Serial Assessment of Hemodynamic and Cerebrovascular Changes after Administration of Mannitol in Intensive Care Unit in Postoperative Neurosurgical patients - A Combined Transthoracic Echocardiographic and Transcranial Doppler Study

Thesis submitted for the partial fulfilment for the requirement of the degree of DM Neuroanesthesia

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DECLARATION

I hereby declare that this thesis entitled "**Serial Assessment of Hemodynamic and Cerebrovascular Changes after Administration of Mannitol in Intensive Care Unit in Postoperative Neurosurgical patients—A Combined Transthoracic Echocardiographic and Transcranial Doppler Study"** has been prepared by me under the able guidance of Prof. Manikandan S, Division Of Neuroanaesthesia, Department Of Anaesthesiology, at Sree Chitra Tirunal Institute For Medical Sciences & Technology, Thiruvananthapuram.

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The secret of getting ahead is getting started.....

Mark Twain

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CONTENTS

LIST OF ABBREVIATIONS

BBB	Blood brain barrier
CBV	Cerebral blood flow
CPP	Cerebral perfusion pressure
CO	Cardiac output
EF	Ejection fraction
ESV	End systolic volume
EDV	End diastolic volume
HR	Heart rate
ICP	Intracranial pressure
LVIDs	Left ventricle internal diameter in systole
LVIDd	Left ventricular internal diameter in diastole
mFV	Mean flow velocity
MCA	Middle cerebral artery
PSV	Peak systolic velocity
PI	Pulsatality index
RI	Resistivity index
SV	Stroke volume
SPECT	Single photon emission computed tomography
TTE	Transthoracic echocardiography
TCCD	Transcranial color duplex

INTRODUCTION

Mannitol is used routinely in neurosurgical unit to reduce intracranial pressure. Management of intracranial pressure is a key component of perioperative management. Experiments and clinical trials have shown that mannitol can attenuate the brain oedema, decrease the intra cranial pressure, and improve the cerebral perfusion. Mannitol is an hyperosmolar agent that extracts water from brain extracellular spaces into the intravascular compartment by altering the osmotic pressure between blood and brain.[1] This increase in intravascular volume can cause significant changes in cardiac output, stroke volume, and blood pressure. Mannitol also alters the rheology, leading to increased cerebral blood flow velocity. Irrespective of the pathology causing increased intracranial pressure and cerebral edema mannitol is used to reduce cerebral blood volume.

Major neurosurgical procedures cause considerable physiological brain insult with significant morbidity and mortality. Up to 20% of patients who undergo craniotomy develop increased intra cranial pressure and hence anti oedema measures are started in the postoperative period. Mannitol causes various circulatory effects altering stroke volume, cardiac output. A bolus infusion of mannitol increases the CO, arterial pressure and cerebral perfusion pressure. Cardiac output rises upto 30% and increases the cerebral blood flow.[2] Transient hypotension is seen after bolus administration whereas fluid overload and pulmonary oedema is seen as delayed effect of mannitol. These changes may not cause significant effect in patients with normal cardiac function but considered detrimental in patients with poor cardiac status. Hence it is necessary to quantify these changes and take appropriate steps to maintain stable haemodynamics. Hemodynamic changes caused by mannitol reflects upon cerebral haemodynamics. Transient hypotension caused by mannitol will reduce cerebral perfusion pressure (mean arterial pressure – intracranial pressure) which further aggravates secondary brain injury.

Conventional hemodynamic variables, such as blood pressure, heart rate, central venous pressure are insensitive and delayed predictors of diminishing circulating blood volume. Following infusion of mannitol during surgeries for the abdominal aorta aneurysm, Sharapova and Vlaikov observed a 12% increase in Cardiac output and lowering of total peripheral resistance of vessels by 11%.[3]

Camishion and Fishman noted similar results with increase in cardiac output by 10% to 35% in normotensive dogs and a significantly greater increase by 46% to 163% in hypotensive dogs.[4] All these are single point measurements with no particular regard to the time course of these changes. Nikki et al observed an increase in stroke volume, cardiac output, and cardiac index transiently after mannitol infusion.[5]

Hemodynamic changes correlates with the changes in cerebral blood flow velocities. Mannitol administration causes cerebral vasoconstriction in distal pial arteries. But alteration in blood rheology improves the cerebral blood flow and by virtue of its osmotic property, it further reduces the brain bulk. Quanlu Wang evaluated the effect of different doses of mannitol on cerebral blood flow velocities in the infarcted hemisphere and compared with non-infarcted hemisphere in stroke patients.[6] Mannitol significantly improved cerebral blood flow and decrease intracranial pressure, in the affected hemisphere of patient with acute large cerebral infarct. This study did not emphasise on cardiovascular effects of mannitol.

Substantial number of studies have evaluated hemodynamic changes after single bolus dose of mannitol in the intraoperative period using thoracic bioimpedance and transesophageal echocardiography. Changes in the cerebral blood flow velocities which exist in the background of hemodynamic changes and as well by the direct action of mannitol on cerebral blood vessels have not been measured. Similarly, studies have employed transcranial Doppler to study the effects of mannitol on cerebral blood flow but did not mention corresponding changes in cardiac output and stroke volume. Apparently no studies have combined these two scenarios to determine the temporal effect of mannitol. At present we could not find studies which investigates the correlation between cerebral and cardiac effects of mannitol in pathological states.

To study the cardiovascular changes produced by mannitol we employed transthoracic echocardiography (TTE). Transthoracic echocardiography is a non-invasive imaging modality routinely used in bedside ICU setting to assess intravascular volume status, contractility of the heart and also fluid responsiveness. Apart from providing information about dynamic indices also helps to identifies structural abnormalities, regional wall motion abnormalities.

Transcranial Doppler is used to assess cerebral blood flow changes following mannitol administration. A 2-MHz pulse-wave Doppler probe is placed on the temporal window, peak systolic velocity (PSV), end diastolic velocity (EDV), mean velocity (Vm) of bilateral middle cerebral arteries before, and at different time points after mannitol infusion is recorded. Combining these two modalities would be ideal to measure the cardiovascular and cerebrovascular effects of mannitol.

PHARMACOLOGY OF MANNITOL

Wise and Carta reported the use of mannitol as a diuretic in 1962, demonstrated several beneficial effects of mannitol.[7] Mannitol is a 6 carbon alcohol with a molecular weight of 183kDa. Prepared by reduction of dextrose. It is available at the concentration of 5%g/100ml to 20%g/100ml with an osmolarity between 274 and 1372 mosm/l.[2]

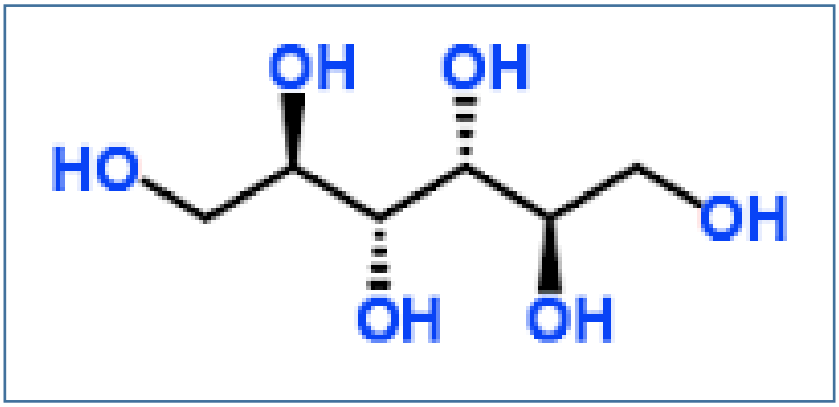

Figure . 1. Structural formula of mannitol

It is filtered at the glomeruli and reabsorbed in the nephron, and excreted unchanged. It has plasma half-life is 2.2-2.4h, onset of action within 15 to 20 minutes. Maximum effect on the brain occurs at 30minutes after administration and lasts for 90 minutes to 6 hours. Primary mechanism of action of mannitol is by increasing the osmotic gradient through the blood brain barrier, causes water to move out to extracellular spaces. This osmotic effect of mannitol reduces the cerebral oedema, improves cerebral blood flow, increases oxygen consumption and decreases cerebral spinal fluid pressure.[8] Mannitol is an effective way to reduce ICP. Bolus of mannitol produces increase in intravascular volume and increase in blood pressure which leads to autoregulatory vasoconstriction reducing the cerebral blood volume. Second mechanism by which mannitol acts is by altering the blood rheology. Mannitol administration causes constriction of both arterioles and venules on the surface of the brain. Reducing the blood viscosity increasing the red cell deformability

improves oxygen delivery, reflex vasoconstriction and fall in CBV. This effect is independent of any changes in the haematocrit due to haemodilution.

There is no ICP threshold above which mannitol is indicated. Rosner et al demonstrated that when ICP>30 and CPP<70 mannitol produced greater decrease in ICP.[9] There is no fixed dose of mannitol for ICP reduction. Long lasting response is seen at the dose between 0.5 and 1.4g/kg is administered. Mannitol also has several cardiovascular effects. Rapid administration of mannitol causes transient arterial hypotension. It leads to reduced afterload with transient increase in preload improving the cardiac output. The significant risk associated with the use of mannitol include electrolyte abnormalities, pulmonary oedema, acidosis, acute renal failure, congestive cardiac failure.[10]

Class 3 evidence exists for use of mannitol in intracranial hypertension during impending herniation as assessed by signs and symptoms.[11] The significant risk associated with mannitol is rebound phenomenon with increased ICP. The loss of BBB continuity has been demonstrated leads to decreasing gradient and accumulation of mannitol in the tissues leading to aggravation of ICP, that may eventually be reverted.[12] The electrolyte abnormality seen with repeated mannitol administration is raised osmolarity, hypernatremia, hypokalaemia. Highest rate of hyper osmolarity occurs on the first day of mannitol administration and that subsequently its rate reduced, although it still remains high.[13] Mannitol becomes less effective with repeated doses. Multiple doses of mannitol leads to unacceptably high serum sodium and osmolarity that is associated with neurological complications, including osmotic demyelination syndromes.[1]

REVIEW OF LITERATURE

The brain utilizes about 20% of available oxygen for its normal function making it vulnerable even for a short periods of reduced blood flow. Tight regulation of blood flow and oxygen supply is of utmost priority for survival of the brain. The adult brain constitutes about 2% of body weight derives about 15% of cardiac output with 20% of total body oxygen consumption. With the high metabolic rate of oxygen consumption, neurones produce ATP almost entirely by oxidative metabolism with very limited capacity for anaerobic metabolism.[14] In the absence of oxygen, oxidative metabolism is abolished leading to irreversible cell injury and death. Hence adequate cerebral blood flow is very crucial for delivery of oxygen and substrates and to remove the waste products of metabolism. Normal cerebral blood flow is about 50ml/100gm/min. Perfusion of the brain is dependent on the pressure gradient between arteries and veins. This gradient is termed as (CPP) cerebral perfusion pressure. CPP is the difference between mean arterial pressure and ICP. CPP is affected by anything that affects MAP and ICP. Blood loss, dehydration, anesthetic drugs, vasodilatory drugs, diuretics all reduce MAP while intracranial pathologies like mass lesion, TBI, stroke, surgical induced brain injury increase ICP. When both reduced MAP and raised ICP co exists leads to a catastrophic fall in CPP causing ischaemia. The radius of arterial vessels is equally important in maintaining cerebral blood flow. Cerebral blood flow when modelled from physics implies that flow in a tube is laminar and uniform throughout the thin walled non distensible tubes.[15] This does not apply to larger blood vessels. Ohms law states that flow is proportional to the difference between in inflow and outflow pressure(ΔP) divided by the resistance to flow (R). In brain (ΔP) is the CPP[14] is estimated by Poiseuielles law that states flow is directly related to (ΔP), length of blood vessel, and inversely related to radius to fourth power. Flow= (8*n*L)/r.[4] Hence radius is the most powerful determinant of blood flow and even small changes in the diameter has significant effects on cerebral blood flow and it is by this mechanism vascular

resistance rapidly changes to alter global and regional cerebral blood flow. The brain requires a constant flow of blood over a range of pressures and this is achieved by the process of autoregulation. Autoregulation of cerebral blood flow is the ability of the brain to maintain relatively constant blood flow despite changes in perfusion pressure. In normotensive patients cerebral blood flow is maintained at ~50ml/100gm/min provided CPP is in the range of 60 to 160mmhg.Above and below this limit autoregulation is lost and cerebral blood flow becomes dependent on MAP in a linear manner. The stimulus for autoregulation is CPP and not MAP. In adults with normal ICP, CPP and MAP are very similar and CBF remains constant at a CPP of 60-160mmhg. Clearly the higher the ICP the more CPP deviates from MAP. At the lower limit of autoregulation, cerebral vasodilation is maximal, and below this level vessel collapse and CBF falls passively with the fall in MAP. At the upper limit of autoregulation, cerebral vasoconstriction is maximal and beyond this the elevated intraluminal pressure may force the vessels to dilate leading to increase in CBF and damage to BBB. Pressure autoregulation is impaired in many pathological conditions like tumour, subarachnoid haemorrhage, stroke or head injury.[16]

Sharma et al observed that large supratentorial tumour, midline shift of more than 5mm is associated with impaired autoregulation.[17] In these case Autoregulation is not restored within 24 hours following craniotomy. As mentioned earlier ICP is also an important determinant of CPP. The skull is a rigid box, containing blood and CSF. According to Monroe Kelly doctrine increase in the volume of one of these constituents there must be a compensatory decrease in volume of one or more of these remaining components otherwise ICP will increase tremendously.[18] Compensatory mechanism includes movement of CSF into spinal space, increased reuptake of CSF, compression of venous sinuses. Brain tumour, cerebral oedema secondary to trauma, infection, infarction, hyponatremia. Cerebral abscess, contusions increase the volume of brain tissue leading to raised ICP. As the ICP increases, CPP falls to a point where there is no cerebral blood flow, no perfusion leading to brain death. The aim of the management of raised ICP is to reduce brain tissue volume by resection of tumour, steroids, mannitol to reduce intracellular

volume. Reduce the blood volume by avoiding hypercarbia, hyperthermia, hypotension.

Osmotic agents are widely used to lower the elevated ICP. Guidelines recommend the use of mannitol in head injury, intracerebral haemorrhage and ischaemic stroke, postoperatively to reduce ICP.[1]

The effect of mannitol on cerebral blood flow has been studied in the past using several modalities like Magnetic resonance imaging, Single Photon Emission Computer Tomography, Brain tissue oxygen monitoring, ICP measurement, Micro dialysis. However, all these techniques are invasive not widely used on day to day basis. TCCD is a non-invasive, bed side, real time monitoring and diagnostic tool. The use of TCCD has expanded immensely over the past three decades has emerged as cost effective tool for evaluating cerebral haemodynamics, detecting stenosis collateral flow pattern, cerebral autoregulation and embolization.[19]

A 2 MHz transducer is used in the ultrasound system to perform TCCD, has an advantage of providing parenchymal imaging with structural flow map of cerebral blood vessels.

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. Through the trans temporal window, the flow velocities of middle cerebral artery, anterior cerebral artery, posterior cerebral artery and posterior communicating artery can be obtained. By placing the transducer probe over the temporal area just above the zygomatic arch and in the front of the tragus of the ear the screen is filled with colour signals between 30 to 80 mm depth. A red colour signal at the depth of 45 to 60 mm signifies the ipsilateral MCA figure 2. The Doppler spectral pattern provides important information about the flow characteristics in the arterial segment.[20]

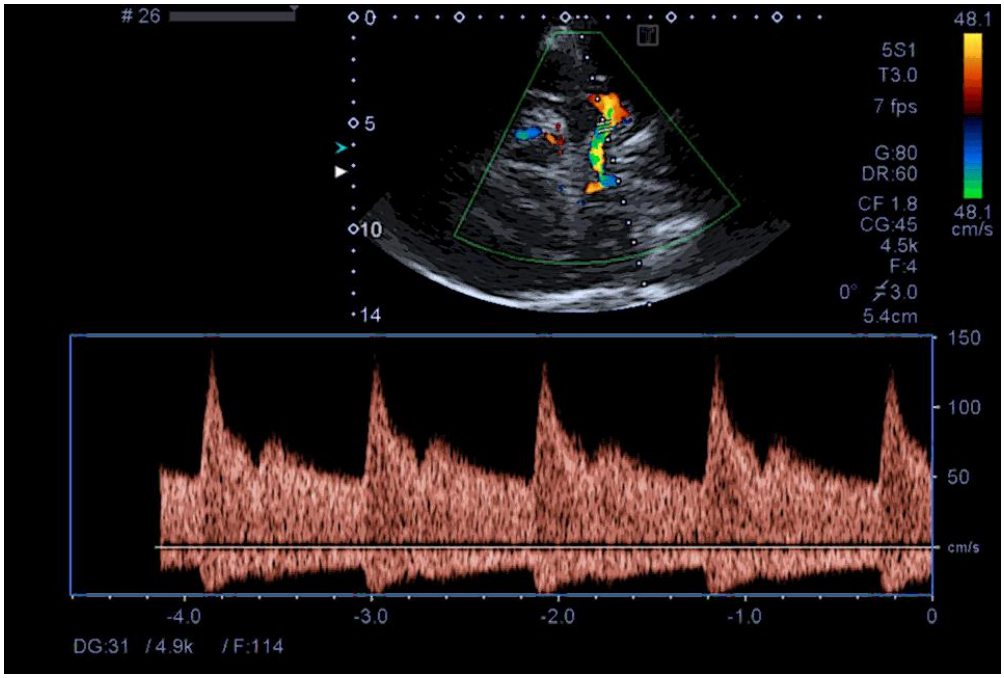

Figure 2. Red signals at the depth of 5cms – indicating ipsilateral MCA flow

The normal spectral waveform shows a sharp systolic upstroke and stepwise deceleration with positive end diastolic flow. Peak systolic velocity is the first peak on the on a TCD waveform from each cardiac cycle. The end diastolic velocity lies between 20 to 50% of the peak systolic velocity indicating the low resistance pattern of intracranial arteries. The insonation characteristics of MCA is that the transducer is directed superiorly and anteriorly to get the signal at the depth of 30 to 65mm with flow towards the probe.

TCCD indices: The various indices are Mean flow velocity, Gosling's pulsatality index, The Pourcelot resistivity index. Mean flow velocity is the central parameter of TCCD and is equal to PSV+EDV*2/3. The normal mFV of MCA is about 55$\pm$12.

Gosling's pulsatality index (PI) provides information on downstream cerebral vascular resistance and is equal to (PSV-EDV)/MFV. Normal values of PI lie within the range of 0.5 to 1.19. PI positively correlates with ICP; a PI change of 2.4% is reflected by a 1 mmHg change in ICP. Pulsatality derived ICP can be used as a surrogate marker of ICP. The use of TCD as a predictor of ICP was first described by Klinghoffer et al. Middle cerebral artery (MCA) flow velocities and PI may help

to assess the progression of the injury, correlate well with ICP and guide the treatment protocols[21]. In the observational study of Bellner et al, 81 patients with various diagnoses including aneurysmal subarachnoid haemorrhage, head injury and encephalitis had an intraventricular catheter for ICP monitoring.[22] Multiple TCD measurements were performed parallel to the ICP recordings. Independent of the intracranial pathology, a significant correlation between PI and ICP and between flow velocity and ICP was found. PI ≥ 1.26 could reliably predict CSF-P ≥ 20 cm H2 0 (sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were 81.1%, 96.3%, 93.8%, 88.1%, and 90.1% respectively).[23]

TCD is defined highly sensitive with a medium specificity. The sensitivity decreases and specificity increased with values over 20 mmHg. PI measurements therefore provide a good estimate of ICP. Formula to calculate ICP from PI is 10.93*PI-1.28.[22]

The Pourcelot resistivity index (RI) is equal to (PSV-EDV)/PSV with values 0.8 indicating increased downstream resistance. Derangements of RI reflect similar disease patterns as observed with an abnormal PI.

Estimated cerebral perfusion pressure: Method of direct calculation of CPP as MAP-ICP, does not always adequately expresses brain perfusion. Schimdt investigated an alternative method based waveform analysis of MCA.[24] Time averaged values of arterial blood pressure, mean and diastolic blood flow velocities were calculated and eCPP was computed as ABP *EDV/mFV +14. An absolute difference between real CPP and eCPP was less than 10 mmhg in 82% and less than 13 mmhg in 90% of measurements. This method is of potential benefit for the continuous measurements and continuous monitoring of changes in cerebral perfusion where the direct measurement of CPP is not available.

Major limitations of TCD is the fact that It is highly operator dependent, with the handheld technique requiring detailed three-dimensional knowledge of cerebrovascular anatomy and its variations.

The use of TCD is also hampered by the 10 to 15% rate of inadequate acoustic windows due to increased thickness and porosity of the bone around the acoustic windows and attenuation of the ultrasound energy transmission. TCD measurements are also limited to the large basal arteries and can only provide an index of global rather than local cerebral blood flow velocity.[25]

Similarly echocardiography is a non-invasive bedside monitor. Transthoracic echocardiography (TTE) provides the clinician with a tool that has potential to give a rapid, non-invasive assessment of the hemodynamic status of the critically ill patient at the bedside. Echocardiography uses sound waves to create images of the heart and other structures. Adult echocardiography utilises the frequencies of 2 to 7 MHz. TTE employs low frequency (2 to 7Hz) transducers, which allows deeper penetration through the chest wall but at the expense of image quality. Basic imaging modalities of echocardiography are M-mode(motion mode) depicts the structures along the path of single line of ultrasound beam. M mode has excellent axial resolution compared to 2D images. The low powered ultrasound beam cannot image the entire heart entirely in its natural position behind the sternum. Hence left lateral position that shifts the heart laterally is the ideal position to obtain optimum images.

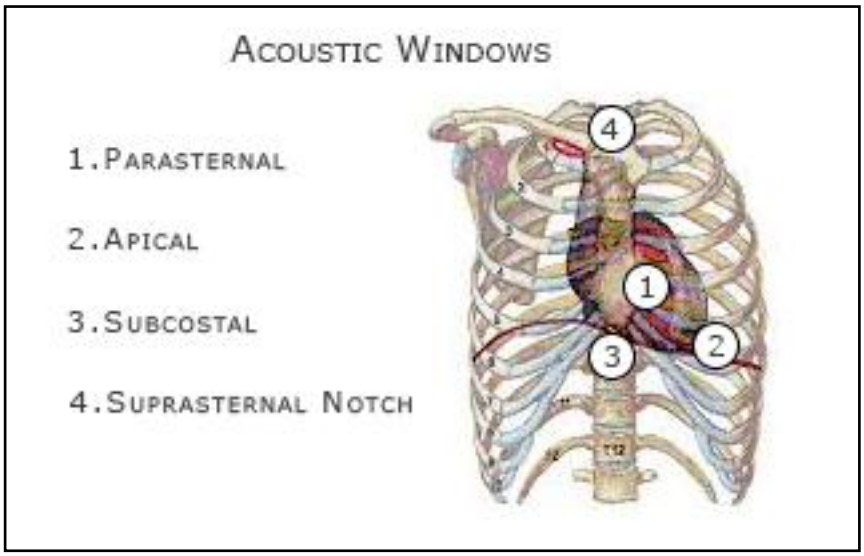

Figure. 3. Transthoracic echocardiographic: Acoustic windows

TTE can be used to assess left ventricular systolic function, diastolic function, contractility, valves, filling status of chambers, chamber wall thickness. The basic five transthoracic echocardiography views are parasternal long-axis view, parasternal short-axis view, apical four-chamber view, subcostal view, suprasternal view (figure 3). For the parasternal long axis view patient is positioned in left lateral position with traducer placed at third or fourth intercostal space notch facing towards right shoulder. Structures visualized are left atrium, left ventricle, left ventricle outflow tract, right ventricle outflow tract, Aorta, mitral valve and aortic valve. This view is of paramount importance in making standardized set of measurements by 2D and M mode imaging modalités (figure 4).

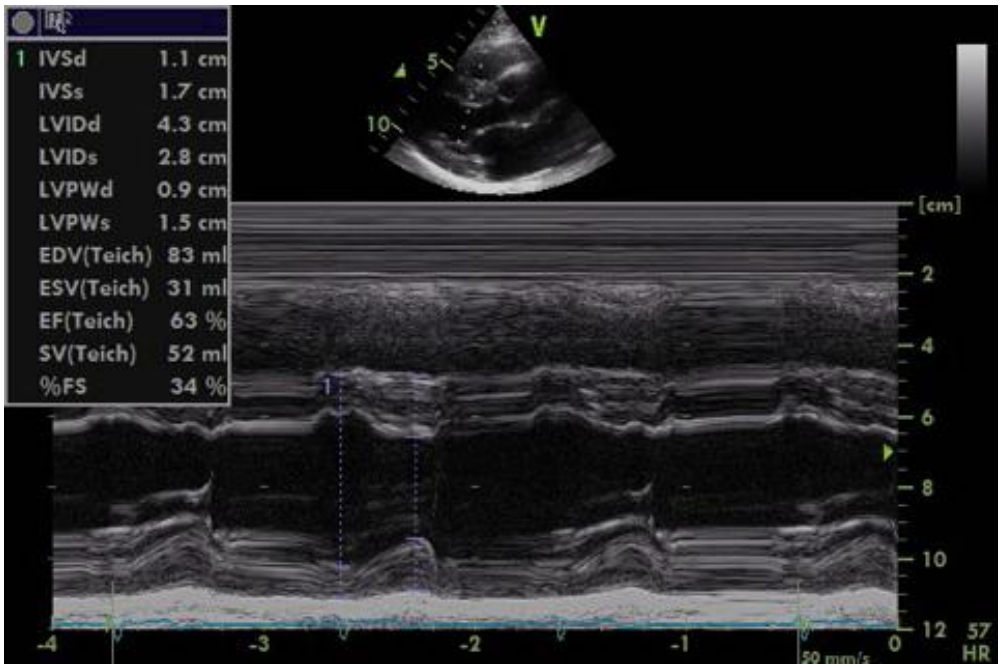

Figure. 4. M-mode measurements of left ventricle in PLAX view

Thereafter, apical four chamber and two chamber views will be acquired to trace LV endocardial borders at end diastolic and end systolic frames in the same cardiac cycle. Ejection fraction is derived from subtracting end systolic volume from end diastolic volume and dividing the result by end diastolic volume. It is appropriate to use modified Simpson's method which assumes that LV is composed of 20 discs and its volume is integral function of summation of volume of individual discs. In cases where there is no problem in endocardial border detection, this method

provides the best estimate of LV EF. Furthermore, stroke volume (SV) will be calculated in apical five chamber view using spectral Doppler. As, Doppler has limitation of angle dependency, the interrogation line has to be aligned parallel to the LVOT flow with the cursor at 5-10 mm below the aortic annulus. By tracing the contour of envelope, velocity time integral (VTI) will be measured. So, SV will be the product of cross sectional area of LVOT and VTI across it. Similarly, the product of SV and patient's heart rate will depict the cardiac output of that cycle. The limitations of TTE in the ICU relate to the patient, the pathology, and the ability of the operator (both technical and in interpreting the study). Patient factors include immobility, the effects of positive-pressure ventilation, the presence of dressings and drains, and obesity - all of which limit the diagnostic windows and increase the challenge to the operator.

Several studies have been conducted in the past to study the effects of mannitol on cerebral vasculature and haemodynamic parameters in various clinical scenarios like tumour, ischaemic stroke, subarachnoid haemorrhage and intracranial hypertension.

Kassel et al studied the effects of high dose of mannitol on CBF in dogs with normal intracranial pressure.[26] They administered 2g/kg bolus of mannitol over 7 minutes to male mongrel dogs. CBF was measured by radioactive microspheres techniques with radioactive labels at 5, 10, 15 and 30 minutes. At the end of study CBF was measured by sacrificing the animal. Soon after administration of mannitol abrupt increase in end tidal carbon di oxide was seen, ventilation was adjusted to maintain partial pressure of carbon di oxide at 30 mmhg. Mean arterial pressure increased after 5 minutes of mannitol administration from 115 to 125 mmhg returned to baseline by 30 minutes. Heart rate changed from 81 to 115beats/min at the end of 60 minutes. Total mean cerebral blood flow increased from 42 to 46ml/100gm/min at five minutes and then declined to 34 ml/100gm/min at 30 minutes and remained same till the end of the study. Similar pattern of change was seen in cerebral hemisphere, cerebellum, and brain stem. Cerebrovascular resistance increased from 2.7 units to 3.4 at 30 minutes and 3.9 units at 180 minutes. They hypothesized that the protective action of mannitol is due to reduction of swelling of endothelial cell and pericapillary oedema. The haemodynamic changes observed in the study is not

statistically significant except heart rate. The increase in the cerebral blood flow was due to increase in the intravascular volume and cardiac output. But the fall in cerebral blood flow could not be attributed to hemodynamic changes cause they adjusted ventilation to maintain partial pressure of carbon di oxide less than 30mmhg. The limitation of the study was that the dose of mannitol administered is very high compared to routine dosage in clinical practice. Such high doses of mannitol would have caused significant diuresis leading to dehydration and reduced cerebral blood flow.

Mendelow et al analysed the cerebral blood flow and cerebral perfusion pressure changes in head injury after mannitol administration.[27] A total of 55 patients were included in the study. The study group was further divided into focal and diffuse injury group. CBF was measured by sinctigraphy and ICP was measured by intra ventricular catheter. A bolus of 20% mannitol was administered was given intravenously over 15 to 20 minutes. On analysis of results they had 18 patients with diffuse injury and 9 patients with focal injuries. They further created a sub group of high ICP (>20) group and low ICP (<20) group. The mean CBF for all the patients was 43.9ml/100gm/min. On considering each subcatgory the patients with diffuse injury had mean CBF of 50.2 ml/100gm/min and in focal injury group mean CBF was 39.8 ml/100gm/min. Mean flow was lower in patients with focal injury compared to diffuse injury group. Mean flow was also higher in low ICP group. Following Mannitol in fusion global CBF increased from 50.2 to 58.7 ml/100gm/min. On comparing the affected and unaffected hemisphere, less damaged hemisphere had greater increase in CBF from 37ml/100gm/min to 45ml/100gm/min whereas in affected hemisphere CBF did not show much increase, 37 to 41ml/100gm/min only. Mannitol increased CBF in patients with low ICP group. They hypothesized that diffuse injury is associated with hyperaemia secondary to raised CBV. But change in cerebral blood volume alone may not be responsible for the severe cerebral oedema seen in diffuse injury group.

The increase in cerebral blood volume following mannitol administration may be due to loss of auto regulation as CBF becomes pressure dependent with absent autoregulation. Mannitol reduces the circulatory blood volume and produces

hypotension over a period of time. The study demonstrates that mannitol is of benefit in patients with focal injuries with high ICP. The limitation of the study was also that haemodynamic change, urine losses following diuretic action of mannitol was not enumerated. Hypotension can also lead to further reduction in cerebral perfusion pressure. The cause of reduced CPP was a reduced MAP or raised ICP could not be distinguished.

Kalitha et al conducted a SPECT study to determine the changes in regional cerebral blood flow after mannitol administration in patients with intracerebral haemorrhage.[28] The study population consisted of 20 patients with 12 in the study group and 9 in the control group. All patients with computed tomography proven intracerebral haemorrhage were enrolled into the study. Baseline SPECT study was done in all patients. After SPECT study mannitol was administered over 20 minutes. The control group received sham infusion. Second SPECT study was carried out 60 minutes following mannitol infusion. They performed semi quantitative measure of cerebral perfusion in the region of basal ganglia, frontal and parietal and occipital regions and expressed as asymmetry index. Asymmetry index was reduced following mannitol administration compared to sham infusion group. Conclusion of this study was that mannitol does not alter the regional cerebral blood flow as assessed by SPECT in patients with intracerebral haemorrhage. The subset of patients who underwent the study had small or medium sized haematoma. The patients with large haematoma with haemodynamic perturbations were not suitable for SPECT study. Changes in cerebral blood flow, ICP, oedema occurs over several minutes to hours, SPECT cannot be performed repeatedly to assess these changes.

Vincenzi et al studied the effects of the single mannitol bolus in patients with intracerebral haemorrhage.[29] They studied the blood flow velocity changes in the middle cerebral artery, after mannitol administration. Transcranial Doppler measurements were taken upto 90 minutes after mannitol administration. The MCA flow velocity and pulsatality index was recorded. They compared the mean flow velocity between the affected and unaffected hemisphere. They timed the Doppler measurements such that they matched the clinical timings. They excluded the patients receiving less than 4 hourly mannitol to prevent mannitol accumulation.

They measured Doppler upto 2.2 days after the symptom onset. No significant blood pressure changes occurred during the study. MFV was significantly higher and PI lower on affected side compared to healthy side. The increase in MFV started at the end of infusion and persisted upto end of 60 minutes. No changes in the MCA flow velocity and PI on the healthy side. The results on day 2 is not elaborated and is summed up as a whole and expressed as baseline, 10 minutes after infusion and 60 minutes after infusion.

Anthony F Kauffman et al analysed the pharmacokinetics of mannitol administered for the treatment of vasogenic oedema.[30] They anesthetised 23 adult cats maintained them on mechanical ventilation. Vasogenic cerebral oedema was produced by probe cooled at -50 degree and applied to the intact Dura through left parietal craniectomy. Evans blue was infused intravenously over 30 minutes to study the progression of cerebral oedema. Mannitol treatment was initiated one hour after the cold injury either by single dose or five doses at 4 hour interval. Animals were sacrificed at the end of the study. The concentration of radiolabelled mannitol was determined scintillator counting. They observed rapid clearance of mannitol with no differences between single or multiple doses. About 73% after single dose and 83% after multiple doses of mannitol was excreted. But however mannitol did accumulate in oedematous tissue. Concentration of mannitol in the oedematous tissue is 0.046 after multiple doses and after single dose was 0.028 mg/gm. There was fivefold increase in mannitol concentration after repeated administration compared to single dose. They concluded that after single dose of mannitol vasogenic oedema did not increase justifying its clinical use to reduce cerebral bulk but the same results could not be extrapolated for the use of multiple doses of mannitol.

Von Berenberg et al conducted a similar study obtained different results. Multiple doses of mannitol was administered during the development of cerebral oedema in sprague dawley rats.[31] The first series of 8 rats received four doses of 20% mannitol at 30 minutes, 3, 6 and 9 hours after trauma. Twelve hours after trauma the animals were sacrificed and analysed. The second series of rats received 8 doses of mannitol at 30 minutes' interval.

In the 8 doses mannitol group hemispheric swelling was 8.9 versus 10.1 in the control rats. Whereas hemispheric swelling after four doses of mannitol was 7.2 compared to 7.6 in the control animals. Water content of the mannitol group was 80.5 compared to saline group 80.8%. Taken together these result indicate that multiple doses of mannitol do not aggravate total hemispheric swelling nor global water content following induction of cerebral oedema.

Hong et al conducted a study with two different doses of mannitol 125 and 250 ml in patients with intracerebral haemorrhage.[31] They included 30 patients in the study group. All patients received 125 ml 20% mannitol intravenously over 15 minutes followed by 250 ml of mannitol after 6 hours. They assessed mean flow velocity (Vm) of MCA using TCD derived PI from the TCD recordings. TCD measurements were taken at 0, 30, 60, 90, 120, 180 and 240 minutes. After 125 ml mannitol infusion, mean flow velocity increased significantly at 30 minutes about 58cm/sec to 54cm/sec at 60 minutes compared to 54 cm/sec at baseline. Baseline PI was 1.08 reduced to 1.03 at 30 minutes and 1.05 at 60 minutes. After 250 ml mannitol infusion Vm of affected MCA increased from 52cm/sec to 62cm/sec at 30 minutes maximum increase was seen at 60 minutes Vm was about 59cm/sec. PI reduced from 1.08 to 1.00 at 30 minutes remained at 1.02 at 60 minutes. Vm of unaffected MCA after 250 ml mannitol remain elevated from 50 to 60 cm/sec at 30 minutes and was 57cm/sec at 60 minutes. PI in unaffected MCA decreased significantly from 60 minutes to 120 minutes and then elevated. The difference in Vm caused by mannitol existed more with 250 ml mannitol bolus and was more powerful in reducing oedema and improving cerebral blood flow.

There are several studies in the past that dealt with cerebral haemodynamic after mannitol administration. They answered several questions about rebound phenomenon, reduction in ICP, improvement in cerebral blood flow. The cardiovascular changes secondary to mannitol administration was never emphasized nor investigated, about its relevance in altering the cerebral blood flow.

Though we could find many studies that saw only cardiovascular changes following mannitol infusion they did not mention on cerebral hemodynamic.

Chatterji et al performed systolic function assessment after mannitol administration in neurosurgical patients undergoing craniotomy.[32] They included 15 patients without cardiac illness into the study group. After standard anaesthesia induction patients received single dose of mannitol was infused over 15 minutes before the dural opening. They assessed left ventricular systolic function with tranesophageal echocardiography. The single dose of mannitol altered CVP at 5 minutes but not other times. Thereafter CVP decreased at 15 minutes and was lower at 45 minutes. However the CVP difference was not statistically significant. MAP and HR showed unremarkable changes across all times. There was increase in EDA at 5 minutes after mannitol infusion. LVOT (VTI), SV, CO, CI all increased significantly at 5 and 15 minutes after infusion.

Nikki et al conducted a similar study to Chatterji et al[32] assessed cardiovascular changes after mannitol administration using non invasive cardiac output monitoring. They measured all variables at 1, 2, 5, 10, 15, 20, 25, 30, 35 and 40, 45 minutes after termination of mannitol. There was decease in heart rate over 45 minutes, SBP and DBP was always less than pre mannitol values. Stroke volume increased at 15 minutes after mannitol administration and was lower at 30 minutes. CO also showed similar changes with a significant increase at 1 minute to 10 minutes and a decrease at 40 to 45 minutes.

No study to date has enumerated the effect of mannitol in postoperative period after repeated administration. Postoperative period is very crucial, stable haemodynamics, adequate hydration must be maintained. But however due to fluid shifts, continued blood loss, diuretic state, electrolyte and water imbalance, can complicate postoperative period. In the premise of these underlying changes will mannitol behave as the same way as bolus dose of mannitol or produces enhanced hemodynamic changes must be studied.

AIMS AND OBJECTIVES

The aims of the current study are;

1. Serial assessment of effect of mannitol on the cardiovascular and cerebral haemodynamics assessed by transcranial doppler and transthoracic echocardiography
2. To compare the differences in cerebrovascular effects between operated and non-operated side.
3. To determine the temporal course of these changes on the brain and heart in postoperative period in patients who underwent neurosurgical procedures

MATERIALS AND METHODS

A total of 25 patients undergoing supratentorial craniotomy for tumor surgeries from department of neurosurgery were enrolled into the study. The study was approved by institutional ethics committee and written informed consent was obtained from patient relatives.

Inclusion criteria

Patients aged between 18 to 60 years

American Society of Anaesthesiologist (ASA) grade 1 and 2 undergoing elective supratentorial surgery were included in the study.

Further recruitment into the study group was made if patient was started on mannitol in the postoperative period by the surgeon.

Exclusion criteria

Patients refusing to participate in the study

Emergency surgeries

ASA grade 2 and 3

Pregnant and nursing mothers

Obese patients with poor acoustic window

Acute neurological deterioration

Anaemia

Coronary artery disease

Renal dysfunction

Mechanical ventilation

Fever

Sepsis

Inotrope support

Ventriculostomy

Coagulopathy

Surgeries for aneurysm arteriovenous malformation were excluded from the study.

Patients satisfying the inclusion criteria were explained about the study pattern, echo and doppler screening following mannitol administration. Doppler and echo cardiographic recordings were made on day one and day two in intensive care unit (ICU) following administration of mannitol over 15 minutes. Vital parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure(DBP) and mean arterial pressure (BP), Plethysmography (spO2%) were recorded before mannitol administration and at regular intervals of 5, 15, 30, 60 minutes following mannitol administration. Urine output before and after one hour of mannitol administration was noted. Simultaneously, a comprehensive transthoracic echocardiography (TTE) examination and transcranial colour duplex sonography (TCCD) was performed by the principle investigator/co-principal investigator at baseline and at intervals of 5, 10, 15, 30 and 60 minutes.

TTE Measurements

Patients are supine or in left lateral position for TTE examination. A 3-Mhz transducer probe is used to acquire images.

Left ventricle (LV) dimensions, global LV function (Ejection fraction) is assessed in the parasternal long axis and apical views.For parasternal long axis view, the transducer is placed 2 to 3 inches to the left of the sternum in the 4th or 5th rib interspace. The notch on the transducer should be facing the 10 o'clock position toward the right shoulder.

Thereafter, apical four chamber and two chamber views are acquired to trace LV endocardial borders at end diastolic and end systolic frames in the same cardiac cycle. Stroke volume (SV) is calculated in apical five-chamber view using spectral doppler. As doppler has a limitation of angle dependency, the interrogation line has to be aligned parallel to the LVOT flow with the cursor at 5 to10 mm below the aortic annulus. By tracing the contour of envelope, velocity time integral (VTI) is measured. SV is the product of cross sectional area of LVOT and VTI across it. Similarly the product of SV and patient's heart rate depicts the cardiac output of that cycle.

TCCD measurements

A 2-Mhz transducer is used in the ultrasound system to perform TCCD. TCCD has an advantage of parenchymal imaging with structural flow map of cerebral vessels. A trans-temporal window is chosen to insonate middle cerebral artery (MCA).Temporal window is an area delineated by a line drawn from tragus to the lateral canthus of the eye, 2 cm above this line probe and is directed anteriorly and superiorly to insonate MCA. Probe is adjusted such that screen is filled with colour signals between 30 to 80 mm of depth. A red colour signal at the depth of 40 to 60 mm represents the same side MCA. Normal spectral waveform consists of peak systolic velocity (PSV) and a positive deceleration of end diastolic flow.

Peak systolic velocity (cm/sec): From each cardiac cycle this is the first peak on TCCD.

End diastolic velocity (cm/sec): Lies between 20% and 50% of PSV indicate a low resistance circuit of cerebral vasculature.

Mean flow velocity (cm/sec): Is derived from PSV and EDV. MCA has the highest mFV. The mean flow velocity waveform shows least variation and is a commonly used TCCD parameter.

mFV = EDV+1/3(PSV-EDV)

Pulsatality index of Gosling determines the cerebrovascular flow resistance. PI is derived from difference between PSV and EDV divided by mFV. PI is independent of angle of insonation, hence it is not expressed in units. Normal PI value ranges between 0.8 and 1.2. A value greater than 1.2 represents high resistance to cerebral blood flow.

A significant correlation exists between PI and ICP. An increased ICP will reduce the compliance of cerebrovascular system and augments the velocity variation, increasing the denominator of PI. PI is extremely sensitive to ICP changes and hence can be used as a surrogate marker of ICP.

ICP can be derived from PI using the formula

$$ICP=11.1\times (PI) -1.43$$

Regression equation applied to the above formula calculated ICP is ±2 SD with 95% confidence interval of 4.2. The sensitivity and specificity of calculated ICP reduces with raised ICP.

Resistance index (RI) is a TCCD parameter that represents the flow resistance distal to the site of insonation. RI is calculated by subtracting EDV from PSV and then dividing the result by PSV. Normal value of RI is less than 0.75.

To summarize the following hemodynamic parameters were estimated from TCCD:

1. Mean flow velocity (mFV)
2. Pulsatility index [PI = (systolic FV – diastolic FV)/mean FV],
3. Resistivity index = (systolic FV – diastolic FV)/PSV
4. Estimated cerebral perfusion pressure (eCPP = MAP×EDV/mFV + 14)
5. Calculated ICP=11.1× (PI) – 1.43.

Haemodynamic values derived from transthoracic echocardiography are:

1. Left ventricular internal diameter in systole
2. Left ventricular internal diameter in diastole
3. Left ventricular end systolic volume
4. Left ventricular end diastolic volume
5. Ejection fraction
6. Stroke volume
7. Cardiac output

STATISTICAL ANALYSIS

The software SPSS version 17 (Chicago, inc) was used for statistical analysis. This was designed as a prospective pilot study, no similar studies were available in the past. Hence no power analysis could be prior to the study. Results obtained from the study are expressed as mean ±SD. A paired t test was applied to compare between operative and non-operative side at different time intervals. Adverse reactions during the study were documented.

Repeated measures were compared using repeated measures ANOVA. A "p" value less than 0.05 was considered statistically significant and less than 0.01 as highly significant.

RESULTS AND OBSERVATIONS

The total number of patients enrolled in study group was 25. Out of 25 patients undergoing supratentorial craniotomy 3 patients had poor accoustic window and 2 of them underwent re-exploration and therefore excluded from the study group. Finally, 20 patients constituted the study cohort and 2 of them were hypertensive and three patients were diabetic.

The observations like vital parameters, Doppler and echocardiographic changes were recorded at baseline, 5, 15, 30, 45 and 60 minutes' interval on day 1 and day 2 of the postoperative period.

Further the effect of mannitol was assessed between operated site and non-operated site for Doppler velocities and compared the difference in the effect of mannitol on day 1 and day 2.

Table 1. Age distribution in the study group

Age in years	Frequency	Percent
< 30	7	35.0
30 - 49	8	40.0
>50	5	25.0
Total	20	100.0

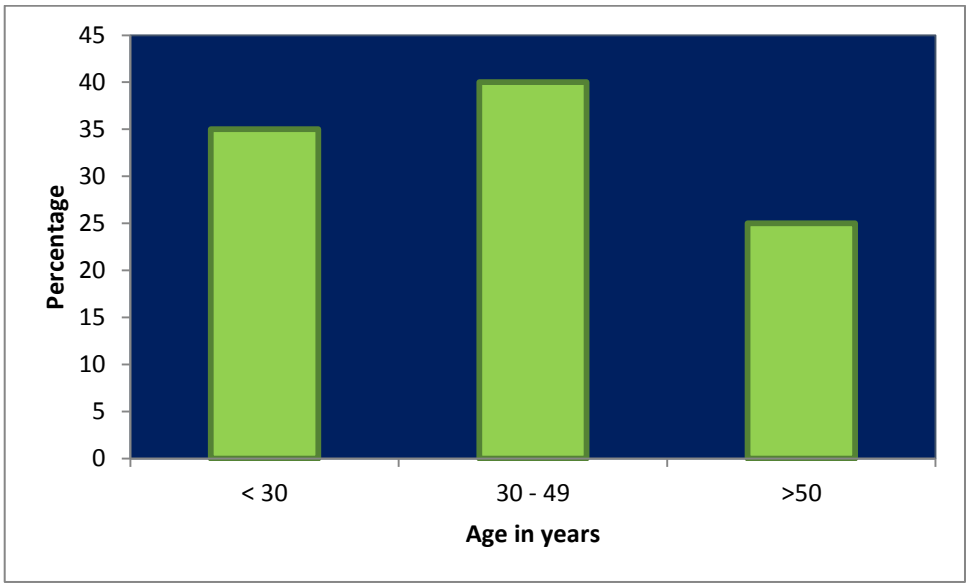

Chart 1. Age distribution in the study group

Study group contained 30% of population less than 30 years, 40% were between 30 and 50 years, whereas only 25% were above 60 but within 65 years.

Table 2. Gender distribution in the study group

Sex	Frequency	Percent
Male	8	40.0
Female	12	60.0
Total	20	100.0

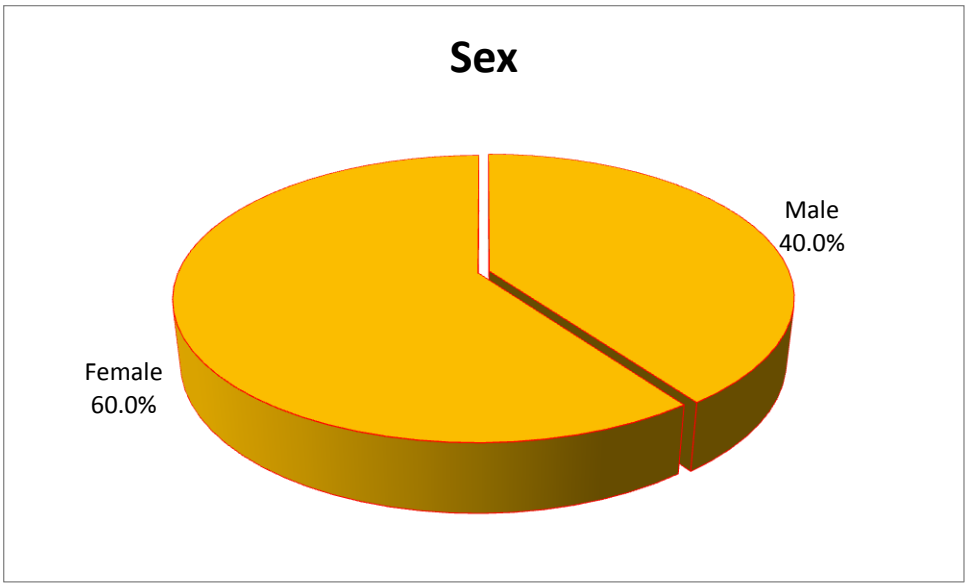

Chart 2. Gender distribution pattern

In the group of 20 patients 8 were men and 12 were female patients (chart 2).

Vital parameters

Heart rate, Systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and spo2% were measured at the baseline 5, 15, 30, 45 and 60minutes after mannitol administration both on day one and two.

Table 3. Heart rate on day 1 and day 2

	Heart rate				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	82.5	14.5	83.4	18.0	-0.243	0.811
After 5 minutes	82.4	16.9	83.3	14.1	-0.214	0.833
After 15 minutes	81.9	17.3	82.1	16.3	-0.053	0.958
After 30 minutes	81.2	15.6	80.5	16.4	0.201	0.843
After 45 minutes	83.0	15.3	83.5	18.3	-0.127	0.900
After 60 minutes	85.2	11.9	82.3	18.8	0.714	0.484

Table 4. Repeated measure ANOVA Comparing heart rate on day 1 and day 2

	F	p
Day 1	1.044	0.396
Day 2	.566	0.726

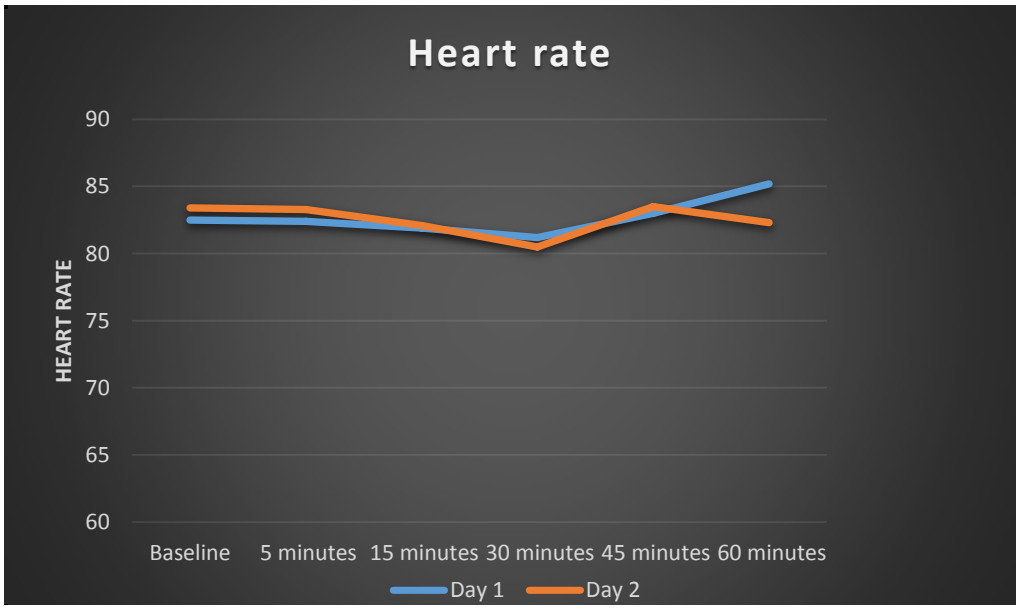

Chart 3. Comparison of Heart rate changes on day 1 and day 2

The results are expressed as mean ± standard deviation. Heart rate did not show any changes at all the time intervels on both day 1 and day 2. Heart rate changes are shown in Table 3, Chart 3. On comparing the heart rate on both days, repeated measure ANOVA did not show any statistically significant difference (Table 4). Day 1 $F= 1.044$ $P= 0.396$ and on day 2 $F = 0.566$ and $P = 0.726$.

Table 5. Mean arterial pressure on day 1 and day 2

	MAP				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	80.2	8.8	80.3	12.5	-0.045	0.965
After 5 minutes	81.4	13.9	80.2	13.1	0.275	0.787
After 15 minutes	85.8	13.9	79.1	15.5	1.636	0.118
After 30 minutes	83.0	9.7	79.7	11.7	1.204	0.243
After 45 minutes	82.8	9.7	77.9	13.8	1.361	0.189
After 60 minutes	85.3	8.2	80.2	11.5	1.681	0.109

Table 6. Repeated measure ANOVA

	F	p
Day 1	2.226	0.508
Day 2	0.583	0.713

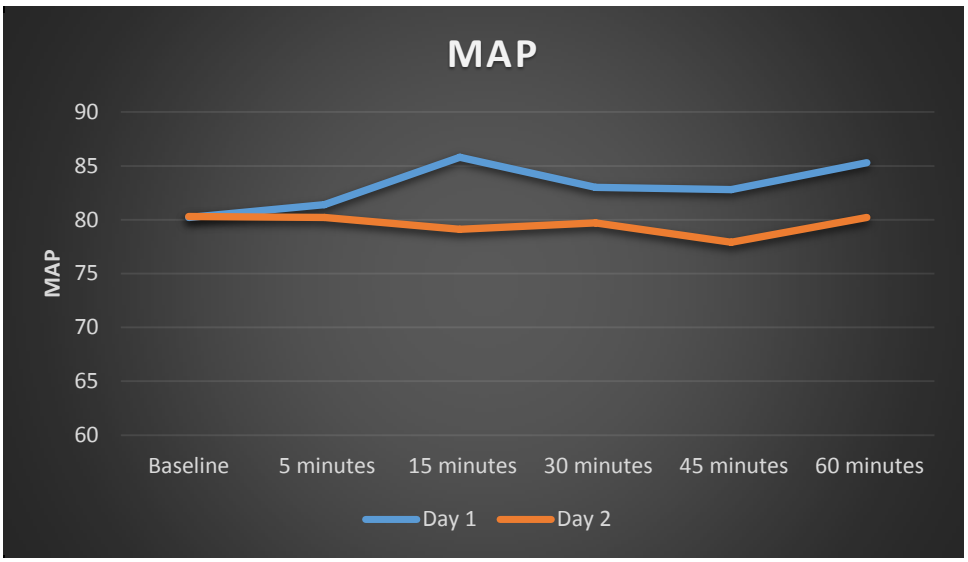

Chart 4. Changes in mean arterial pressure on day 1 and day 2

Table 5: Indicates changes in MAP at Basline 5, 15, 30, 45 and 60 minutes. Paired t- test applied did not show any statistically significant difference between day 1 and day 2. No p value was < 0.05 at any time period.

Table 6: Repeated measure ANOVA noticed no significant difference between day 1 and day 2.

F = 2.26 on day 1 and p= 0.508. on day 2 F= 0.583 and p= 0.713

Comparison between day 1 and day 2 MAP is depicted in chart 4

Table 7. SPo2% changes on day 1 and day 2

	SPO2(%)				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	100.0	0.0	100.0	0.0		
After 5 minutes	100.0	0.0	99.8	0.6	1.453	0.163
After 15 minutes	100.0	0.0	99.8	0.6	1.453	0.163
After 30 minutes	100.0	0.0	99.9	0.4	1.000	0.330
After 45 minutes	99.9	0.7	100.0	0.2	-1.000	0.330
After 60 minutes	99.9	0.7	100.0	0.2	-1.000	0.330

Table 8. Repeated measure ANOVA

	F	p
Day 1	1.000	0.422
Day 2	1.669	0.149

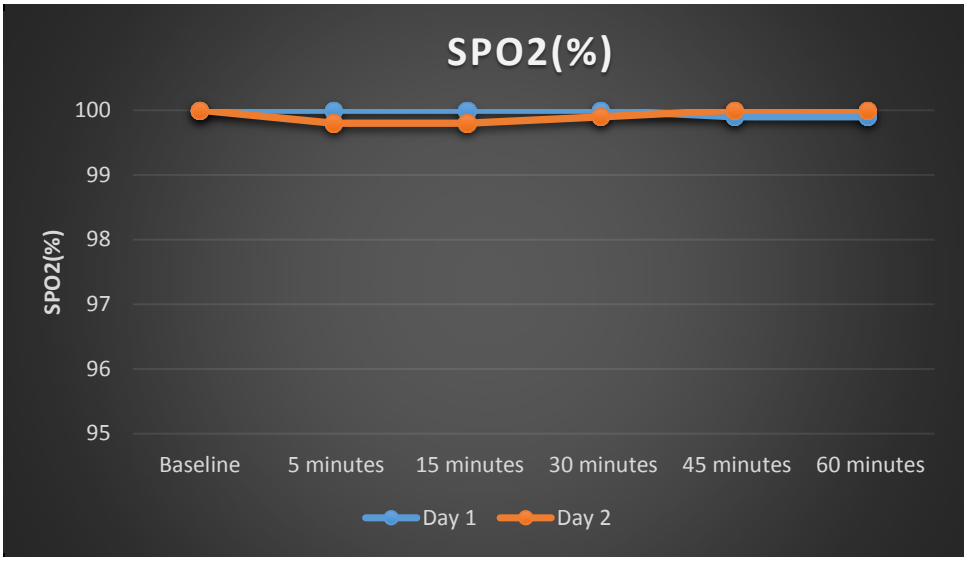

Chart 5. comparison of changes in SPo2% on day 1 and day 2

SpO2% did not show any changes in all time points on day one and two.

SpO2 changes on day 1 and day 2 is seen in Table 7. No significant changes is seen on both day 1 and day 2.

Repeated measure ANOVA did not reveal any difference. F = 1.000, p 0.149 (Table 8). SpO2% did not show any changes at all time points on day 1 and day 2 (Chart 5)

Transcranial Doppler velocities

Mean flow velocity (mFv)

Table 9. Mean flow velocity on day 1

	Mean Flow Velocity in cm/sec (Day 1)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	49.2	9.2	50.8	9.3	-0.944	0.357
After 5 minutes	86.1	14.8	53.3	13.8	17.139	<0.001
After 15 minutes	135.4	24.4	50.9	13.8	17.399	<0.001
After 30 minutes	80.6	11.0	107.9	22.7	-21.176	<0.001
After 45 minutes	83.3	14.0	108.3	23.9	-7.536	<0.001
After 60 minutes	139.7	24.8	107.7	25.0	5.817	<0.001

Table 10. Repeated measure ANOVA comparing operated and non operated side on day 1

	F	p
Operated	175.841	<0.001
Non operated	76.829	<0.001

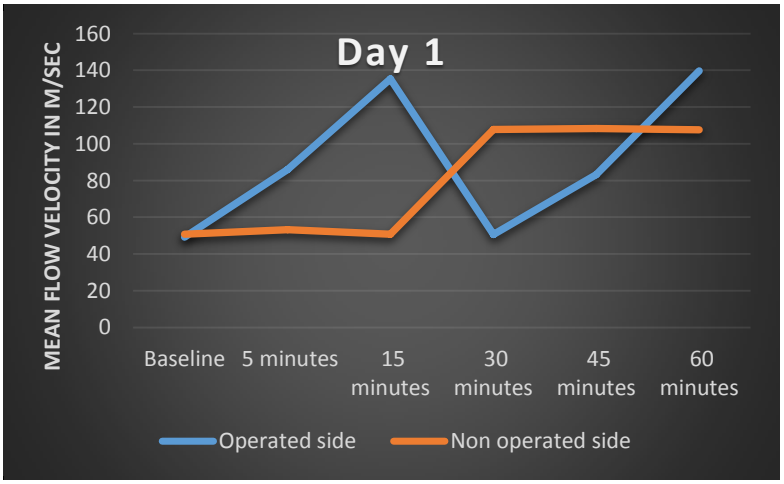

Chart 6. Comparison of changes in mFv on day 1 between operated and nonoperated side

Mean flow velocities of MCA on day 1 and day 2 is shown in Table 9.

mFv increases at 5 minutes on the operated side, $p < 0.001$. At 30 minutes onwards significant increase is seen in both operated and non operated side.

Table 10 shows results of repeated measure ANOVA shows $F = 175$ $p = <0.001$ on day 1 on day 2 $F = 76.829$ $p < 0.00132$. significant difference is seen on both operated and non operated side.

Chart 6 shows comparison between operated and non operaetd side on day 1

Table 11. Mean Flow Velocity on Day 2

	Mean Flow Velocity in m/sec (Day 2)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	51.6	10.3	57.4	16.6	-1.707	0.104
After 5 minutes	58.2	16.9	55.7	12.3	0.550	0.589
After 15 minutes	52.0	11.0	52.9	7.9	-0.480	0.637
After 30 minutes	50.8	10.0	53.9	14.2	-0.902	0.379
After 45 minutes	50.8	10.0	55.6	9.2	-1.793	0.089
After 60 minutes	52.9	13.0	52.8	11.7	0.038	0.970

Table 12. Repeated measure ANOVA on comparing operated and non operated side

	F	P
Operated	1.765	0.128
Non operated	0.802	0.551

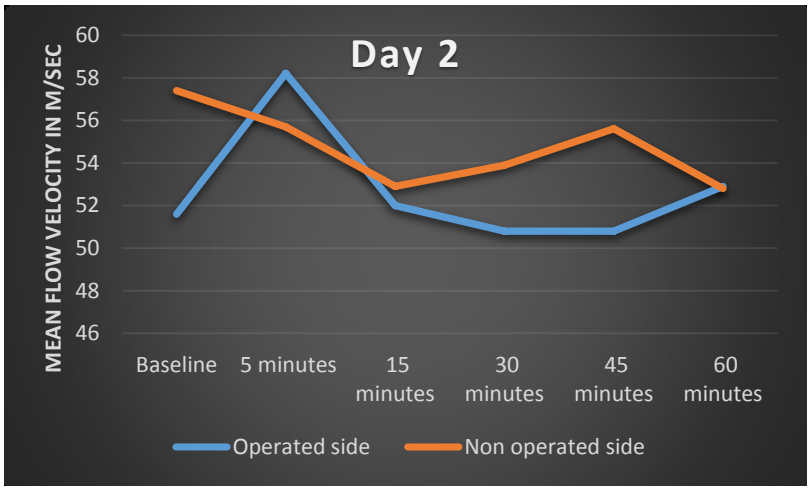

Chart 7. Comparison of mFV between operated and nonoperated side on day 2

On both operated side and non operated side mFv on day 2 did not show any change from baseline (Table 11, Chart 7).

Repeated measure ANOVA (Table 12) did not show significant difference between operated and non operated side.

Table 13. Comparison of PI between operated and nonoperated side on day 1

	Pulsatality Index (Day 1)				Paired t test	
	Operated side		Non operated side		t	p
	mean	Sd	mean	sd		
Baseline	1.00	0.32	0.97	.29	.408	0.688
After 5 minutes	0.97	0.30	0.94	.26	.702	0.491
After 15 minutes	0.87	0.29	0.94	.28	-1.362	0.189
After 30 minutes	0.92	0.22	0.92	.22	.014	0.989
After 45 minutes	0.92	0.25	0.93	.32	-.102	0.920
After 60 minutes	0.96	0.37	1.02	.35	-.878	0.391

Table 14. Repeated measure ANOVA comparing operated and non operated side

	F	p
Operated	1.460	0.210
Non operated	1.076	0.379

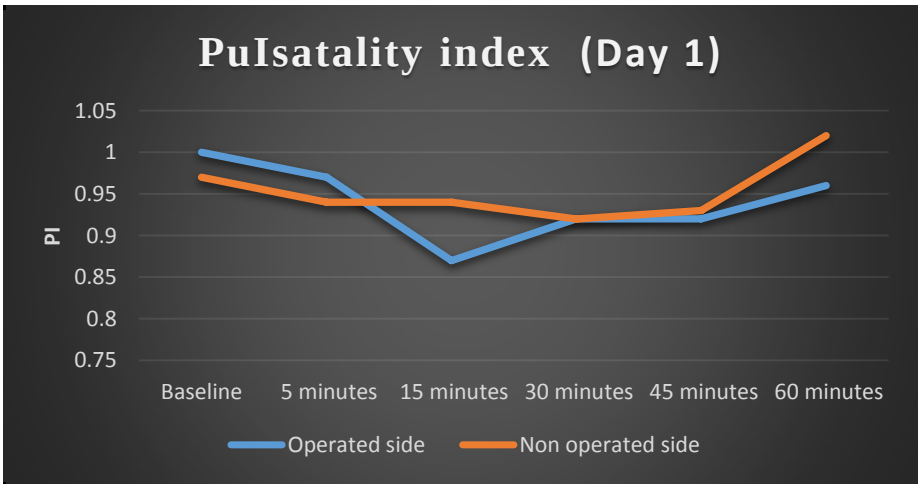

Chart 8. Comparision between operated and nonoperated side PI

PI on 1st post operative day showed decrease from baseline but was not statistically significant (Table 13). P value was not < 0.05 at any given point.

Repeated measures ANOVA comparing operated and non operated side (Table 14) did bnot show any difference.

F = 1.460 p = 0.210 on operated side

F = 1.076 p = 0.379 on non operated side day 1

Table 15. Comparison of PI between operated and nonoperated side on day 2

	Pulsatality index (Day 2)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	1.05	.34	1.10	0.26	-.790	0.439
After 5 minutes	.94	.28	1.06	0.28	-1.527	0.143
After 15 minutes	.99	.31	1.02	0.32	-.806	0.430
After 30 minutes	1.07	.36	1.08	0.29	-.209	0.837
After 45 minutes	1.00	.25	1.00	0.21	.081	0.936
After 60 minutes	1.03	.32	1.01	0.18	.297	0.770

Table 16. Repeated measure ANOVA comparing operated and non operated side.

	F	p
Operated	0.785	0.563
Non operated	2.085	0.165

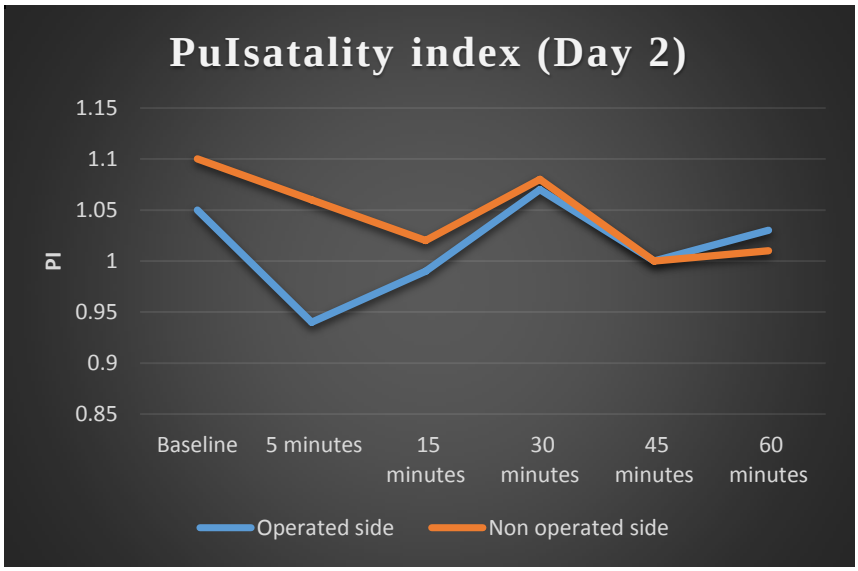

Chart 9. Comparison between operated and non operated side PI on day 2

PI did not show significant change between operated and non operated side on day 2 (Table 15, Chart 9).

Repeated measure ANOVA on 2nd post operative day did not show significant difference between operated and non operated side (Table 16). The p value $\leq$ 0.563 on operated side and on non operated side p $\geq$ 0.165.

Table 17. Resistivity Index on day 1

	Resistivity Index (Day 1)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	0.60	0.1	0.60	0.1	0.183	0.856
After 5 minutes	0.71	0.1	0.62	0.1	1.185	0.251
After 15 minutes	0.62	0.1	0.66	0.1	-0.076	0.940
After 30 minutes	0.61	0.1	0.64	0.1	1.620	0.122
After 45 minutes	0.63	0.1	0.63	0.1	1.144	0.267
After 60 minutes	0.65	0.1	0.66	0.1	0.069	0.946

Table 18. Repeated measure ANOVA for Day 1

	F	p
Operated	1.102	0.365
Non operated	1.659	0.152

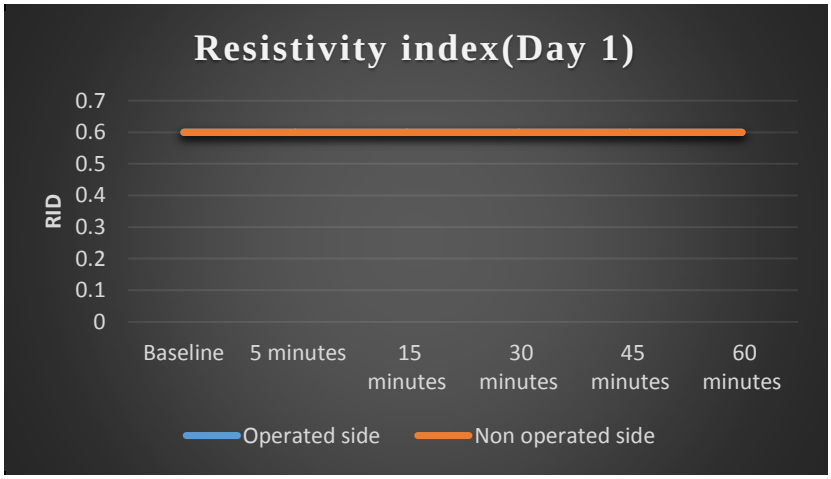

Chart 10. Comparison of Resisitivity Index between operated and Non operated side on day 1

Resistivity index on day 1 did not show any statistically significant difference (Table 17, Chart 10).

Repeated measure ANOVA (Table 18) comparing operated and non operated side did not show any difference on day 1.

Table 19. Resistivity Index on day2

	Resistivity Index (Day 2)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	0.6	0.1	0.6	0.1	-0.886	0.387
After 5 minutes	0.6	0.1	0.6	0.1	-0.951	0.354
After 15 minutes	0.7	0.1	0.7	0.2	0.278	0.784
After 30 minutes	0.7	0.1	0.7	0.1	0.415	0.682
After 45 minutes	0.7	0.2	0.6	0.1	1.599	0.126
After 60 minutes	0.7	0.1	0.7	0.1	0.223	0.826

Table 20. Repeated measure ANOVA comparing operated and non operated side.

	F	p
Operated	1.727	0.136
Non operated	0.784	0.564

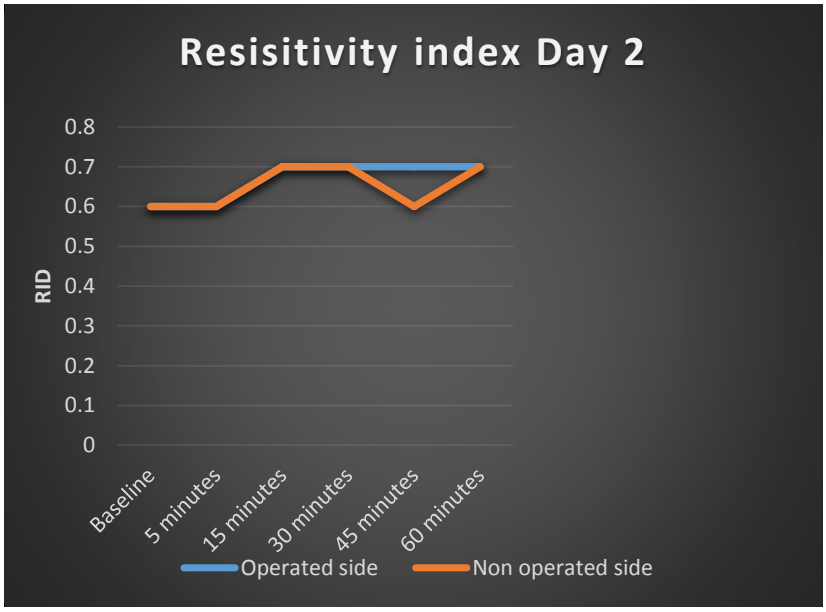

Chart 11. Comparison of Resisitivity Index on operated and nonoperated side on day 2

Resistivity index on day 2 did not show any statistically significant difference between operated and non operated side (Table 19, Chart11).

Repeated measure ANOVA did not show any difference between operated and non operated side (Table 20) on day 2.

Table 21. Estimated Intracranial pressure on day 1

	ICP (Day 1)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	9.6	3.5	9.3	3.2	0.408	0.688
After 5 minutes	9.3	3.3	9.0	2.8	0.702	0.491
After 15 minutes	8.2	3.2	9.0	3.0	-1.362	0.189
After 30 minutes	8.7	2.4	8.7	2.4	0.014	0.989
After 45 minutes	9.2	4.0	8.8	3.5	0.489	0.630
After 60 minutes	9.2	4.0	9.9	3.9	-0.878	0.391

Table 22. Repeated measure ANOVA of day 1

	F	p
Operated	1.362	0.245
Non operated	1.076	0.379

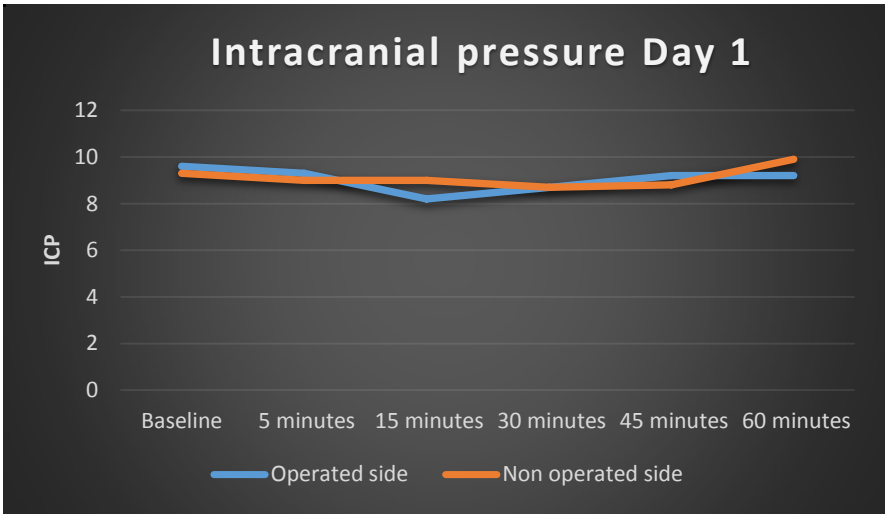

Chart 12. Comparison between operated and non operated side ICP

Estimated intracranial pressure on day 1 showed difference but was not significant (Table 21, Chart 12). p value was always > 0.05.

Repeated measures ANOVA comparing ICP between operated and non operated side did not show statistically significant difference (Table 22).

Table 23. Estimated Intracranial pressure on day 2

	ICP (Day 2)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	10.2	3.8	10.8	2.8	-0.790	0.439
After 5 minutes	9.0	3.1	10.3	3.1	-1.527	0.143
After 15 minutes	9.6	3.4	9.8	3.5	-0.476	0.639
After 30 minutes	10.4	3.9	10.6	3.1	-0.209	0.837
After 45 minutes	9.7	2.8	9.6	2.3	0.081	0.936
After 60 minutes	10.0	3.5	9.8	1.9	0.222	0.827

Table 24. Repeated measure ANOVA comparing operated and non operated side

	F	p
Operated	0.752	0.587
Non operated	1.971	0.090

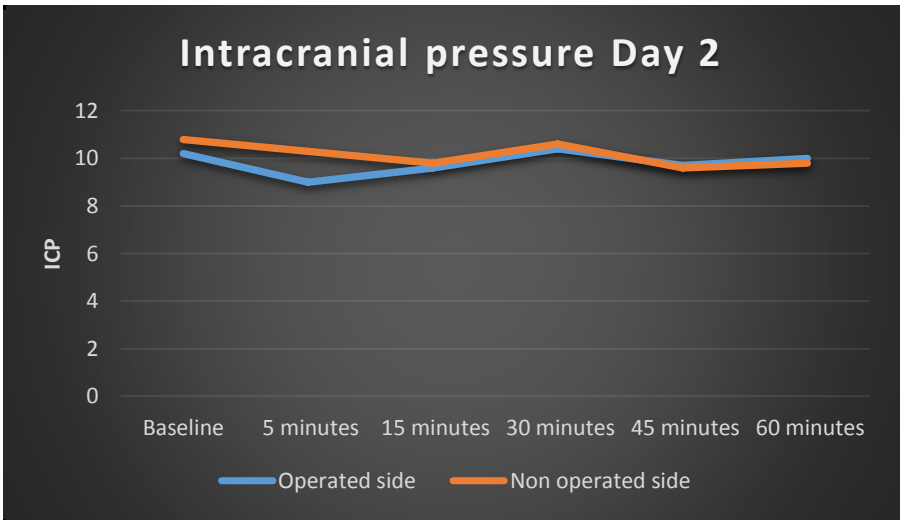

Chart 13. Comparison of ICP between operated and nonoperated side on day 2

Estimated intracranial pressure on day 2 (Table 23, Chart 13) did not show statistically significant difference on both operated and non operated side.

Repeated measures ANOVA comparing both operated and non operated side did not show difference on day 2 (Table 24).

Table 25. Estimated cerebral perfusion pressure (eCPP) on day 1

	CPP (Day 1)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	66.9	10.0	66.9	18.6	-0.007	0.995
After 5 minutes	55.9	13.7	69.4	10.3	-3.436	0.003
After 15 minutes	60.0	16.7	72.1	10.9	-4.869	<0.001
After 30 minutes	67.7	8.2	56.3	16.8	2.553	0.019
After 45 minutes	53.4	10.0	53.0	13.6	0.096	0.925
After 60 minutes	59.0	8.2	57.2	15.6	0.481	0.636

Table 26. Repeated measure ANOVA of day 1

	F	p
Operated	7.937	<0.001
Non operated	7.032	<0.001

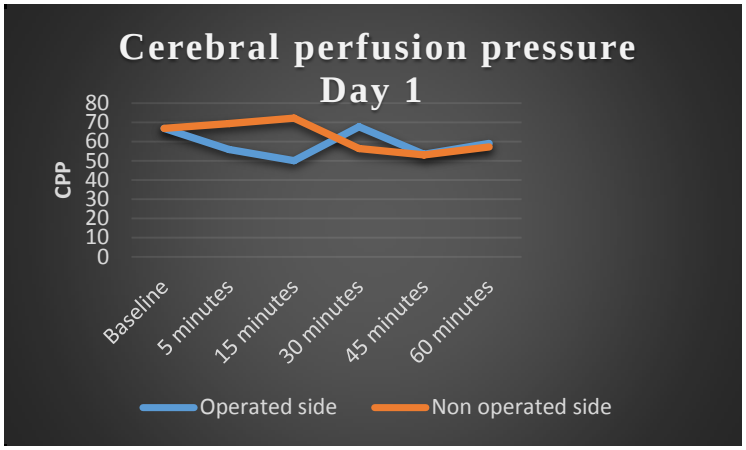

Chart 14. eCPP comparison between operated and nonoperated side on day 1

Estimated cerebral perfusion pressure eCPP on day 1 (Table 25) reduced at 5 minute on the operated side, but increased from 15 minute onwards.

Repeated measure ANOVA (Table 26) showed significant difference between operated and non operated side.

$F = 7.937$ $p = <0.001$ on operated side.

On non operated side

$F = 7.032$ $p < 0.001$

Table 27. Estimated cerebral perfusion pressure on day 2

	CPP (Day 2)				Paired t test	
	Operated side		Non operated side		t	p
	mean	sd	mean	sd		
Baseline	56.4	12.9	59.4	21.1	-0.723	0.479
After 5 minutes	71.9	17.3	59.8	27.6	1.633	0.119
After 15 minutes	74.8	20.8	61.7	21.3	1.931	0.069
After 30 minutes	57.8	12.2	71.4	22.0	-3.311	0.004
After 45 minutes	68.5	21.2	71.8	19.7	-1.488	0.153
After 60 minutes	68.2	25.5	94.9	11.5	-5.259	<0.001

Table 28 .Repeated measure ANOVA between operated and non operated side.

	F	p
Operated	4.443	0.001
Non operated	13.258	<0.001

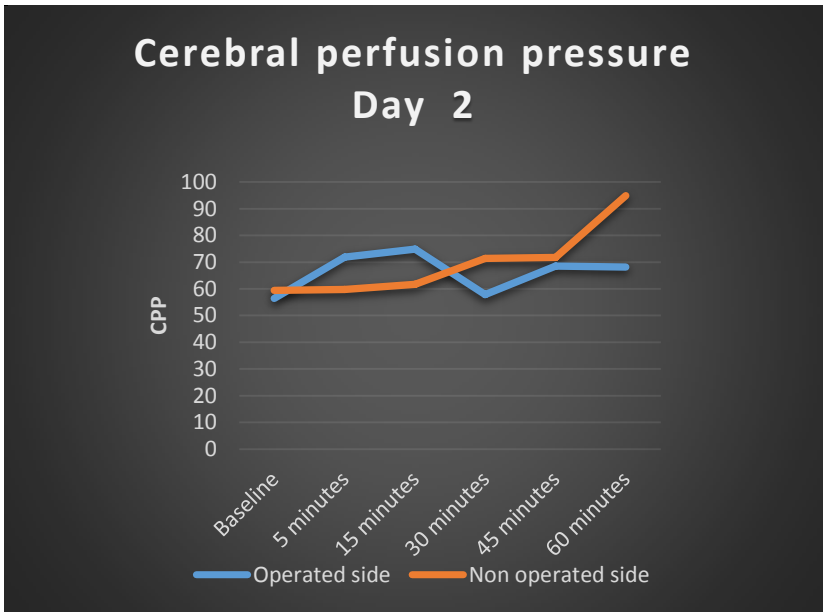

Chart 15. eCPP comparison between operated and nonoperated side on day 2

eCPP on day 2 (Table 27) increased in both operated and non operated side at 30 minutes remained elevated upto 60 minutes (Chart 15).

Repeated measure ANOVA (Table 28) shows significant change in eCPP on day 2.

Significant increase eCPP in the non operated side at the end of 60 minutes

Transthoracic echocardiographic parameters

Table 29. Left ventricular internal diameter in systole on day 1 and day 2

	LVIDs				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	3.2	0.9	2.9	0.5	1.486	0.154
After 5 minutes	3.3	1.0	2.8	0.6	1.987	0.061
After 15 minutes	3.2	0.9	2.7	0.4	1.960	0.065
After 30 minutes	3.3	0.9	2.7	0.5	2.739	0.013
After 45 minutes	3.1	0.9	2.9	0.5	0.573	0.574
After 60 minutes	3.0	0.7	3.0	0.6	-0.338	0.739

Table 30.Repeated measure ANOVA

	F	p
Day 1	0.774	0.571
Day 2	2.053	0.078

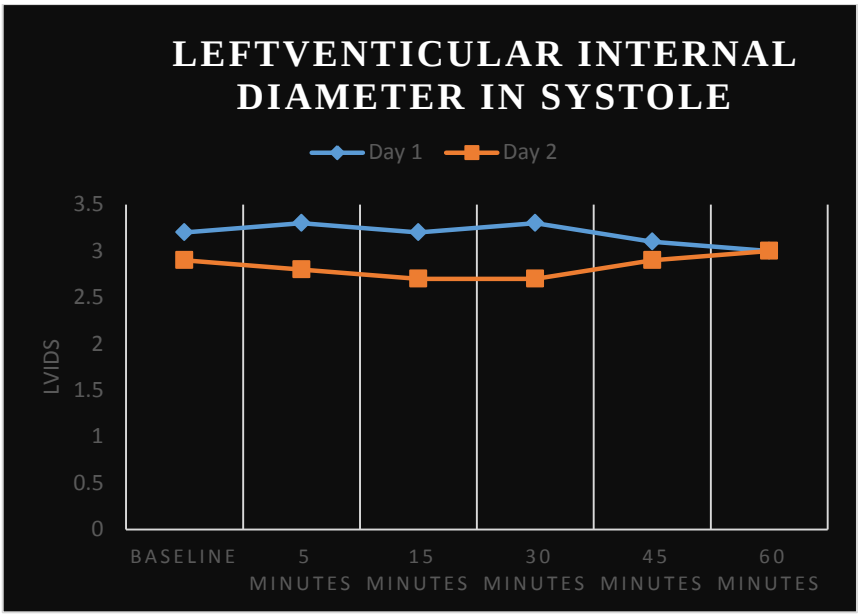

Chart 16. Comparison between Left ventricular internal diameter in systole on day 1 and day 2

Left ventricular internal diameter did not show change in diameter on day 1 and day 2 (Table 29, Chart 16).

Repeated measure ANOVA comparing day one andy day 2 (Table 30) did not show statistically significant difference

Table 31. Left ventricle internal diameter in diastole on day 1 and day 2

	LVIDd				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	4.6	1.0	4.4	0.7	0.639	0.531
After 5 minutes	4.4	0.9	4.4	0.8	0.309	0.761
After 15 minutes	4.3	0.9	4.3	0.7	0.013	0.990
After 30 minutes	4.5	0.9	4.3	0.7	0.932	0.363
After 45 minutes	4.4	0.7	4.4	0.7	0.000	1.000
After 60 minutes	4.6	0.8	4.3	0.7	1.279	0.216

Table 32. Repeated measure ANOVA

	F	p
Day 1	.458	0.807
Day 2	.242	0.943

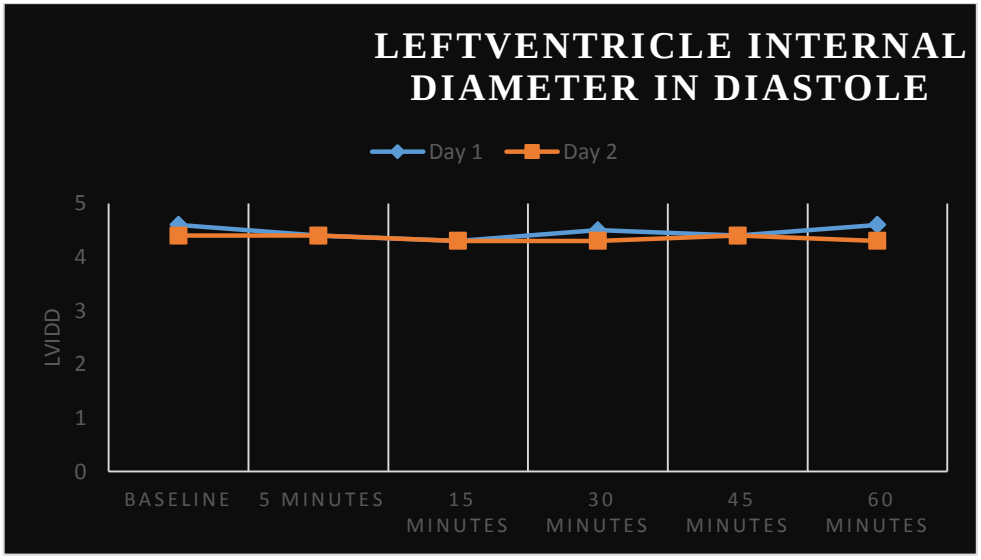

Chart 17. Comparison between Left ventricle internal diameter in diastole on day 1 and day 2

Left ventricular internal diameter in diastole (Table 31, Chart 17). Did not show any difference between day 1 and day 2 at any time interval.

Repeated measure ANOVA comparing day 1 and day 2 (Table 32) did not show and difference.

Table 33. End systolic volume on day 1 and day 2

	End Systolic Volume				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	32.3	13.6	36.3	10.3	-0.797	0.435
After 5 minutes	37.1	15.2	39.7	12.6	-1.233	0.233
After 15 minutes	38.2	14.4	37.6	11.3	-1.446	0.164
After 30 minutes	34.2	13.1	35.7	15.1	-0.534	0.599
After 45 minutes	34.4	10.8	41.2	13.0	0.110	0.914
After 60 minutes	35.4	11.2	40.5	11.7	0.799	0.434

Table 34. Repeated measure ANOVA

	F	p
Day 1	1.190	.320
Day 2	1.295	.273

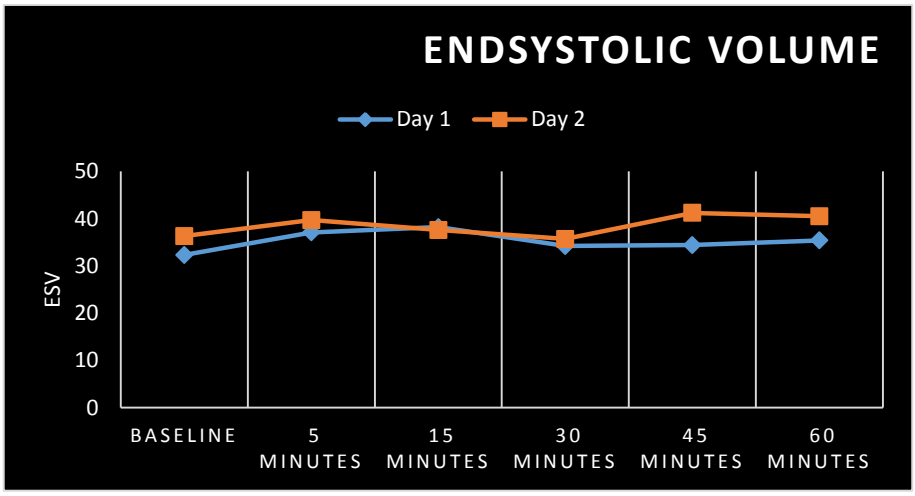

Chart 18. Comparison between End systolic volume on day 1 and day 2

End systolic volume did not change on day 1 and as well day 2 $p > 0.05$ at all time points (Table 33, Chart 18).

Repeated measures ANOVA did not show difference between day 1 and day 2 (Table 34).

Table 35. End diastolic volume on day 1 and day 2

	End diastolic volume				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	89.6	29.5	90.2	31.9	-1.271	0.219
After 5 minutes	92.1	22.4	95.3	36.0	-0.646	0.526
After 15 minutes	84.7	24.3	107.4	38.0	0.184	0.856
After 30 minutes	77.6	25.8	103.3	33.8	-0.325	0.748
After 45 minutes	86.0	16.9	98.5	28.8	-1.860	0.078
After 60 minutes	91.4	28.4	95.0	23.7	-1.939	0.067

Table 36. Repeated measure ANOVA

	F	p
Day 1	1.137	0.346
Day 2	1.500	0.197

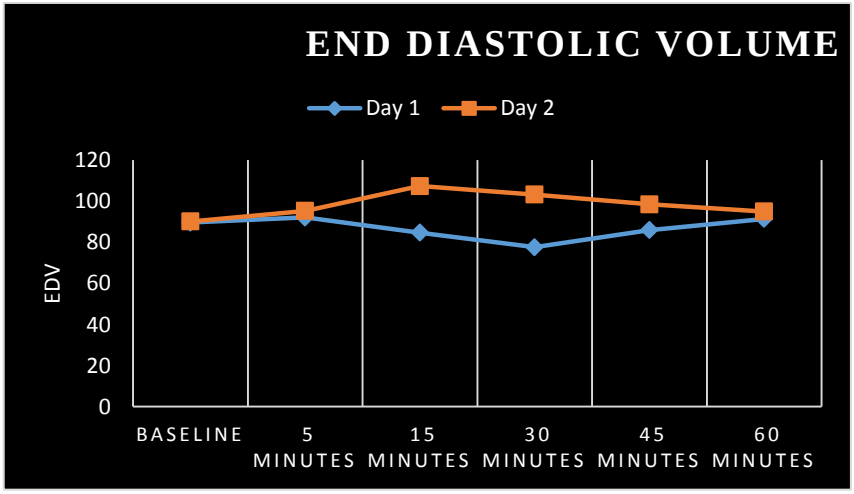

Chart 19. Comparison between End diastolic volume on day 1 and day 2

End diastolic volume also did not change after manitol administration (Table 35, Chart 19).

Repeated measure ANOVA, did not show statistically significant difference between day 1 and day 2 (Table 36).

Table 37. Stroke volume on day 1 and day 2

	Stroke Volume				Paired t test	
	Day 1		Day 2		T	p
	mean	sd	mean	sd		
Baseline	48.5	14.1	48.8	9.8	-0.123	0.904
After 5 minutes	49.0	11.8	48.9	10.0	0.036	0.972
After 15 minutes	50.5	10.1	49.6	10.2	0.284	0.780
After 30 minutes	52.0	11.4	50.5	9.3	0.425	0.675
After 45 minutes	50.4	9.1	48.8	9.0	0.698	0.494
After 60 minutes	53.1	9.2	49.4	11.7	1.647	0.116

Table 38. Repeated measure ANOVA

	F	p
Day 1	0.856	0.514
Day 2	0.150	0.980

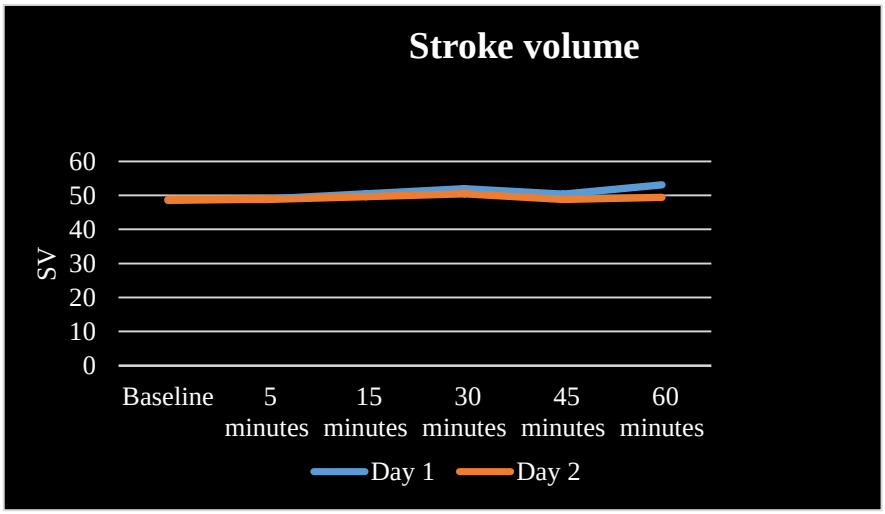

Chart 20. Comparison between Stroke volume on day 1 and day 2

Stroke volume on day 1 and day 2 did not increase or decrease on day 1 as well on day 2 (Table 37, Chart 20).

Repeated measures ANOVA did not show difference after manitol administration on both day 1 and day 2(Table 38).

Table 39. Ejection fraction on day 1 and day 2

	EF				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	64.3	11.4	66.8	8.1	-0.066	0.948
After 5 minutes	64.7	12.5	68.6	9.8	-0.421	0.678
After 15 minutes	60.7	12.4	66.7	12.7	-2.326	0.031
After 30 minutes	65.9	10.7	67.2	8.6	-2.602	0.018
After 45 minutes	67.5	9.0	67.2	7.8	11.208	0.000
After 60 minutes	69.6	8.2	68.0	10.3	-0.576	0.571

Table 40. Repeated measure ANOVA

	F	p
Day 1	1.608	0.165
Day 2	0.114	0.989

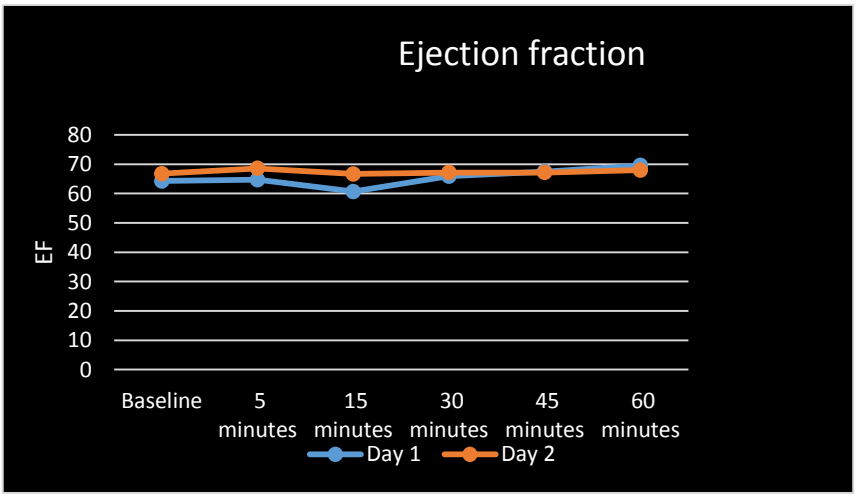

Chart 21. Comparison between Ejection fraction on day 1 and day 2

Ejection fraction did not alter after manitol administration (Table 39, Chart 21), no statistically significant difference was seen.

Repeated measures ANOVA did not show difference between day 1 and day 2 (Table 40).

Table 41. Cardiac output on day 1 and day 2

	Cardiac output				Paired t test	
	Day 1		Day 2		t	p
	mean	sd	mean	sd		
Baseline	4.1	1.0	4.1	1.0	-0.083	0.935
After 5 minutes	4.3	1.4	4.3	1.3	0.168	0.868
After 15 minutes	4.1	1.0	4.2	1.2	-0.104	0.918
After 30 minutes	4.0	1.1	4.1	1.2	-0.631	0.536
After 45 minutes	3.7	0.9	4.1	1.0	-1.738	0.098
After 60 minutes	4.1	0.9	4.2	1.0	-0.368	0.717

Table 42. Repeated measure ANOVA

	F	p
Day 1	1.253	0.291
Day 2	1.143	0.982

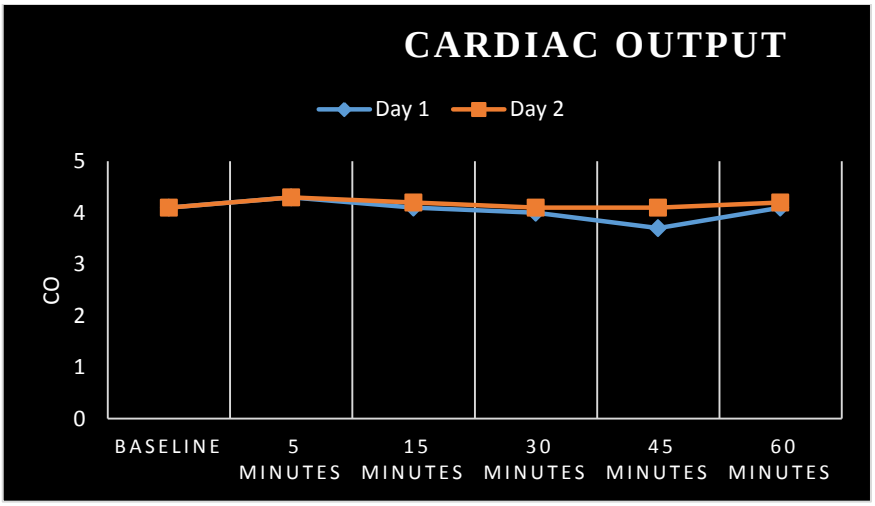

Chart 22. Comparison between Cardiac output on day 1 and day 2

Cardiac out put on both day 1 and day 2 (Table 41, Chart 22) did not change after manitol administration.

Repeated measures ANOVA (Table 42) was not statistically significant between day 1 and day 2.

Observations

Vital parameters : HR, MAP, SpO2: No changes were seen in HR, MAP Spo2% following mannitol administration at different time intervals. No significant difference was seen between these two postoperative days.

Transcranial Doppler Velocities:

Day 1: Mean flow velocity increased in both operated and non-operated side. The change was more significant on the non-operated compared to operated side.

Pulsatality Index: decreased from baseline but was not statistically significant.

Resistivity Index: did not show significant decrease.

ICP: Baseline ICP was normal, statistically significant decrease was not seen on both sides.

eCPP: increase in estimated CPP was significant at 5 minutes on the operated side persisted upto 15minutes.

Day 2: No significant change in mFV, PI, RI, ICP seen on second day.

Echocardiographic variables:

LVIDs and LVIDd did not change following mannitol administration. No significant difference was seen between day one and two.

ESV, EDV,SV,CO did not change significantly following mannitol infusion throughout the study period. No difference was seen between day 1 and 2.

DISCUSSION

Synopsis of the results: In this prospective observational study we observed that 0.5 g/kg of mannitol significantly altered the cerebral haemodynamics measured by TCCD on the first postoperative day. However, on the 2nd postoperative day administration of similar dose of mannitol did not affect the cerebral haemodynamics significantly. On both PODs, administration of mannitol during the study period did not alter the systemic haemodynamics as well as echocardiographic variables from the baseline values.

At the doses of 0.5 mg/kg does not produce significant cardiovascular changes that are seen at the dose range of 0.5 to 2 gm/kg bolus infusion.[32]

Justification for the study

Mannitol since its introduction in 1960 is the most widely used osmotherapy agent worldwide. Mannitol being the main stay in clinical practice of pre hospital care of TBI patients, treat impending herniation's, provide intraoperative slack brain during removal of tumour. Mannitol has been used as both bolus dose as well infusion. Magnitude of effect produced by mannitol is determined by the dose, baseline level of ICP, and also on rate of infusion. Studies have shown that bolus dose is more effective in reducing ICP compared to continuous infusion. The recommended dose of mannitol for reduction of ICP is 0.25 to 1g/kg body weight. Most of the studies reviewed administered mannitol in the dose range of 0.25 to 1gm/kg. Nincevic et al used a very low dose mannitol 0.3gm/kg, pulsatality index and blood flow velocity increased at these low doses.[33] Cerebral blood flow changes is seen at very low doses of mannitol however, the effect of mannitol is more pronounced at higher doses. In our study patients received 0.5gm/kg mannitol three times a day. Administration of mannitol brings about changes in ICP, cerebral perfusion and

cerebrovascular resistance. To date the changes in the cerebral blood flow after mannitol administration is poorly understood.

Several animal studies are done in past to study the changes in the cerebral blood flow after mannitol administration. Measurements of cerebral blood flow in these studies was invasive as well animals were sacrificed at the end to study the effect of mannitol. Human studies comprised of different pathologies like stroke, TBI, tumours. Changes were measured using various modalities like micro dialysis, SPECT scan, MRI, Invasive ICP monitoring. All these monitoring cannot be a reality in day to day practice. Hence we employed TCCD to monitor cerebrovascular changes. In our study we noticed change in mean flow velocity on both operated and non operated side increased soon after mannitol administration. On first POD the mean flow velocity increased at 5 minutes on the operated side and non-operated side. In the first 15 minutes the change was significant on the operated side compared to non-operated side. Following which there was a brief decrease in mFV at 30 min and 45 min in the operated side. At 60 minutes there was a second peak in mFV in the operated side. In the non operated side there was a gradual increase in the mFV from 30 min to 60 min. We believe that there was a defective autoregulation in the operated side causing initial increase in mFV immediately following the mannitol administration due to increased cerebral blood flow which was not seen in the non operated side. The second peak increase mFV correlates with osmotic action of mannitol, improved rheology etc. Quala wang et al evaluated two different doses of mannitol 125 and 250 ml and its effect on ICP and CPP in intracerebral haemorrhage.[34] Mean flow velocity increased in both affected and non-affected hemisphere from 30 to 120 mins. The changes in mean flow velocity was similar to our studies. Compared to this study the dose of mannitol administered in our study is less.

Vincenzi et al differed in their results following mannitol administration. The higher MCA flow velocity was seen on the affected side (in ICH)at the baseline and during the infusion period compared to the non affected side.[29] They attributed this changes to reduced perilesional oedema. The biphasic response seen in our study was not noted in their study.

No changes in the mFV was noticed during 2nd postoperative day. We believe that the cerebral homeostasis was returned to normal during the second POD which is responsible for the action seen in 2nd POD.

Mannitol acts by reducing ICP .PI measured by TCD can be reflect of ICP. Mannitol reduces cerebrovascular resistance of distal arterioles. As the resistance decreases flow increases and thus improves the cerebral perfusion in the affected areas. In our study PI gradually decreased on both operated and non-operated side. The decrease was not however statistically significant. The decrease in PI can be considered as indirect evidence of reduced ICP and improved perfusion produce by mannitol. Similar decrease in PI was seen by Wang et al.[35] Vincenzi et al did not find any difference in PI, probably due to preserved pulsatality.[29] On 2nd postoperative day in our study PI did not show any change.

ICP derived from PI showed gradual decrease from baseline both on operated side and non-operated side, decrease is not statistically significant. These studies did not derive ICP from PI. Hence ICP results cannot be compared.

In our study repeated administration of mannitol did not alter MAP at any point on both the days. Dhringer also noticed that boluses of mannitol dose not consistently raise the blood pressure.[34] Chatterji et al also had similar finding of no change in MAP and heart rate after mannitol administration.[32]

But all these beneficial effects of mannitol do not translate to good clinical outcome. Cochrane review on mannitol in head injury 2007 concluded lack of evidence for recommendation of mannitol. In addition, Cochrane review on stroke made no recommendations for routine use of mannitol.[36] Outcome studies following mannitol administration in head injury patients did not show difference on 6months follow up.[10] Several randomized studies in the past have focussed only on effect of mannitol in head injuries, ischaemic stroke, intraoperative brain relaxation and few in vivo models of brain injury. We did not find any studies emphasizing on cerebrovascular effects of mannitol administration in the postoperative period.

Mannitol administration brings about significant cardiovascular changes. Central venous pressure and cardiac preload increased 5 to 15 minutes after mannitol

administration.[32] Bratton et al stated that acute infusion of mannitol induces rise in cardiac output and filling pressure , temporary increase in MAP and cerebral perfusion pressure.[2] Cardiac output increases by 30% increasing cerebral blood flow .Rapid bolus administration of mannitol can precipitate hypotension.The cardiovascular and respiratory complications are common after supratentorial surgeries. Supraventricular tachycardia, hypertension, hypotension is commonly seen in the postoperative period. In a study by Gilsanz et al out of 145 patients 66 of them had significant hypotension secondary to hypovoluemia.[37] Hypovoluemia is more pronounced in the postoperative period due to fluid shifts, ongoing blood loss, use of diuretics, glycosuria. Mannitol administration in the postoperative period will further compound this effect and lead to acute renal failure, pulmonary oedema, acidosis, electrolyte imbalance leading to adverse clinical outcome. This warrants careful administration of mannitol in patients with cardiac illness. Mean arterial pressure is the main determinant of CPP. Fall in MAP following mannitol bolus administration can reduce cerebral perfusion and precipitate ischaemia in vulnerable regions of the brain. No studies have simultaneously analysed the action of mannitol on cerebrovascular system and cardiovascular system. Our study laid focus on both these systems on two consecutive postoperative days and tried to analyse the action of mannitol in a panoramic view.

Earlier literature on the issue

Mendelow et al observed the increase in cerebral blood flow following 2g/kg mannitol administration in head injury patients.[27] On comparing the affected and unaffected hemisphere less damaged hemisphere had greater increase in cerebral blood flow.

CPP being a surrogate marker for cerebral blood flow measurements. In the absence of raised ICP, CPP changes reflect alterations in MAP. Either a decrease in MAP or an elevation in ICP will alter CPP.

eCPP increased at 15 minutes on day 1 on the non operated side and increased at 30 minutes on day 2($p<0.005$). Muizelaar et al studied the effect of mannitol on global CBF.[38] The investigators concluded that mannitol did not rise CBF in patients with

intact autoregulation after head injury. CBF increased in patients with defective autoregulation and those whose basal CBF was less than 25ml as in hypo perfusion. Sharma et al observed impaired autoregulation after supratentorial craniotomies.[17] Which probably was the causative factor for our observations.

We did not observe any changes in vital parameters with 100ml bolus mannitol administration. Mannitol administered in small boli repeatedly lowers the ICP, increases the intracranial compliance and alters the rheology of blood and improves the cerebral perfusion. Vincenzi et al Observed increase in mean flow velocities in MCA in ICH patients following mannitol administration started 10minutes after infusion and lasted upto 60 minutes.[29] No changes in velocity was seen on the healthy side. PI increased on the heathy side alone but not in the affected hemisphere. Mannitol induces flow gradient between brain parenchyma and vascular compartment removes the interstitial fluid reducing the cerebral oedema.[39] Due to reduction in the perilesional and interstitial oedema following mannitol the increase in mean flow velocities can be an indirect sign of improved cerebral perfusion thus explains the restoration of perfusion pressure following the initial decrease. Preoperative cerebral autoregulation is impaired in patients with large supratentorial tumour and midline shift of more than 5mm[17] they continue to have impaired autoregulation and vasomotor reactivity in the first 24 hours following craniotomy. Paulson et al reported the loss of autoregulation in the unaffected cerebral hemisphere in their series of 6 patients.[40] Cerebral perfusion pressure at the upper limit of autoregulation cerebral resistance arterioles are close to maximally constricted and ability to rise in CBF is response to change in viscosity is limited. Due to loss of autoregulation in the postoperative period, and due heterogeneity between the cerebral hemisphere, the fall in the brain volume could be due to reduced brain water content and not reduced cerebral blood volume in response to vasoconstriction alone.[41]

In our study soon after mannitol infusion no change occurred in left ventricular systolic function on both day 1 and day 2. Left ventricular systolic diameter in systole and diastole remained similar to baseline values from the start of the study upto 60 minute. End diastolic volume showed increase at 60 minutes but is not statistically significant. Mannitol did not produce any significant changes Of stroke volume, cardiac output and ejection fraction on both days.

Where as Chatterji[32] et al observed increase in the end diastolic area, CO, SV at 5 and 15 minutes. The dose of mannitol administered in this study was 1 g/kg over 15 minutes which is much higher than the dose used in our study i.e 0.5 gm/kg.

Under the effect of general anaesthetics the haemodynamic changes of mannitol could be more pronounced and cannot be solely attributed to mannitol. Similar changes were not seen in our study. HR, MAP, remained unaltered as seen in study by chatterji et al [32]. Niki et al measured haemodynamic variables like CVP, CO, SV during craniotomy at regular intervals. Mannitol at the dose of 1 g/kg reduced MAP, HR in the t1rst 45 minutes.

The probable cause of all these changes can be due to osmotic intravascular expansion followed by diuresis. The factors that affected both these studies could be larger dose of mannitol compared to our study, anesthetic effects which is absent in the postoperative period, intraoperative blood loss. Deep seated lesions require good brain relaxation hence warrants the use of higher doses compared to the postoperative period. The error of measurement is about 26.4% in an non-invasive cardiac output monitors hence may not be true measure of the changes in cardiovascular parameters. Echocardiographic assessment correlates well with results obtained from thermos dilution techniques. These changes in CO, SV, EDV can be detrimental in patients with limited cardiac reserve. In patients with cardiac illness, adequate measures must be taken to choose the dose and timing of mannitol administration.

Why we chose trans cranial Doppler and transthoracic echocardiography to assess the effect of mannitol:

Transcranial Doppler (TCD) ultrasonography is an inexpensive, non-invasive real-time measurement of blood flow characteristics and cerebrovascular haemodynamics within the cerebral blood vessels. The physiologic data obtained from these measurements are complementary to structural data obtained from invasive methods of cerebral blood flow measurements. TCD is the most convenient way to monitor vascular changes in response to interventions during acute cerebrovascular events at the bedside. Invasive ICP monitoring is not warranted in low risk group and carried increased incidence of infection and increased mortality. TCD derived indices is used as a surrogate marker on par to invasive methods of estimation of cerebral blood flow.

Transoesophageal echocardiography being an invasive modality cannot be a monitoring option in the postoperative period. Whereas TTE being a non-invasive simple bedside monitoring tool provides accurate findings similar to transoesophageal echocardiography. Hence we used TTE to quantify the changes produced by mannitol.

In summary, we found that caution needs to be exercised in administering mannitol in the immediate postoperative period especially in large doses as it may increase the cerebral blood flow disproportionately despite maintenance of normal systemic hemodynamics. This can paradoxically increase the CBF can lead to edema and haemorrhage. This is probably due to altered autoregulation in the operated side. However the effects are normalized in the second POD. Future studies needs to address the effects of mannitol on regional cerebral blood flow and whether cerebral perfusion pressure and autoregulation in the immediate postoperative period. Till the question is answered, our study shows mannitol should be used judiciously in this scenario.

CONCLUSION

1. Mannitol infusion in postoperative period is associated with significant increase in mean flow velocities in both hemispheres indicating improved perfusion following mannitol infusion.

2. No benefit of repeated administration of mannitol is seen. On 2nd postoperative day mannitol did not produce any change in the mean flow velocities.

3. eCPP decreased transiently on the first postoperative day at 15 and 30 minutes ‘on both the sides returned to normal by 45 minutes. On second post-operative day eCPP increased significantly at 30 and 60 minutes in both sides.

4. No rebound increase in ICP was noticed following repeated administration of mannitol.

5. Mannitol maintained resistivity and pulsatality indices in both cerebral hemispheres.

6. Mannitol at the dose of 0.50gm/kg produces no significant cardiovascular changes. On both day 1 and 2 cardiac indices like CO, SV, EF, EDV, ESV, did not change following mannitol administration.

7. Repeated administration of mannitol in the postoperative period does not produce significant cerebral haemodynamic changes compared to single bolus dose of mannitol.

8. Mannitol at the dose of 0.50gm/kg can safely be administered to reduce ICP without adverse cardiovascular effects.

LIMITATIONS

An important limitation of this study is the absence of comparison between invasive and non-invasive techniques of measurement of CPP, CBF, and also CO. However invasive monitoring like ICP, PA catheter is not warranted in low risk group ASA 1 and 2.

TCCD can be performed only intermittently but ICP catheter provides a real time monitoring of ICP. Being an operator dependent monitor TCCD is prone for technical errors and as well inter observer variability. Large case series are published supporting the TCCD derived indices as surrogate markers of cerebrovascular homeostasis against the gold standard ICP measurement.

Our study included less number of patients and only those undergoing surgery for decompression of tumour. The results cannot be authentically extrapolated to surgeries due to other pathologies like trauma, stroke, congenital anomalies with different mechanism of brain injury. Assessment of autoregulation would have added more strength to the study. Our study not being an outcome study, did not analyse the effect of mannitol on clinical improvement.

The various factors in postoperative period like fluid shifts, diuresis, electrolyte imbalance, blood loss, fever can alter the haemodynamic status. The cardiovascular effects seen during mannitol administration can be confounded by these postoperative variables. Meticulous attention was given to maintain these factors relatively constant.

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