middle cerebral artery flow velocity (MCA FV) amongst normal adults, falls between 35 to 90 cm/s when subjected to normal physiological conditions.(61) This variability, despite constant cerebral blood flow (CBF), is mainly the reflection of variability in the diameter of the MCA or the angle of insonation.

On a temporal scale, the cyclic variation of MCA FV is estimated to be approximately 10%. (62) The evaluation of variation from side to side has been conducted and variances that surpass 14% should be contemplated as abnormal. (61) Furthermore, daily variation should not exceed 10 cm/s for 95% of the population. It has been reported that inter-observer variability can reach approximately 7.5% on the same day and increase to about 13% on different days. (62) The velocity of the middle cerebral artery (MCA FV) is impacted by age. In newborns, MCA FV is roughly 24 cm/s, but it rises to 100 cm/s by the ages of 4 to 6. Subsequently, it diminishes constantly to around 40 cm/s by the seventh decade. (63)

2.2.3 Measures of cerebrovascular resistance

The examination of FV waveform has been executed using various methods for the purpose of approximating cerebrovascular resistance (CVR). There have been three commonly utilized indicators of CVR:

Pulsatility Index (PI) - also referred to as Gosling's Index. This index was developed to summarize data from systolic and diastolic velocities, providing a numerical representation of alterations in the pulsatility properties of blood vessels as downstream resistance increases.(64) When faced with increased resistance downstream, such as in instances of vasospasm or heightened intracranial pressure, the systolic upstroke of the intracranial pressure pulse undergoes an increase in both slope and magnitude, while the diastolic downstroke experiences a decrease in magnitude. This discrepant behavior between systolic and diastolic velocities leads to a rise in pulsatility. The calculation of the pulsatility index (PI) can be determined through the following formula:

$$\mathbf{PI=FVs-FVd/\ FVm}$$

An elevation in intracranial vascular resistance induces a corresponding rise in systolic velocity (SV) and a reduction in diastolic velocity (DV), coupled with a mild decline in mean velocity (MV). Such changes give rise to an increase in the pulsatility index (PI), a crucial parameter due to its resistance to the angle of insonation. The normal range of PI is generally between 0.5 to 1.19. The stenosis or occlusion of proximal vessels causes downstream vasodilation, leading to a decrease in PI below 0.5. Conversely, an increase in downstream resistance, such as vasospasm or heightened intracranial pressure, causes PI to rise above 1.19. In certain cases, such as arterio-venous malformations or in arteries functioning as feeders, PI may also be reduced below 0.5.

Resistance index (RI) - initially described by Pourcelot(65) this is also based on a similar concept and is calculated as:

$$\mathbf{RI = FVs-FVd/\ FVs}$$

In addition to autoregulatory assessment, the utilization of indices such as the Pulsatility index (PI) and Resistant index (RI) can prove to be beneficial in the evaluation of the reaction of distal cerebral vasculature towards various stimuli such as drugs and pathological processes.

The values of PI and RI are subjected to the influence of various factors, such as vascular compliance, arterial pressure, and $PaCO_2$.(66)

2.2.4 Estimation of ICP from TCD

The potential application of transcranial Doppler (TCD) in non-invasive intracranial pressure (ICP) monitoring was initially recognized by Hassler et al. They noticed that as the ICP escalated, the waveform morphology of TCD underwent characteristic changes.(67) Klingelhofer and colleagues were the first to establish a correlation between ICP and TCD-derived flow velocities.(68,69) They established that an increase in ICP corresponds to a decrease in TCD-derived flow velocities and a rise in Pourcelot index or resistance index.

In 2004, Bellner *et al.*(70) conducted a prospective study to evaluate the relationship between ICP and TCD-derived PI. TCD recordings were carried out on a daily basis, while the ICP was observed via an intraventricular catheter. The results obtained revealed a marked association between the two values, with the statistical analysis showing a significant correlation ($P < 0.0001$, $r = 0.938$, for the formula $ICP = 10.93 \times PI - 1.28$). The researchers concluded that regardless of the underlying pathology, the two indices were highly correlated, implying that one could be used as a proxy for the other.(70) In a study conducted by Wakerley et al. in the year 2014, transcranial Doppler (TCD) was investigated as a potential noninvasive technique for monitoring intracranial pressure (ICP).(71) The authors aimed to evaluate the feasibility of using TCD as a modality for ICP monitoring and to establish its accuracy compared to the invasive techniques currently employed. The researchers carried out their investigation on a cohort of 78 individuals, procuring the transcranial Doppler (TCD) spectra from either middle cerebral artery (MCA) and subsequently gauging the cerebrospinal fluid (CSF) pressures via an invasive method of lumbar puncture (LP) after a time interval of 5 minutes. The researchers discovered that a PI value greater than or equal to 1.26 was a highly reliable predictor of CSF-p values greater than or equal to 20 cm H2O, with sensitivity at 81.1%, specificity at 96.3%, positive predictive value at 88.1%, and negative predictive value at 90.1%. As a result, they suggest that the TCD-derived PI may serve as a valuable tool for monitoring purposes.(71)

2.3 Assessment Of Autoregulation

All evaluations pertaining to autoregulation in the brain measure the fluctuations in the velocity of such flow which arise as a consequence of modifications in cerebral perfusion pressure.(72) The phenomenon of autoregulation possesses diverse characteristics that provide the basis for these evaluations. These features comprise the limits of autoregulation encompassing the upper and lower values of CPP that uphold constant blood flow, the speed of autoregulation, which denotes the time interval between shifts in CPP and the restitution of blood flow, and the gradient of autoregulation, which indicates the extent to which FV remains uniform despite variations in perfusion pressure within the limits of autoregulation. These attributes are critical for the precise evaluation of cerebral autoregulation and may facilitate the diagnosis of certain medical conditions.Although newer modalities like MRI, PET scan and NIRS have been described described for assessment of cerebral autoregulation with varying sensitivity and specificity, TCD is still the most common method used for bedside assessment of autoregulation.

2.3.1 TCD assisted autoregulation assessment

The correlation between changes in blood flow and changes in flow velocity can be observed in cases where the diameter of the large cerebral vessels remains constant. To assess flow velocity, TCD will be utilized with varying cerebral perfusion.(73) There exist a variety of techniques to manipulate cerebral perfusion pressure, comprising the administration of vasoactive substances, positional alterations (e.g., sit-to-stand or bed tilt), the Valsalva maneuver, the cold pressor test, isometric exercises of the upper limb, lower body negative pressure, quick deflation of inflated thigh cuffs, and compression of the common carotid arteries located in the neck. TCD continuously monitors changes in cerebral blood flow velocity (CBFV), and several techniques and indices have been described for the assessment of autoregulation. By utilizing these methods and indices, researchers can gain a better understanding of cerebral blood flow dynamics and their relationship to other physiological variables.

Static autoregulation

This refers to the evaluation of autoregulatory plateau with respect to a small range of changes in arterial pressure (73) order to measure this, the velocity of flow in the middle cerebral artery is assessed using TCD, under normal physiological conditions. This measurement is then repeated after inducing a steady state increase of 20-30mmHg in the mean arterial pressure (MAP) through the administration of phenylephrine infusion. The index of autoregulation is then calculated as the percentage change in the cerebrovascular resistance (CVR) per percentage change in the MAP. It is considered that autoregulation is functioning properly, if the index is 1, whereas a value of less than 0.4 indicates inadequate autoregulation. This method of assessment is valuable in gaining insight into the integrity of autoregulation in various clinical scenarios.

Dynamic autoregulation

Dynamic autoregulation refers to the ability of the cerebral vasculature to maintain constant cerebral blood flow despite changes in systemic blood pressure. The flow velocity (FV) response to sudden changes in perfusion pressure induced by various methods can be used to assess dynamic autoregulation. One of the methods used to assess dynamic autoregulation is the thigh cuff method.(74) This method involves continuously measuring MCA flow velocity while rapidly deflating bilateral thigh tourniquets, resulting in a transient lowering of arterial pressure. Autoregulation can be assessed by observing the recovery of FV and mean arterial pressure (MAP). If autoregulation is intact, FV recovers more quickly than MAP due to vasodilation. If autoregulation is impaired, FV recovery follows passively the recovery of MAP. An autoregulation index (ARI) is calculated based on the observed changes in FV and MAP. A normal value for ARI is 5±1. The thigh cuff method has several advantages, including minimal age-related effects and the ability to assess transient changes in MAP without the use of vasoactive agents.

Another method used to assess dynamic autoregulation is the transient hyperaemic response test.(75) This test involves the continuous recording of middle cerebral artery flow velocity (MCA FV). A brief compression of the ipsilateral common carotid artery is applied, resulting in a sudden reduction in MCA FV and presumably perfusion pressure. If autoregulation is intact, this provokes vasodilation in the vascular bed distal to the MCA, resulting in a transient increase in MCA FV on release of compression. Two indices are assessed in this test, namely the Transient Hyperaemic Response Ratio (THRR) and the Strength of Autoregulation (SA). The THRR and SA indices are used to assess the gradient and limits of the autoregulatory plateau without differentiating between the two. The THRR is calculated as the ratio of the peak increase in MCA FV to the baseline MCA FV after release of compression. The SA is calculated as the slope of the linear regression between the change in MCA FV and corresponding changes in MAP during the first 5-10 seconds after release of compression(76,77) The THRR has been validated against the measurement of static autoregulation and dynamic autoregulation with the thigh cuff method.

Transfer function analysis

Computer-generated models that employ continuous evaluation of cerebral perfusion pressure, transcranial Doppler flow velocities, and the dynamic correlation (Mx) between these two determinants are utilized for the purpose of autoregulation assessment.(78)

The transfer function between the oscillations in BP and CBFV is characterized by three parameters: gain (or magnitude), phase shift, and coherence.

a) Gain: The gain is a measure of the damping effect of autoregulation on the magnitude of the blood pressure (BP) oscillations. A low gain value indicates an efficient autoregulation mechanism, which is able to effectively dampen BP oscillations. In contrast, an increase in gain value represents a diminished efficiency of the dynamic process of autoregulation, which can lead to larger BP oscillations

b) Phase shift: In cases where autoregulation is intact, changes in cerebral blood flow velocity (CBFV) recovers quickly compared to the changes in BP, leading to the appearance of CBFV oscillations before BP oscillations. This phenomenon is known as "phase lead". The phase shift is usually expressed in degrees from 0° to 360°, or in radians ranging from 0 to 2 π. In patients with complete impairment of autoregulation, the phase shift between CBFV and BP is expected to nearing 0°, as CBFV changes in parallel to the change in, i.e. in phase.

c) Coherence function: The coherence function is utilized to assess the linearity of the relationship between the input and output of BP/CBFV. A coherence value that approaches unity within a defined frequency range implies a linear association in this domain, while coherence values that approximate zero may suggest an absence of relationship between the signals. To calculate gain values and phase shifts, a majority of researchers have employed coherence thresholds of greater than 0.4 or 0.5.

2.4 Transient Hyperaemic Response Test

This method of autoregulatory assessment, initially introduced by Giller, has been widely implemented in both research and clinical settings.(75)

Physiology

The test involves a continuous measurement of the flow velocities of the middle cerebral artery (MCA FV). A brief compression of the ipsilateral common carotid artery, lasting between three to ten seconds, is initiated, which leads to a sudden reduction in the MCA FV and perfusion pressure. It is presumed that if autoregulation is preserved, this compression would stimulate vasodilation in the vascular bed situated distal to the MCA. The resultant vasodilation would lead to a decrease in cerebral vascular resistance as well as a transient increase in MCA FV upon the release of compression.

Factors analysed:

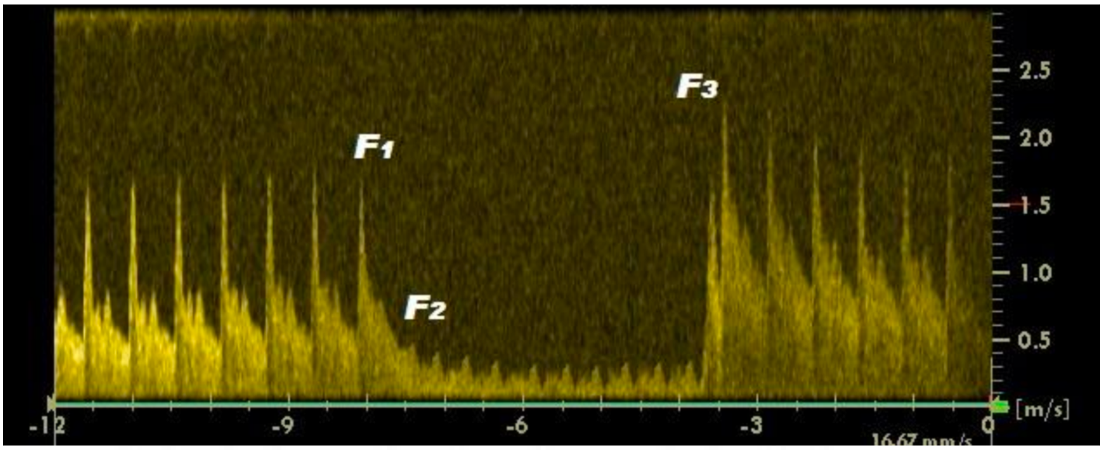
Standard criteria must be employed for the identification of the MCA with TCD. Firstly, a good recording of the waveform must be obtained. Following this, the ipsilateral common carotid artery must be compressed for a period of 3 to 10 seconds before being suddenly released. Throughout this process, flow velocity waveforms must be continuously recorded.

The THR test is deemed acceptable if it meets the following criteria:

- Sudden decrease in flow velocity is observed upon onset of compression
- Heart rate and Blood pressure remains stable throughout the test
- Flow transits after compression are absent
- The power of the reflected Doppler signal is constant indicating that the diameter of MCA remains unchanged.

For analysis time-averaged mean of the outer envelope of the flow velocity profile preceding the compression (F1), immediately after compression (F2), and immediately after the release of compression (F3) are selected.

Fig 3: THRR analysis waveform with flow velocity profile preceding the compression (F1), immediately after compression (F2), and immediately after the release of compression (F3) marked.



The analysis involves the selection of the time-averaged mean of the flow velocity profile's outer envelope before compression (F1), immediately subsequent to compression (F2), and immediately following the release of compression (F3).

The calculation of Compression ratio (CR) serves as a quantification of the extent to which blood flow velocity decreases during the compression of the common carotid artery and is calculated using the formula:

$$CR = \frac{(F_1 - F_2) \times 100}{F_1}$$

Research indicates that an optimal compression ratio of approximately 40% is required in order to obtain accurate THRR and SA values.(79)

The following two autoregulatory indices have been described.

Transient hyperaemic response ratio (THRR): The THR ratio pertains to the relationship between the flow velocity subsequent to the cessation of compression and the flow velocity preceding the beginning of compression.

A number of validation and clinical studies have been carried out to ascertain the regular value of THRR, which has been determined to be roughly 1.36±0.09. The alteration of autoregulatory response on a clinical level is indicated by a variance beyond two standard deviations from the norm.(79)

$$\mathbf{THRR} = \frac{\mathbf{F_3}}{\mathbf{F_1}}$$

Strength of Autoregulation (SA): The determination of the strength of autoregulation involves the normalization of the THRR with regards to alterations in the MAP of the MCA at the commencement of compression.

$$\mathbf{SA} = \frac{\mathbf{F_3 \ x \ P_2}}{\mathbf{MAP \ x \ F_1}}$$

Where P_2 =MAP x F_2/F_1 or 60mmHg whichever is greater (assumed lower limit of autoregulation).

The normal range for strength of autoregulation is around 0.8 – 1.1. A reduction in SA index indicates towards an impaired autoregulatory mechansim.(79)

2.4.1 Validity of THRR based autoregulation assessment

This test has been validated against easurement of static and dynamic autoregulation.(77,80) Smielewsky et al. have demonstrated that the Transient hyperaemic response ratio is a reliable indicator that possesses comparable sensitivity to the leg-cuff technique, as delineated by Aaslid et al., for discerning alterations in cerebral autoregulation brought about by distinct systemic carbon dioxide concentrations.(80) The THR test has the potential to evaluate both the gradient and the limits of the autoregulatory plateau without distinguishing between them. It is noteworthy that its variability is considerably lower (with a coefficient of variation less than 10%) when compared to other tests, which makes it ideal for comparison purposes.

The advantages of utilizing THRR-based autoregulatory assessment include its reproducibility, simplicity, and non-involvement of pharmacological intervention. Nonetheless, a major drawback is the likelihood of carotid artery atheroma embolization.

Experimental variables, such as the duration for which the carotid artery is compressed and the degree of reduction in blood flow velocity during compression, can have an impact on the THR ratio. Past research efforts have implemented compression durations ranging from five to fifteen seconds. Healthy volunteer subjects, as studied by Cavill et al, have suggested that a minimum of ten seconds of compression is necessary to achieve an optimal response, as a result of the inherent autoregulatory delay that can last between six to ten seconds.(79)

In the modelling study conducted by Smielewski et al, compression ratio (CR) values ranging from 36 to 57% were used to assess the THRR. It was assumed that all volunteers had normal blood pressure. The results indicated that a CR of 36-57% could lead to an approximate reduction of 40 to 64 mmHg in MCA perfusion pressure, which is well below the lower limit of autoregulation (~ 60mmHg).(80) The findings of a study carried out by Cavill et al indicate that as CR surpasses 40%, the correlation with THRR begins to level off. The authors have proposed that a CR of 40% or higher is indicative of the point at which the autoregulatory capacity of normotensive healthy volunteers is maximally tested.(79)

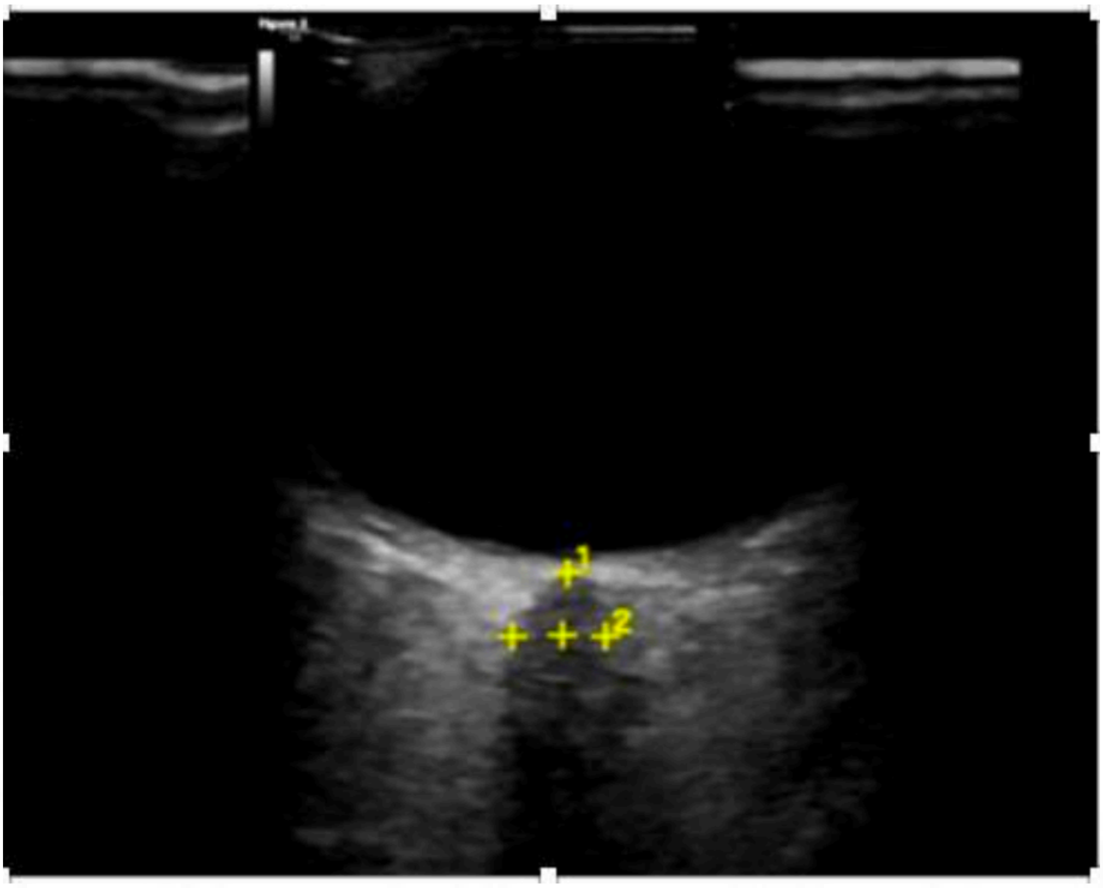
2.5 Optic nerve sheath diameter (ONSD)

Ocular ultrasonography is currently recognized as a safe, rapid, accurate, and repeatable method for measuring the optic nerve sheath diameter (ONSD), which is a promising method for determining ICP. The leptomeningeal sheath, which is extensible in the anterior portion and located behind the globe, protects the optic nerve, which is an extension of the central nervous system. This dural covering expands as ICP increases because cerebrospinal fluid (CSF) is pushed towards the periphery of the narrow subarachnoid gap between the sheath and the nerve. These alterations are more evident in the front section of the nerve sheath behind the globe. The ONSD alters dynamically in response to variations in ICP, much like any other physiological change. At 3 mm from the globe, the widening is most noticeable; beyond this distance, the presence of arachnoid trabeculations hinders further widening of the optic nerve sheath(81). As a result, the ONS may distend and the optic nerve may protrude or the posterior globe may flatten as a consequence of the accumulation of CSF in the perineural space brought on by an elevation in ICP.(82) Apart from its use in measurement of ICP in intracranial hemorrhage, ischemic stroke, meningitis, encephalitis, idiopathic intracranial hypertension, it's use has also been extended to acute mountain sickness, reversible encephalopathy syndrome, ischemic optic neuritis and symptomatic intracranial hypotension.(5,6)

2.5.1 Measurement of ONSD

The learning curve for experienced sonologists might involve as few as 10 tests, whereas novice sonologists might require up to 25 scans.(83) The lowest acoustic power required to insonate the optic nerve sheath is used to carry out an ultrasonic measurement of the ONSD utilizing a 7.5–10.5MHz linear ultrasound probe.(84) The patient is to be positioned supine with 30 degree head elevation and a thick layer of ultrasonic gel is applied to the eye. The patient is asked to look forward with eyes closed to delineate anatomy better. In the axial plane, the optic nerve can be visualized posterior to the globe. ONSD is measured 3 mm behind the globe, in each eye perpendicular to the optic nerve axis, using an electronic calliper and an axis perpendicular to the optic nerve. ONSD is measured between the outer hyperechogenic borders of the subarachnoid space.(85) The mean of three measured values is computed, to reduce the intra-observer variability.

Fig 4: Optic nerve sheath diameter



Dynamic assessment of the ONSD has also been done in cases like spontaneous intracranial hypotension (SIH) and normal pressure hydrocephalus. It can be done at two different time points in two different positions, first in supine position followed by two minutes after standing. It can also be done 5 minutes after lumbar puncture.(86)

2.5.2 Correlation between ONSD and other invasive and non-invasive ICP measurements

Optic nerve sheath ultrasound is a simple, safe, easy and bedside diagnostic test and has the potential to replace invasive ICP monitoring in cases of raised intracranial hypertension.(83) Helmke and Hansen used ultrasound in cadavers to prove that in the area just behind the eyeball, elevated pressure can increase the sheath diameter by >50%.(81)

The cut-off value for normal ONSD, measured 3 mm posterior to the globe, ranges from 5.2 to 5.9 mm. Tamburrelli et. al, used 4.5 mm as the cut-off for normal and found a sensitivity of ONSD to identify an ICP >15 mmHg of 88% and a specificity of 90%.(86) Romagnuolo, et. al, showed that the ONSD does not change with patient position.(87) Interobserver variation is quite low and the measurements are highly reproducible, even for novice operators taught in a single training session. Robba, et. al, studied the effect of prone position on ICP with the help of TCD and ONSD in 30 patients undergoing spine surgery which concluded a significant increase in ICP from supine to prone.(88) They also stated that the mean ONSD measurement was the most effective technique in distinguishing a hypothetical change in ICP between supine and prone positioning.

Previous studies have demonstrated that ONSD can be used as a non-invasive indicator of raised ICP. Tayal et. al, conducted a prospective, double-blind study in 55 patients and found that an ONSD of 5.0 mm or more correlated with CT findings suggestive of raised ICP.(83) Sahoo and Deepak Agrawal have reported a cut-off of 6.3 mm for predicting an ICP >20 mmHg in patients of neurocritical care by using Codman intraparenchymal probes (n = 20).(89)

Cranial CT findings of shift, edema or effacement suggestive of elevated ICP were used to evaluate ONSD accuracy. In the recent clinical studies, ONSD has been correlated with clinical symptoms and CT abnormalities, both surrogate indicators of elevated ICP.(90,91) A systematic review revealed that ONSD is a good diagnostic test for accurately detecting raised ICP compared to CT, for ruling out raised ICP in a low-risk group and high specificity for ruling out raised ICP in a high-risk group. ONSD measured by ultrasound has also been correlated with ONSD by MRI.(92)

ONSD has been used in a multitude of conditions to predict intracranial pressure indirectly and also to predict outcomes. A prospective, blind, observational study conducted by Moretti R et. al, in 53 adult patients with primary intracranial hypertension and subarachnoid hemorrhage showed ONSD threshold of 5.2 mm as a predictor of ICP >20mm Hg proved to be an attractive combination of sensitivity and specificity (94% and 76%, respectively) and proved the reliability of ONSD for noninvasively measuring ICP.(93)

Singer et al did a study comparing 4 non-invasive ICP measurement technologies in traumatic brain injury patients by categorizing them into non-trauma patients with ICP monitoring, trauma patients without TBI, trauma patients with mild TBI, and trauma patients with severe TBI with ICP monitoring. In comparing ONSD values in patients with mild TBI, non-TBI trauma patients, and patients with severe TBI, ONSD was found to differ significantly and bilaterally on post-injury days 2 and 3. ONSD as well as the dynamic measurements of pupillometry reliably differentiated severe TBI from more mild brain injuries on post-injury days 2 and 3. Interestingly, however, these same measurements did not correlate to ICP in patients with severe TBI. The TCD measurements did not show consistent or bilateral differences between severe TBI compared with mild and moderate TBI although it correlated well with ICP.(94)

In a study by Patel et al in-stroke patients with both ischemic and hemorrhagic, Bilateral ONSD were measured on arrival and within the first 2 days of admission. Outcomes were measured as inpatient survival, Cerebral Performance Category, and modified Rankin Scale at 3 and 6 months. They concluded that elevations in ONSD were associated with increased in-hospital mortality and poor functional outcome at 6 months. For every 0.1 cm increase in optic nerve sheath diameter, the odds ratio for death was 4.2 among ischemic stroke (95% CI, 1.32-13.64; $p = 0.015$), and the odds ratio was 6.2 among ischemic or haemorrhagic patients (95% CI, 1.160-33.382; $p = 0.033$).(95)

Toscano M, et. al, retrospectively analyzed data from ultrasound ONSD in 21 sedated critical patients with neurological diseases to identify early malignant hypertension with brain death found to reliably predict the impending brain death where it showed higher ONSD values as compared with control.(96) Their main conclusion was that routinely monitoring ONSD daily is useful in ICU when invasive ICP monitoring is not available, to recognize intracranial hypertension in neurocritical patients.

Correlation between TCD measured non-invasive ICP based on two-depth TCD technology from the ophthalmic artery velocities and ONSD was done by Ragauskas et al in neurocritical care patients and the correlation with ICP was measured through a lumbar puncture. The diagnostic sensitivity of 37.0%, specificity of 58.5%, and the area under the ROC curve (AUC) of the ONSD method for detecting elevated intracranial pressure (ICP .14.7 mmHg) were 0.57, calculated using a cut-off point of ONSD at 5.0 mm. The diagnostic sensitivity, specificity, and AUC for the non-invasive absolute ICP measurement method were calculated at the same ICP cut-off point of 14.7 mmHg and were determined to be 68.0%, 84.3%, and 0.87, respectively. The TCD technology was observed to have better diagnostic than the ONSD method when expressed by the sensitivity and specificity for detecting elevated ICP > 14.7 mmHg. (97)

ONSD and PI derived from TCD were correlated in traumatic brain injury patients postoperatively by Chang et al to predict intracranial hypertension. They found a correlation between ONSD and ICP and this remained when ONSD > 5mm. Also, there was a strong interrelationship between PI and ICP on post-surgery days 3,4 and

5. For predicting intracranial hypertension with PI ≥ 1.2 mm or ONSD ≥ 5 mm or a combination of them, the AUC was 0.729, 0.900, and 0.943, respectively ($p < .001$

MATERIALS AND METHODS

3 MATERIALS AND METHODS

This is a prospective observational study designed to assess the effect of SNP infusion on cerebral blood flow, cerebral vascular reactivity, cerebral autoregulation and intracranial pressure in patients undergoing posterior fossa surgeries.

Setting: Neurosurgical operation theatre (NSOT) at Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, Kerala a specialized tertiary referral center.

Institutional Ethics Committee Approval: This study was approved by our Institutional Ethics Committee (SCT/IEC/1804/JANUARY/2022)

Study period: Patients were enrolled from Jannuary 2022 to March, 2023 for the study.

Study Design: Prospective observational case study. The total number of participants are sixty.

The patients for the study were selected from elective neurosurgical operation theatre list and recruited after fulfilling the following inclusion and exclusion criteria. Informed written consent was obtained from those who fulfilled the recruitment criteria and those willing for the study were included in the study.

Inclusion criteria:

- Postoperative patients who have undergone elective posterior fossa surgeries who receive SNP infusion for the control of postoperative hypertension.

- Age 18-60yrs
- ASA class 1 and 2
- GCS 15 prior to the surgery

Exclusion criteria

- Patient refusal
- Age<18yrs,>60yrs
- Patients extubated immediately after the surgery
- Long standing uncontrolled diabetes mellitus, systemic hypertension on multiple drugs, cardiovascular disease, COPD, bronchial asthma, liver disease, chronic kidney disease
- Patients with carotid atherosclerotic plaques, vascular diseases, stroke
- Patients with hydrocephalus/haematoma in the postoperative CT scan
- Difference of MCA MFV of more than 10% between the two sides

Study protocol

After IEC approval and informed patient consent, patient will be recruited for the study

- On the day prior to surgery, the hemodynamic parameters including heart rate, blood pressure and oxygen saturation of the patient were recorded and these parameters will be taken as baseline
- On the day of surgery, the patient was shifted to operation theatre. Safety

checklist was filled as per protocol.

- Before induction of anaesthesia, haemodynamic parameters including pulse rate, blood pressure, oxygen saturation will be noted
- Carotid ultrasound was performed bilaterally to rule out for carotid plaques using 10 MHz probe (Esaote MylabTM guide, Italy)
- Transcranial doppler (TCD) is performed at this point through the trans-temporal acoustic window. All patients were placed in supine with head positioned with support and in neutral position. The 2 Mhz TCD probe was placed in front of tragus above the imaginary line drawn from outer cantus of the eye to the tragus on the right side. The depth was preset to 40-60 mm with gain setting of 8 and power of 50%. The middle cerebral artery (MCA) flow was identified in the M-mode window showing the red color. The doppler flow was obtained from the dedicated window for the same and the values were recorded The observed parameters viz. peak systolic flow velocity (PSV), end diastolic flow velocity (EDV), mean flow velocity (MFV), Pulsatility index (PI),and Resistivity index (RI) are recorded for a period of 15 seconds and average value was noted. The similar technique was used for the left side. If the difference in mean velocity of more than 10% was observed between the two sides, the patient was excluded from the study.

The pulsatility index (PI), or Gosling index, is calculated as follows:

$$\mathbf{PI} = \frac{\mathbf{(PSV-EDV)}}{\mathbf{PSV}}$$

The intracranial pressure was calculated from the formula proposed by Bellner et al(70)

$$\mathbf{ICP = 10.93 \times PI - 1.28}$$

The cerebrovascular resistance index was calculated from the formula:

$$\mathbf{CVRi = MAP/MCA\ MFV(98)}$$

- Cerebral autoregulation was assessed by transient hyperaemic response test and a 10% increase in MCA MFV after 10 seconds of common carotid artery compression was taken as significant. Transient hyperaemic response ratio (THRR) of less than 1.1 was be considered as impaired autoregulation.(99)
- Technique of Optic Nerve sheath diameter (ONSD) measurement - For ONSD, a thick layer of gel was be applied over the closed upper eyelid. A 10 MHz probe (Esaote MylabTM guide, Italy) was placed only on the temporal area of the eyelid to prevent pressure being exerted on the eye. The eye was checked for proper closure to prevent any corneal or conjunctival injury. The position of the probe was adjusted to give a suitable angle for displaying the entry of the optic nerve into the globe. The power of ultrasound was reduced to 75%. ONSD was measured 3 mm behind the globe using an electronic calliper along an axis perpendicular to the optic nerve. Three measurement for ONSD of each eye was taken & average of all reading was considered. ONSD of more than 5 mm was considered to be increased ICP(100)
- Anesthesia was induced as per the discretion of the attending anesthesiologist and institutional practice

- Additional monitors like intraarterial canula was introduced in the radial artery for continuous blood pressure monitoring along with temperature and urine output monitors as per the institutional practice. The difference between arterial blood pressure and non-invasive blood pressure was noted. Adequate IV access was obtained using a peripheral cannula and/or central venous access as per the case.
- Anaesthesia was discontinued at the end of the procedure and patient was shifted to postoperative care unit. A CT scan was done in the immediate postoperative period. If there are any features of raised intracranial pressure/hydrocephalus were present in the postoperative CT scan, the subject will be excluded from the study.
- Postoperative baseline TCD and ONSD readings (T1) was obtained after the patient is stabilised in the ICU and mechanically ventilated with a $PaCO_2$ value adjusted to 35-40mmHg. Postoperative haemodynamic parameters including pulse rate, blood pressure, oxygen saturation was noted.
- Post-operative hypertension was defined as systolic blood pressure of above 140mm Hg or an increase in systolic blood pressure of more than 20% from the baseline and SNP infusion was started at 2mcg/kg/min to achieve systolic blood pressure of less than 20% of baseline or SBP of less than 120 mm Hg whichever is higher.
- At the point when the systolic blood pressure returns to less than 20% of baseline blood pressure or systolic blood plressure falls below 120 mmHg and stabilized for 10 minutes, TCD parameters, ONSD value and haemodynamic parameters (T2) were assessed and recorded.

- After 12 hours of initiation of SNP or when the SNP infusion is terminated, TCD parameters, ONSD value and haemodynamic parameters were reassessed and recorded (T3).

Data collection: The following observations were manually entered into the study proforma

1. Baseline Heart rate, Systolic blood pressure (SBP), Diastolic Blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO2) on day prior to surgery
2. MCA MFV, P.I, R.I, CVRi, THRR prior to induction of anaesthesia, end of surgery (T1), after reduction of blood pressure to within 20% of baseline blood pressure with SNP infusion (T2), and at end of 12 hours of SNP infusion/ termination of SNP infusion (T3)
3. SBP, DBP, MAP, SpO2, PaCO2 at induction of anaesthesia, end of surgery (T1), after reduction of blood pressure to within 20% of baseline blood pressure with SNP infusion (T2), and at end of 12 hours of SNP infusion/ termination of SNP infusion (T3)
4. ONSD values prior to induction of anaesthesia, end of surgery (T1), after reduction of blood pressure to within 20% of baseline blood pressure with SNP infusion (T2), and at end of 12 hours of SNP infusion/ termination of SNP infusion (T3)

STATISTICS

Sample size calculation

Sample size was calculated by using the formula:

$$N = (Z\alpha)^2.(S)^2 / (d)^2$$

$Z\alpha$ - 1.96 at 95% level of significance

S – standard deviation of 8.48 was assumed based on previous study(101)

d – Margin of error of 3

The calculated sample size was calculated to be n =31. Considering dropout, we intended to take sample size as 45

Data analysis

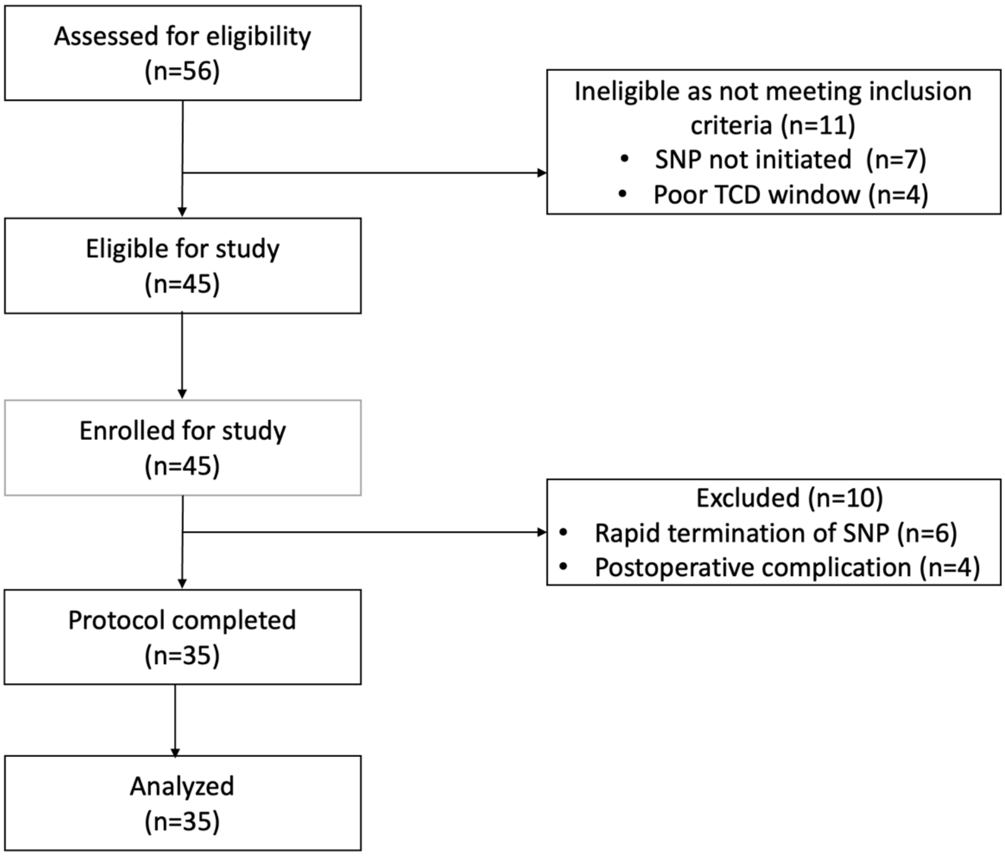
Data was manually entered into the proforma by the investigators. It was not analysed to understand, gender, caste, class, ethnicity and race difference All statistical analyses were performed using IBM SPSS Statistics software version 29.0 for Macintosh (Armonk, NY: IBM Corp). Descriptive data were expressed in frequency, percentage, mean and standard deviation. Kolmogorov Smirnoff was done to check whether the distribution of data was normal. One–way repeated measures variance analysis (ANOVA) was used for the inter- comparison of relative changes in cerebral blood velocities, P.I., R.I, ICP, THRR, CVRi from TCD, ONSD and hemodynamics with different time points.. Significance was accepted when probability value was ≤ 0.05 level with post hoc Bonferroni corrections for minimizing type I error for multiple comparisons. For data with non-normal distribution related-samples Friedman's two-way analysis of Variance by ranks was done. A p value of ≤ 0.05 was considered as significant after the siginificance value has been adjusted by the Bonferroni correction for multiple tests. Relative differences were measured as percent change between the different time points. Cerebral autoregulation was assessed by linear regression of percentage changes in cerebral vascular reactivity index (CVRi) in responses to percentage changes in mean arterial pressure (MAP). A linear regression slope of ≈ 0 for ΔCVRi% or ΔCVR% would suggest impaired autoregulation, whereas a slope of ≈ 1.0 indicates intact autoregulation.(102)

RESULTS

4 RESULTS

Fifty-six patients were evaluated in order to ascertain their eligibility for participation in the study. The results of this evaluation indicated that forty-five patients met the criteria for enrollment, as depicted in Figure. The remaining eleven patients were deemed ineligible, with ten of these being excluded from the study due to the presence of either hydrocephalus or operative site hematoma in the postoperative CT scan. The remaining patient was excluded due to the termination of SNP infusion prior to the subsequent TCD recordings. Despite these exclusions, the study was successfully completed with the participation of all thirty-five enrolled patients.

Figure 5: Flow chart presenting the enrolment, study inclusion, and data analysis



4.1 Demographics

Table 2 : Showing demographic data of patients

Variable	Total subjects = 35
Age (years) Mean ± SD	43.65 ± 12.16
Gender (%) Female Male	58.1% 41.9%
ASA Grade (%) ASA I ASA II	61% 39%

Figure : Gender distribution of the subjects

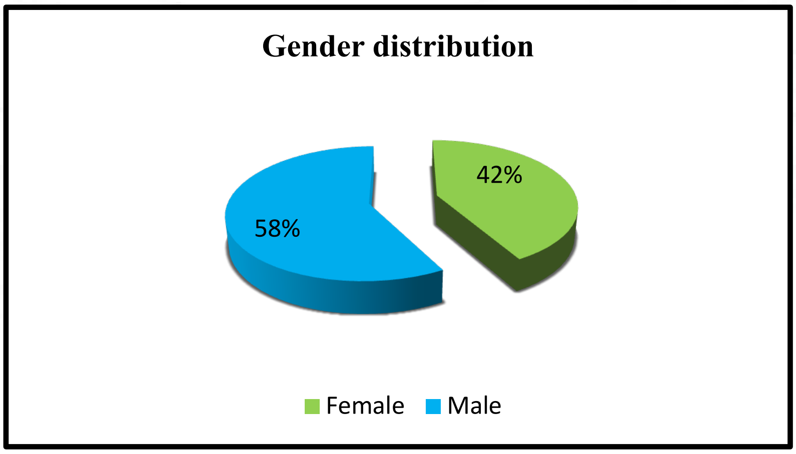


Figure 6: ASA grading distribution of subjects

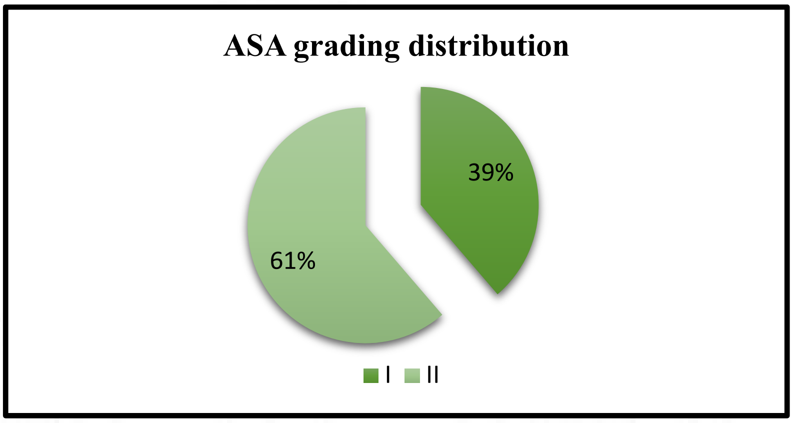
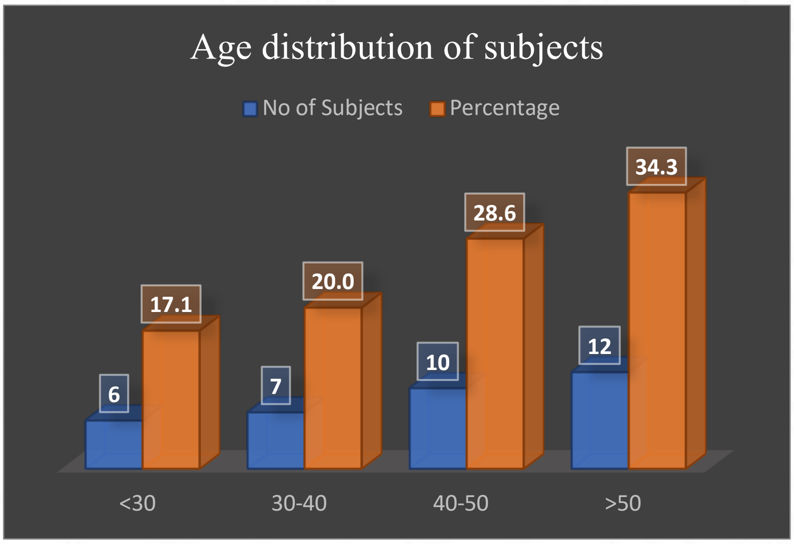


Figure 7: Age distribution of subjects



The demographic details of the 35 patients enrolled are shown in Table . The mean age was 43.65 ± 12.16 years. 34.3% were between 51-60 years as shown in Figure . Fifty eight percent were females. 61% of the patients were ASA grade 1 while 39% were ASA II. The study was completed successfully in the 35 recruited patients.

Table 3 . Pre-operative diagnosis of the subjects

Diagnosis	No. of subjects	Percentage
CP angle schwannoma	12	34.3%
CP angle meningioma	6	17.1%
Trigeminal neuralgia	8	22.9%
Cerebellar vermian lesion	3	8.6%
Cerebellar convexity meningioma	4	11.4%
CP angle epidermoid tumour	2	5.7%

As described in Table 34.3% of the patients underwent surgery for cerebello-pontine (CP) angle schwannomas followed by microvascular decompression for trigeminal neuralgia (22.9%).

4.2. Haemodynamic parameters

Heart rate (HR) and Mean arterial pressure (MAP) of the study group have been demonstrated in table

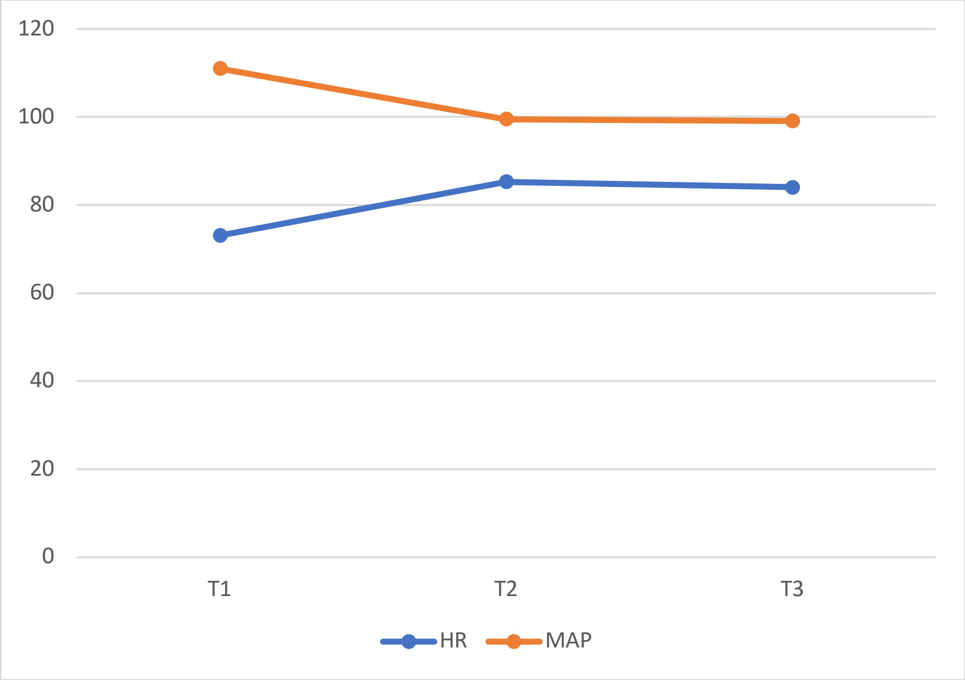
Table 4: Shows the HR and MAP of the subjects at the different time points

N = 35	T1	T2	T3	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
HR (beats/min)	73.1 ±10.38	85.26 ±9.96	84.06 ±10.26	.0005*
MAP (mm Hg)	111.0 ± 7.33	99.52 ± 6.89	99.10 ± 6.48	.0005*

HR = Heart rate ; MAP = Mean arterial pressure ; Analysis using Repeated measure ANOVA with Bonferroni correction ; p-value of < .05 is considered as significant level.

The mean heart rate at T1 was found to be 73.1 ± 10.38 /minute which increased to 85.26 ± 9.96/minute at T2 after initiation of SNP infusion and 84.06 ± 10.26/minute at T3 which was statistically significant (p-value < 0.05). The mean arterial pressure decreased from 111 ± 7.33 at T1 to 99.52 ± 6.68 at T2 and 99.1 ± 6.48 at T3. This change was also statistically significant with p-value < 0.001

Figure 8: Comparison of HR and MAP velocities at different time points



The analysis of SPO2 and PaCO2 values at the different time points did reveal any difference fom time points T1 to T3 as shown in Table (p value > 0.05)

Table 5: Shows the SPO_2 and $PaCO_2$ of the subjects at the different time points

N = 35	T1	T2	T3	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
SPO_2 (%)	99.839 ± 0.374	99.581 ± 0.720	99.645 ± 0.608	.143
$PaCO_2$ (mm Hg)	37.381 ± 1.455	37.542 ± 1.208	37.813 ± 1.236	.304

SPO_2 = peripheral oxygen saturation ; MAP = Mean arterial pressure ; Analysis using Repeated measure ANOVA with Bonferroni correction ; p-value of < .05 is considered as significant level.

4.3. Transcranial doppler velocities

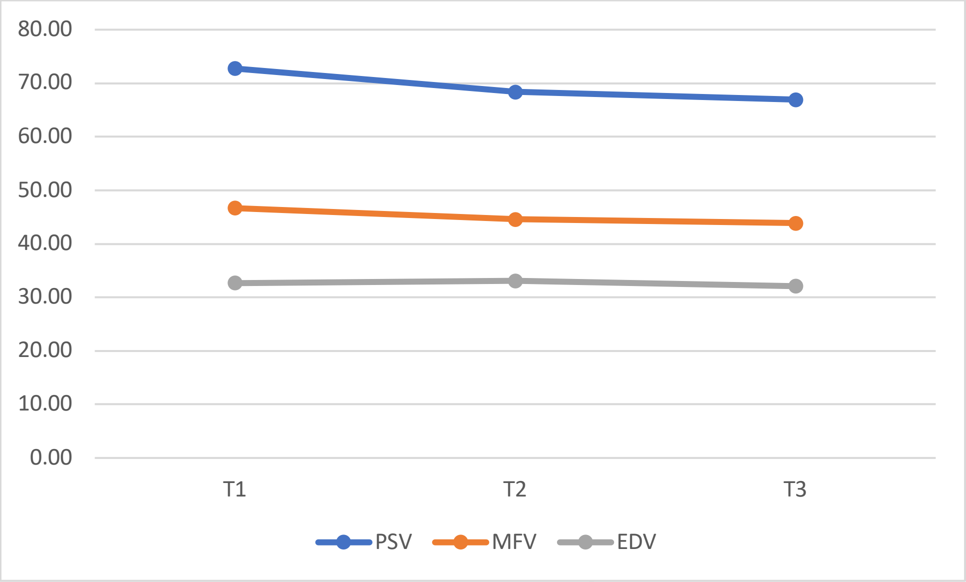
The repeated measures ANOVA analysis showed that the PSV decreased significantly from 72.72 ± 15.91 cm/s at T1 to 66.94 ± 13.25 cm/s at T 3 (p-value < 0.01). However the decrease of MFV from 46.61 ± 11.17 cm/s at T1 to 43.88 ± 10.90 cm/s at T3 was not found to be statistically significant (p-value – 0.138). The end diastolic velocity also decreased from 32.68 ± 9.01 cms at T1 to 32.09 ± 8.22 cm/s at T3but was not statistically signifant (p-value – 0.70)

Table 6: Shows the TCD velocities (PSV, MFV and EDV) of the subjects at the different time points

N = 35	T1	T2	T3	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
PSV (cm/sec)	72.74 ± 15.91	68.39 ± 13.97	66.94 ± 13.25	.0005*
MFV (cm/sec)	46.61 ± 11.17	44.58 ± 11.46	43.88 ± 10.90	.138
EDV (cm/sec)	32.68 ± 9.01	33.09 ± 10.31	32.09 ± 8.22	.700

PSV = Peak systolic velocity ; MFV = Mean flow velocity ; EDV = End diastolic velocity; Analysis using Repeated measure ANOVA with Bonferroni correction ; p-value of < .05 is considered as significant level.

Figure 9: Comparison of TCD velocities at different time points



The results of the data analysis indicate that there was no significant variation in PI from T1 (0.82 ± 0.13) to T3 (0.814 ± 0.15) , as evidenced by the p-value which 0.748. Moreover, the alteration in RI from T1(0.54 ± 0.07) to T3 (0.53 ± 0.06) was not observed to be statistically significant, as indicated by the p-value of 0.613. Additionally, the ICP did not demonstrate any statistically significant change from T1 (7.42 ± 1.75 mm Hg) to T3 7.38 ± 1.90 mm Hg) with a p-value of 0.70.

Table 7: Shows the PI, RI and ICP of the subjects at the different time points

N = 35	T1	T2	T3	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
PI	.822 ± .133	.825 ± .156	.814 ± .146	.748
RI	.536 ± .068	.532 ± .083	.527 ± .063	.613
ICP	7.42 ± 1.75	7.49 ± 1.98	7.38 ± 1.90	.700

PI = Pulsatility index ; RI = Resistivity index ; ICP = Intracranial pressure ; Analysis using Repeated measure ANOVA with Bonferroni correction ; p-value of < .05 is considered as significant level.

The CVRi, THRR and ONSD data was analayzed using Friedman's analysis of repeated measures and a significant p-value was adjusted by Bonferroni's correction for repeated measures. The findings of the analysis of the data reveal that there was no significant alteration in CVRi from T1 (2.49 ± 0.57) to T3 (2.41 ± 0.62), and this was supported by the p-value of 0.248. Furthermore, the difference in THRR from T1

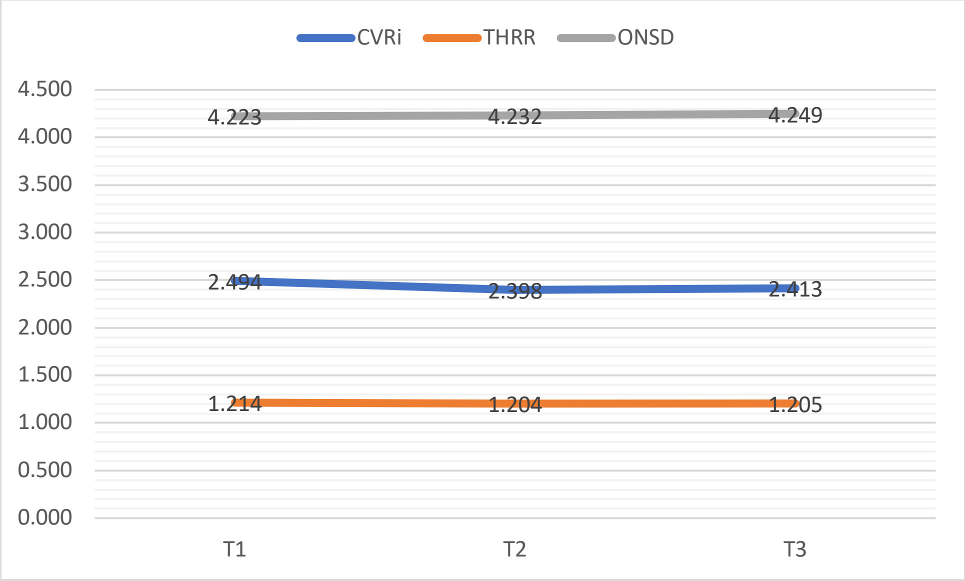
(1.214 ± 0.05) to T3 (1.205 ± 0.05) was not observed to be statistically significant, as the p-value was 0.186. In addition, the ONSD did not reveal any statistically significant change from T1 (4.22 ± 0.37 mm) to T3 (4.24 ± 0.33 mm), as evidenced by the p-value of 0.443

Table 8: Shows the CVRi, THRR and ONSD of the subjects at the different time points

	T1	**T2**	**T3**	**p-value**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
CVRi	2.494 ± 0.565	2.398 ± 0.615	2.413 ± .0.615	.248
THRR	1.214 ± 0.046	1.204 ± 0.048	1.205 ± 046	.186
ONSD	4.22 ± .368	4.32 ± .375	4.24 ± .326	.443

CVRi = Cerebrovascular resistance index; THRR = Transient hyperaemic response ratio; ONSD = Optic nerve sheath diameter. Analysis using Repeated measure ANOVA with Bonferroni correction ; p-value of < .05 is considered as significant level.

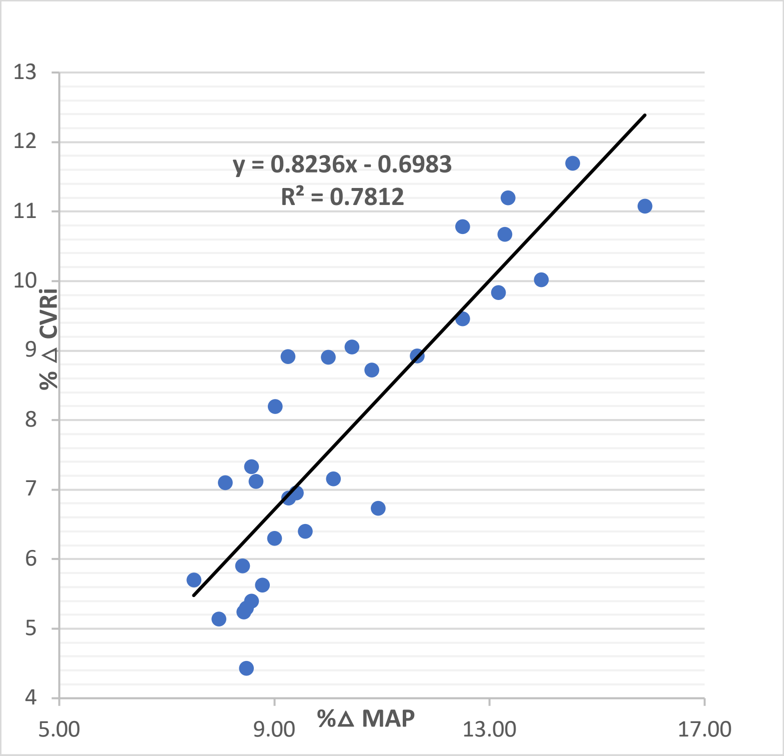
Figure 10 : Comparison of CVRi, THRR and ONSD at different time points



Regression analysis of percentage change in CVRi and MFV to percentage change in MAP

We performed linear regression analysis of changes in CVRi in response to changes in arterial pressure btween different time points

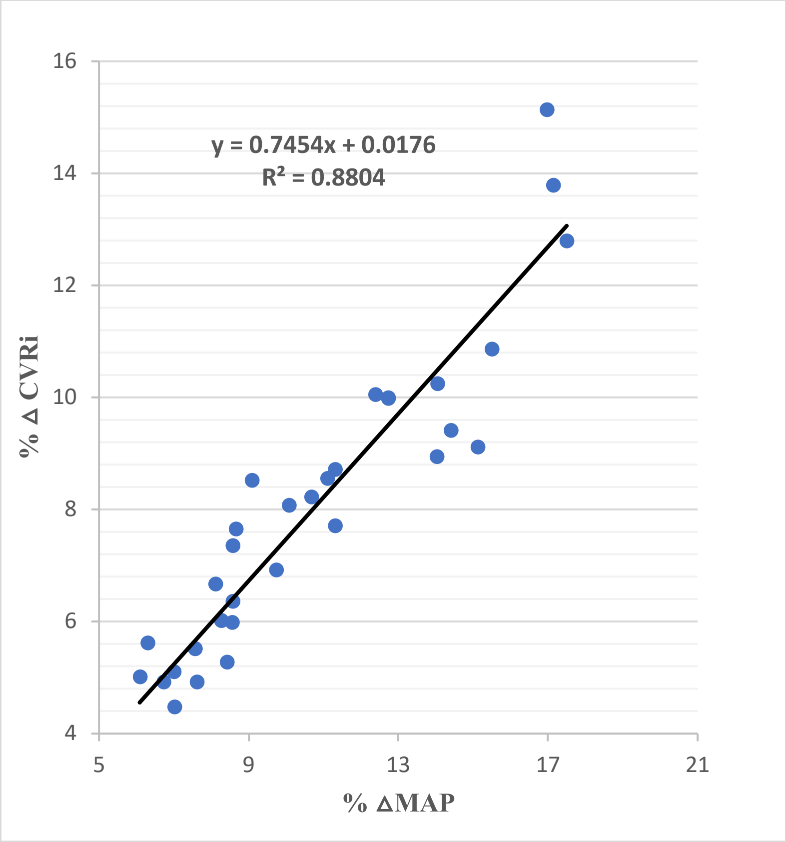
Figure 11: Linear regression analysis of % ∆ CVRi to % ∆ MAP between time points T1 and T 2



Regression Statistics	
Multiple R	0.88
R Square	0.78
Adjusted R Square	0.77
Standard Error	0.99
p-value	<0.05

The analysis showed a linear regression slope of 0.82 and an adjusted R square of 0.77 with a p-value of < 0.05 compared to baseline (T1)

Figure 12: Linear regression analysis of % ∆ CVRi to % ∆ MAP between time points T1 and T 3



Regression Statistics	
Multiple R	0.94
R Square	0.88
Adjusted R Square	0.88
Standard Error	0.94
p-value	<0.05

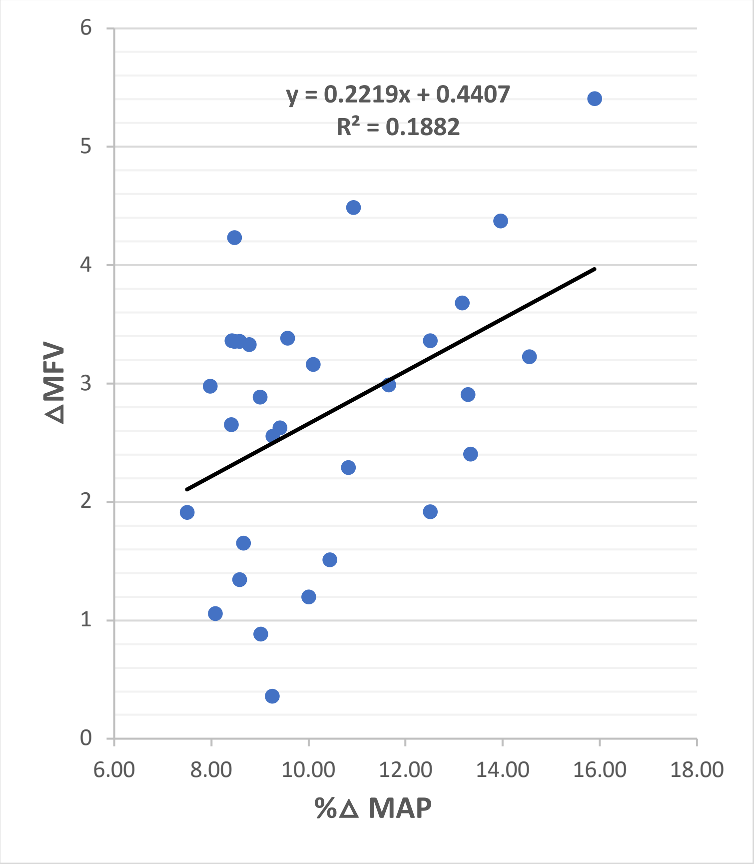
The analysis showed a linear regression slope of 0.75 and an adjusted R square of 0.88 with a p-value of < 0.05 compared to baseline (T1)

Regression analysis of percentage change in CVRi and MFV to percentage change in MAP

We performed linear regression analysis of changes in MCAMFV in response to changes in arterial pressure btween different time points

The analysis showed a linear regression slope of 0.22 and an adjusted R square of 0.16 with a p-value of 0.06 compared to baseline (T1)

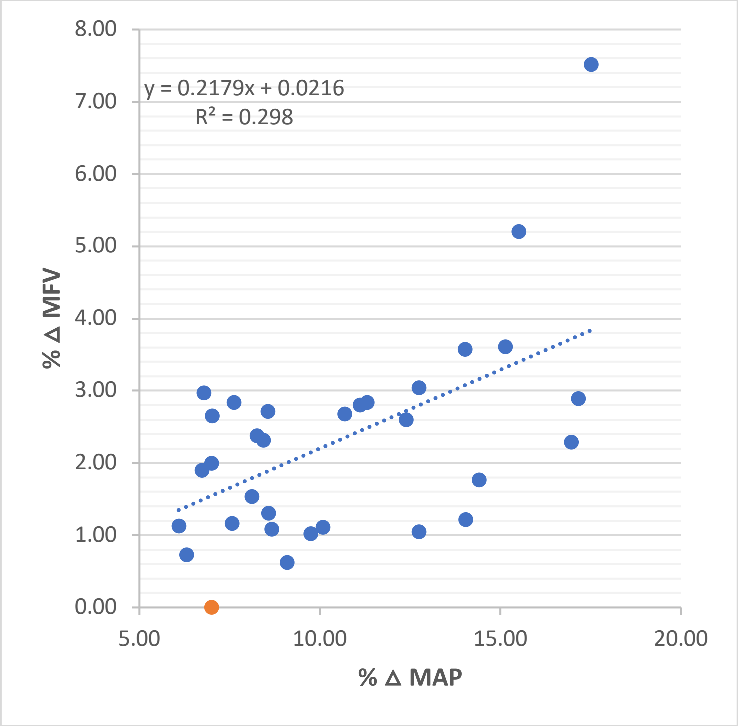
Figure 13 : Linear regression analysis of % ∆ MFV to % ∆ MAP between time points T1 and T 2



Regression Statistics	
Multiple R	0.43
R Square	0.19
Adjusted R Square	0.16
Standard Error	1.05
p-value	0.064

The regression analysis between T3 and T1 of % ∆ MFV to % ∆ MAP revealed a linear regression slope of 0.21 but with an adjusted R square of 0.29 and p - value of 0.055

Figure 14: Linear regression analysis of % ∆ MFV to % ∆ MAP between time points T1 and T 3



Regression Statistics	
Multiple R	0.55
R Square	0.30
Adjusted R Square	0.29
Standard Error	1.02
p-value	0.055

DISCUSSION

5 DISCUSSION

One crucial aspect of the neurointensive care of neurosurgical patients in the immediate post-operative period is to prevent post-operative hypertension, while simultaneously ensuring the preservation of cerebral autoregulation and cerebral oxygenation, and averting any increase in intracranial pressure. Hypertension in patients undergoing posterior fossa surgeries can lead to devastative complications like operative site hematoma, hyperaemia leading to cerebral oedema which can result in significant morbidity and mortality.(18) An appropriate anti-hypertensive medication therefore for use during neurological surgery must possess the characteristics of being easily titratable and should not interfere with the cerebral autoregulation process or promote an increase in cerebral blood volume.

SNP can be deemed efficacious due to its rapid onset of action, taking effect within seconds, and its short half-life which makes it well-suited for bringing about an immediate and regulated decrease in blood pressure.(4) Although SNP possesses superior pharmacokinetics, there exist certain drawbacks that might impede its usage. The administration of nitroprusside intravenously has the potential to not only lower the mean arterial pressure, but also to elevate the intracranial pressure and hinder the process of autoregulation.(54,103,104) However recent studies have questioned these pres-existing notions regarding nitroprusside. Furthermore, it was noticed that a caveat was present in a recent literature that examined the effect of SNP on cerebral haemodynamics in the neurosurgical population using TCD and ONSD . Hense we conducted an observational study with the purpose of assessing the cerebral hemodynamic ramifications of administering SNP in patients for the management of post-operative hypertension subsequent to posterior fossa surgeries. The main objective of our investigation was to assess whether the implementation of SNP in this particular subset patients resulted in the disruption of cerebral autoregulation, consequentially leading to an elevation in intracranial pressure (ICP).

A fundamental prerequisite for recruitment into the study was the confirmation of the patients' unimpaired autoregulation prior to commencement of SNP, which was achieved through a preliminary TCD assessment. Additionally, every patient underwent a postoperative CT scan and ONSD examination to conclusively rule out the possibility of elevated ICP before SNP was initiated. These measures were taken with the utmost care and diligence to ensure patient safety and the validity of the study results.

5.1 Effect of PaCO2 and PaO2

Changes in arterial PCO2 have a significant and independent impact on cerebral blood flow (CBF) and cerebrovascular resistance (CVR). Specifically, during orthostatic hypotension, a decrease in arterial PCO2 by 8mmHg accounts for 25% of the reduction in CBF velocity.(105) It should also be noted that PaO2 within physiologic ranges does not appear to have a direct effect on CBF, although hypoxemia is a potent stimulus for arteriolar dilation due to tissue hypoxia and lactic acidosis.(106) Conversely, hyperoxia decreases CBF, producing a modest 10% to 15% reduction at 1 atmosphere.{Citation} Despite the potential for confounding due to changes in oxygen (spO2) and PaCO2, statistical analysis revealed that the difference between these variables at the three time points was insignificant. Thus, the confounding effect of oxygen and Paco2 on our results was likely negligible.

5.2 Effect on TCD Velocities

The examination of TCD velocities demonstrated a significant reduction in MCA PSV among patients subsequent to the commencement of SNP infusion. Nevertheless, the variation in PSV between time T2 and T3 was discovered to be nonsignificant. However, there was no significant alteration observed in MFV and EDV in these patients across the various time points. Similar results was seen in the study by Lavi et al who studied the role of nitic oxide (NO) in mechanoregulation by use of SNP in 18 healthy subjects and concluded that NO does not have a role in mechanoreulation of CBF.(6) Similary a study by Guo et al in 2012 studying the effects of SNP on cerebral blood velocities in 5 healthy individuals concluded after correction for PetCO2, no clear change in MCA mean velocity could be detected.(7) Given that SNP is unable to pass through the BBB but is capable of liberating NO in the bloodstream, the findings of the present study imply that headache was triggered at the level of extra- or intracerebral blood vessels. The administration of SNP resulted in a significant increase in the diameter of both the STA and the RA, whereas the calculated diameter of the MCA, adjusted for CO2, remained unaltered. These results may suggest that the MCA and intracerebral arteries were not impacted by SNP, while the peripheral and extracranial arteries were clearly dilated.(107)

Simsic et al. conducted a study with the aim to determine the effects of sodium nitroprusside on cerebral blood flow velocity and systemic oxygenation in patients after bidirectional superior cavopulmonary connection, utilizing a prospective patient-controlled approach.(108) The findings of the study revealed that the mean systemic blood pressure decreased from 69±6 mm Hg at baseline to 58±6 mm Hg during the administration of sodium nitroprusside, with a statistically significant p-value of less than 0.05. Even though sodium nitroprusside infusion was associated with a decrease in systemic blood pressure, there was no corresponding change in MCA blood flow velocity, indicating that cerebral blood flow remained stable during sodium nitroprusside administration.

The findings of Xu et al. also indicated that there was no substantial fluctuation in cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA) as measured through transcranial Doppler (TCD) when utilizing SNP-induced hypotension in a cohort of 30 ASA Grade I-II patients.(109)

On the other hand, Immink et al utilized SNP for regulating the blood pressure of patients with malignant hypertensive emergencies, and this resulted in a significant decrease in MFV of MCA. This phenomenon could be attributed to the fact that the blood pressure of patients with malignant hypertenson might exceed the autoregulatory range, thereby rendering the CBF "pressure passive". As a consequence, the regulation of blood pressure through the use of SNP led to a significant reduction in MFV of MCA.(101)

5.3 Effect on TCD Derived Indices

RI is a measure of resistance that is based on two points on the Doppler waveform, and relies on the observation that the diastolic point of a velocity wave will change with changes in downstream vascular resistance. However, PI appears to be a more robust estimate of resistance as it incorporates the entire waveform and is not as heavily reliant on two points. Both RI and PI have been validated through experimental research and have been found to track well with changes in vascular resistance.

Upon analyzing the data collected from our subjects, we found that neither PI nor RI showed any significant variation across the different time points (p-value <0.05). This suggests that there was no significant change in vascular resistance during the study period. We also conducted an analysis of the CVRi across the different time points, which also did not show any significant variation. Our study results were consistent with the research conducted by Immink and colleagues, who explored the impact of SNP and labetalol on cerebral hemodynamics in individuals with malignant hypertension.(101) The team's findings suggested that SNP has a greater effect on peripheral vascular resistance compared to cerebral vascular resistance, which results in a preference for systemic circulation and does not contribute to an increase in CBF.(101)

On the other hand, numerous research studies have exhibited that in anesthetized individuals, the implementation of SNP hypotension led to a significant decrease in cerebrovascular resistance (CVR)(53,110,111) Conversely, when the studies were conducted in patients with basal hypertension or when performed on conscious patients, the reduction in CVR was discovered to be less noteworthy.(7,112,113) Joshi et al. conducted a study on the effects of intracarotid SNP subsequent to the administration of a sympathomimetic agent, phenylephrine, and reported CVR values equivalent to baseline.(49) The possible reason behind the findings of our study also appear to be an increased sympathetic tone of the subjects under investigation.

5.4 Effect on Cerebral autoregulation and Cerebral Blood flow

Our study findings indicated that the average THRR of patients at T1, T2, and T3 were 1.214 ± 0.05, 1.204 ± 0.05, and 1.205 ± 0.05, respectively. The preservation of autoregulation is presumed when the THRR value exceeds 1.09, which was the case for all three time points. Our results reveal that at all three time points, the THRR value exceeded this threshold value, signifying the presence of autoregulation. Furthermore, The Friedman’s test for repeated measures showed a non-significant difference in the

THRR between the three time points, which further corroborates the presumption that autoregulation remained unimpaired.

We conducted an analysis to determine the percentage change of cerebral vascular resistance index (CVRI) to the percentage change in mean arterial pressure (MAP) at two different time points (T2 to T1 and T3 to T1) using linear regression. A slope of zero would indicate impaired autoregulation, while a slope of approximately 1.0 would suggest that autoregulation is functioning perfectly.(114) Our linear regression analysis showed a regression slope of 0.82 from T1 to T2, and a regression slope of 0.75 from T3 to T1. These high positive values for regression slopes indicate results suggest that cerebral autoregulation was well-maintained following the administration of SNP. Our findings align with the findings of Liu et al. who conducted a prospective cohort study on the impact of SNP on autoregulation in 21 healthy volunteers.(102) According to their findings, there was a linear regression slope of ΔCVRi% of MCA to ΔMAP% of 0.77, which led them to conclude that the autoregulation was preserved. Furthermore, they observed that measuring CVRi instead of CVR underestimates the strength of autoregulation, which implies that the strength of autoregulation in our study may also have been underestimated

We also conducted an analysis using linear regression to explore the relationship between percentage change in mean flow velocity (MFV) and percentage change in mean arterial pressure (MAP). A linear regression's slope value of 0 in response to percentage changes in MAP for percentage changes in CBFV represents perfect autoregulation, whereas a slope value of 1 denotes compromised autoregulation.(115)

It has been previously established that the diameter of the middle cerebral artery (MCA) does not vary despite fluctuations in MAP or carbon dioxide (CO2).(116) As a result, changes in ΔMFV% can be considered equivalent to changes in ΔCBF%. Our analysis revealed a regression slope of 0.22 between T2 and T1, and a regression slope of 0.21 between T3 and T1. These findings are consistent with those of Liu et al., who reported a regression slope of 0.239 with no statistical difference from baseline, indicating relatively well-preserved autoregulation.(102) Additionally, Liu et al. reported that the regression slope decreased after accounting for changes in end-tidal CO2 (ETCO2).(102) Similarly the study conducted by Lucas et al. aimed to explore the relationship between changes in cerebral blood flow velocity (CBFV) and mean arterial pressure (MAP) in healthy adults.(115) Their findings revealed a significant positive correlation between the two variables, with a linear slope ranging from 0.5% to 3.0% per 3mmHg−1 within the MAP range of 60 to 150 mm Hg.(115) These results suggest that even in the presence of intact cerebral autoregulation, CBF cannot remain constant in response to fluctuations in arterial pressure.

5.5. Effect on ICP

We conducted an assessment on the impact of SNP on ICP using two distinct techniques. Firstly, we computed the ICP from PI using the formula proposed Bellner et al.(70) Secondly, we measured the ONSD at all three time points. Our analysis of the calculated ICP indicated that there was no statistically significant change from T1 to T3. Similarly, we observed that the alteration in ONSD was also statistically insignificant. These findings contradict the results reported in prior literature.

Cottrell et al conducted one of the initial studies that analyzed the impact of SNP on ICP.(53) Their study focused on the alterations in intracranial pressure (ICP) in patients with intracranial mass lesion after the administration of hypotensive anesthesia using SNP. The findings of the study indicated a significant increase in ICP accompanied by a decline in CPP in the patients. However, it is vital to highlight that the patients already had poor intracranial compliance, and a MAP reduction of 33 percent was observed, which potentially challenged the lower limit of autoregulation. Therefore, it is crucial to consider the pre-existing conditions in patients while evaluating the effects of SNP. Similar to Cottrell, Turner et al. measured intracranial pressure in 45 patients undergoing neurosurgery during the induction of deliberate hypotension using either sodium nitroprusside or trimetaphan. A statistically significant increase in intracranial pressure (ICP) occurred during the infusion of nitroprusside in normocapnic patients. It is to be noted that both the studies were done under anaesthesia

Given the lack of prior research on the impact of SNP on ICP in the context of post-neurosurgical patients with post-operative hypertension, it is not possible to draw comparisons with existing literature. We posit that the augmented sympathetic activity observed during emergence from anesthesia, which contributed to the development of emergence hypertension, acted as a counterbalance to the direct cerebro-vasodilatory effect of SNP, consequently resulting in an unaltered ICP.

We would like to propose two potential explanations for the findings of our study. The first involves the debatable function of nitric oxide in the cerebral circulation of individuals possessing intact cerebral autoregulation. Sodium nitroprusside is a water-soluble sodium salt that consists of Fe 2+ complexed with nitric oxide (NO) and five cyanide anions. Within the body, it operates as a prodrug, engaging with sulfhydryl groups on erythrocytes, albumin, and other proteins to discharge NO. NO, also known as endothelium-derived relaxing factor, stimulates guanyl cyclase to produce cyclic GMP, which sequesters calcium and restricts cellular contraction. These NO effects at the tissue level lead to reduced vascular tone in muscular conduit arteries. The efficacy of intraarterial nitroprusside as a vasodilator in most noncerebral vascular beds of humans indicates that the nitric oxide produced from nitroprusside has the ability to easily permeate vascular endothelium.(117,118) If endothelial nitric oxide (NO) is indeed a significant regulator of cerebral blood flow (CBF), one would expect that physiologically generated NO should be able to penetrate the blood-brain barrier without difficulty since the barrier is positioned between the endothelium and the vascular smooth muscle cell. However, the administration of SNP through intra-carotid injection of SNP, was not found to increase CBF.(49) This lack of response prompts speculation regarding the efficacy of NO transfer across the blood-brain barrier and therefore its role as a major regulator of CBF. Considering the limited evidence in support of the participation of endothelial and neurogenic factors in the regulation of cerebral blood flow (CBF) via mechanoregulation, it is postulated that the primary mechanism responsible for autoregulation is myogenic.(57) Furthermore, animal studies have demonstrated that while nitric oxide (NO) plays a role in chemoregulation, it has no significant impact on pressor-dependent regulation.(119)

The potential explanation for our findings is the involvement of the sympathetic system. In studies conducted on anaesthetised patients, it was observed that CBF either remained stable or increased in response to SNP. However, studies conducted on awake patients revealed that CBF was slightly reduced.(7,112) The plausible explanation for this difference in the action of the sympathetic system is the influence on the large intracranial vessels. Our study involved patients who exhibited emergence hypertension, which was linked to an increase in the sympathetic and renin-angiotensin activity. The excessive vasodilatory effects of SNP were likely countered due to the aforementioned reason.

5.6 Limitations

- Our investigation involved enrolling individuals who displayed an unimpaired cerebral autoregulation at the outset, accompanied by a normal intracranial pressure. Therefore, it is imprudent to generalize our findings to patients who exhibit lowered intracranial compliance and disrupted cerebral autoregulation

- Due to the lack of evaluation on the effects of SNP in posterior circulation, it is not possible to extend the current findings beyond the realm of anterior circulation.

- The lack of a discernible difference in PaCO2 across the various time points notwithstanding, it is plausible that the outcomes of the analysis may have been influenced by the failure to factor in the variations in PacO2.

- Given that our study is an observational one and the sample population is limited, it is imperative to conduct larger randomized control trials to ensure the validity and confirm the reliability of our findings.

SUMMARY & CONCLUSION

6 SUMMARY AND CONCLUSION

This study was conducted with a prospective observational design to investigate the impact of sodium nitroprusside (SNP) on cerebral blood flow, autoregulation, and intracranial pressure in patients who underwent posterior fossa surgeries and were administered SNP for postoperative hypertension management. Our hypothesis was that the use of SNP would not affect the cerebral autoregulatory status or intracranial pressure in patients with an intact basal cerebral autoregulation.The study assessed the middle cerebral artery blood velocities and cerebral autoregulation through transcranial Doppler (TCD) and measured intracranial pressure through optic nerve sheath diameter (ONSD) before and after the initiation of SNP treatment for hypertension control in 35 patients who underwent elective posterior fossa surgery. The parametric data was analyzed using repeated measures ANOVA with Bonferronic correction while the non-parametric data was analyzed using Friedman's two way analysis of variance. We also The anaslysis of our data revealed the following:

1. The use of SNP lead to a significant decrease in MAP along with a significant increase in Heart rate
2. A significant reduction in PSV across the time points, the MFV or EDV did not show significant variation.
3. The changes in PI or RI were also found to be statistically insignificant. The reduction in CVR was also found to be statistically insignificant

4. The ONSD as well as ICP calculated from PI did not show any statistical significant variation across the different time points
5. The logistic linear regression comparing the pervebtage change in CVRi to percentage change in MAP revealed a slope of 0.82 and 0.75. The THRR was also maintained above 1.09 and did not show significant variation across time points.

Based on our findings, we have determined that the utilization of SNP for the treatment of acute post-operative hypertension in patients who underwent elective posterior fossa surgery did not result in a significant impact on cerebral blood flow velocities, while also managing to uphold cerebral autoregulation without causing an escalation in intracranial pressure. We posit that the impact on cerebral vascular resistance is comparatively lower in relation to that of peripheral vascular resistance, possibly due to the reduced influence of NO on mechanoregulation as it is assumed. Additionally, the heightened sympathetic activity observed in patients with acute post-operative hypertension following posterior fossa surgeries may counteract the direct vasodilator properties of SNP. • Given that our study is an observational one and the sample population is limited, it is imperative to conduct larger randomized control trials to ensure the validity and confirm the reliability of our findings.

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ANNEXURES

PROFORMA

TITLE:

Effect of sodium nitroprusside (SNP) infusion on cerebral blood flow velocity and intracranial pressure using Transcranial doppler sonography and Optic nerve sheath diameter in postoperative patients undergoing posterior fossa surgeries – a prospective observational study.

AGE:

GENDER:

DIAGNOSIS:

PREOPERATIVE COMPLAINTS:

ASA GRADE:

DATE OF SURGERY:

BASELINE PARAMETERS:

HEART RATE: BLOOD PRESSURE: SPO2:

CHECKLIST

FACTORS	INCLUDE	EXCLUDE
Patient Consent	YES	NO
Nature of Surgery	ELECTIVE	EMERGENCY
Age	18-60	<18,>60
Long standing uncontrolled DM, hypertension on multiple drugs, liver disease, Ischemic heart disease, chronic renal disease, bronchial asthma or lung diseases	NO	YES
History of vascular diseases or stroke	NO	YES
Presence of carotid atherosclerotic plaques	NO	YES
Difference in MCA MFV of >10% between in right and left side	NO	YES
Immediate Postoperative Extubation	NO	YES
Hydrocephalus/Hematoma in Postoperative CT Scan	NO	YES
Use of SNP in postoperative period	YES	NO

A. **HAEMODYNAMIC PARAMETERS**

	T0	T1	T2	T3
HEART RATE				
BLOOD PRESSURE				
SPO2				
PaCO2				

B. **TCD**

	T0	T1	T2	T3
MCA PSV				
MCA EDV				
MCA MFV				
P I				
ICP				
R I				
CVRi				
THR Ratio				

C. **ONSD:**

	T0	T1	T2	T3
Right Eye				
Left Eye				

- T0 – Baseline, prior to induction
- T1 – At end of surgery and prior to starting SNP infusion
- T2 – At the point where systolic blood pressure returns to less than 20% of baseline after initiation of SNP infusion
- T3 – After 12 hours of starting SNP infusion or at point of termination of SNP infusion

NAME AND SIGNATURE OF THE INVESTIGATOR (with date):

CONSENT FORM

Title: Effect of sodium nitroprusside(SNP) on cerebral blood flow velocity and intracranial pressure using Transcranial doppler sonography and Optic nerve sheath diameter in postoperative patients undergoing posterior fossa surgeries – 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 on the effect of sodium nitroprusside(SNP) on cerebral blood flow velocity and intracranial pressure using Transcranial doppler sonography and Optic nerve sheath diameter in postoperative patients undergoing posterior fossa surgeries. [ ]
- 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:

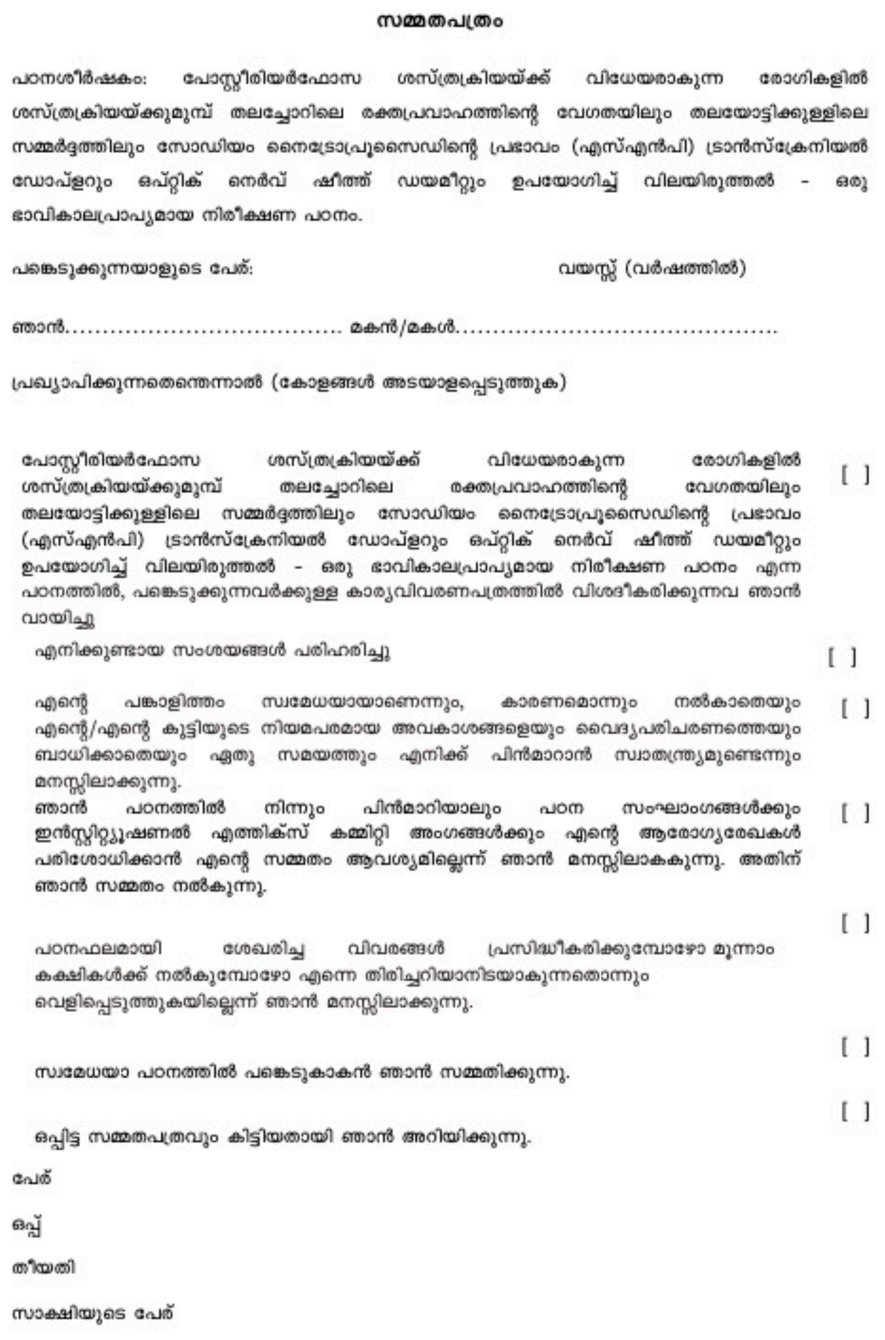
Person Obtaining Consent

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:

CONSENT (MALAYALAM)



സമ്മതപത്രം

പഠനശീർഷകം: പോസ്റ്റീരിയർഫോസ ശസ്ത്രക്രിയയ്ക്ക് വിധേയരാകുന്ന രോഗികളിൽ ശസ്ത്രക്രിയയ്ക്കുമുമ്പ് തലച്ചോറിലെ രക്തപ്രവാഹത്തിന്റെ വേഗതയിലും തലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദത്തിലും സോഡിയം നൈട്രോപ്രൂസൈഡിന്റെ പ്രഭാവം (എസ്എൻപി) ട്രാൻസ്ക്രേനിയൽ ഡോപ്ളറും ഒപ്റ്റിക് നെർവ് ഷീത്ത് ഡയമീറ്റും ഉപയോഗിച്ച് വിലയിരുത്തൽ - ഒരു ഭാവികാലപ്രാപ്യമായ നിരീക്ഷണ പഠനം.

പങ്കെടുക്കുന്നയാളുടെ പേര്: വയസ്സ് (വർഷത്തിൽ)

ഞാൻ.................................... മകൻ/മകൾ...

പ്രഖ്യാപിക്കുന്നതെന്തെന്നാൽ (കോളങ്ങൾ അടയാളപ്പെടുത്തുക)

പോസ്റ്റീരിയർഫോസ ശസ്ത്രക്രിയയ്ക്ക് വിധേയരാകുന്ന രോഗികളിൽ ശസ്ത്രക്രിയയ്ക്കുമുമ്പ് തലച്ചോറിലെ രക്തപ്രവാഹത്തിന്റെ വേഗതയിലും തലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദത്തിലും സോഡിയം നൈട്രോപ്രൂസൈഡിന്റെ പ്രഭാവം (എസ്എൻപി) ട്രാൻസ്ക്രേനിയൽ ഡോപ്ളറും ഒപ്റ്റിക് നെർവ് ഷീത്ത് ഡയമീറ്റും ഉപയോഗിച്ച് വിലയിരുത്തൽ - 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 sodium nitroprusside (SNP) on cerebral blood flow velocity and intracranial pressure using Transcranial doppler sonography and Optic nerve sheath diameter in postoperative patients undergoing posterior fossa surgeries – a prospective observational study

Name of the Investigators:

Dr. Revikrishnan S (PI), Dr.Smita V (Guide and CO-PI), Dr.Ranganatha Praveen C S. (Co guide and CO-PI).

You are being requested to participate in the above titled study which is being conducted to evaluate the effect of sodium nitroprusside on the blood flow to the brain and the pressure inside the brain. The changes in the blood flow to the brain as well as pressure changes in the brain will be estimated non-invasively by Transcranial Doppler. The intracranial pressure will be also measured non-invasively by optic nerve sheath diameter (ONSD) using ultrasound.

We have planned to recruit people with posterior fossa tumours posted for elective neurosurgical procedure at SCTIMST, Trivandrum.

What is Sodium nitroprusside (SNP)?

Sodium nitroprusside injection is used for acutely lowering of blood pressure in adults and children with high blood pressure. It acts by dilating the blood vessels in the body. It is routinely used in our institution for controlling high blood pressure in the postoperative period.

What is Transcranial Doppler?

Transcranial Doppler (TCD) is an ultrasound that detects blood flow in the brain's major arteries when applied to the sides of head. It is routinely performed, safe, non-invasive and requires little to no special preparation.

What is ONSD?

The optic nerve sheath is a covering around optic nerve which is an extension of the covering from the brain. Any pressure rise within the brain causes corresponding changes in the optic nerve sheath diameter. This is measured with the help of ultrasound machine placed over the patients eyelids. It is routinely performed and is safe and non-invasive.

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

On the day before surgery, your vital parameters viz. heart rate, blood pressure and oxygen saturation will be recorded. On the day of surgery, you will be taken inside the Operation Theatre. All routine non invasive monitors to check your heart rate, blood pressure and oxygen saturation level will be attached. The blood flow to your brain as well as the pressure inside your brain will be estimated using TCD and ONSD after which you will be administered with general anesthesia. On completion of the surgery, your cerebral blood flow and intracranial pressure will again be estimated by TCD and ONSD. If SNP has to be started in the postoperative period for blood pressure control, TCD and ONSD will be done to look for changes in blood flow to the brain as well as pressure changes in your brain. TCD and ONSD measurements will be again taken after 12 hours of starting sodium nitroprusside or when the SNP infusion is stopped.

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.

What will happen if you develop any study related injury?

We do not expect any injury to happen to you since the anaesthesia technique and monitoring tools would be same even if you were not part of the study. But if you do develop any side effects or problems due to the study, the side effects will be treated at no cost to you. We are unable to provide any monetary compensation, however.

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

These are used as a part of anaesthesia procedure for surgery. No additional charges will be incurred for participating in the study.

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.

When you read this information, your treating doctor will be available to discuss and answer any questions you may have. If you have any queries please contact:

Dr Revikrishnan S

Senior Resident, Division of Neuroanaesthesiology, Department of Anaesthesiology
Sree Chitra Tirunal Institute for Medical Sciences and Technology Tel: +91
9895911697, Email: revikrishnan@sctimst.ac.in

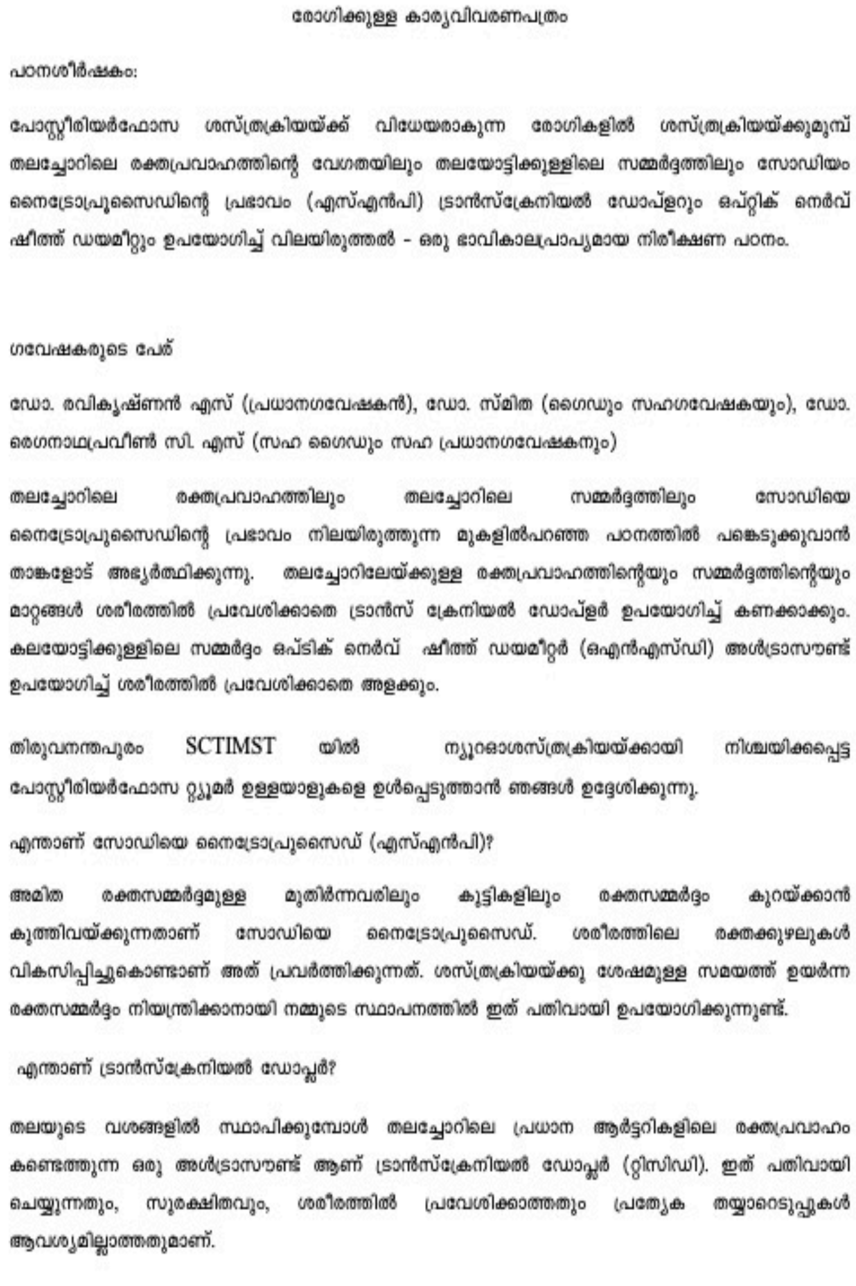
If you have any questions, concerns or complaints about the research please contact:

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

Patient Information Form (Malayalam)



രോഗിക്കുള്ള കാര്യവിവരണപത്രം

പഠനശീർഷകം:

പോസ്റ്റീരിയർഫോസ ശസ്ത്രക്രിയയ്ക്ക് വിധേയരാകുന്ന രോഗികളിൽ ശസ്ത്രക്രിയയ്ക്കുമുമ്പ് തലച്ചോറിലെ രക്തപ്രവാഹത്തിന്റെ വേഗതയിലും തലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദത്തിലും സോഡിയം നൈട്രോപ്രൂസൈഡിന്റെ പ്രഭാവം (എസ്എൻപി) ട്രാൻസ്ക്രേനിയൽ ഡോപ്ളറും ഒപ്റ്റിക് നെർവ് ഷീത്ത് ഡയമീറ്റും ഉപയോഗിച്ച് വിലയിരുത്തൽ - ഒരു ഭാവികാലപ്രാപ്യമായ നിരീക്ഷണ പഠനം.

ഗവേഷകരുടെ പേര്

ഡോ. രവികൃഷ്ണൻ എസ് (പ്രധാനഗവേഷകൻ), ഡോ. സ്മിത (ഗൈഡും സഹഗവേഷകയും), ഡോ. രെഗനാഥപ്രവീൺ സി. എസ് (സഹ ഗൈഡും സഹ പ്രധാനഗവേഷകനും)

തലച്ചോറിലെ രക്തപ്രവാഹത്തിലും തലച്ചോറിലെ സമ്മർദ്ദത്തിലും സോഡിയെ നൈട്രോപ്രുസൈഡിന്റെ പ്രഭാവം നിലയിരുത്തുന്ന മുകളിൽപറഞ്ഞ പഠനത്തിൽ പങ്കെടുക്കുവാൻ താങ്കളോട് അഭ്യർത്ഥിക്കുന്നു. തലച്ചോറിലേയ്ക്കുള്ള രക്തപ്രവാഹത്തിന്റെയും സമ്മർദ്ദത്തിന്റെയും മാറ്റങ്ങൾ ശരീരത്തിൽ പ്രവേശിക്കാതെ ട്രാൻസ് ക്രേനിയൽ ഡോപ്ളർ ഉപയോഗിച്ച് കണക്കാക്കും. കലയോട്ടിക്കുള്ളിലെ സമ്മർദ്ദം ഒപ്ടിക് നെർവ് ഷീത്ത് ഡയമീറ്റർ (ഒഎൻഎസ്ഡി) അൾട്രാസൗണ്ട് ഉപയോഗിച്ച് ശരീരത്തിൽ പ്രവേശിക്കാതെ അളക്കും.

തിരുവനന്തപുരം SCTIMST യിൽ ന്യൂറോശസ്ത്രക്രിയയ്ക്കായി നിശ്ചയിക്കപ്പെട്ട പോസ്റ്റീരിയർഫോസ റ്റ്യൂമർ ഉള്ളയാളുകളെ ഉൾപ്പെടുത്താൻ ഞങ്ങൾ ഉദ്ദേശിക്കുന്നു.

എന്താണ് സോഡിയെ നൈട്രോപ്രൂസൈഡ് (എസ്എൻപി)?

അമിത രക്തസമ്മർദ്ദമുള്ള മുതിർന്നവരിലും കുട്ടികളിലും രക്തസമ്മർദ്ദം കുറയ്ക്കാൻ കുത്തിവയ്ക്കുന്നതാണ് സോഡിയെ നൈട്രോപ്രൂസൈഡ്. ശരീരത്തിലെ രക്തക്കുഴലുകൾ വികസിപ്പിച്ചുകൊണ്ടാണ് അത് പ്രവർത്തിക്കുന്നത്. ശസ്ത്രക്രിയയ്ക്കു ശേഷമുള്ള സമയത്ത് ഉയർന്ന രക്തസമ്മർദ്ദം നിയന്ത്രിക്കാനായി നമ്മുടെ സ്ഥാപനത്തിൽ ഇത് പതിവായി ഉപയോഗിക്കുന്നുണ്ട്.

എന്താണ് ട്രാൻസ്ക്രേനിയൽ ഡോപ്ലർ?

തലയുടെ വശങ്ങളിൽ സ്ഥാപിക്കുമ്പോൾ തലച്ചോറിലെ പ്രധാന ആർട്ടറികളിലെ രക്തപ്രവാഹം കണ്ടെത്തുന്ന ഒരു അൾട്രാസൗണ്ട് ആണ് ട്രാൻസ്ക്രേനിയൽ ഡോപ്ലർ (റ്റിസിഡി). ഇത് പതിവായി ചെയ്യുന്നതും, സുരക്ഷിതവും, ശരീരത്തിൽ പ്രവേശിക്കാത്തതും പ്രത്യേക തയ്യാറെടുപ്പുകൾ ആവശ്യമില്ലാത്തതുമാണ്.

എന്താണ് ഒഎൻഎസ്ഡി

ഒപ്റ്റിക് നെർവിനുചുറ്റും പൊതിഞ്ഞിരിക്കുന്ന തലച്ചോറിൽനിന്നു വ്യപിക്കുന്ന ഒരു കവചമാണ് ഒപ്റ്റിക് നെർവ് ഷീത്ത്. തലച്ചോറിലെ ഏത് സമ്മർദ്ദ വർദ്ധനവും ഒപ്റ്റിക് നെർവ് ഷീത്തിന്റെ വ്യസത്തിൽ അതിനനുസരിച്ചുള്ള മാറ്റമുണ്ടാക്കും. ഇത് രോഗിയുടെ കൺപോളകളിൽ അൾട്രാസൗണ്ട് യന്ത്രം ഘടിപ്പിച്ച് അളക്കും. ഇത് പതിവായി ചെയ്യുന്നതും, സുരക്ഷിതവും, ശരീരത്തിൽ പ്രവേശിക്കാത്തതുമാണ്.

താങ്കൾ പങ്കെടുക്കുകയാണെങ്കിൽ എന്തു ചെയ്യണം

ശസ്ത്രക്രിയയ്ക്ക് ഒരു ദിവസം മുമ്പ്, താങ്കളുടെ ഹൃദയ മിടിപ്പ്, രക്തസമ്മർദ്ദം പ്രാണവായു പൂരിതാവസ്ഥ മുതലായ ജീവനപരമായ ഘടകങ്ങൾ രേഖപ്പെടുത്തും. ശസ്ത്രക്രിയാദിവസം, താങ്കളെ ശസ്ത്രക്രിയാമുറിയിൽ പ്രവേശിപ്പിക്കും. പൃദയമിടിപ്പ്, രക്തസമ്മർദ്ദം പ്രാണവായൂ പൂരിതാവസ്ഥ എന്നിവ പരിശോധിക്കുന്ന ശരീരത്തിൽ പ്രവേശിക്കാതെയുള്ള എല്ലാ പതിവ് നിരീക്ഷണ സംവിധാനങ്ങളും ബന്ധിപ്പിക്കും. റ്റിസിഡിയും ഒഎൽഎസ്ഡിയുമുപയോഗിച്ച് താങ്കളുടെ തലച്ചോറിലേയ്ക്കുള്ള രക്തപ്രവാഹവും തലച്ചോറിലെ സമ്മർദ്ദവും കണക്കാക്കും. അതിനുശേഷം താങ്കളെ പൊതുവായ മയക്കലിനുവിധേയമാക്കും. ശസ്ത്രക്രിയ പൂർത്തിയായയശേഷം റ്റിസിഡിയും ഒഎൽഎസ്ഡിയുമുപയോഗിച്ച് താങ്കളുടെ തലച്ചോറിലേയ്ക്കുള്ള രക്തപ്രവാഹവും തലച്ചോറിലെ സമ്മർദ്ദവും വീണ്ടും കണക്കാക്കും. ശസ്ത്രക്രിയയ്ക്കുശേഷം രക്തസമ്മർദ്ദം നിയന്ത്രിക്കാനായി എസ്എൻപി നൽകേണ്ടതായി വന്നാൽ, റ്റിസിഡിയും ഒഎൽഎസ്ഡിയും ഉപയോഗിച്ച് തലച്ചോറിലെ രക്തപ്രവാഹത്തിലും തലച്ചോറിലെ സമ്മർദ്ദത്തിലും മാറ്റം ഉണ്ടോയെന്ന് പരിശോധിക്കും. സോഡിയം നൈട്രോപ്രൂസൈഡ് നൽകി 12 മണിക്കൂറിനുശേഷമോ എസ്എൻപി നൽകുന്നത് നിർത്തിയശേഷമോ റ്റിസിഡി ഒഎൽഎസ്ഡി അളവുകൾ എടുക്കും.

പഠനമാരംഭിച്ചശേഷം താങ്കൾക്ക് 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.

പഠനവുമായി ബന്ധപ്പെട്ട് താങ്കൾക്ക് പരുക്കുകളെന്തെങ്കിലുമുണ്ടായാൽ എന്ത് സംഭവിക്കും.

താങ്കൾ പഠനത്തിൽ പങ്കെടുത്താലും ഇല്ലെങ്കിലും മയക്കൽ സങ്കേതവും, നിരീക്ഷണ ഉപകരണങ്ങളും ഒന്നുതന്നെയാകയാൽ പഠനത്തിന്റെ ഭാഗമായി ഒരു പരുക്കുമുണ്ടാകുമെന്ന് ഞങ്ങൾ പ്രതിക്ഷിക്കുന്നില്ല. പക്ഷേ താങ്കൾക്ക് എന്തെങ്കിലും പാർശ്വഫലങ്ങളോ പ്രശ്നങ്ങളോ പഠനംമൂലം ഉണ്ടായാൽ അവ താങ്കൾക്ക് ചിലവുണ്ടാകാതെ ചികിത്സിക്കും. എന്തങ്കിലും സാമ്പത്തിക നഷ്ടപരിഹാരം നൽകാൻ ഞങ്ങൾക്കാവില്ല.

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. എന്നിരുന്നാലും, താങ്കൾ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിക്കുകയാണെങ്കിൽ താങ്കളുടെ ചികിത്സാരേഖകൾ പഠനവുമായി ബന്ധപ്പെട്ടവർ താങ്കളുടെ അധികമായ സമ്മതമില്ലതെ അവലോകനം ചെയ്തേക്കാം.

താങ്കൽ ഈ വിവരങ്ങൾ വയിക്കുമ്പോൾ താങ്കളെ ചികിത്സിക്കുന്ന ഡോക്ടർ താങ്കൾക്കുണ്ടാകുന് ഏത് ചോദ്യത്തിനും ഉത്തരം നൽകാൻ സന്നിഹിതമായിരിക്കും. താങ്കൾക്ക് ചോദ്യങ്ങളുണ്ടെങ്കിൽ ബന്ധപ്പെടുക
ഡോ. രവികൃഷ്ണൻ എസ്
സീനിയർ റസിഡന്റ്, ന്യൂറോഅനസ്തിഷ്യോളജി വിഭാഗം, അനസ്തീഷ്യോളജി ഡിപ്പാർട്ട്മെന്റ്

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി,
തിരുവനന്തപുരം, ഫോൺ: 91 9895911697ഇമെയിൽ: revikrishnan@sctimst.ac.in

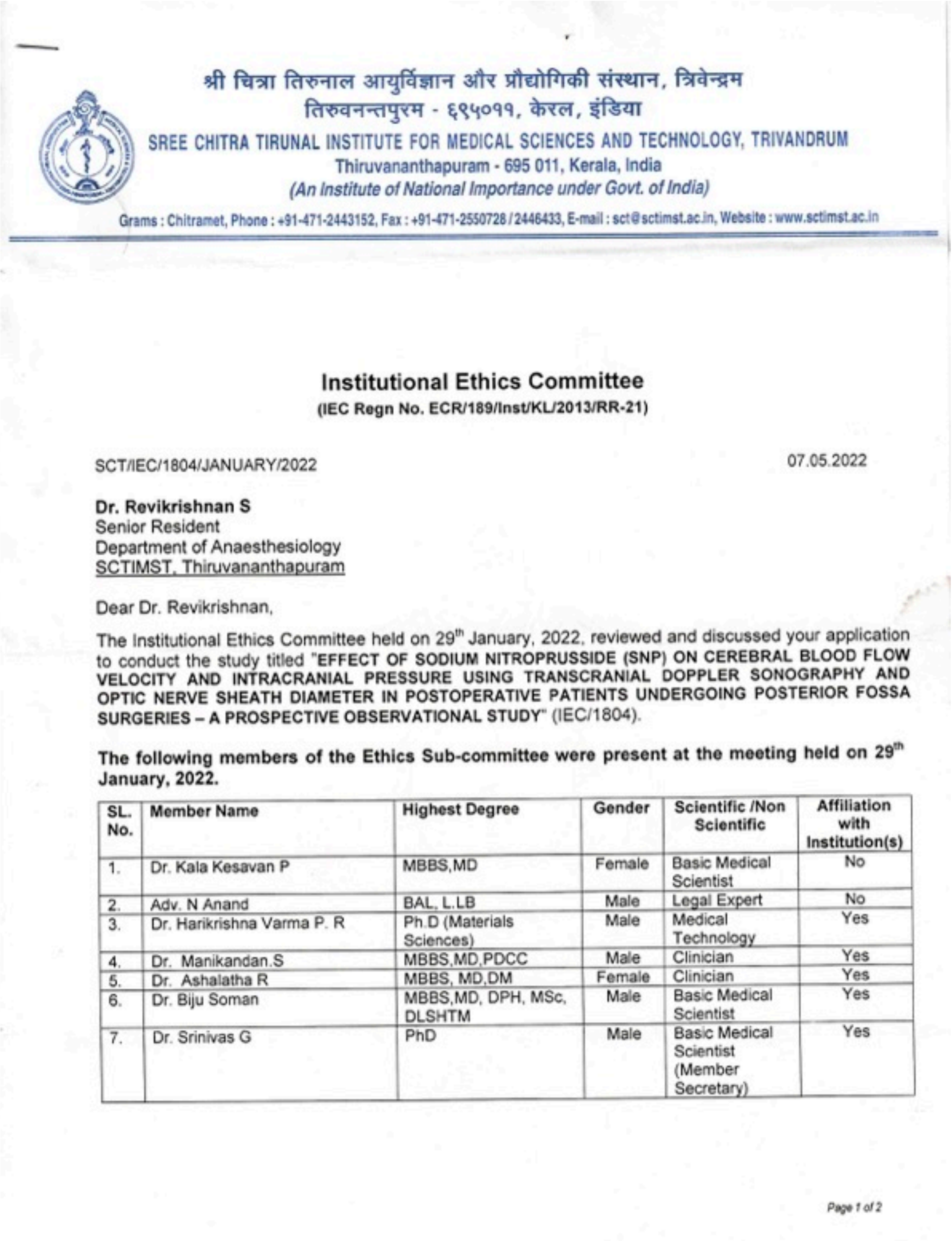
ഗവേഷണത്തെപ്പറ്റി ചോദ്യങ്ങളോ, ഉത്കണ്ഠകളോ, പരാതികളോ ഉണ്ടെങ്കിൽ ജയവായി ബന്ധപ്പെടുക

ഡോ. ശ്രീനിവാസ് ജി

മെമ്പർ സെക്രട്ടറി

ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മറ്റി

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി, ഫോൺ: 0471-2524689ഇമെയിൽ: iec.mem.sec@sctimst.ac.in



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

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

SCT/IEC/1804/JANUARY/2022

07.05.2022

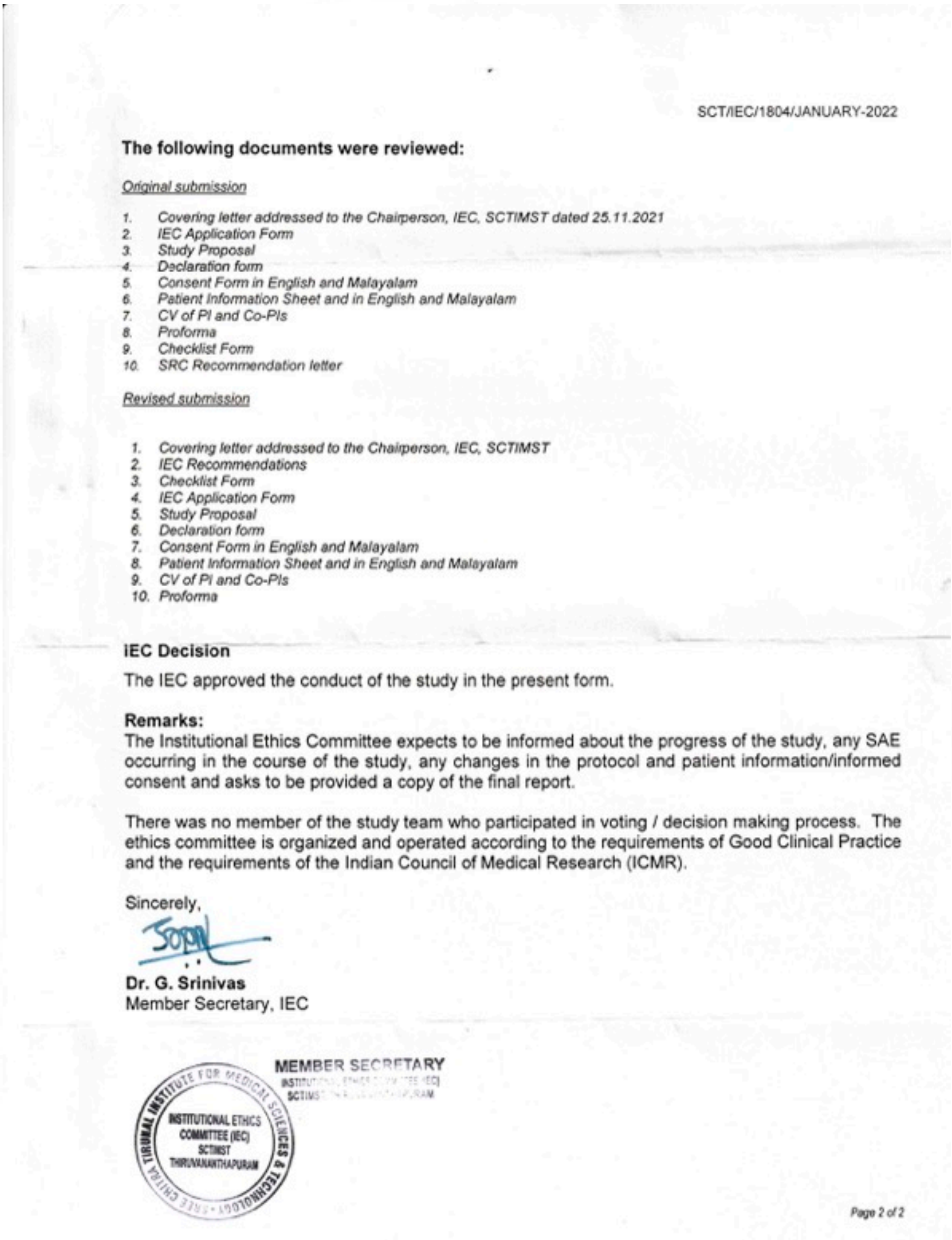
Dr. Revikrishnan S
Senior Resident
Department of Anaesthesiology
SCTIMST, Thiruvananthapuram

Dear Dr. Revikrishnan,

The Institutional Ethics Committee held on 29th January, 2022, reviewed and discussed your application to conduct the study titled "**EFFECT OF SODIUM NITROPRUSSIDE (SNP) ON CEREBRAL BLOOD FLOW VELOCITY AND INTRACRANIAL PRESSURE USING TRANSCRANIAL DOPPLER SONOGRAPHY AND OPTIC NERVE SHEATH DIAMETER IN POSTOPERATIVE PATIENTS UNDERGOING POSTERIOR FOSSA SURGERIES – A PROSPECTIVE OBSERVATIONAL STUDY**" (IEC/1804).

The following members of the Ethics Sub-committee were present at the meeting held on 29th January, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
3.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
4.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
5.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
6.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes



SCT/IEC/1804/JANUARY-2022

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 25.11.2021*
2. *IEC Application Form*
3. *Study Proposal*
4. *Declaration form*
5. *Consent Form in English and Malayalam*
6. *Patient Information Sheet and in English and Malayalam*
7. *CV of PI and Co-PIs*
8. *Proforma*
9. *Checklist Form*
10. *SRC Recommendation letter*

Revised submission

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

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

INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

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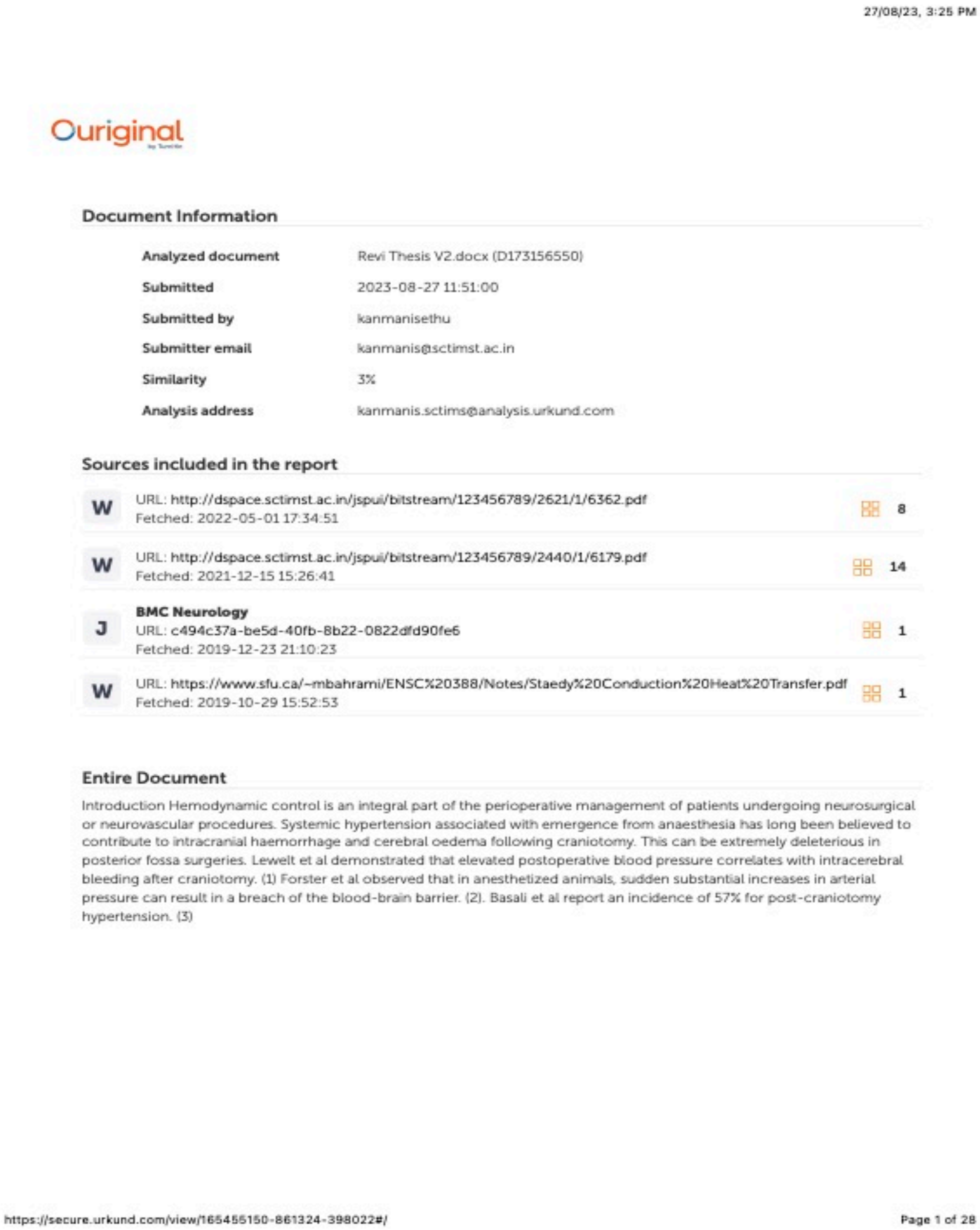

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Analysis address	kanmanis.sctims@analysis.urkund.com

Sources included in the report

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W	URL: http://dspace.sctimst.ac.in/jspui/bitstream/123456789/2440/1/6179.pdf Fetched: 2021-12-15 15:26:41	14
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Introduction Hemodynamic control is an integral part of the perioperative management of patients undergoing neurosurgical or neurovascular procedures. Systemic hypertension associated with emergence from anaesthesia has long been believed to contribute to intracranial haemorrhage and cerebral oedema following craniotomy. This can be extremely deleterious in posterior fossa surgeries. Lewelt et al demonstrated that elevated postoperative blood pressure correlates with intracerebral bleeding after craniotomy. (1) Forster et al observed that in anesthetized animals, sudden substantial increases in arterial pressure can result in a breach of the blood-brain barrier. (2). Basali et al report an incidence of 57% for post-craniotomy hypertension. (3)

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					HR			MAP			SPO2			PaCO2			MCA PSV			MCA EDV			MCA MFV			PI			ICP			RI			CVRi			THRR			ONSD		
Sl No	Age	Gender	Diagnosis	ASA Grade	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
1	29	F	RT VESTIBUL	1	85	98	90	100	91	93	100	100	100	35.70	38.00	38.20	59.90	53.10	54.90	27.77	25.86	28.09	30.60	27.83	28.44	1.05	1.04	0.99	10.19	10.08	9.54	0.54	0.55	0.54	3.27	3.48	3.27	1.24	1.24	1.23	4.80	4.80	4.70
2	49	M	RT CP ANGL	2	84	88	85	95	87	87	100	100	100	38.10	37.90	38.30	74.50	78.50	71.70	26.86	32.84	30.60	55.40	50.73	50.73	0.86	0.90	0.81	8.12	8.56	7.57	0.64	0.60	0.57	1.71	1.71	1.71	1.18	1.15	1.14	4.40	4.50	4.50
3	59	M	RT TRIGEMI	2	56	74	80	118	108	101	100	100	100	39.00	37.00	39.00	56.30	52.20	51.90	15.97	9.87	11.68	37.00	33.86	31.67	1.09	1.25	1.27	10.63	12.38	12.60	0.72	0.78	0.66	3.19	3.19	3.19	1.19	1.12	1.14	4.90	5.10	5.00
4	53	M	RT CP ANGL	2	70	84	77	103	91	92	100	100	100	37.00	38.00	38.00	91.80	84.00	82.60	46.68	42.89	39.78	70.50	62.29	62.97	0.64	0.66	0.68	5.70	5.90	6.20	0.49	0.61	0.50	1.46	1.46	1.46	1.20	1.18	1.18	3.90	3.90	4.10
5	65	M	LT CP ANGLE	2	63	85	90	120	111	99	100	99	99	36.20	39.20	39.70	61.80	53.00	49.80	29.49	23.45	26.99	35.90	33.21	29.62	0.90	0.89	0.77	8.56	8.44	7.13	0.60	0.56	0.53	3.34	3.34	3.34	1.23	1.18	1.20	4.50	4.40	4.20
6	23	M	RT CP ANGL	1	94	98	105	105	91	87	100	100	99	35.70	35.70	37.00	92.50	70.40	73.70	58.08	36.98	42.13	45.90	39.78	38.03	0.75	0.84	0.83	6.92	7.90	7.80	0.55	0.41	0.47	2.29	2.29	2.29	1.33	1.30	1.30	4.20	4.30	4.30
7	54	M	CREBELLAR	2	83	100	104	110	94	96	100	100	100	38.20	39.40	38.70	50.40	40.80	44.60	23.44	18.31	23.31	32.10	27.43	28.01	0.84	0.82	0.76	7.90	7.70	7.30	0.53	0.54	0.53	3.43	3.43	3.43	1.27	1.26	1.27	3.80	3.90	3.90
8	53	M	RT CP ANGL	2	68	86	90	104	91	97	100	100	100	37.00	37.00	36.00	48.10	47.20	45.40	21.46	22.14	13.10	33.30	29.14	31.06	0.80	0.86	1.04	7.46	8.12	10.08	0.55	0.56	0.64	3.12	3.12	3.12	1.26	1.27	1.21	4.10	4.10	4.20
9	49	F	LT CEREBELL	1	80	98	90	112	98	93	100	100	100	39.00	36.00	38.00	95.10	89.40	90.10	51.53	51.78	55.85	58.10	50.84	48.24	0.75	0.74	0.71	6.92	6.81	6.48	0.51	0.50	0.53	1.93	1.93	1.93	1.18	1.15	1.16	3.70	3.70	3.80
10	40	F	RT VESTIBUL	1	70	87	88	119	106	101	99	99	99	36.40	35.20	38.20	48.10	47.20	45.40	21.46	24.06	22.79	33.30	29.66	28.26	0.80	0.78	0.80	7.46	7.24	7.46	0.55	0.50	0.49	3.57	3.57	3.57	1.20	1.19	1.22	4.20	4.20	4.20
11	20	F	LT CP ANGLE	1	82	92	87	99	91	90	100	100	100	36.10	38.60	38.50	69.60	74.20	70.70	45.66	54.60	49.83	32.80	30.15	29.82	0.73	0.65	0.70	6.10	5.90	6.40	0.39	0.38	0.36	3.02	3.02	3.02	1.25	1.14	1.21	4.00	4.00	4.10
12	32	M	RT CEREBELL	1	80	85	82	104	95	95	100	99	100	37.40	39.20	39.00	86.20	77.70	70.10	37.99	31.88	38.07	48.70	44.49	44.49	0.99	1.03	0.72	9.54	9.80	6.60	0.60	0.63	0.50	2.14	2.14	2.14	1.24	1.22	1.23	4.70	4.70	4.52
13	54	F	LT TRIGEMIN	2	82	90	94	114	104	106	99	100	99	38.70	37.60	36.50	48.60	45.70	49.20	17.28	20.61	21.85	38.20	34.85	35.52	0.82	0.72	0.77	7.50	6.90	7.20	0.52	0.58	0.58	2.98	2.98	2.98	1.30	1.26	1.28	4.30	4.20	4.20
14	37	M	LT CP ANGLE	1	75	84	78	115	103	108	100	100	100	38.10	37.50	37.00	93.30	80.20	76.40	48.34	47.03	36.16	52.90	47.38	49.68	0.85	0.70	0.81	8.02	7.35	8.12	0.55	0.53	0.53	2.17	2.17	2.17	1.20	1.23	1.19	3.90	4.20	4.00
15	57	F	LT CP ANGLE	2	80	94	94	119	108	107	100	100	100	40.00	38.20	39.30	99.10	80.40	82.70	44.11	32.62	36.41	58.50	53.09	52.60	0.94	0.90	0.88	8.90	8.60	8.30	0.55	0.58	0.60	2.03	2.03	2.03	1.29	1.26	1.24	4.60	4.30	4.50
16	49	F	SOLITARY CE	2	66	80	84	105	96	97	100	100	100	35.10	36.60	36.80	66.80	61.50	59.40	32.64	27.14	27.05	42.70	39.04	39.45	0.80	0.88	0.82	7.50	8.30	7.70	0.51	0.62	0.58	2.46	2.46	2.46	1.22	1.18	1.20	3.80	3.80	4.00
17	45	F	LT TRIGEMIN	2	62	78	74	113	104	102	99	100	100	37.90	38.50	38.10	72.50	64.90	60.40	38.30	31.57	26.35	50.30	46.29	45.40	0.68	0.72	0.75	6.20	6.60	6.90	0.47	0.54	0.57	2.25	2.25	2.25	1.16	1.15	1.20	3.90	4.00	4.00
18	38	M	LT VESTIBUL	1	76	88	82	114	99	98	100	100	100	39.40	38.10	39.00	75.90	66.80	63.90	47.72	37.62	33.61	54.20	47.07	46.59	0.52	0.62	0.65	5.30	5.50	5.80	0.43	0.48	0.53	2.10	2.10	2.10	1.14	1.17	1.14	3.60	3.60	3.80
19	63	M	LT POST FOS	2	60	74	77	118	108	110	100	100	100	35.50	37.80	36.50	83.70	72.30	74.50	39.64	36.71	39.46	64.80	59.31	60.41	0.68	0.60	0.58	6.20	5.30	5.20	0.52	0.51	0.49	1.82	1.82	1.82	1.20	1.20	1.18	4.00	3.80	4.00
20	30	M	RT VESTIBUL	1	58	70	68	107	90	92	100	100	100	36.60	38.30	35.80	90.90	72.50	66.90	49.32	45.02	36.26	59.40	49.96	51.07	0.70	0.55	0.60	6.20	4.80	5.30	0.46	0.42	0.50	1.80	1.80	1.80	1.16	1.15	1.14	3.60	3.60	3.60
21	18	M	RT CEREBELL	1	68	80	78	111	99	102	100	100	100	37.50	38.20	38.00	72.80	77.40	75.80	35.69	45.59	43.47	48.20	42.99	44.29	0.77	0.74	0.73	4.21	4.14	4.12	0.51	0.45	0.47	2.30	2.30	2.30	1.17	1.15	1.16	4.20	4.10	4.10
22	63	F	RT TRIGMIN	2	76	88	90	129	111	109	99	99	98	39.20	36.80	37.40	68.80	71.10	70.50	26.00	35.17	36.54	52.20	44.92	44.11	0.82	0.80	0.77	4.30	4.20	4.20	0.62	0.52	0.53	2.47	2.47	2.47	1.19	1.21	1.23	4.30	4.20	4.20
23	54	M	LT TRIGEMIN	2	58	70	76	117	106	107	100	99	99	35.20	38.70	39.00	60.20	63.20	62.50	34.56	40.66	38.71	37.70	34.16	34.48	0.68	0.66	0.69	6.30	6.00	6.20	0.42	0.37	0.38	3.10	3.10	3.10	1.22	1.24	1.21	4.00	3.90	4.00
24	33	F	RT VESTIBUL	1	74	90	90	111	101	104	100	99	100	38.30	39.10	39.00	80.20	78.60	83.50	37.26	40.29	42.48	42.10	38.31	39.45	1.02	1.00	1.04	9.90	9.70	10.10	0.53	0.51	0.55	2.64	2.64	2.64	1.25	1.20	1.19	4.80	4.70	4.80
25	38	F	LT CP ANGL	2	82	96	90	110	99	96	100	99	100	37.40	36.20	39.10	90.60	92.60	88.00	36.88	42.55	41.67	63.20	56.88	55.16	0.85	0.88	0.84	8.00	8.30	7.90	0.59	0.62	0.57	1.74	1.74	1.74	1.17	1.20	1.16	4.30	4.40	4.40
26	50	F	LT CEREBELL	2	80	102	98	113	98	99	99	97	98	35.20	35.70	36.10	50.20	55.60	55.00	21.02	28.98	28.44	37.90	32.87	33.20	0.77	0.81	0.80	7.10	7.50	7.40	0.58	0.54	0.54	2.98	2.98	2.98	1.24	1.22	1.25	4.20	4.30	4.30
27	39	F	LT CP ANGLE	2	90	94	88	108	98	96	100	100	100	37.90	36.40	38.10	70.20	66.50	65.30	30.69	30.25	30.96	43.90	39.84	39.02	0.90	0.91	0.88	8.56	8.67	8.34	0.56	0.56	0.54	2.46	2.46	2.46	1.18	1.22	1.25	4.50	4.50	4.40
28	45	M	CEREBELLAR	2	62	70	62	119	109	110	100	98	99	35.20	37.60	35.60	90.70	86.80	85.20	47.21	45.31	43.88	60.40	55.32	55.83	0.72	0.75	0.74	4.10	4.17	4.15	0.48	0.51	0.51	1.97	1.97	1.97	1.23	1.28	1.28	4.10	4.20	4.10
29	63	M	LT TRIGEMIN	2	70	68	71	115	104	102	100	100	100	39.40	36.80	37.20	66.50	70.30	65.00	34.12	39.48	34.39	42.60	38.53	37.78	0.76	0.80	0.81	7.03	7.46	7.57	0.49	0.42	0.44	2.70	2.70	2.70	1.19	1.16	1.22	4.20	4.30	4.30
30	64	M	LT TRIGEMIN	2	76	82	78	109	98	100	100	99	99	37.90	35.50	35.60	80.70	85.30	78.80	32.44	40.08	34.99	50.80	45.67	46.61	0.95	0.99	0.94	9.10	9.50	9.00	0.59	0.57	0.57	2.15	2.15	2.15	1.21	1.26	1.23	4.60	4.70	4.70
31	28	M	RT CP ANGL	1	56	70	66	105	96	96	100	100	100	38.50	39.00	39.50	58.90	60.70	61.20	24.36	28.51	29.62	32.90	30.08	30.08	1.05	1.07	1.05	10.19	10.41	10.20	0.58	0.54	0.53	3.19	3.19	3.19	1.14	1.17	1.13	4.80	4.80	4.80

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