A COMPARISON OF EQUIOSMOLAR CONCENTRATIONS OF COMBINATION OF MANNITOL AND HYPERTONIC SALINE VS MANNITOL ALONE TO ASSESS BRAIN RELAXATION, HEMODYNAMIC PROFILE AND ELECTROLYTE CHANGES IN PATIENTS UNDERGOING ELECTIVE SUPRATENTORIAL CRANIOTOMY
A RANDOMISED CONTROL TRIAL

Dissertation submitted in partial fulfillment of the requirement of the Tamil Nadu Dr. M. G. R. Medical University for the M.D Branch X (Anesthesiology) Examination to be held in May 2018

A COMPARISON OF EQUIOSMOLAR CONCENTRATIONS OF COMBINATION OF MANNITOL AND HYPERTONIC SALINE VS MANNITOL ALONE TO ASSESS BRAIN RELAXATION, HEMODYNAMIC PROFILE AND ELECTROLYTE CHANGES IN PATIENTS UNDERGOING ELECTIVE SUPRATENTORIAL CRANIOTOMY
A RANDOMISED CONTROL TRIAL

Dissertation submitted to the

THE TAMIL NADU DR.MGR MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirements for the degree of

MASTER OF MEDICINE

IN

ANAESTHESIOLOGY

By

SNEHA E

Register Number: 201620360

DEPARTMENT OF ANAESTHESIOLOGY

CHRISTIAN MEDICAL COLLEGE

VELLORE

CERTIFICATE

This is to certify that "**A COMPARISON OF EQUIOSMOLAR CONCENTRATIONS OF COMBINATION OF MANNITOL AND HYPERTONIC SALINE VS MANNITOL ALONE TO ASSESS BRAIN RELAXATION, HEMODYNAMIC PROFILE AND ELECTROLYTE CHANGES IN PATIENTS UNDERGOING ELECTIVE SUPRATENTORIAL CRANIOTOMY-A RANDOMISED CONTROL TRIAL"** is the bonafide work of Dr. Sneha E under my supervision in the department of Anesthesiology, Christian Medical College, in partial fulfillment of the requirements for the M.D Anesthesiology Examination Branch X of the Tamil Nadu Dr. M.G.R Medical University to be held in May 2018 and no part thereof has been submitted for any other degree.

Dr.Georgene Singh (MD, DM)

Professor

Department of Anesthesiology

Vellore Christian Medical College

15/10/2018 Vellore -632004

CERTIFICATE BY THE HEAD OF THE DEPARTMENT / PRINCIPAL

This is to certify that "**A COMPARISON OF EQUIOSMOLAR CONCENTRATIONS OF COMBINATION OF MANNITOL AND HYPERTONIC SALINE VS MANNITOL ALONE TO ASSESS BRAIN RELAXATION, HEMODYNAMIC PROFILE AND ELECTROLYTE CHANGES IN PATIENTS UNDERGOING ELECTIVE SUPRATENTORIAL CRANIOTOMY-A RANDOMISED CONTROL TRIAL"** is the bonafide work of Dr. Sneha E under the supervision of Dr. Georgene Singh, Professor, Department of Anesthesiology, Christian Medical College, Vellore.

Dr. Sajan Philip George, MD,DNB.
Professor and Head .
Department of Anesthesiology.
Christian Medical College.
Vellore.

Dr. Anna Pulimood.
Principal.
Christian Medical College .
Vellore.

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

Dr. George Thomas, M.B.B.S., D. Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., MA (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

February 07, 2016,

Dr. Sneha E,
PG Registrar,
Department of Anesthesia,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Grant: -**
Comparison of equiosmolar concentrations Of combination of mannitol and hypertonic Saline vs mannitol alone to assess hemodynamic profile, brain relaxation and electrolyte abnormalities in patients undergoing elective supratentorial craniotomy--A Randomised Control Trial.
Sneha E, Employment Number:21134, Post Graduate registrar, Dr.Georgene Singh, Professor, Emp. No.28474, Dr. Ramamani Mariappan, Employment number: 50916, Professor, Department of Anesthesia, Ms. Reka k, Senior Demonstrator, Employment No.:32547, Department of Biostatistics.

Ref: IRB Min No: 10389 [INTERVEN] dated 30.11.2016

Dear Dr. Sneha E,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Cc: Dr.Georgene Singh, Department of Anaesthesia, CMC, Vellore.

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

Dr. George Thomas, M.B.B.S., D. Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., MA (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

February 07, 2016,

Dr. Sneha E,
PG Registrar,
Department of Anesthesia,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Grant: -**
Comparison of equiosmolar concentrations Of combination of mannitol and hypertonic Saline vs mannitol alone to assess hemodynamic profile, brain relaxation and electrolyte abnormalities in patients undergoing elective supratentorial craniotomy--A Randomised Control Trial.
Sneha E, Employment Number:21134, Post Graduate registrar, Dr. Ramamani Mariappan, Employment number: 50916, Professor, Department of Anesthesia, Ms. Reka k, Senior Demonstrator, Employment No.:32547, Department of Biostatistics.

Ref: IRB Min No: 10389 [INTERVEN] dated 30.11.2016

Dear Dr. Sneha E,
The Institutional Review Board (**Silver**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Comparison of equiosmolar concentrations Of combination of mannitol and hypertonic Saline vs mannitol alone to assess hemodynamic profile, brain relaxation and electrolyte abnormalities in patients undergoing elective supratentorial craniotomy--A Randomised Control Trial" on November 30th 2016.

The Committee reviewed the following documents

1. IRB Application form
2. CV's of Drs. Georgene, Ramamani.
3. Consent and Information sheets
4. Data Sheet
5. No. of documents 1-4.

The following Institutional Review Board (**Silver**, Research & Ethics Committee) members were present at the meeting held on November 30th 2016 in the BRTC Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Name	Qualification	Designation	Affiliation
Dr. George Thomas	MBBS, D Ortho, PhD	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB, Chennai	External, Clinician
Dr. Vinod Joseph Abraham	MBBS, MD, MPH	Professor, Community Medicine, CMC, Vellore	Internal, Clinician
Dr. Suceena Alexander	MBBS, MD, DM	Associate Professor, Nephrology, CMC, Vellore	Internal, Clinician
Dr. Abhay Gahukamble	MS, D Ortho, DNB(Ortho)	Associate Professor, Paediatric Orthopaedics, CMC, Vellore	Internal, Clinician
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Additional Vice Principal (Research), Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore.	Internal, Clinician
Rev. Dr. T. Arul Dhas	MSc, BD, DPC, PhD(Edin)	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. AshishGoel	MBBS, MD, DM	Professor, Hepatology, CMC, Vellore	Internal, Clinician
Dr. Binu Susan Mathew	MBBS, MD	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
Dr. P. Zachariah	MBBS, PhD	Retired Professor, Vellore	External, Clinician
Dr. RV. Shaji	BSc, MSc, PhD	Professor, Heamatology, CMC, Vellore	Internal, Basic Medical Scientist

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bio-Engineering, CMC, Vellore	Internal,Basic Medical Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Shirley David	MSc, PhD	Professor, Head of Fundamentals Nursing Department, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Sathya Subramani	MD, PhD	Professor, Physiology, CMC, Vellore	Internal, Clinician
Mrs. Ruma Nayak	M Sc (Nursing)	Professor, Head of Paediatric Nursing & Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Prasanna Samuel	MSc, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist &Epidemiologist
Dr. D. J. Christopher	BSc, MBBS, DTCD DNB, FRCP(Glasg), FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Jiji Elizabeth Mathews	MBBS, MD, DGO	Professor, Head of OG unit - 5, CMC, Vellore.	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Comparison of equiosmolar concentrations Of combination of mannitol and hypertonic Saline vs mannitol alone to assess hemodynamic profile, brain relaxation and electrolyte abnormalities in patients undergoing elective supratentorial craniotomy--A Randomised Control Trial" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

IRB Min No: 10389 [INTERVEN] dated 30.11.2016

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 50,000/- INR(Rupees Fifty Thousand only) will be granted for 12 months.

Yours sincerely

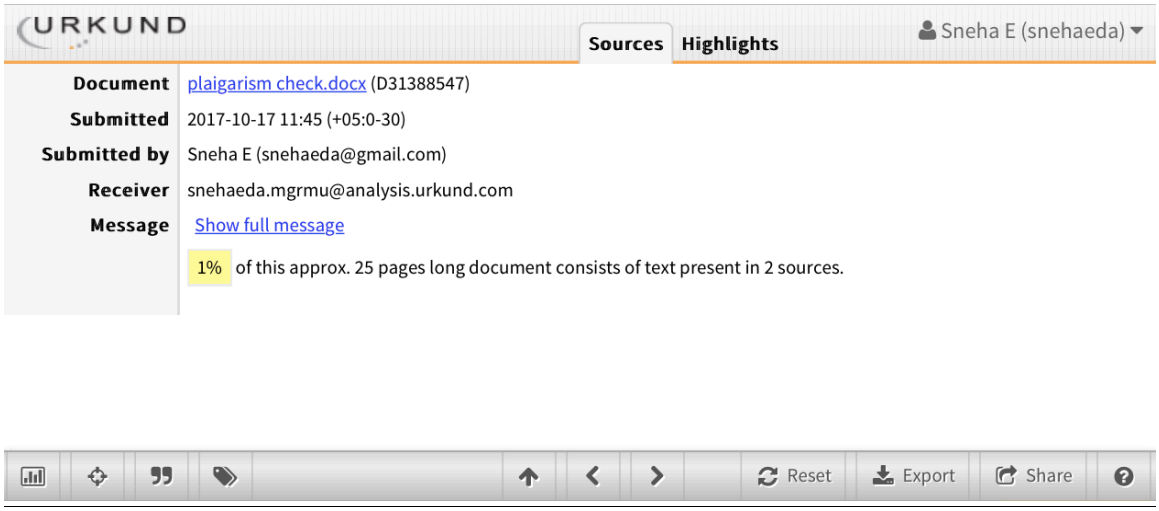
Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 10389 [INTERVEN] dated 30.11.2016

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Urkund Plagiarism Certificate



Acknowledgements

I thank God Almighty for giving me the opportunity to do this thesis.

I wish to express my sincere gratitude to my guide Dr. Georgene Singh, Professor, Christian Medical College. I truly thank her and consider myself blessed to have an approachable, friendly, kind, accomplished and inspiring guide such as her. I would also like to thank her for taking such a keen interest in showing me how to go about doing research, and for accompanying me right from presentation of thesis proposal in the department of neurosurgery, to the Institutional Review Board, for helping me recruit patients and collecting data in the neurosurgery theatres.

I would like to thank Dr Sajan Philip George, Head of the Department of Anesthesia, Christian Medical College for providing the necessary facilities for doing research.

I am grateful to Dr.Ramamani Mariyappan who helped me with carrying out many of the cases in the neurosurgery theatres whenever I couldn't be there myself.

I thank Professor Dr. V. Rajsekhar, Head of Neurosurgery unit 2,for giving me valuable advice and opinions regarding this research project. I thank, Professor Dr. Krishnaprabhu, Head of Neurosurgery unit 1 for his encouragement and support for going ahead with this dissertation topic. Dr. Mathew Joseph, Head of

Neurosciences, was of immense help in the post-operative follow-up of the patients in this study.

I reserve a special word of gratitude to the remarkably proficient staff anesthesia technicians in the Neurosurgical theatres, who set aside time to collect samples for ABG of the patients involved in the study, in addition to their other responsibilities. Special word of thanks to Dr.Vinayak Shukla, Professor and Head of Cardiothoracic Surgery, for letting me use their ABG machine to process my samples. I thank Mr.Bijesh Yadav my statistician, for their help in preparing the statistical tables and for accommodating me in his demanding schedule and helping me beyond working hours.

Last, but far from least, I reserve special appreciation for my parents and my family and friends for their constant love and support through these years of training.

Sneha E

ABSTRACT

Background and Objectives

This study aims at comparison of equiosmolar concentration of a combination of mannitol with hypertonic saline vs. mannitol to assess brain relaxation on opening of dura by surgeons and to compare hemodynamic profile(HR,SBP,DBP,MAP),use of vasopressor support , total fluid input and output, electrolyte abnormalities, between the two groups.

Patient and Methods

This study was initiated after getting approval from the Institutional Review Board (IRB) and Ethics Committee of our institution. After obtaining informed patient consent, a total of 58 patients who fulfilled the inclusion criteria were recruited for this study during the time period March - September 2017. Patients were divided into 2 groups, one group received mannitol and the other received equiosmolar concentration of mannitol and hypertonic saline.

Patients are assessed preoperatively and anaesthetized according to our standard institutional protocol. Apart from routine noninvasive monitoring,(ECG,HR, et CO_2) hemodynamics is monitored using an invasive arterial line and the depth of anesthesia was monitored using Bispectral index monitor. The ventilation is adjusted to maintain a $PaCO_2$ of 30-35 mm of Hg. Osmotic diuretic agents either

mannitol or equiosmolar concentration of mannitol with hypertonic saline combination @ a calculated dose of 4 ml/kg is administered during craniotomy .The hemodynamics and need for vasopressor support are noted during serial intervals for 2 hours after administration of the drugs. Serum electrolyte levels (sodium and potassium),serum lactate levels and blood sugar levels were also measured at baseline and at end of one hour from the time of administration of study drug.

Surgeons assessment of brain relaxation was noted on a four point scale (1.Perfectly relaxed:2.Satisfactorily relaxed:3.Firm brain:4.Bulging brain).The need for additional osmotherapeutic agents was also studied.Total fluid input and urine output were noted at the end of procedure.

Results

60 patients who satisfied inclusion criteria were included in the study. Of the 60 patients, 2 patients were not included for analysis due to insufficient data. Of which ,29 patients received combination of mannitol with hypertonic saline and 29 patients received mannitol alone as osmotherapy during craniotomy. The two groups were comparable in distribution of age, sex, weight, BMI, tumor location and tumor pathology. There was no statistically significant difference in brain relaxation score, hemodynamic profile,use of vasopressors,electrolye abnormalities, intake and output between the groups .Although biochemically

mild hyponatremia,increased vasopressor use and need for additional osmotherapeutic agent were observed in the group which received mannitol alone no statistical significance was noted .

CONCLUSION

We conclude that the equiosmolar combination of mannitol and hypertonic saline is a safe and comparable option to mannitol for providing adequate brain relaxation. There is a tendency for increased vasopressor use , need for additional osmotherapeutic agent and hyponatermia in the mannitol group.

Key words:

Supratentorial craniotomy, osmotheraphy, mannitol, 3%hypertonic saline, brain relaxation, hemodynamics.

TABLE OF CONTENTS

INTRODUCTION

Majority of the intracranial neoplasm are supratentorial (>80%) of which most common are glioma (36%) and meningioma (32. 1%). They generally present with features of raised intracranial pressure such as headache, vomiting and blurring of vision. These tumors are generally associated with surrounding brain edema and midline shift on preoperative CT scans . It is essential to reduce intracranial pressure as a part of the anesthetic management to prevent herniation of brain and to minimize secondary brain injury due to retraction. Moreover, they also require maximal reduction of brain tension to facilitate surgical access. To facilitate brain relaxation, various techniques are in practice. One of most commonly used method is control of brain tension via control of cerebral blood flow and cerebral metabolic requirement, i.e,the , ***'chemical brain retractor concept'***.

This concept involves use hyperosmotic agents such as mannitol and hypertonic saline. These agents can't cross blood brain barrier and creates an osmolar gradient drawing fluid from brain tissue into intravascular compartment and reduces brain edema which in turn reduces intracranial pressure. This can be assessed clinically by surgeon on opening of dura on a four-point scale,1: Perfectly relaxed. 2:Satisfactorily relaxed. 3:Firm brain. 4: Bulging brain. Mannitol is a time-tested drug and had been in use for reducing intracranial pressure. In addition to the osmotherapeutic mechanism it also has other mechanisms by which it reduces intracranial pressure. It increases blood rheology,

decreases blood viscosity, increases blood volume. All these effects in turn contribute to reduction of intracranial pressure. However, it is associated with hyponatremia, hyperkalemia and acute hypervolemia which are deleterious in patients with congestive heart failure, chronic kidney disease, diseases involving liver.

Another alternative is hypertonic saline. Recent evidence has shown that equiosmolar dose of hypertonic saline may also be used with better brain relaxation and more hemodynamic stability. In addition to its osmotic action, it also has other mechanisms such as hemodynamic, vasoregulatory, immunological, and neurochemical effect and causes endothelial shrinkage which decreases intracranial pressure. It is also associated with side effects such as hypernatremia, decreased platelet aggregation and hyperchloremic metabolic acidosis.

Since it is the serum osmolarity playing an important role in regulating intracranial pressure we would like to combine both the drugs while maintaining the osmolar load ,to reduce the side effects associated with either one of them when used alone. To our knowledge we have not come across any study with similar objective.

AIMS AND OBJECTIVES

Aim:

To compare equiosmolar concentrations of combination of mannitol with hypertonic saline vs mannitol alone to assess brain relaxation, hemodynamic profile and electrolyte abnormalities in patients undergoing elective supratentorial craniotomy-

Objectives:

1) To assess for brain relaxation between two groups

2) To compare equiosmolar concentration of combination of mannitol with hypertonic saline vs. mannitol to assess any significant changes in hemodynamic variables. (HR, BP)

3) To compare changes in serum electrolyte levels (sodium and potassium).

4) To compare changes in serum lactate, blood glucose levels between the two groups.

5) To compare total fluid intake and urine output between the two groups.

Hypothesis

Equiosmolar concentration of combination of mannitol with hypertonic saline will not cause significant changes in brain relaxation, hemodynamic profile and electrolyte levels in patients undergoing elective supratentorial craniotomy as compared to mannitol alone.

REVIEW OF LITERATURE

Intracranial tumors constitute most of the neurosurgical conditions that present for elective neurosurgery. The most common tumors in adults are gliomas(36%), meningiomas(32.1%), and pituitary adenomas(8.4%)(1). More than 50% of tumors are malignant and 80% of tumors are supratentorial in origin. These tumors can be primary or secondary. The most common sources for the metastatic lesions are breast, kidney, colorectal, lung and melanoma.

Patients with intracranial tumors or lesions present with symptoms associated with raised intracranial pressure such as bradycardia, drowsiness, headache, blurring of vision, projectile non- bilious vomiting and seizures.

Anesthetizing patients for supratentorial craniotomies require a thorough understanding of neuroanatomy, pathophysiology of elevated intracranial pressure, regulation and maintenance of cerebral perfusion, effects of anesthetic on intracranial pressure, cerebral blood flow ,metabolism and therapeutic options available for decreasing intracranial pressure, brain bulk and edema preoperatively.

Pathophysiology of intracranial pressure

Intracranial pressure is the pressure exerted by cranial contents on the dural envelope. The intracranial pressure is the final result of a complex interaction of hemodynamic, metabolic and anatomical factors.

Intracranial pressure is derived from 2 components, the circulation of cerebral

blood (vasogenic) and cerebrospinal fluid (CSF).

The component of ICP derived from the circulation of CSF is responsible for the baseline ICP.

The circulatory CSF component may be expressed using **Davson's equation**.(2)

ICP (CSF) = (RESISTANCE TO CSF OUTFLOW) * (CSF FORMATION) + (PRESSURE IN SAGITTAL SINUS)

Vascular component is derived from the pulsation of the cerebral blood volume. Variables such as the arterial pressure, auto regulation, and cerebral venous outflow contribute to the vascular component. The vasogenic component of ICP is associated with continuous small fluctuations of cerebral blood volume. Vasogenic increases in ICP are caused by hyperpnoea, increase in cerebral metabolism and cerebral hyperemia

Normal ICP ~10-15 mmHg in adults, 3-7 mm of Hg in children and 1.5-6mm of Hg in term infants.(supine at the level of Foramen of Monroe).In vertical position intracranial pressure is negative of -10mmHg but not more than -15mmHg.(3)Normal intracranial pressure is pulsatile and fluctuates with respiration.

ICP volume curve

Relationship between intracranial volume and intracranial pressure is represented by a non linear curve.(4) There are three parts to the curve.

A flat part representing good compensatory reserve (A–B), where ICP remains low despite increases in intracerebral volume.

An exponential part representing reduced compensatory reserve (B–C). At this point the compliance is critically reduced and any increase in intracerebral volume causes a substantial increase in ICP.

A final flat part representing terminal derangement of cerebrovascular responses at high ICP (C–D). Dilatation of cerebral arterioles in response to a decrease in CPP is exhausted signifying a loss of compensation.

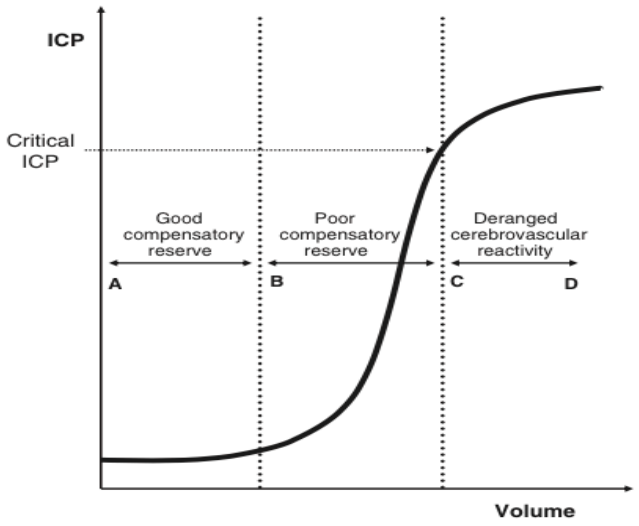


Figure 1. ICP Pressure Volume Curve

Compliance

Compliance or elastance of the intracranial space are used to describe relationship between intracranial volume and intracranial pressure.

Pressure volume index (PVI) is a measure of intracranial compliance. PVI of 22-30 ml was considered normal,18ml pathologic and 13 ml or less indicated a critically low cerebral compliance.

Compliance is expressed as dV/dP and is the amount of 'give' available within the intracranial space. This represents the accommodative potential of the intracranial space. A brain that has a decreased compliance, i.e. very little space for expansion within the intracranial space, would be reflected by a small change in volume producing a large change in ICP and vice versa.

Elastance

Elastance is the inverse of compliance (dP/dV). It is the change in pressure observed for a given change in volume and it represents the resistance offered to expansion of a mass or of the brain itself .

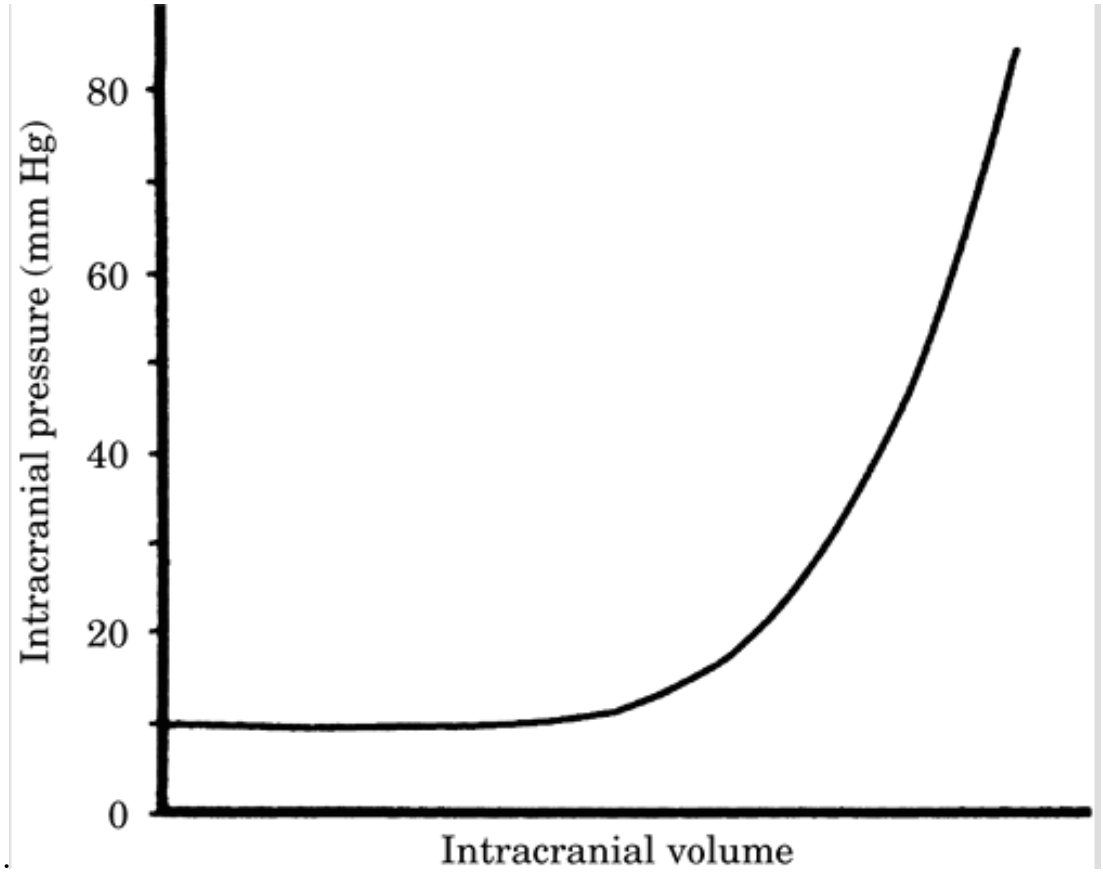


Figure 2. Compliance curve

The **MONROE KELLIE** hypothesis suggests that cranial vault is a closed structure, and the sum of intracranial volumes of brain(~80%) blood (~10%)and CSF(~10%) is constant and that an increase in any one of these must be offset by an equal decrease in another or else intracranial pressure increases.(5)

In 1783 **MONROE** described the skull as a rigid structure containing incompressible brain and stated that the volume of blood must remain constant

unless: '***water or other matter is effused or secreted from the blood-vessels' in which case 'a quantity of blood, equal in bulk to the effused matter will be pressed out of the cranium'***. (5)

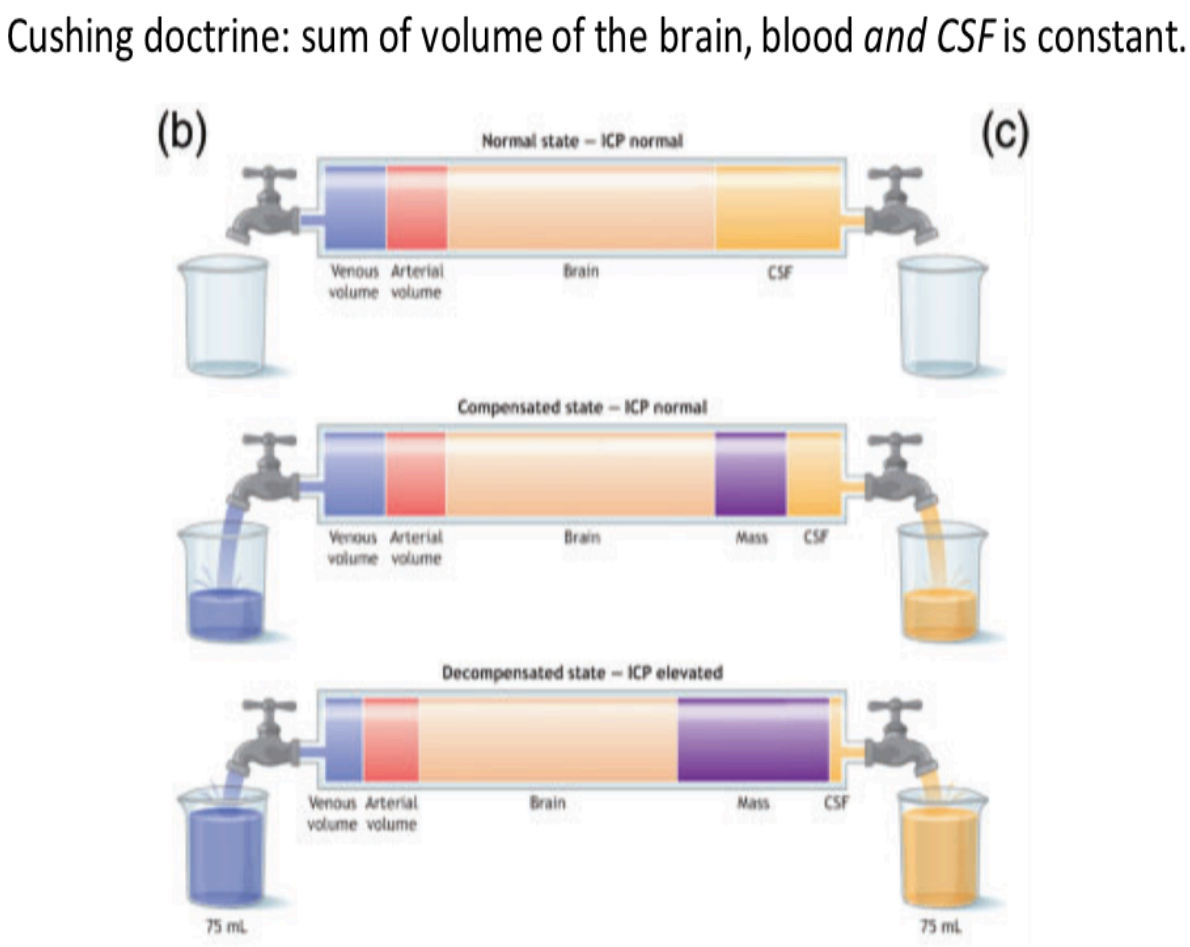
In 1824 **GEORGE KELLIE** confirmed **MONRO'S** doctrine in human and animal studies: cerebral (in particular, venous) blood volume was similar, no matter what the cause of death (hanging, exsanguination) was. (5)

Its total volume is 1600 ml, and that increase in any one of these components can be achieved only at the expense of another.

V. INTRACRANIAL = V. BRAIN (80%)+ V. CSF (8%)+ V. BLOOD (12%)

The ability of homeostatic mechanisms to compensate for increase in ICP depends on volume of the mass and speed of expansion. For rapidly expanding neoplasms , the intracranial pressure volume curve shifts markedly to left. Initially, it's compensated by extracranial shift of intracranial blood followed by displacement of cerebrospinal fluid. Once compensatory mechanisms gets exhausted or tumor size increases rapidly then there is increase in intracranial pressure.

Figure 3. MULLER MONROE THEORY



Physiology of intracranial pressure and factors regulating intracranial pressure

Brain completely depends on the oxidative metabolism of glucose and ketone bodies for ATP production. Therefore adequate cerebral blood flow should be maintained for constant supply of glucose and oxygen. The driving force for cerebral circulation is cerebral perfusion pressure. Increase in intracranial pressure due to expanding neoplasm will compromise cerebral perfusion as

cerebral perfusion pressure depends on mean arterial pressure and intracranial pressure.

CPP=MAP-ICP

Normal CPP is about 80mmhg

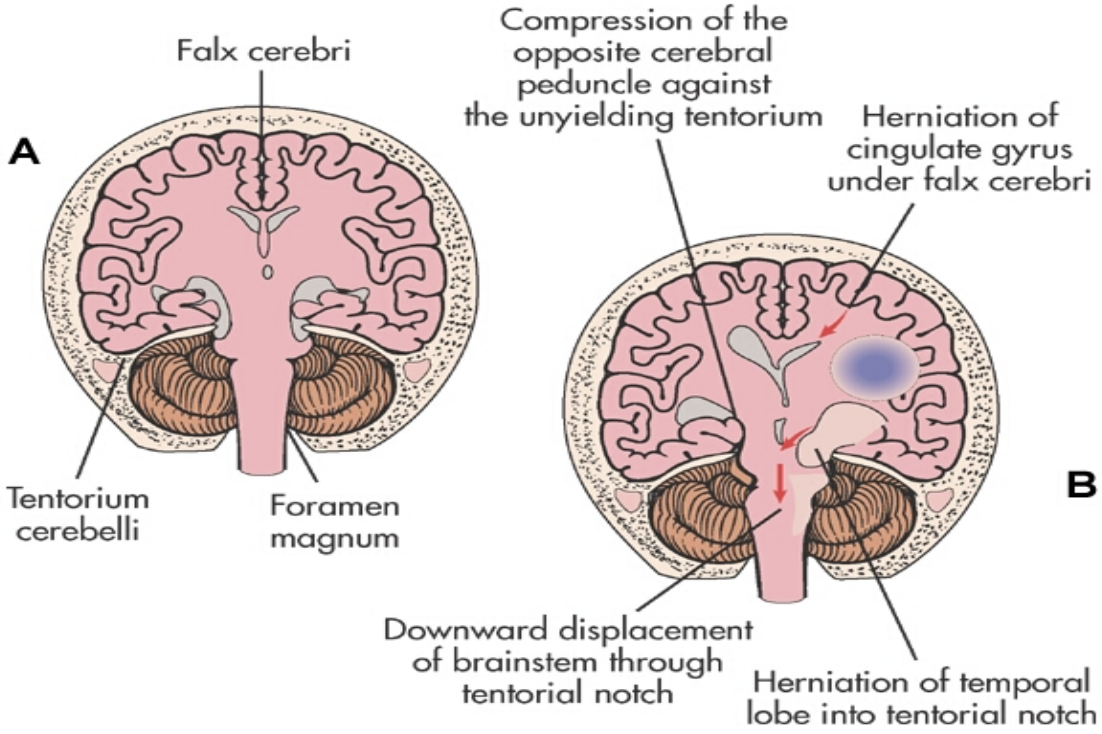
Effects of increased intracranial pressure

Headache, vomiting and visual disturbances are most common symptoms associated with elevated intracranial pressure. It can cause downward displacement of brainstem and upper cervical cord through foramen magnum and causes compression of cardiac and respiratory centers. Critical compression of these structures can cause Cushing's triad (hypertension bradycardia and kussumal pattern of respiration), which precedes the herniation of brain. Most common herniations are transtentorial (either lateral or central), tonsillar, and subfalcine. Lateral tentorial herniation presents with features of third nerve palsy (ptosis, decreased pupillary reflex), False localizing (ipsilateral) hemiparesis (Kernohan's notch), Decreased level of consciousness from reticular formation compression and potentially posterior cerebral artery occlusion resulting in a homonymous hemianopia.

Central tentorial herniation presents with features of upward gaze palsy results from compression on the pretectum and superior colliculi. Decreased level of consciousness is observed due to compromise of blood supply to the diencephalon and midbrain. They may also develop diabetes insipidus due to traction on the

pituitary stalk and hypothalamus.

Tonsillar herniation presents with features of neck stiffness as the cerebellar tonsils compress against the foramen magnum. Elevated blood pressure and bradycardia indicate progressive brainstem compression. Decreased level of consciousness and respiratory arrest will follow persistent compression.



Cerebral pressure auto regulation

The process by which cerebral arterioles maintain constant blood flow in face of changing cerebral perfusion pressure is known as cerebral autoregulation. Cerebral blood flow is relatively constant between CPP 50-150 mmHg. Outside this range cerebral blood flow depends on CPP.

The two underlying mechanisms responsible for cerebral auto regulation are shear stress and transmural pressure as explained by metabolic and myogenic hypothesis.

Metabolic hypothesis states that regulation of cerebral blood flow is mediated by effect of chemical mediators on precapillary sphincters in metaarterioles. The principal chemical mediators are CO_2, O_2, potassium, calcium and H^+ ions.(6)

Myogenic hypothesis was originally formulated by Bayliss in 1902.(7)

After discovery of isolated vessel mechanisms, it caused differentiation from neural metabolic and endothelial mechanisms.(8) It states that arterioles contract and dilate in response to transmural pressure changes. Rapid change in pressure causes changes in actin and myosin filaments of arteriolar smooth muscle.

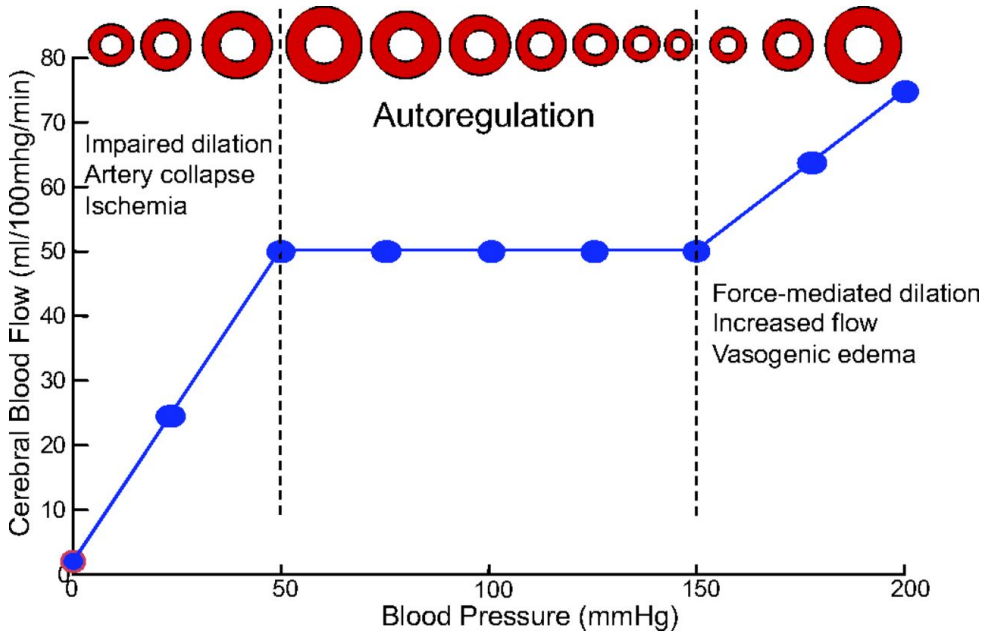


Figure 4. Auto regulation curve

Effect of carbondioxide on cerebral blood flow

There is a linear relationship between partial pressure of carbon dioxide in arterial blood ($paCo_2$) and cerebral blood flow till $paCo_2$ is 80mm Hg. Beyond that point there is no further increase in cerebral blood flow as arterioles are maximally dilated. Similarly below $paCo_2$ <20 mm hg cerebral blood flow cannot be decreased as arterioles are maximally constricted.(9)As $paCo_2$ crosses cell membrane, increase in intracellular $paCo_2$ causes increase in H^+ ions which causes vasodilation(10)(11). Later, this is further mediated by nitric oxide, prostanoids and potassium channels. The arteriolar response to $paCo_2$ is one of the methods to decrease ICP. By decreasing $paCo_2$ there is decrease in cerebral blood flow which further decreases cerebral blood volume and intracranial pressure.

Effect of oxygen on cerebral blood flow

Clinically used paO_2 has minor effects on cerebral blood flow. Cerebral blood flow will increase when paO_2 <50mmHg. It acts by releasing adenosine from endothelium and causing vasodilation which increases cerebral blood flow and an increase in intracranial pressure.

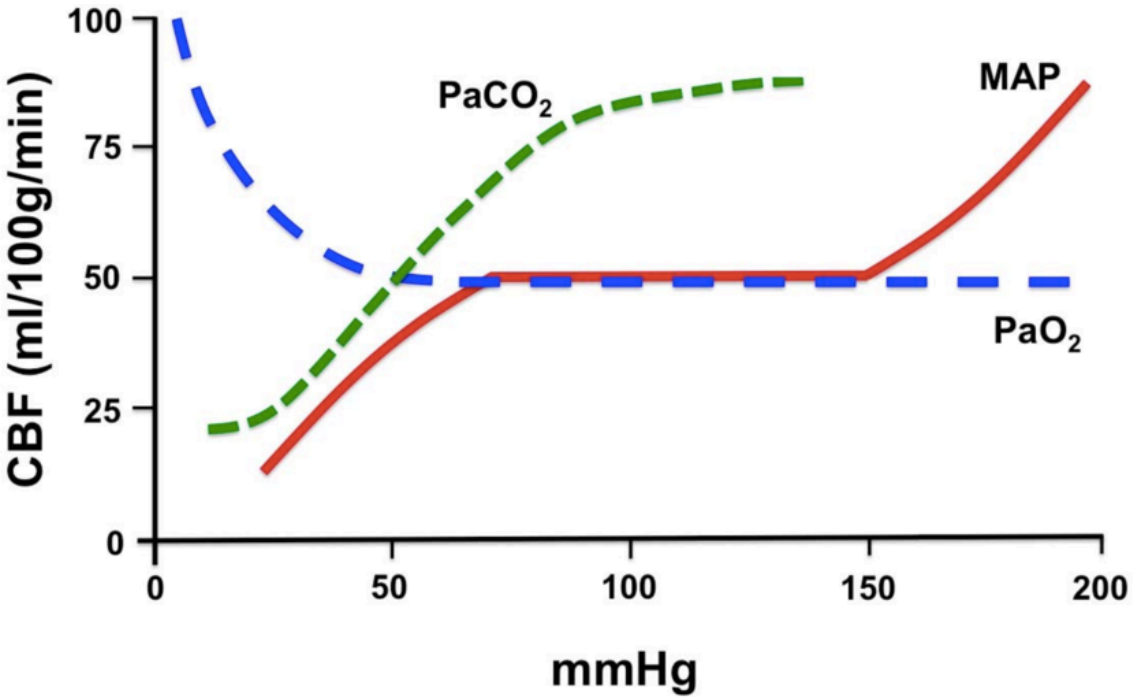


Figure 5. Effect of $paCo_2$ and pO_2 on cerebral blood flow

Cerebral metabolism

Cerebral blood flow increases with increase in cerebral metabolic rate. (Flow Metabolism Coupling). With increased synaptic transmission , there are increases in potassium and hydrogen ions which increase blood flow by acting on ATP sensitive potassium ions and on by causing vasodilation respectively.(12) As cerebral synaptic activity increases, there are increased levels of adenosine which directly causes vasodilation and increases blood flow

Various techniques to reduce intracranial pressure

Prevention

- Euvolemia
- Avoiding laryngoscopy response
- Smooth induction and intubation
- Adequate plane of anesthesia and analgesia during noxious stimulus like pin application, skin incision, burr hole application and periosteum elevation.
- Head-up positioning.(13)
- No compression/kinking of jugular veins.
- Osmotic agents such as mannitol and hypertonic saline(14)
- Steroids to reduce perilesional edema
- Adequate ventilation paO_2>100 mm of hg; $paCo_2$ 35 mm of hg
- Avoiding high intrathoracic pressure
- Hyperventilation before induction(15)
- Use of intravenous anesthetic agents for induction and maintenance

Treatment

- Drainage of cerebrospinal fluid using lumbar catheter
- Osmotic agents mannitol and hypertonic saline.(14)
- Hyperventilation(15)

- Maintenance of anesthesia using total intravenous anesthesia
- Facilitating venous drainage using head up position,(13)
- No positive end expiratory pressure and decreasing inspiratory time.

Intracranial neoplasms are commonly associated with surrounding brain edema. They require maximal reduction of brain tension to facilitate surgical access. One of the most commonly used technique to reduce intracranial pressure is **chemical brain retractor concept.**

This concept utilizes

1) Osmotic agents

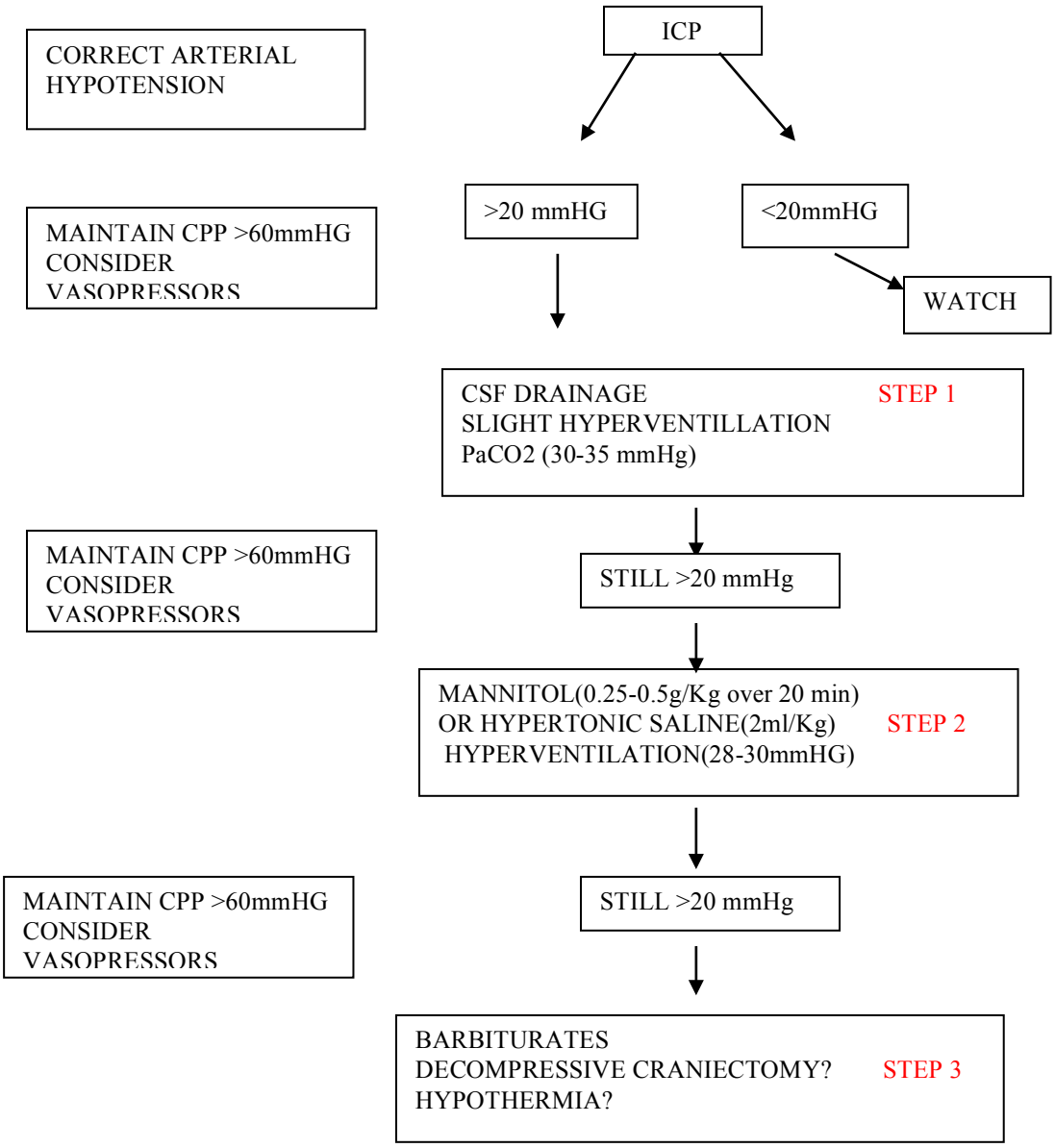
2) Maintenance with total intravenous anesthesia

3) Mild hyperventilation

4) Mild hyperoxygenation.

Management of raised intracranial pressure should aim at decreasing secondary insults to brain. Secondary insults such as hypotension, hypoxia, hypercarbia and acidosis should be avoided.

Concept of **three-tier therapy** is used for management of intracranial pressure.



Osmotic diuresis

Osmotic agents such as mannitol and hypertonic saline are one of mainstream therapy in management of cerebral edema. Osmotherapy works only on undamaged brain regions because it requires an intact blood brain barrier to maintain osmotic gradient.

Osmotic diuretics are freely filtered at the glomerulus, undergo minimal reabsorption by the renal tubules, and are relatively pharmacologically and metabolically inert.

These agents can't cross blood brain barrier thereby creating osmolar gradient drawing fluid from brain tissue into intravascular compartment and reduces brain edema.(16)

Mannitol is the most commonly used osmotic agent. Recent evidence has shown that equiosmolar dose of hypertonic saline may also be used with better brain relaxation and more hemodynamic stability.

Mannitol

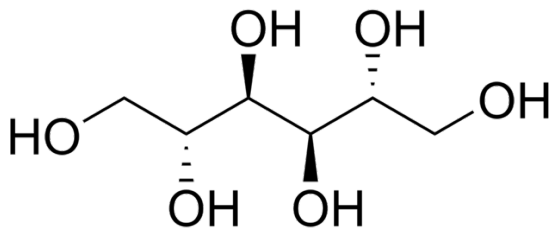
Mannitol is an obligatory osmotic diuretic.

Mannitol is a naturally occurring alcohol found in fruits and vegetables.

It is prepared by reduction of glucose.

It is a 6-carbon sugar alcohol.

Chemical structure is $C_6H_{14}O_6$.



Molecular weight is 182.

Mannitol occurs as a white, odorless, crystalline powder, or free flowing granules.

Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

Mannitol shows polymorphism.

It is metabolically inert in humans.

It is commercially available as 10% and 20% mannitol solution.

The ph is adjusted with hydrochloric acid and sodium hydroxide.

	Composition (mannitol BP)	**Osmolality** mOsmol/kg	**pH**
10% mannitol	10gm/100ml	596	5.5(4.5 to 7.0)
20% mannitol	20gm/100ml	1192	5.0(4.5 to 7.0)

Mechanism of action

1) It acts primarily by causing osmotic dehydration of brain secondary to reduction in cerebral water content. It was thought that mannitol shifts fluid from brain tissue to intravascular compartment thereby reducing brain tissue edema,(14)But later it was shown that mannitol decreases water content only by 2%.

Therefore, other mechanisms have been suggested. Mannitol has other effects that reduce ICP more than its osmotic effects.

2) It causes transient hypervolemia thereby decreasing blood viscosity and in turn increases cerebral blood flow, which triggers vasoconstrictor regulators and causes cerebral vasoconstriction and decreases cerebral blood volume and reduces brain bulk. It causes hemodilution, and improves red blood cell rheology.(17)

3) It increases cardiac output and decreases systemic vascular resistance. These effects increase oxygen delivery at tissue level.(18)

4) It has free radical scavenging properties.

The end results of these effects is reflex cerebral vasoconstriction.

It decreases CSF production. The net effect is decrease in the volume of CSF and increase in intracranial pressure.

Pharmacokinetics

Volume of distribution corresponds to extracellular water that is 20% of body weight.

$T_{1/2}$ elimination is about 30 to 60 mins for doses.

It is rapidly excreted in urine.

The most important determinant of mannitol clearance is renal function.

Dose

0.5-1gm/kg.

Serum osmolarity is monitored during administration of mannitol. A serum osmolarity >320mosm indicates withdrawal of therapy due to concerns of osmotic nephrosis and renal failure.(19)

Serum mannitol levels are measured by osmolar gap. Osmolar gap is the difference between calculated serum osmolarity and measured serum osmolarity.(20) Increased levels indicates mannitol accumulation. While monitoring hyperosmolar therapy osmolar gap of 55msom/kg is targeted(21,22)

Indications

1) Reduction of intracranial pressure by reducing brain tissue volume.

2) As a diuretic to prevent or treat oliguric phase of renal failure.

3) Reduction of intraocular pressure when other methods have failed

4) To create osmotic diuresis in management of poisoning.

5) Preservation of perioperative renal function in patients undergoing major vascular and cardiac surgery and in those with jaundice

6) To promote diuresis and minimize the risk of acute renal failure in patients after renal transplantation

7) Preservation of renal function in rhabdomyolysis secondary to crush injuries and compartment syndrome

8) Bowel preparation before colorectal surgery, colonoscopy, and barium enemas

Contraindications

1) Hypersensitivity to mannitol

2) Pre-existing plasma hyperosmolarity

3) Severe heart failure

4) Disturbance of the blood-brain barrier

5) Severe renal disease

6) Severe pulmonary congestion or frank pulmonary edema

7) Active intracranial bleeding except during craniotomy

8) Severe dehydration

9) Progressive renal damage or dysfunction after institution of mannitol therapy, including increasing oliguria and azotemia.

10) Progressive heart failure or pulmonary congestion after institution of mannitol therapy.

Side effects

Gastrointestinal system: nausea, vomiting

Hypersensitivity reactions: Local pain

Skin necrosis

Thrombophlebitis at the site of intravenous infusion

Angio-oedema

Allergic reaction

Anaphylactic shock

Neurological reactions: Chills, urtricaria

Fever , headache and dizziness.

Circulatory effects: Hypotension, Hypertension, and Tachycardia

Cardiac arrhythmia

Angina-like chest pain

Pulmonary congestion and edema

Convulsions

Congestive cardiac failure

Renal effects: Osmotic nephrosis.

Alveolar nephrosis

Large doses of mannitol have been known to cause acute

renal failure even in patients with satisfactory pre-treatment renal function

Excessive diuresis

Fluid and electrolyte disturbance: Hypernatremia

Dehydration and haemoconcentration

Hyponatremia

Hypokalemia

Hyperkalemia

Other electrolytes imbalances

Metabolic acidosis

Metabolic alkalosis

Drug interactions

Potentiation effects: Concurrent use of other diuretics potentiates effects of mannitol and dose adjustment is required.

Inhibition effects: Mannitol decreases responsiveness to lithium and methotrexate by increasing their elimination.

1) It potentiates ototoxic effects of aminoglycosides.

2) It enhances neuromuscular blocking effects.

3) It reduces effects of oral anticoagulants by increasing clotting factors secondary to dehydration.

4) It potentiates digoxin toxicity if hypokalemia follows mannitol treatment.

3% HYPERTONIC SALINE:

3% hypertonic saline is a sterile non-pyrogenic solution of sodium chloride in water.

The preparation doesn't contain antimicrobial agent or buffer.

During sterilization small amount of hydrochloric acid can be formed making solution acidic.

	Composition (mg/dl)	Sodium (meq/l)	Chloride (meq/l)	Osmolarity (mosm/l)	ph
3% hypertonic saline	30	513	513	1027	5 (4.5-7)

Mechanism of action

Sodium is a major cation of extracellular fluid and it principally regulates extracellular fluid electrolytes and osmotic pressure of fluid compartment. Chloride is also a major extracellular anion which closely follows sodium cation in maintenance of tonicity and electrodynamic properties.

There are several mechanisms by which hypertonic saline reduces intracranial pressure:

1) **Osmotic:** Hypertonic saline causes an osmotic gradient and causes shift of fluid from cerebral tissue to intravascular space and reduces edema. (23)

2) **Hemodynamic:** Hypertonic saline increases blood volume thereby reduces blood viscosity. And increases cerebral tissue oxygenation.(24)As blood viscosity decreases autoregulatory mechanisms of brain causes vasoconstriction of cerebral blood vessels and decreases blood flow thereby decreases intracranial pressure.

As 3% saline is hypertonic it increases tonicity of plasma which facilitates CSF absorption.(25)

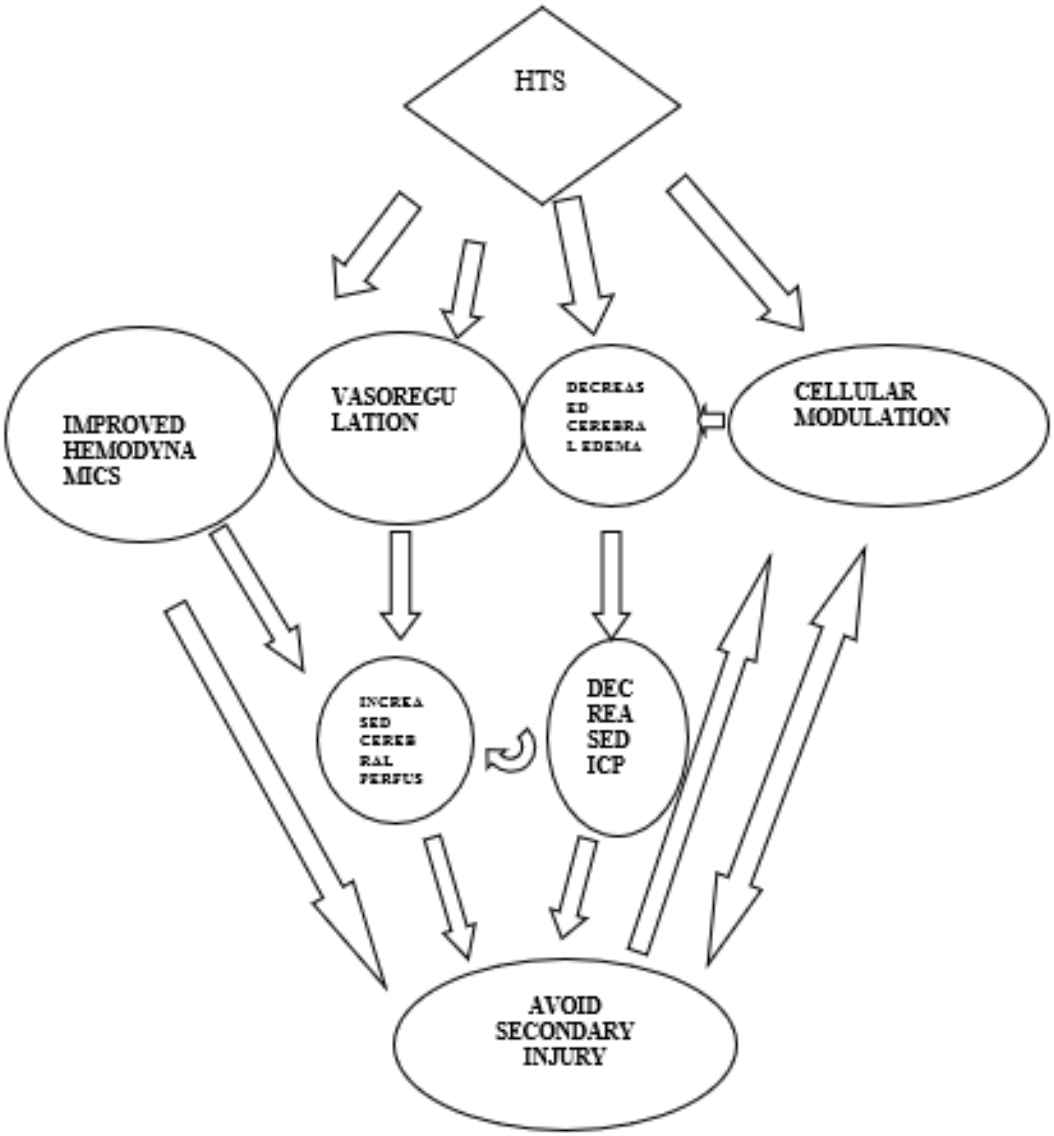
3) Vasoregulatory: It causes cerebral endothelial cells and erythrocyte dehydration thereby increases regional brain tissue perfusion.(26,27) It has positive inotropic effect.

4) Immunologic: Hypertonic saline causes decreased inflammatory response and

reduces edema.(28,29)

5) Neurochemical: Brain injury increase extracellular glutamate levels. It normalizes intracellular sodium and chloride ions and restores normal membrane potential and prevents pathological release of glutamate.

Multiple actions of hypertonic saline



Pharmacokinetic properties

It is administered intravenously.

It has 100% bioavailability.

Dose

Cerebral edema: Administered 3-5ml/kg over 10-20 minutes.

For hyponatremic seizures:1ml/kg till sodium>125mmol/l

Indications

Hyponatremic seizures.

Cerebral edema and raised intracranial pressure.

Contraindications

Hypernatremia

Severe Hyponatremia

Side effects

Intracranial complications

Patient can develop rebound edema after discontinuation of continuous infusion.

It can disrupt blood brain barrier as it causes dehydration of cells and causes loosening of tight junctions.

Theoretical possibility of excess neuronal cell death.

Severe hypernatremia (>375mosm/l) can cause venous and capillary congestion, intracerebral and subarachnoid bleeding.

If preexisting hyponatremia exists and it is corrected rapidly it can cause central pontine myelinolysis.

Systemic complications

It can cause transient hypotension following a rapid infusion, but blood pressure will increase due to increase in blood volume and contractility. It causes decreased platelet aggregation and increases prothrombin time and plasma thromboplastin time. It causes hypokalemia and hyperchloremic metabolic acidosis when infused in large doses.

Major anesthetic concerns in supratentorial craniotomy

Preoperative assessment

Preoperative assessment involves assessment of the neurological state of patient and general state of patient, discussion with neurosurgeon and formulating planned operative intervention.

Neurological state of patient

History regarding symptoms of increased intracranial pressure such as headache, nausea, vomiting, blurred vision should be noted down. We should also be aware of any history suggestive of loss of consciousness, any focal neurological deficits and seizures.

Physical examination should include neurological status assessment, patient's degree of orientation, any neurological deficits and Glasgow coma scale. Particular attention should be made to note any signs of raised intracranial pressure such as **Cushing's response** (hypertension, bradycardia) and papilloedema.

Elucidate patient's drug history and duration as they affect intracranial compliance and pharmacokinetics and dynamics of anesthetic drugs.

CT and MRI should be examined for tumor size , location and signs of raised intracranial pressure. Signs of intracranial pressure include effacement of lateral ventricle by tumor mass, midline shift>5mm,lateral ventricular extension due to obstructive hydrocephalus.

General state of patient

Preoperative assessment of cardiovascular and respiratory functions are vital as supratentorial tumors significantly alter their function. Supratentorial craniotomies are associated with significant blood loss, hypotension and hypovolemia. Malignant tumors are also associated with coagulation disorders and have high chance of thromboembolism. Renal function should be assessed as the patients are routinely on diuretics and have subsequent changes in electrolytes.

Planning operative intervention

A detailed discussion with the neurosurgeon regarding size of tumor and its location, positioning of patient and surgical approach is required. Combination of a large size tumor in a difficult location requiring radical excision makes it a technically demanding surgery and entails maximum reduction of brain volume.

Premedication

Sedative premedication is routinely avoided as they can cause hypercarbia, hypoxia and increase intracranial pressure. Premedication with benzodiazepines will unmask or worsen preexisting neurological deficits.(30) and continue steroids on day of surgery. As increased intracranial pressure causes delayed gastric emptying time and increased acid secretion it is advisable to administer H2 blockers and gastric prokinetic agents. Anticonvulsants are continued on day of surgery.(31,32)

Vascular access

At least two wide bore IV access should be secured. Central venous access is indicated only if we anticipate major blood loss for administering vasoactive agents, for aspirating air in sitting craniotomies, for CVP monitoring and in patients with cardiovascular compromise. Either brachial PICC line or subclavian catheter is preferred as internal jugular vein can compromise cerebral perfusion. Invasive arterial blood pressure monitoring is preferred to have tight control of cerebral perfusion pressure and for repeated arterial sampling.

Monitoring

Close hemodynamic monitoring plays a vital role in postoperative outcome. It includes 5 lead ECG,SPO_2,beat to beat intrarterial blood pressure monitoring,$ETCO_2$,pulse pressure variation,CVP.$ETCO_2$ monitoring to detect air embolism. temperature and urine output is closely monitored. Transesophageal echo is indicated in patients with cardiovascular compromise and anticipating air embolism. air embolism can be detected by precordial doppler.(33)close monitoring of blood glucose levels are essential in neuroanaesthesia as hyperglycemia can worsen neurological damage during ischemia.(34–36)

Anesthetic management

Standard monitoring and vascular access mentioned above should be secured,

A smooth and gentle induction with mild hyperventilation to avoid hypercarbia and hypoxemia is preferred. Preoxygenation with 100% oxygen for five minutes till eto2>90%.is routinely done. Fentanyl 2-3mcg/kg is administered. It can be replaced with alfentanyl (5-10mcg/kg followed by infusion 5-10mcg/kg/hour) for hemodynamic control or sufentanil (0.5-1mcg/kg followed by infusion 0.1-0.2 mcg/kg/hr) for rapid awakening.(37–39). Patient is induced with propofol 2-3mg/kg or thiopentone 3—6mg/kg. Etomidate can be used in patients with significant cardiovascular compromise.Patient adequately paralyzed with non-depolarising muscle relaxant like Vecuronium/Rocuronium and controlled ventilated maintaining Paco2 around 35mm of hg. Use of depolarizing muscle relaxants like succinylcholine should be reserved only for patients with difficult airway and rapid sequence intubation is mandated. Succinylcholine causes transient increase in cerebral blood flow, cerebral metabolic requirement and intracranial pressure. This can be controlled by hyperventilation and by deepening plane of anesthesia.

Long acting non-depolarizing muscle relaxants such as Pancuronium is routinely avoided as neurosurgical patients are susceptible to myorelaxant hangover.

One of most nociceptive stimulus is application of skull pins. Hemodynamic response can be prevented by deepening plane of anesthesia with propofol 0.5mg/kg, fentanyl 1-3mcg/kg/ alfentanyl 10-20mcg/kg.Local anesthetic using 2%

lignocaine is administered at the pin application site.(41) Careful monitoring for air embolism as pin application is associated with higher risk of air embolism..

Mild head up positioning is preferred to facilitate venous drainage and to reduce intracranial pressure. At least two fingers breadth should be maintained between chin and nearest bony prominence to avoid extreme extension or flexion, and endotracheal kinking and impairment of cerebral venous drainage. In pteronial and frontotemporal craniotomy head is turned laterally, opposite shoulder should be elevated to avoid damage to brachial plexus.

Anesthesia can be maintained either by using inhalational agents or intravenous agents(Total intravenous anesthesia). Intravenous anesthetic agents decrease cerebral blood flow and cerebral metabolic requirement of oxygen i.e. coupling and thereby decreases intracranial pressure. In contrast to intravenous agents, inhalational agents increases cerebral blood flow and cerebral metabolic requirement thereby increases intracranial pressure. Maintaining anesthesia by total intravenous anesthesia is ideal as it causes adequate brain relaxation by decreasing intracranial pressure.

Brain tension is reduced by altering cerebral metabolic rate and intracranial pressure, which is widely known as *chemical brain retractor concept*.

Chemical brain retractor concept includes mild hyperventilation, mild hyperoxygenation, and normovolemic status, not to use vasodilators, mild hypertension, and use of hypertonic agents. Most commonly used hypertonic solutions are *mannitol and hypertonic saline*.

HYPEROSMOLAR SOLUTIONS TO REDUCE INTRACRANIAL PRESSURE : CURRENT STAND

Craniotomies for excision and biopsy of supratentorial tumors are common neurosurgical procedures. Often the combination of large size of tumor, associated edema and the raised intracranial pressure, and narrow corridor for approach requires techniques to reduce the ICP. Reduced ICP prevents intraoperative brain bulge, thereby reduces the risk for cerebral ischemia, herniation, structural damage due to shear forces. This would in turn minimize the secondary insult to the brain and translate to better neurological outcome following neurosurgical procedures.

Various treatment strategies as described previously have been in practice to minimize ICP (such as head end elevation, steroids, CSF drainage, osmotherapy). The '*chemical brain retractor concept'* aims to decrease cerebral blood flow and cerebral metabolic requirement of oxygen thereby decreasing intracranial pressure. Osmotherapy is an integral part of this concept.

The history of osmotherapy stretches back to the early 20th century. Initially people tried and injected cats with hypertonic saline and noted that their thecal sacs had become flaccid, making it difficult to acquire CSF from them. Mannitol became popular from then.

Shenkin demonstrated a rise in serum osmolality by 20-30 mOsm/L, and a fall in ICP by 30-60% in his patients with use of mannitol.

Use of hyperosmotic agents such as mannitol and hypertonic saline increases the serum osmolarity, which creates an osmolar gradient between intravascular space and brain tissue favoring movement of water from latter into former thereby decreasing the brain edema, facilitating brain retraction.

Mannitol has been used as the agent of choice in dose of 0.5-1gm/kg.(42).It is indicated as a temporary measure in management of acute intracranial hypertension with symptoms and signs of impending herniation.(42,43).There is no preset threshold before which mannitol therapy is started.ICP targeted therapy with targeting ICP<25 is indicated.(43–45).

James et al demonstrated that patients with higher ICP responded better to mannitol therapy than patients with marginally elevated ICP.(46)

It also has beneficial effect of improving blood rheology. However it is associated with hypotension requiring use of vasopressors, hyponatremia, hyperkalemia and acute hypervolemia which are deleterious in patients with congestive heart failure. Other alternative is hypertonic saline.

Recent evidence has shown that equiosmolar dose of hypertonic saline may also be used with better brain relaxation and more hemodynamic stability.(47,48)hypertonic saline reduces intracranial pressure associated with tumors(49),traumatic brain injury,(24,50–54)subarachnoid hemorrhage, stroke. Studies have shown that mannitol and hypertonic saline have same effect in causing brain relaxation when used initially as a single agent(55) and hypertonic

saline reduces intracranial pressure in patients not responding to mannitol.(50,56,57)

A randomized cross over trial comparing mannitol and hypertonic saline showed hypertonic saline is better than mannitol in terms of reduction of intracranial pressure and its durability a recent metaanalysis revealed that hypertonic saline is better than mannitol in reduction of intracranial pressure.(58)

Ching-tang wu et al did a randomized control trial comparing mannitol with 3% hypertonic saline and demonstrated that 3% hypertonic saline provided more satisfactory brain relaxation than mannitol,mannitol had more prominent diuretic effect and 3% hypertonic saline caused hypernatremia.

Prabhakar and associates had done a cochrane systemic review which included *6 RCT with 527 participants* which suggested hypertonic saline significantly reduces risk of brain tension during craniotomy. (59)Hypertonic saline increases preload and reduces afterload thereby increases cardiac output.(60)In addition to an osmotic action, hypertonic saline has hemodynamic, vasoregulatory, immunological, and neurochemical effects. (61)In particular, hypertonic saline relaxes arteriolar vascular smooth muscle and, in association with a reduction in cerebral endothelial cell edema, improves cerebral microcirculatory flow. It also expands intravascular volume, thereby potentially augmenting CPP.

Pros and cons of both the agents are summarized below.

	PROS	CONS
MANNITOL	1.Decreases edema. 2.Improves microvascular circulation. 3.Decreases blood viscosity. 4.Improves blood rheology. 5.Promotes free scavenging. 6.Inhibits apoptosis. 7.Fairly cheap. 8.Rapid onset of action.	1.Fluid and electrolyte imbalance—particularly hyponatremia. 2.Metabolic acidosis. 3.Pulmonary congestion. 4.Hypovolaemia,Hypotension 5.Thrombophlebitis. 6.Skin necrosis if extravasation occurs 7.Allergic reactions, including anaphylaxis 8.Rebound increases in ICP 9.Torrential diuresis.

Hypertonic saline	1.Reflection coefficient 1 (mannitol 0.9, theoretically better than mannitol for relaxation) 2.Improves brain oxygenation 3.Better cerebral hemodynamics 4.Cheap 5.Stable in storage 6.Have intrinsic anti-inflammary 7.Less potent for hypovolemia.	1.Volume overload 2.Coagulopathy 3.Hypernatremia 4.Hyperchloremic metabolic acidosis 5.Need for central venous access for administration. 6.Can cause seizures due to wide fluctuation in sodium. 7.Altered platelet aggregration.

MATERIALS AND METHODS

Patient Selection and Methodology

Settings

This study was carried out in the three Neurosurgery operating theatres and Neurosurgery Intensive Care Unit of Christian Medical College and Hospital, Vellore.

Inclusion Criteria

1) Supratentorial tumors.

2) ASA 2

3) Patient not on diuretics.

4) Age 18-65 years.

Exclusion Criteria

1) Age<18year

2) ASA 3-5

3) Preoperative hyponatremia Serum **Na<130**

4) Preoperative hypernatremia **Serum Na >145**

5) Treatment with any hyperosmotic fluid (mannitol/hypertonic saline/diuretics) in previous 24hrs.

6) Congestive heart failure/chronic kidney disease.

Sample Size

Sample size is calculated based on the data collected over a period of two months in 2016.It is hypothesized that the study drug would provide for similar brain relaxation and a 50% reduction in the use of vasopressors. With a 5% alpha error and 80% power the calculated sample size is 67 patients in each arm**.**

$$n = \frac{2\,(z_{\alpha}+z_{1-\beta})^2\ \sigma^2}{\Delta^2}$$

where

n = required sample size.

Zα, *Z* is a constant (set by convention according to the accepted α error and whether it is a one-sided or two-sided effect) as shown below

α-error	5%	1%	0.1%
2-sided	1.96	2.5758	3.2905
1-sided	1.65	2.33	

For $Z_{1-\beta}$,Z is a constant set by convention according to power of the study as shown below:

Power	80%	85%	90%	95%
Value	0.8416	1.0364	1.2816	1.6449

In the above-mentioned formula

σ is the standard deviation (estimated), as per the retrospective study 45% patients required vasopressor support (.45)

Δ is the difference in effect of two interventions which is required (estimated effect size-50% reduction in use of vasopressor support)

Using the above formula, calculated sample size is 62 patients in each arm. Calculating an 8% drop out rate, total sample size estimated is 67 patients per arm. We could only recruit 60 patients in time available and hence an interim analysis was performed.

Methodology

All patients who met the inclusion criteria for the study were considered for the study.The principal investigator met the patient in person, explained about the study in their language and obtained their consent. After obtaining consent they were recruited and standard anesthesia protocol was followed as given below.

No sedative premedication was given. Routine dose of anticonvulsants and dexamethasone were continued as per schedule.

After wheeling the patient into the operating room, standard monitors ECG, SpO_2, NIBP, were connected. 18 or16 G peripheral line, 20 G arterial line were started under local anesthesia. An arterial blood gas sample was taken for checking the serum sodium, potassium, lactate and glucose levels. After adequate preoxygenation with 6 L/min of 100% oxygen, patients were induced with 3-5 μg/kg of fentanyl, 2 mg/kg of propofol and paralysed with 0.15 mg/kg of vecuronium. Central line (either PICC or Central venous catheter as indicated) was inserted as per standard requirements.

Patient's were intubated using appropriate size endotracheal tube. Anaesthesia was maintained using total intravenous anesthesia technique using propofol infusion at a dose of 100-200mcg/kg/min targeting BIS 40-60, vecuronium infusion was titrated to two twitches in train of four stimulus using neuromuscular monitor and $paCo_2$ was maintained in the range of 30 to 35mm of Hg.

Temperature was monitored using a nasophayngeal probe.Additional dose of fentanyl and propofol were given intravenously along with local anesthetic infiltration at pin site at the time of insertion of skull pins. Intermittent boluses of fentanyl upto 7-10μg/kg used for analgesia.

Hemodynamic variables which were monitored were heart rate and systolic,diastolic and mean arterial blood pressure(MAP).If MAP<25% from baseline, vasopressor support was initiated. Initially boluses of phenylephrine 50μg were given. If patient requires more than 5 boluses of phenylephrine, noradrenaline infusion at dose of 0.05-0.1μg/kg/min titrated to maintain MAP was started. If vasopressor support (noradrenaline infusion) had already been started after induction before administration of study drug then any increase in the dose after administration of study drug was noted.

A computer generated randomization allocated patients into two groups. One group received mannitol alone, and the other group received equiosmolar concentration of a combination of mannitol with hypertonic saline over 15 mins. Both the anesthetist and surgeon were blinded to type of solution administered.

Mannitol dose administered was 0.75gm/kg body weight which corresponds to 4ml/kg of 20% mannitol. This dose is equiosmolar to 4ml/kg of 3% hypertonic saline .

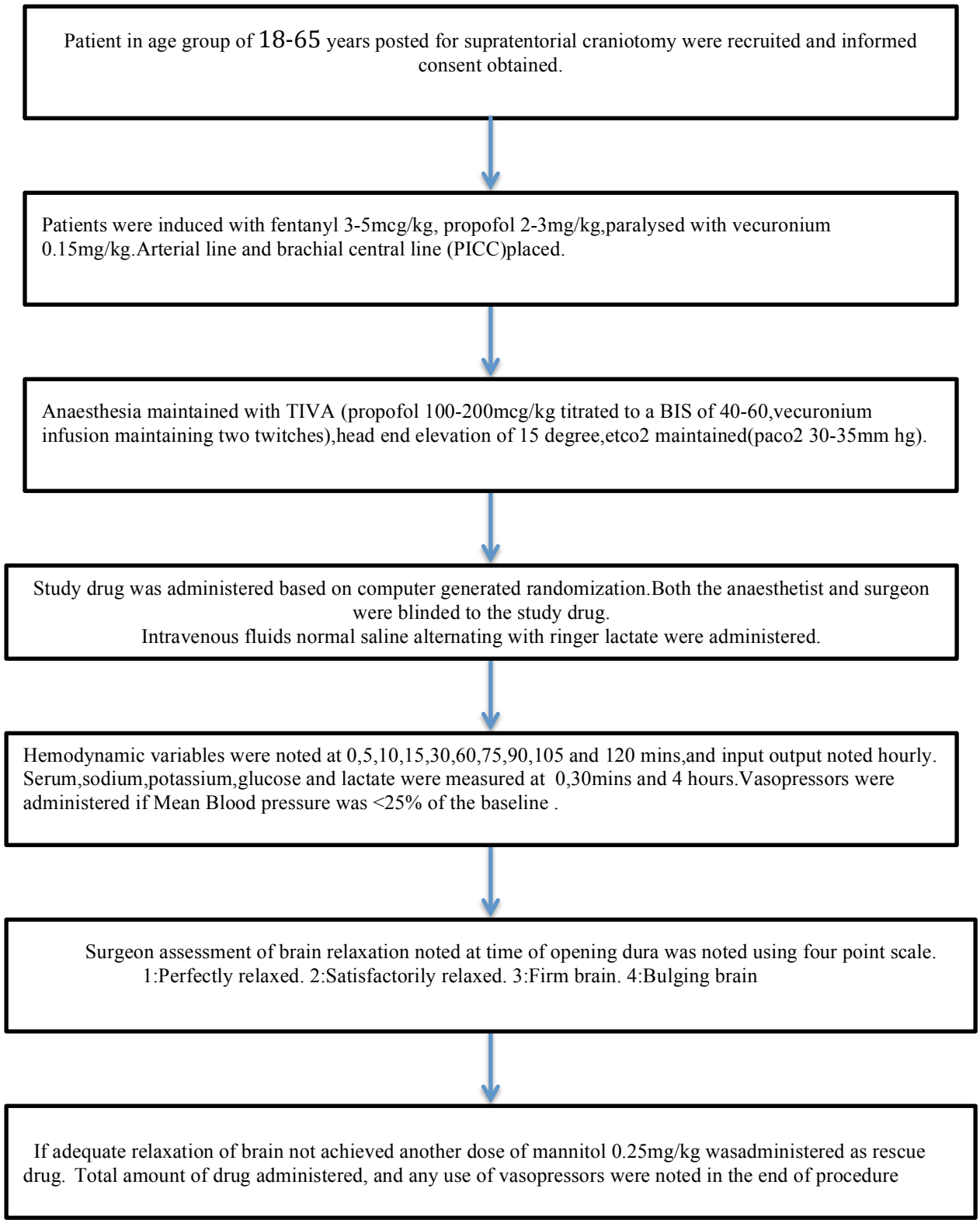
In the combination group ,dose of mannitol was 0.375 mg/kg which corresponds to 2ml/kg of 20% mannitol +2ml/kg body weight of 3% hypertonic saline was administered over 15 minutes. Brain relaxation was assessed by the operating surgeon at the time of opening of dura on a four-point scale (1. perfectly relaxed:2.satisfactorily relaxed:3.firm brain:4.bulging brain). If brain relaxation was not adequate on surgeons assessment , a second dose of 0.25gm/kg of mannitol was administered

Hourly fluid input/output is monitored and total fluid input and output were noted at the end of procedure. Repeat arterial blood gas analysis was done one hour after start of administration of drug and changes in serum sodium, potassium, lactate and glucose levels were noted. At the end of procedure total amount of hyperosmotic agent administered and use of vasopressors were noted.

At the end of procedure haemostasis was achieved. Volatile anesthetics were cut off after removal of pins and neuromuscular blockade was reversed. Patients were extubated once they attained adequate neuromuscular recovery.

After extubation, they were monitored in post anesthesia recovery room for full recovery and transferred to neurosurgical critical care unit for monitoring.

ALGORITHM DESCRIBING PROTOCOL OF STUDY



RESULTS

This study was conducted from April 2017 to September 2017.During this period, 60 patients who fulfilled the inclusion criteria were recruited, of which , 2 pateints were not included in analysis due to insufficient data. Among the rest,29 patients in **Group A** received **equiosmolar concentration of mannitol with hypertonic saline** and 29 patients in **Group B** received **mannitol alone**.

Group A: COMBINATION OF MANNITOL WITH HYPERTONIC SALINE

Group B: MANNITOL

Table 1. Comparison of demographic data between the two groups

Variable	**Mean - Group A**	**Mean-Group B**
AGE (years)	39.35	38.07
WEIGHT(kg)	63.5	63.1
HEIGHT (cm)	161.5	159.6
BMI	24.3	24.9
MALE	17	16
FEMALE	12	13

Demographic Characteristics

58 patients who underwent supratentorial craniotomy for excision of intracranial mass were recruited.

The age of the study patients ranged from 18-70years.The mean age of population in **Group A** is 39.55years and the mean age of population in **Group B** is 38.07 years.

There is no difference in age distribution between the two groups.

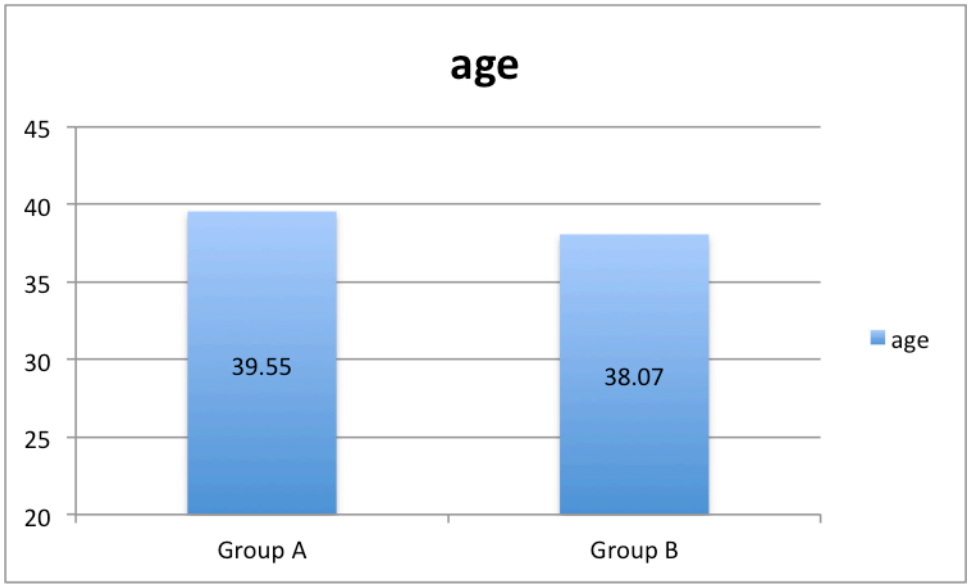


Figure 6. Age distribution between Group A and Group B

Gender

Of the 29 patients in **Group A** ,17 were males and 12were females. Of the 29 patients in **Group B** 16 were males and 13 were females. Both the groups were comparable in terms of sex distribution.

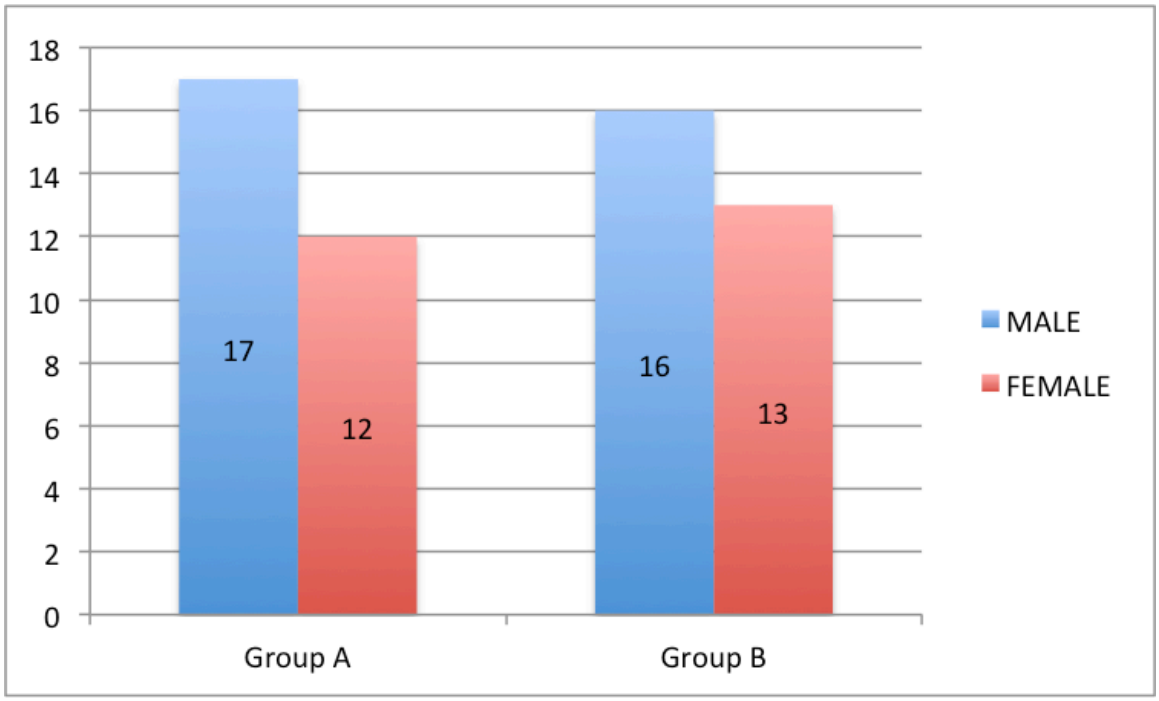


Figure 7. Sex distribution among Group A and Group B

Weight Height and BMI

The mean body weight was 63.48kilogram for **Group A** and 63.13kilogram for **Group B.** There was no difference in body weight between the two groups.

The mean height of patients in **Group A** was 161.5cms and the mean height of patients in **Group B** was 159.6.cms. There was no difference in height between the two groups.

The mean BMI of patients in **Group A** was 24.3 and the mean height of patients in **Group B** was 24.9. There was no difference in BMI between the two groups.

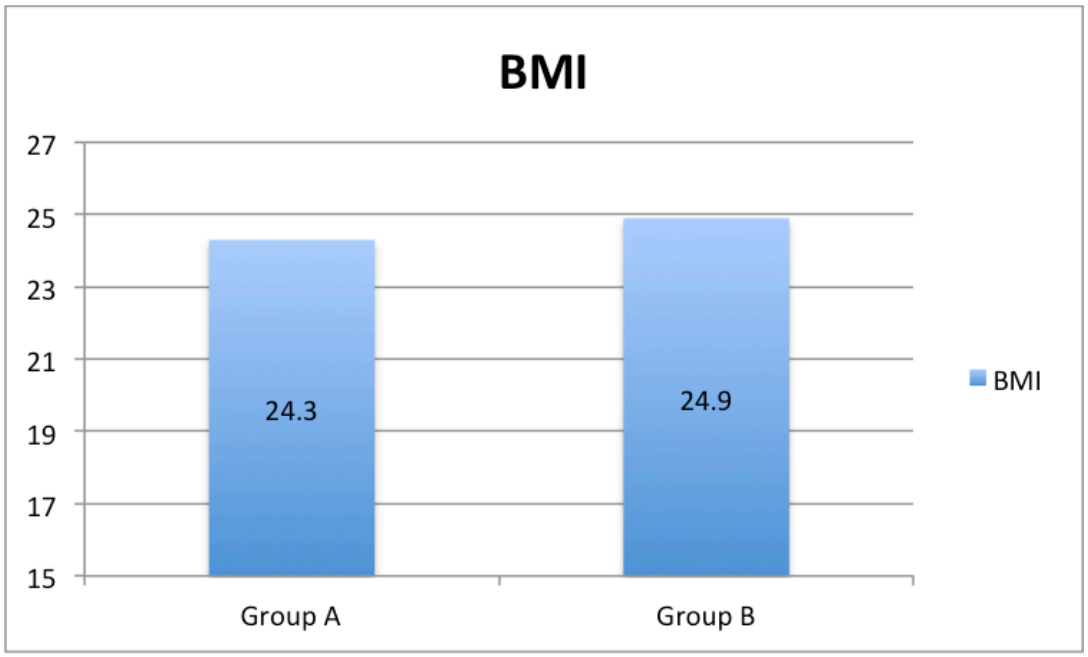


Figure 8. BMI distribution among Group A and Group B.

Tumour location

Tumour location also has a significant impact on technique of surgeryand the need for brain relaxation. Tumours located on certain areas of brain eg.suprasellar region are very difficult to access and requires maximum reduction of intracranial pressure as they are technically challenging for the surgeon. Most patients in both the groups had tumours located superficially as in the frontal region followed by tumours in the parietal tregion. There was no significant difference in location of the tumour between the two groups.

Table 2. The distribution of tumour location between the two groups .

	Group A(%)	**Group B(%)**
FRONTAL	13(44.8%)	16(55.1%)
PARIETAL	7(24.1%)	9(31.03%)
TEMPORAL	9(31.0%)	4(13.7%)

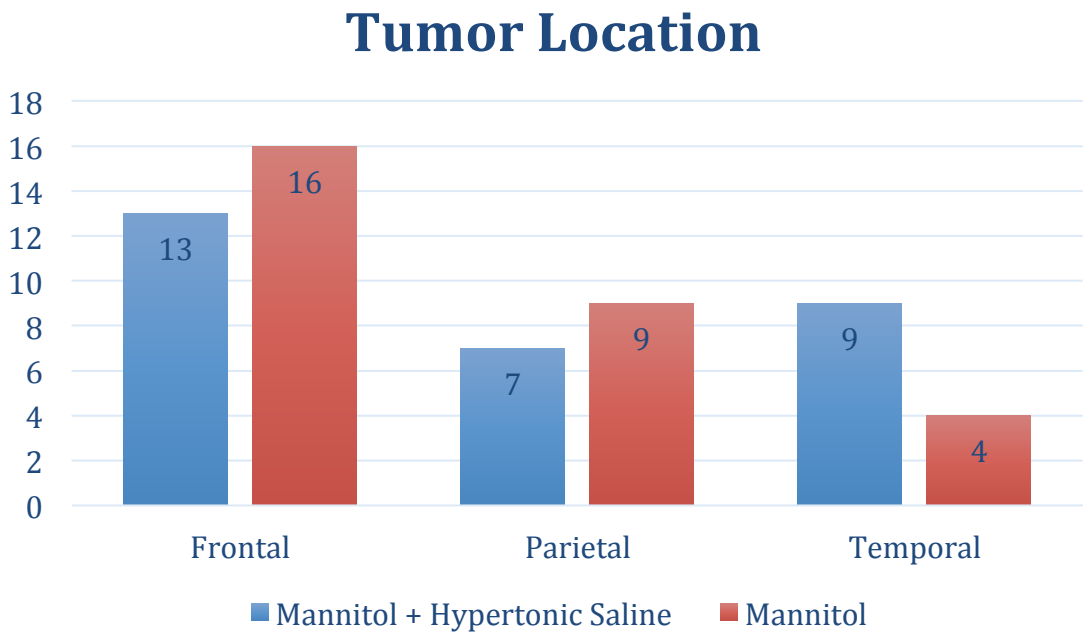


Figure 9. Distribution of tumour location in Group A and Group B

Tumour Pathology

Slow growing tumors are likely to have increases in ICP with adequate compensatory mechanisms unlike the fast growing ones. In our study, there was no significant difference in distribution of tumour pathology between the two groups. Most of the patients in both the groups had meningioma, which is one of the most common slow growing and benign intracranial lesions. Following meningioma, glioma was the second common tumour type seen in both the groups. Table 3 /Figure10 shows the distribution of tumour pathology between the two groups.

Table 3. Distribution of tumour pathology between both groups

	Group A(%	Group B(%)
Meningioma	14(48.2%)	13(44.8%)
Glioma	7(24.1%)	10(34.4%)
Craniopharyngoma	4(13.7%)	2(6.8%)
Others	4(13.7%)	4(13.7%)

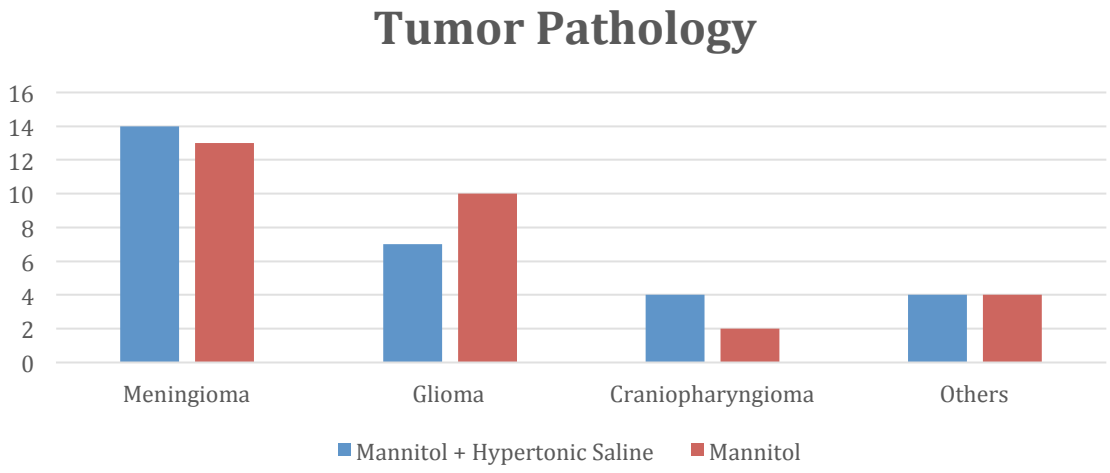


Figure 10. Distribution of tumour pathology in both groups.

Presence of preoperative edema and midline shift

Presence of preoperative edema and midline shift of more than 0.5mm on CT scan and edema are risk factors for intracranial hypertension and indicates the need for perioperative measures to reduce intracranial hypertension. Of the 29 patients in **Group A** ,13 patients had midline shift of more than 0.5mm in preoperative CT scans and of the 29 patients in **Group B** ,10 patients had midline shift of more than 0.5mm in preoperative CT scans.Of the 29 patients in **Group A** 25 patients had preoperative edema on CT scans and of the 29 patients in **Group B** 23 patients had preoperative edema on CT scans.

Table 4. Number of patients with preoperative midline shift on CT scans in both groups

Preoperative midline shift	**Group A**	**Group B**	P value
Present	13	10	0.648
Absent	16	19	

Table 5. Number of patients with preoperative edema on CT scans in both groups

Preoperative edema	**Group A**	**Group B**	**P value**
Present	25	23	0.483
Absent	4	6	

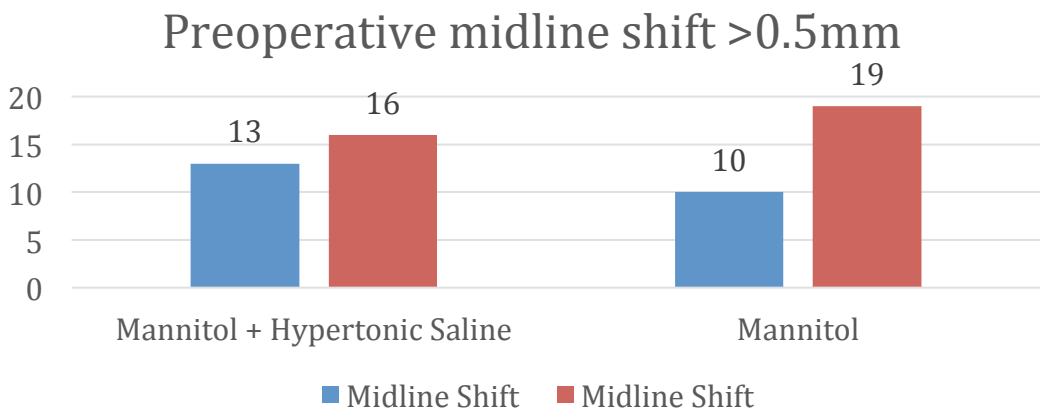


Figure 11. Comparision of distribution of preoperative midline shift in Group A and Group B

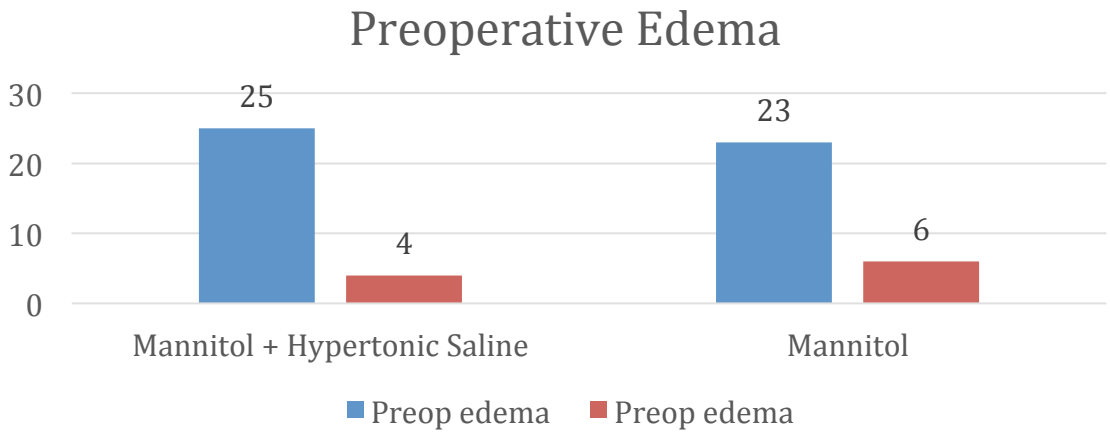


Figure 12. Comparision of distribution of preoperative edema in Group A and Group B

Effect of mannitol with hypertonic saline and mannitol on heart rate

Heart rate was recorded at baseline and at 0,5,10,15,30,60mins and 2 hours.

The mean baseline heart rate in **Group A** is 88.37bpm and mean baseline heart rate in **Group B** with mannitol is 88.41bpm.

The mean heart rate in **Group A** is 95.9 bpm and the mean heart rate in **Group B** is 86.9bpm.Trends in heart rate in **Group B** is lower than group a but there is no statistical difference between the two groups in terms of heart rate.

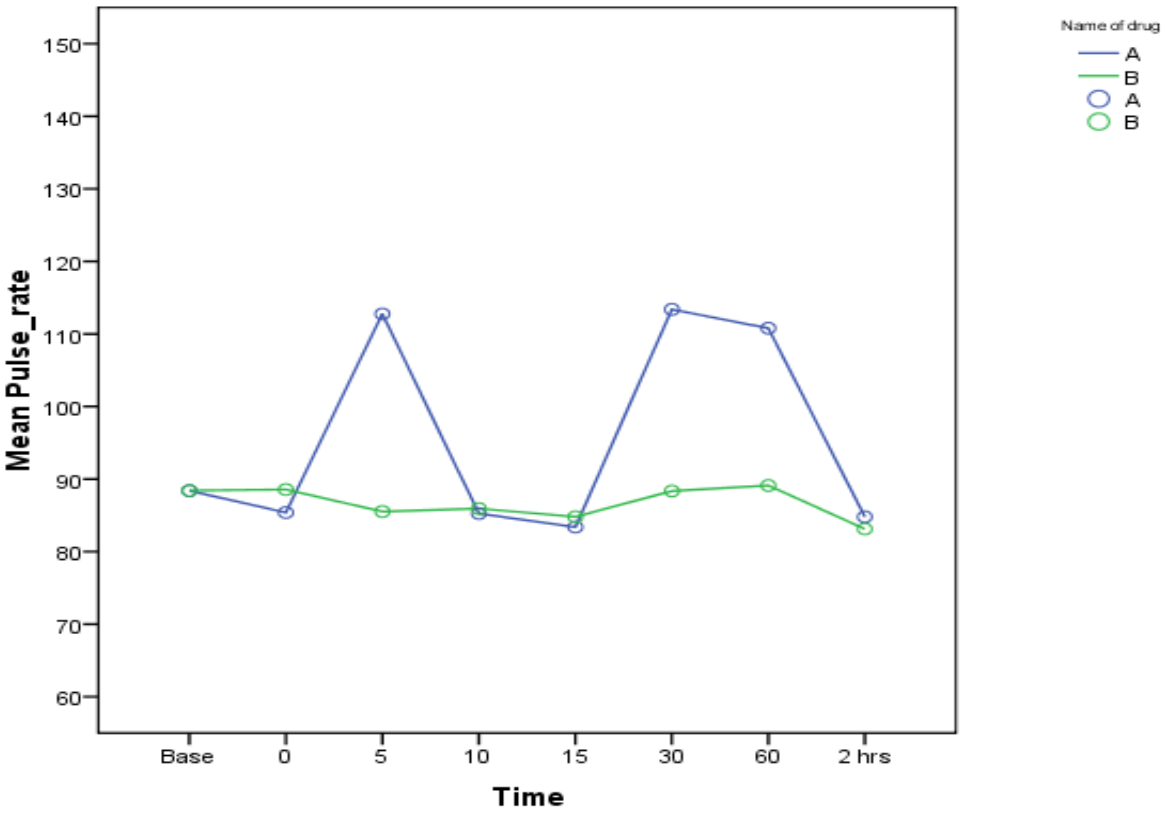


Figure 13. Dot plot comparing heart rate in Group A and Group B.

Effect of mannitol with hypertonic saline and mannitol on systolic blood pressure

Systolic blood pressure was recorded baseline and at 0,5,10,15,30,60mins and 2 hours. The mean baseline systolic blood pressure in **Group A** is 131.62 mm of Hg and mean baseline systolic blood pressure in **Group B** is 130.71mm of Hg.The mean systolic blood pressure in **Group A** is 118.71mm of Hg and the mean systolic blood pressure in **Group B** is 119.56 mm of Hg.There is no statistical difference between the two groups in terms of systolic blood pressure.

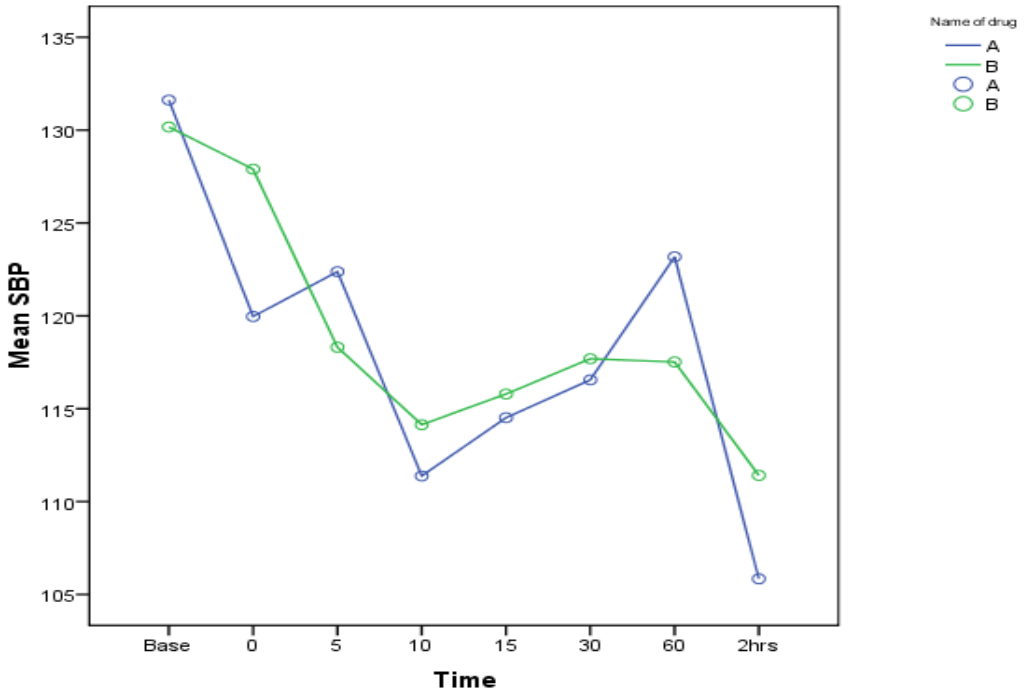


Figure 14. Dot plot comparing systolic blood pressure between Group A and Group B

Effect of mannitol with hypertonic saline and mannitol on diastolic blood pressure

Diastolic blood pressure was recorded baseline and at 0,5,10,15,30,60mins and 2 hours. The mean baseline diastolic blood pressure in **Group A** is 73.75 mm of Hg and mean baseline systolic blood pressure in **Group B** is 75.41 mm of Hg.The mean diastolic blood pressure in **Group A** is 68.88 mm of hg and the mean diastolic blood pressure in **Group B** is 68.84 mm of hg.There is no statistical difference between the two groups in terms of diastolic blood pressure.

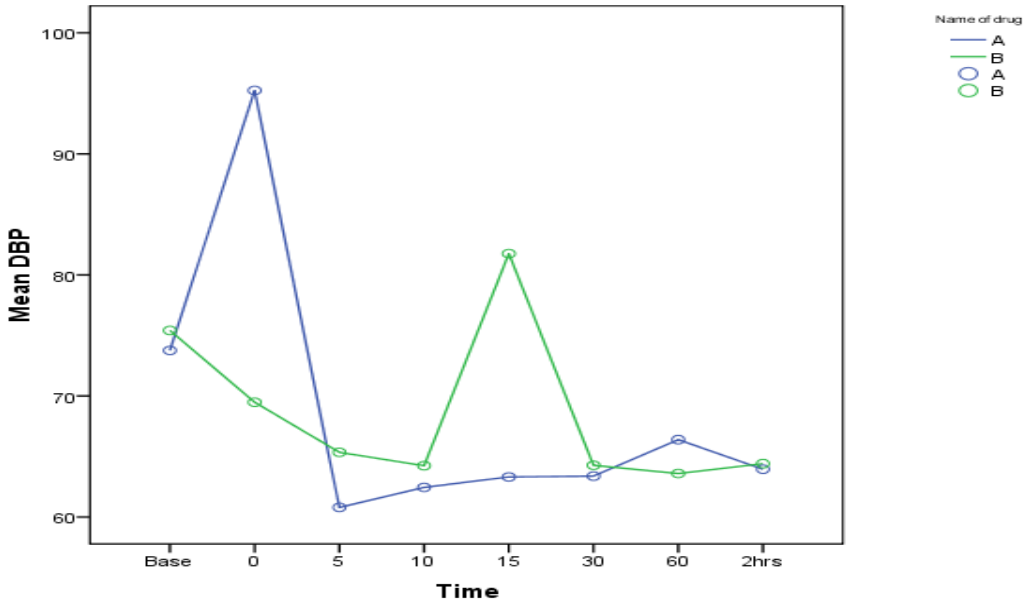


Figure 15. Dot plot comparing diastolic blood pressure between Group A and Group B

Effect of mannitol with hypertonic saline and mannitol on mean blood pressure

Mean blood pressure was recorded baseline and at 0,5,10,15,30,60mins and 2 hours. The mean of baseline mean blood pressure in group with mannitol with hypertonic saline is 90.51 and mean of baseline mean blood pressure in group with mannitol is 92.41. The mean of mean blood pressure in group received combination of mannitol with hypertonic saline is 82.52 and the mean of mean blood pressure in group received mannitol alone is 83.85.There is no statistical difference between the two groups in terms of mean blood pressure.

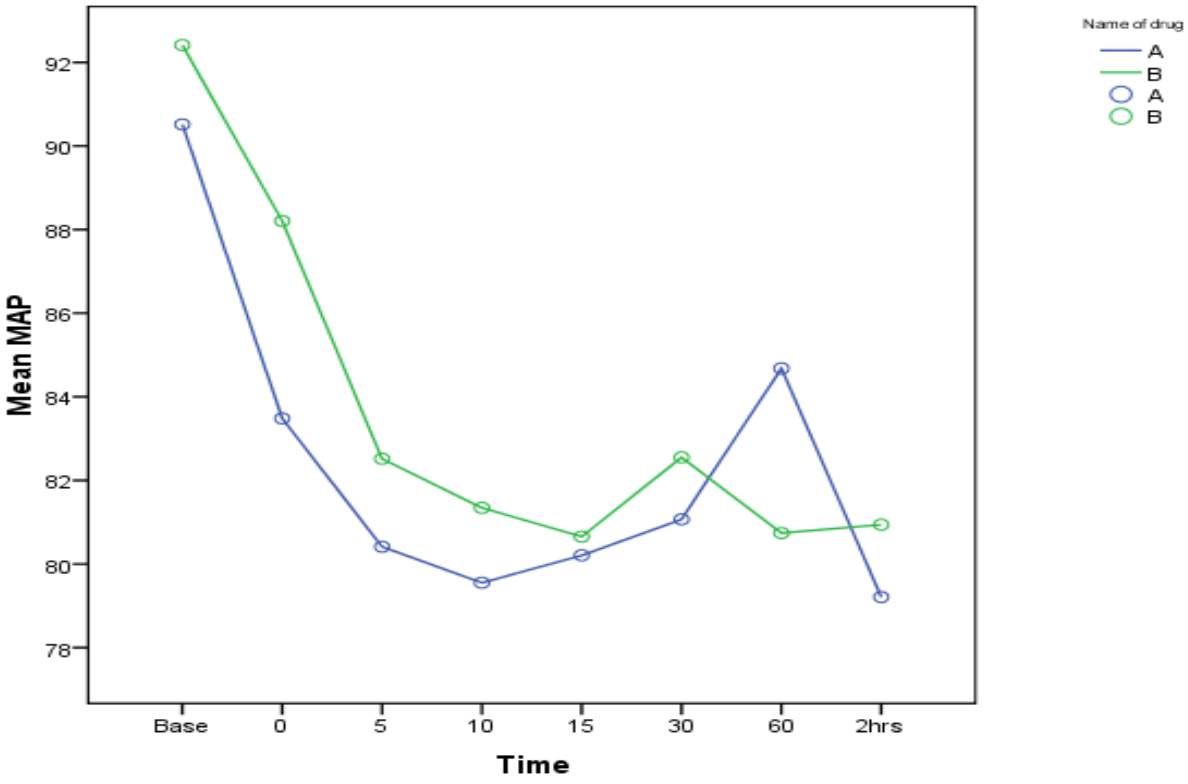


Figure 16. Dot plot comparing mean blood pressure between Group A and Group B

Effect of mannitol with hypertonic saline and mannitol on requirement of vasopressor use

Of the 29 patients in **Group A** only 3 patients (10.3%)required use of vasopressor and 26 patients didn't require vasopressor support. Of the 29 patients in **Group B** 6 (20%)patients required vasopressor support and 23 patients didn't require vasopressor support.Although there is a higher incidence of need for vasopressor support in the **Group B**,it is statistically not significant. (p value -0.832.)

Table 6. NUMBER OF PATIENTS REQUIRING VASOPRESSOR SUPPORT IN BOTH GROUPS.

Vasopressor support	**Group A**	**Group B**	p value
Required	3	6	0.832
Not required	26	23	

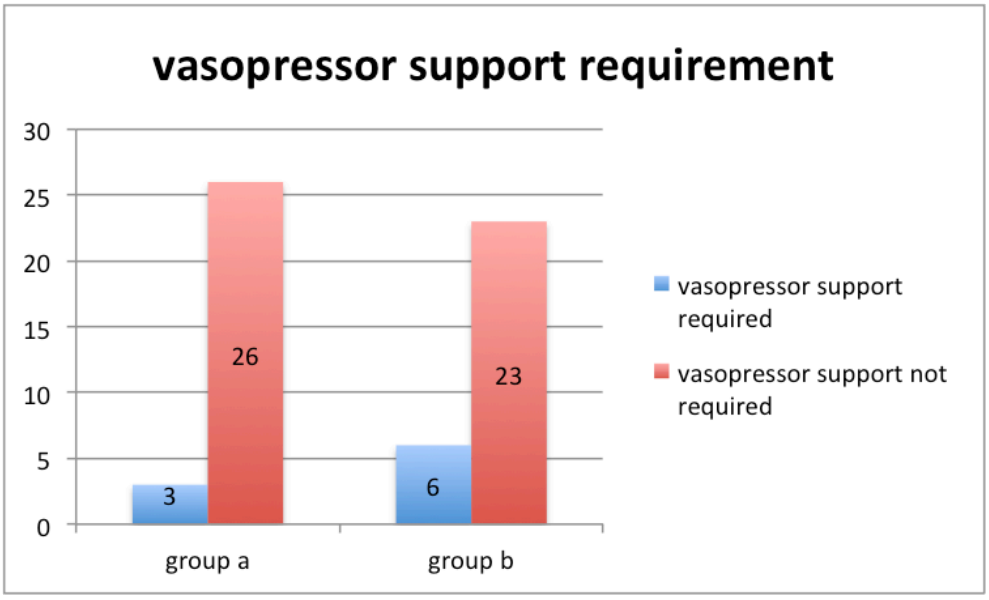


Figure 17. Comparision of requirement of vasopressor support between Group A and Group B

Effect of mannitol with hypertonic saline and mannitol on total fluid intake

The mean of total fluid intake in **Group A** is 2434.48 ml and the mean of total fluid intake in **Group B** is 2734.45.Although there is a tendency to have required larger volume of fluids in the **Group B,** there is no statistical difference in fluid intake between two groups (pvalue:0.291).None of our patients required transfusion of blood or blood products. There was no use of colloids.

Table 7. Comparision of Group A and Group B in terms of total fluid intake and urine output.

	Group A(mean)	**Group B(mean)**	p value	SE	95%Confidence Intervals	
					Upper limit	Lower limit
Total fluid intake	2434.48	2734.45	0.291	352.7	-1006.5	406.58
Urine output.	1217.93	1235.00	0.997	160.3	-338.23	304.09

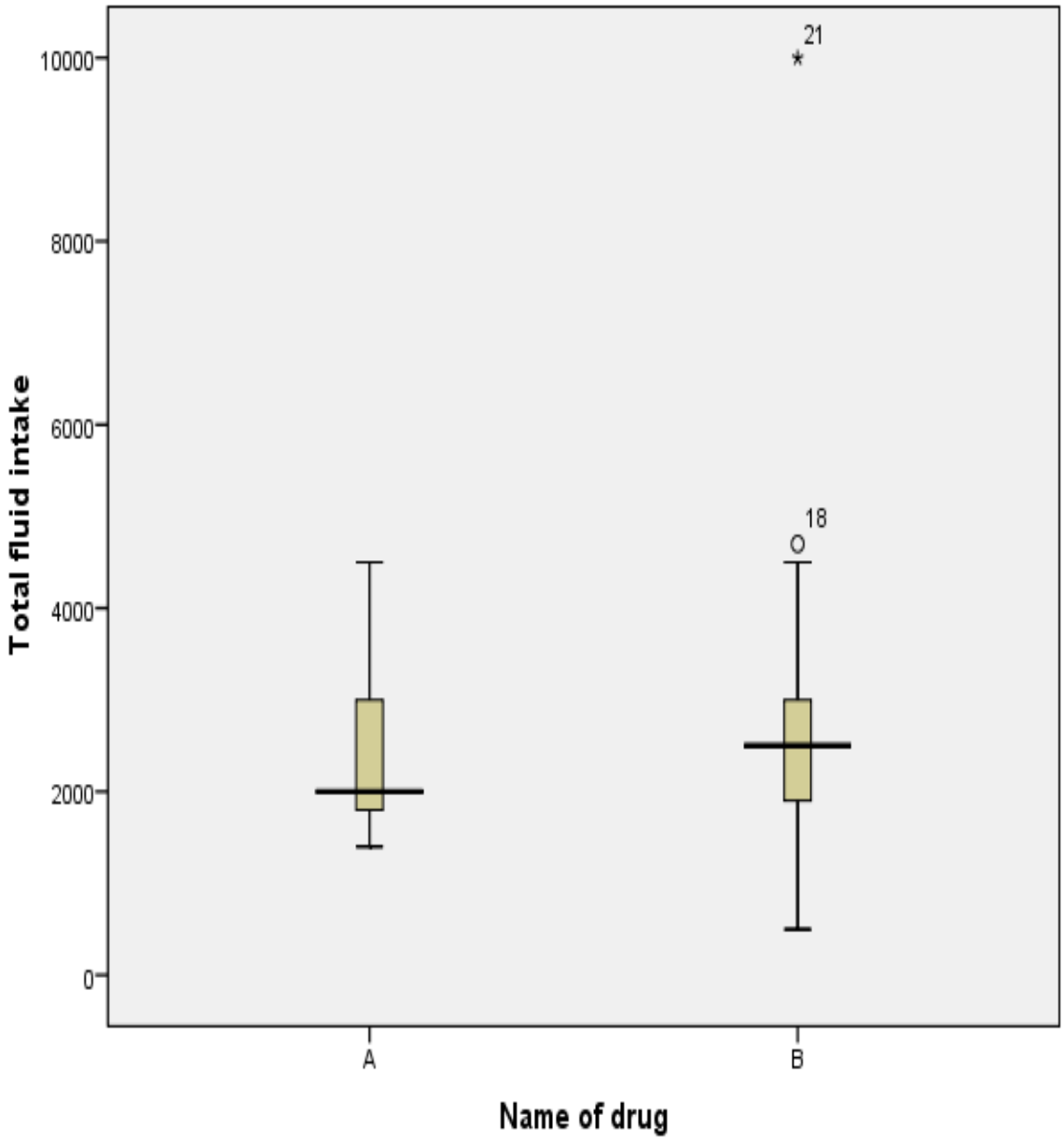


Figure 18. Box plot showing the total fluid input in Group A and Group B

Effect of mannitol with hypertonic saline and mannitol on total urine output

The mean of total urine output in **Group A** is 1217.93 ml and the mean of total urine output in **Group B** is 1235.There is no statistical difference in fluid intake between two groups (pvalue-0.997).

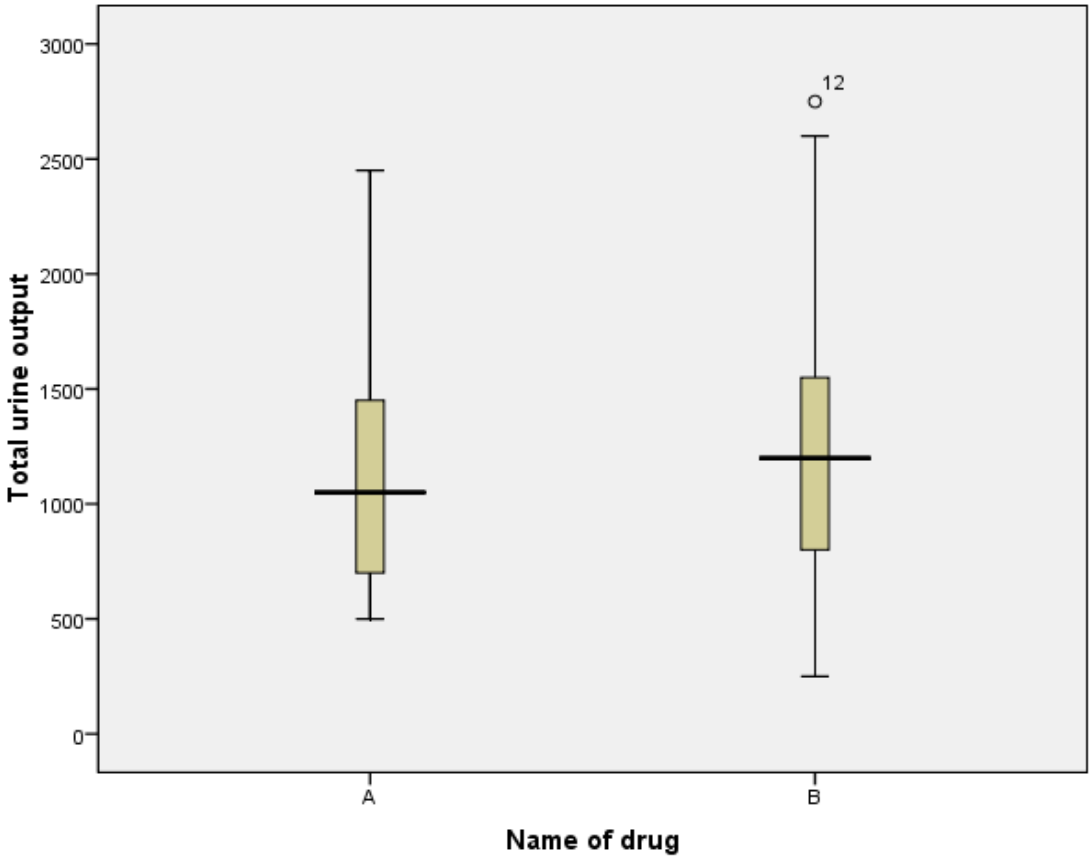


Figure 19. Box plot showing the urine output in Group A and Group B

Effect of mannitol with hypertonic saline and mannitol on serum sodium levels

The mean of baseline serum sodium in **Group A** is 137.48 meq/l and at the end of one hour is 136.48meq/l.(p value:0.425).The mean of baseline serum sodium in **Group B** is 135.58 meq/l and at the end of one hour is 132.44 meq/l(p value:0.397).Although we observed there is a tendency to develop hyponatremia in the group which received mannitol alone after one hour(mean=132.44) ,there is no statistical difference in between two groups p-value, probably because of the smaller sample size. Although this biochemical abnormality may not be clinically significant, it will assume significance in those with lower serum sodium levels as their baseline.

Table 8. Change in serum sodium levels one hour from baseline in both groups

	Group A(mean)	**Group B(mean)**	p value	SE	95%Confidence Intervals	
					Upper limit	Lower limit
Sodium (baseline)	137.48	135.58	0.425	0.76	0.36	3.42
Sodium(1 hour)	136.48	132.44	0.397	0.81	2.40	5.66

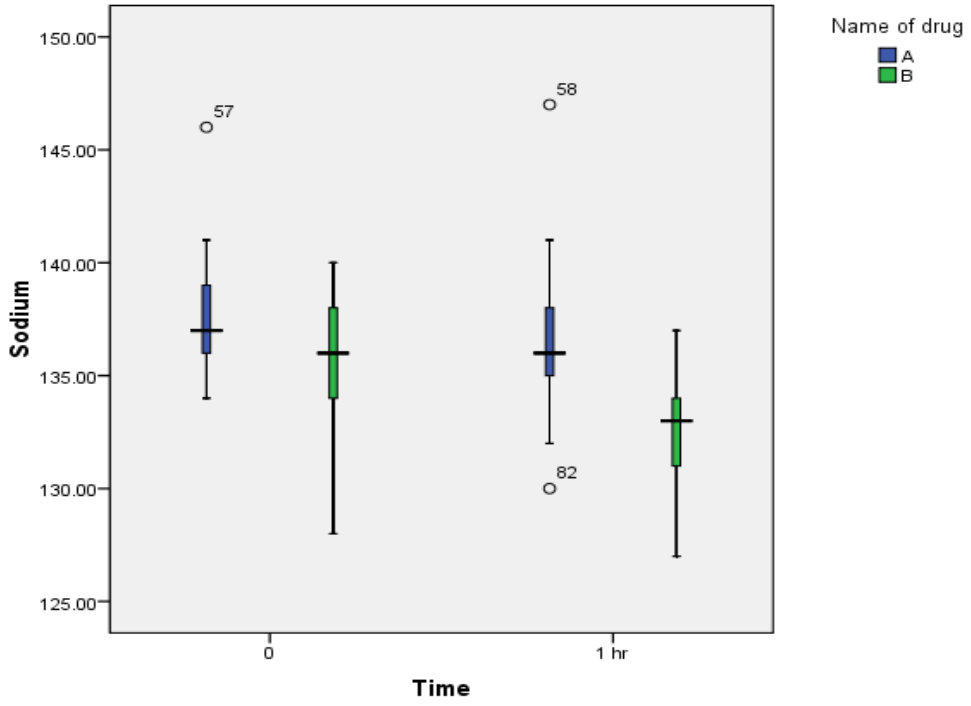


Figure 20. Box plot showing the serum sodium levels in Group A and Group B at baseline and at end of one hour.

Effect of mannitol with hypertonic saline and mannitol on serum potassium levels

The mean of baseline serum potassium in **Group A** is 3.64 meq/l and at the end of one hour is 4.12meq/l(p value:0.752). The mean of baseline serum potassium in **Group B** is 3.60 meq/l and at the end of one hour is 3.91meq/l (p value:0.620). There is no statistical difference in between two groups in terms of changes in potassium levels.

Table 9 . Change in serum potassium levels one hour from baseline in both groups

	Group A(mean)	**Group B(mean)**	p value	SE	95%Confidence Intervals	
					Upper limit	Lower limit
Potassium (baseline)	3.64	3.60	0.752	0.12	-0.202	0.278
Potassium (1 hour)	4.12	3.91	0.620	0.13	-0.04	0.47

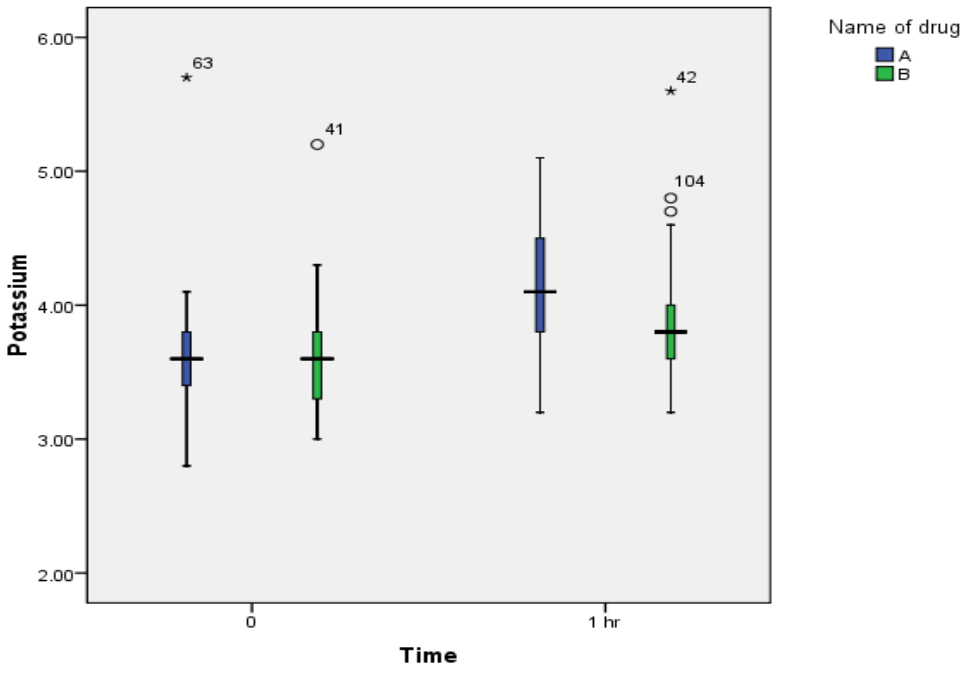


Figure 21. Box plot showing the serum potassium levels in Group A and Group B at baseline and at end of one hour.

Effect of mannitol with hypertonic saline and mannitol on serum lactate levels

The mean of baseline serum lactate levels in **Group A** is 2.45 and at the end of one hour is 2.85.(p value:0.733).The mean of baseline serum lactate levels in **Group B** is 2.22 and at the end of one hour is 2.65(p value:0.120). There is no statistical difference in between two groups in terms of changes in serum lactate levels.

Table 10. Change in serum lactate levels one hour from baseline in both groups

	Group A(mean)	**Group B(mean)**	p value	SE	95%Confidence Intervals	
					Upper limit	Lower limit
Serum lactate (baseline)	2.45	2.22	0.733	0.26	-0.299	0.76
Serum lactate (1hour)	2.85	2.65	0.120	0.34	-0.49	0.89

Effect of mannitol with hypertonic saline and mannitol on serum glucose levels

The mean of baseline serum glucose levels in **Group A** is 130.6 mg/dl and at the end of one hour is 139.2mg/dl(p value:0.522). The mean of baseline serum glucose levels in **Group B** is 130.96mg/dl and at the end of one hour is 142.2mg/dl (p value:0.960). There is no statistical difference in between two groups in terms of changes in serum glucose levels.

Table 11. Change in serum glucose levels one hour from baseline in both groups

	Group A(mean)	**Group B(mean)**	p value	SE	95%Confidence Intervals	
					Upper limit	Lower limit
GRBS (baseline)	130.6	130.9	0.522	7.81	-16.00	15.31
GRBS (1 hour)	139.2	142.2	0.960	7.66	-18.42	12.28

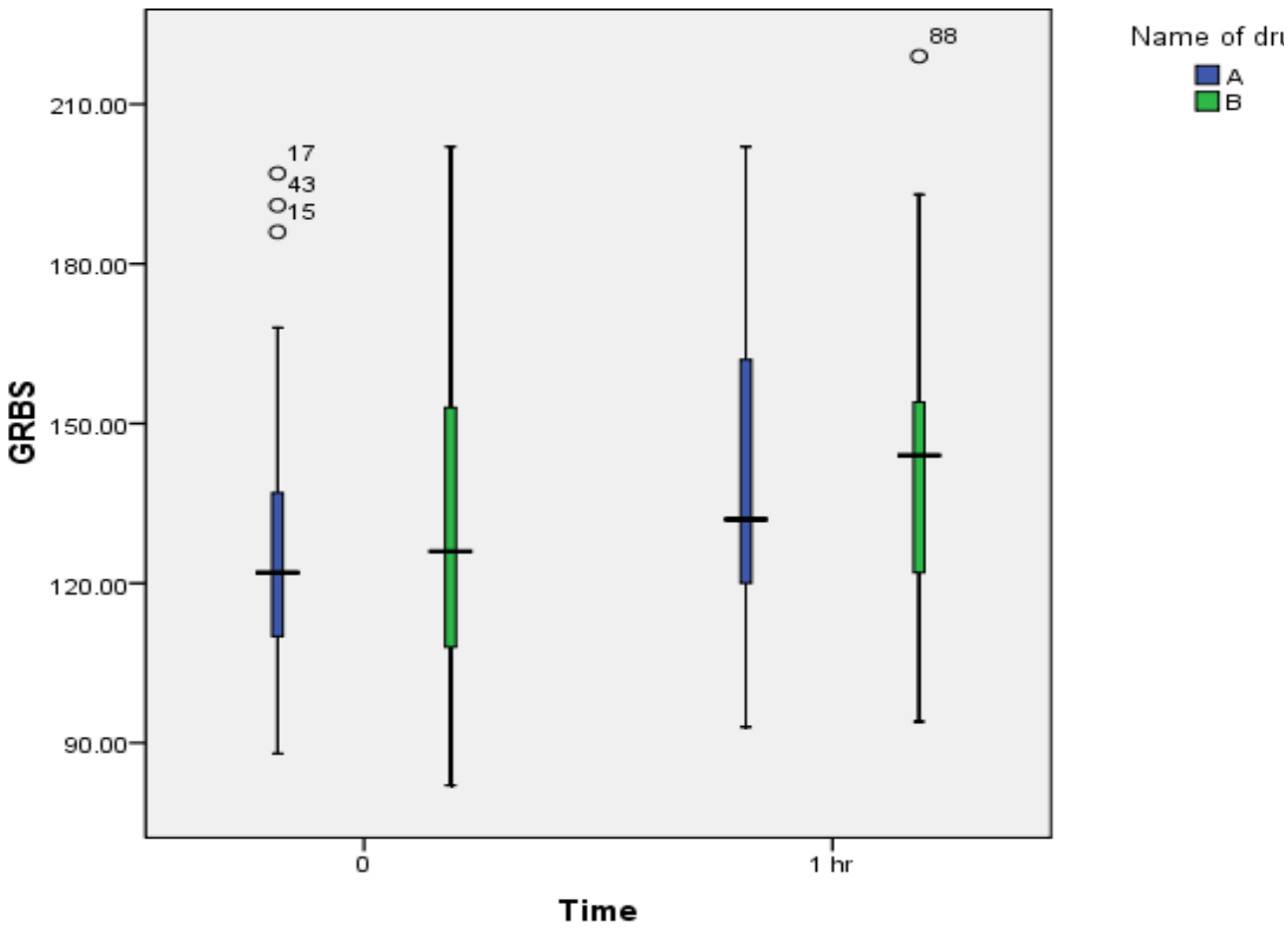


Figure 22. Box plot showing the serum GRBS levels in Group A and Group B at baseline and at end of one hour.

Effect of mannitol with hypertonic saline and mannitol on surgeons assessment of brain relaxation on dural opening

At the opening of dura surgeons assessment of brain relaxation was recorded on a four point score:

1. Perfectly relaxed
2. Satisfactorily relaxed:
3. Firm brain:
4. Bulging brain

Out of 29 patients in ***Group A***

6 patients brain was perfectly relaxed,

13 patients brain was satisfactorily relaxed,

8 patients brain was firm,

2 patients brain was bulging.

Out of 29 patients in ***Group B***

7 patients brain was perfectly relaxed,

13 patients brain was satisfactorily relaxed,

5 patients brain was firm,

4 patients brain was bulging

Table 12. Comparision of Group A and Group B in terms of brain relaxation

	Group A(%)	Group B(%)	p value
Perfectly relaxed	6(20.68%)	7(24.13%)	1
Satisfactorily relaxed	13(44.82%)	13(44.82%)	1
Firm	8(27.585%)	5(17.24%)	0.43
Bulging	2(6.89%)	4(13.79%)	0.56

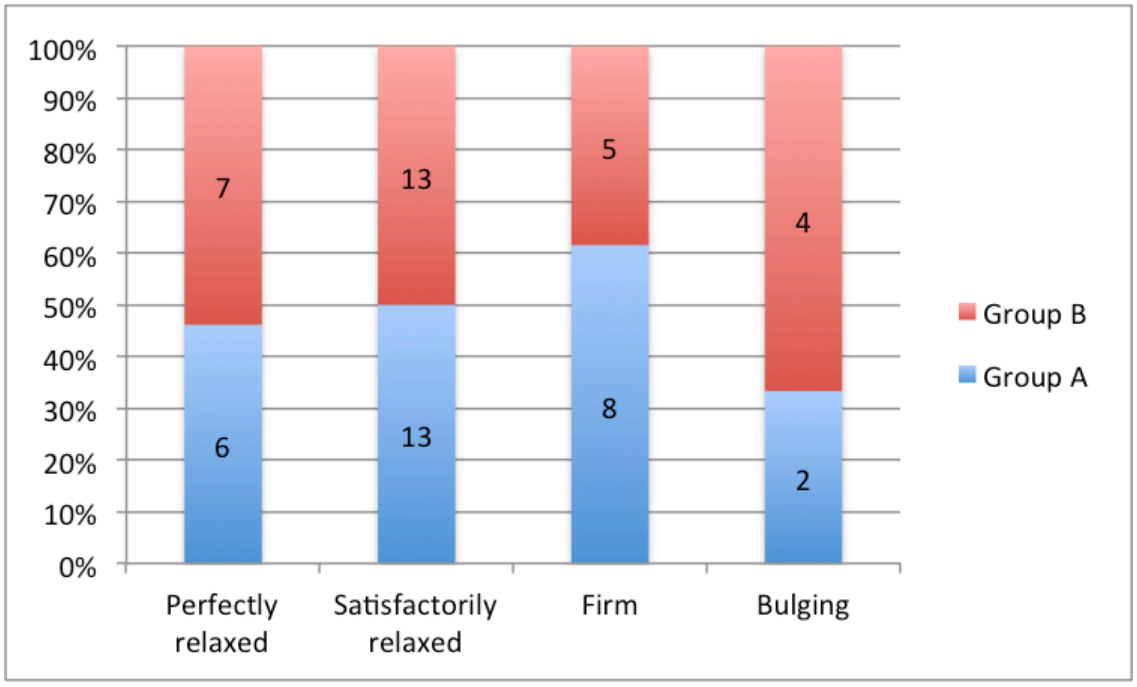


Figure 23. Comparision of brain relaxation in Group A and Group B

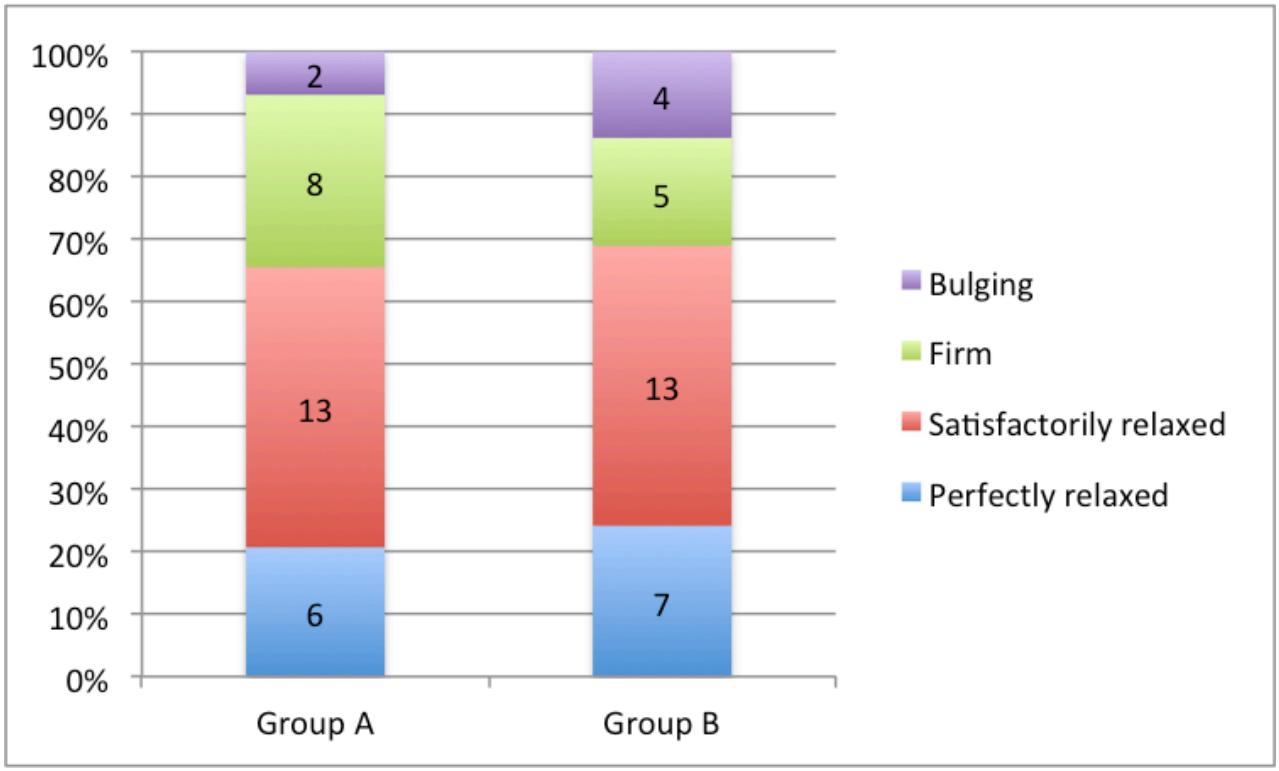


Figure 24. Stacked column comparing Group A and Group B in terms of brain relaxation

Group A:COMBINATION OF MANNITOL WITH HYPERTONIC SALINE
Group B:MANNITOL

Comparing the requirement of additional dose of hyperosmotic agent in Group A and Group B

Table 13. Number of patients requiring additional dose of hyperosmotic agents.

Additional dose of mannitol	**Group A**	**Group B**	p value
Required	5(17.2%)	8(27.6%)	0.892
Not required	24(82.8%)	21(72.4%)	

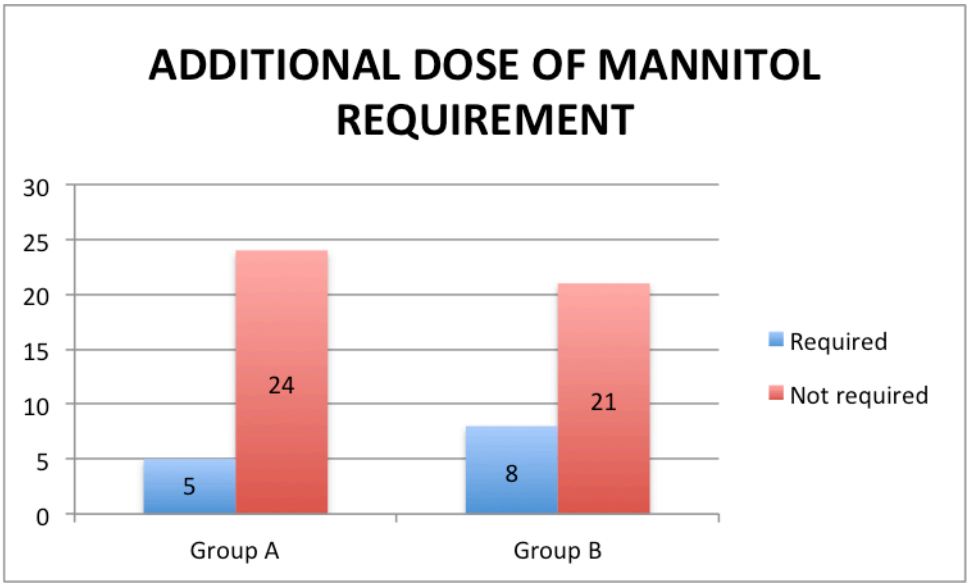


Figure 25. Additional dose of mannitol requirement

Table 14. Summary of comparsion of Group A and Group B on fluid balance, serum electrolyte levels.

	Group A(mean)	**Group B(mean)**	p value	Std Error	95%Confidence Intervals	
					Upper limit	Lower limit
Total fluid intake	2434.48	2734.45	0.291	352.7	-1006.5	406.58
Urine output	1217.93	1235.00	0.997	160.3	-338.23	304.09
Sodium (baseline)	137.48	135.58	0.425	0.76	0.36	3.42
Sodium(1 hour)	136.48	132.44	0.397	0.81	2.40	5.66
Potassium (baseline)	3.64	3.60	0.752	0.12	-0.202	0.278
Potassium(1 hour)	4.12	3.91	0.620	0.13	-0.04	0.47

Table 15. Summary of comparison of Group A and Group B on serum lactate and serum glucose levels.

	Group A(mean)	**Group B(mean)**	p value	Std Error	95%Confidence Intervals	
					Upper limit	Lower limit
Serum lactate (baseline)	2.45	2.22	0.733	0.26	-0.299	0.76
Serum lactate(1hour)	2.85	2.65	0.120	0.34	-0.49	0.89
GRBS (baseline)	130.6	130.9	0.522	7.81	-16.00	15.31
GRBS(1 hour)	139.2	142.2	0.960	7.66	-18.42	12.28

	P value
Vasopressor support	0.832
Brain relaxation	1.436
Additional dose of mannitol	0.892

DISCUSSION

The corner stone of anesthetic management in supratentorial craniotomy is adequate brain relaxation, thereby providing optimal conditions for the adequate resection of the tumour with minimal brain retraction. The most commonly practiced technique , which has withstood the test of time is the chemical brain retraction technique, which uses osmotherapeutic agents to achieve brain relaxation.

The two commonly used osmotherapeutic agents are mannitol and hypertonic saline. Until recently, Mannitol has been the more commonly used drug.

The problems associated with the use of mannitol such as electrolyte imbalance, hemodynamic disturbance, rebound edema ,kidney injury have prompted the search for better osmotherapeutic agents.

It has been clearly shown that in the chemical brain retraction concept of ICP reduction, it is the osmolar load which determines the efficiency of hyperosmolar solute. This depends on the Reflection Coefficient(RC). RC is a factor which determines the relative impermeability of the blood brain Barrier to the solute. The RC of Mannitol is 0.9 and that of the HTS is 1.0 ,which means in theory that HTS is better than mannitol.

In our study which is a double blinded randomized study, we compared the effects of 2 equivolemic , equiosmolar solutions, a combination of 3%hypertonic saline and 20%mannitol and 20%mannitol alone on brain relaxation, hemodynamic profile and electrolyte levels.

There are various intraoperative factors that affect intracranial pressure such as positioning of patient during surgery, hypoxia, hypercarbia, mean arterial pressure and choice of anesthetic technique. These factors have been standardized between the two groups. All the patients included in the study were positioned with head end elevation of 15 degrees, ventilated maintaining $paCo_2$ between 30-35 mm of Hg.and anesthesia was maintained with intravenous anesthesia using propofol infusion .Hemodynamics were maintained with vasopressors and fluids and vasopressor supports were initiated when there was decrease in MAP of <25%.

We found that that the equiosmolar solutions of both groups had a similar effect on brain relaxation. However, in the subgroup of patients with firm and bulging brains, we found that more patients in the mannitol group had bulging brains. It was also observed that patients in the mannitol group required additional rescue osmotherapy as compared to the combination group.

Two prospective studies, by ***Gemma et al and De Vivo et al*** have shown similar brain relaxation with mannitol and hypertonic saline, however with different osmolar loads. It was ***Rozet et al*** who first compared equiosmolar loads of mannitol and hypertonic saline . Although this study used a very small sample size of patients, with varying pathologies and a non standardized anesthesia protocol,they demonstrated that equiosmolar loads provided comparable brain relaxation. The mannitol group also showed less positive fluid balance and increased lactatemia. However, patients remained haemodynamically stable without significant changes in the mean arterial blood pressure.

In a very similar study, done on a larger sample size on a more homogenous patient population by **Wu et al,** better brain relaxation was observed with the use of hypertonic saline during elective supratentorial tumour surgery. However,it did not affect ICU stay or hospital stay. They also observed that Serum Sodium levels were higher in the Hypertonic saline Group.

Ever since, multiple studies have shown that hypertonic saline is as good or better than mannitol in terms of brain relaxation and reduction of ICP not only in tumour surgery but also in ICH,SAH.

Recently a Cochrane review has conclusively shown that , that there is a definite reduction in the incidence of brain bulge with the use of hypertonic saline.(RR of 0.6,95%CI 0.44-0.83)

HTS solutions have evolved as an alternative to mannitol in the management of refractory intracranial hypertension. However . high osmolar fluid loads are associated with an increased risk of the potentially deleterious consequences of hypernatremia or may induce osmotic BBB opening, with possible harmful extravasation of the hypertonic solution into the brain tissue.

The increase in sodium associated with the use of hypertonic saline , stimulates the release of ADH leading to the absorption of free water from the kidney which explains the lower diuretic effect of the HTS.

In our study , the diuresis in both the groups were almost comparable, the mannitol group required more vasopressor support, more intravenous fluids and more hyponatremia as compared to the combination group. This may probably be due to the the not so high serum sodium levels observed in the combination group. Although none of these observations achieved statistical significance, probably because of the smaller sample size, the emergence of trends was observed which is in concordance with that observed by Irene et al and Wu et al .

The hydreoelectrolytic changes with mannitol and HTS have been described by ***Boas et al***. Mannitol is known to cause dilutional serum hyponatremia due to volume overload and hyperkalemia. This was also reflected in our study,where we found mild hyponatremia in the group receiving mannitol alone. The mean serum sodium levels are 132.4.in the mannitol group and in the combination group,the mean serum sodium levels observed are 136.4.

Rozet et al. also demonstrated lower sodium serum levels 15 and 30 minutes after mannitol administration. Changes in serum levels of chloride, calcium, and hemoglobin after mannitol administration are most likely dilutional with longer lasting calcium and hemoglobin changes since solutions containing calcium or red blood cells were not administered.

Wu et al has showed that 3% HTS was associated with significantly higher levels of serum sodium and a decreased diuretic effect compared with mannitol. But since, we had used a combination of mannitol and hypertonic saline, we did not observe any significant hypernatremia or a reduction in diuresis.

Combination of mannitol and hypertonic saline in equiosmolar concentrations have not been studied to the best of our knowledge. The only

one instance is the study done by De Vivo et al which has used differing osmotic loads of 2 different hyperosmolar agents..As has been shown in our study, the combination of mannitol and hypertonic saline provides adequate brain relaxation and a superior electrolyte profile as compared to mannitol alone.

Limitations

1) One of the major limitations of our study was small sample size. So, our study results have to be interpreted with caution. We are planning to continue the study in future to increase the sample size and the power of the study. Then our results can be interpreted better and can bring about a change in clinical practice on day to day basis.

2)Patients with preexisting cardiac dysfunction, chronic kidney disease and electrolyte abnormalities were not included in the study and hence the results can not be generalized for the above group of patients.

3) One of the limitation of study was assessment of brain relaxation objectively. Since there is no validated technique available to measure brain relaxation, the brain relaxation was assessed subjectively by the primary surgeon on a 4 point scale.

4) Serum electrolyte levels were not measured post operatively due to financial constraints

5)An another additional arm with only hypertonic saline would have been beneficial but since it is not the routine practice in our institution, we had not used3% HTS.

References

1. Cottrell JE, Young WL. Cottrell and Young's Neuroanesthesia. Elsevier Health Sciences; 2016. 481 p.

2. Davson H, Hollingsworth G, Segal MB. The mechanism of drainage of the cerebrospinal fluid. Brain J Neurol. 1970;93(4):665–78.

3. Monitoring and interpretation of intracranial pressure | Journal of Neurology, Neurosurgery & Psychiatry [Internet]. [cited 2017 Sep 26]. Available from: http://jnnp.bmj.com/content/75/6/813

4. Löfgren J, von Essen C, Zwetnow NN. The pressure-volume curve of the cerebrospinal fluid space in dogs. Acta Neurol Scand. 1973;49(5):557–74.

5. Wilson MH. Monro-Kellie 2.0: The dynamic vascular and venous pathophysiological components of intracranial pressure. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2016 Aug;36(8):1338–50.

6. Kuschinsky W, Wahl M. Local chemical and neurogenic regulation of cerebral vascular resistance. Physiol Rev. 1978 Jul 1;58(3):656–89.

7. Bayliss WM. On the local reactions of the arterial wall to changes of internal pressure. J Physiol. 1902 May 28;28(3):220–31.

8. Kuo L, Davis MJ, Chilian WM. Myogenic activity in isolated subepicardial and subendocardial coronary arterioles. Am J Physiol. 1988 Dec;255(6 Pt 2):H1558–62.

9. Hertz MM, Paulson OB. Heterogeneity of cerebral capillary flow in man and its consequences for estimation of blood-brain barrier permeability. J Clin Invest. 1980 May;65(5):1145.

10. al KH et. Analysis of vasoactivity of local pH, PCO2 and bicarbonate on pial vessels. - PubMed - NCBI [Internet]. [cited 2017 Sep 19]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16363

11. Influence of changes in the acid-base composition of the ventricular system on cerebral blood flow in cats | SpringerLink [Internet]. [cited 2017 Sep 19]. Available from: https://link.springer.com/article/10.1007/BF00586213

12. Nielsen AN, Lauritzen M. Coupling and uncoupling of activity-dependent increases of neuronal activity and blood flow in rat somatosensory cortex. J Physiol. 2001 Jun 15;533(Pt 3):773–85.

13. Mavrocordatos P, Bissonnette B, Ravussin P. Effects of neck position and head elevation on intracranial pressure in anaesthetized neurosurgical patients: preliminary results. J Neurosurg Anesthesiol. 2000 Jan;12(1):10–4.

14. Muizelaar JP, Lutz HA, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. J Neurosurg. 1984 Oct;61(4):700–6.

15. Gelb AW, Craen RA, Rao GSU, Reddy KRM, Megyesi J, Mohanty B, et al. Does hyperventilation improve operating condition during supratentorial craniotomy? A multicenter randomized crossover trial. Anesth Analg. 2008 Feb;106(2):585–94, table of contents.

16. Saraswat VA, Saksena S, Nath K, Mandal P, Singh J, Thomas MA, et al. Evaluation of mannitol effect in patients with acute hepatic failure and acute-on-chronic liver failure using conventional MRI, diffusion tensor imaging and in-vivo proton MR spectroscopy. World J Gastroenterol WJG. 2008 Jul 14;14(26):4168–78.

17. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. J Neurosurg. 1983 Nov;59(5):822–8.

18. Rosner MJ, Coley I. Cerebral perfusion pressure: a hemodynamic mechanism of mannitol and the postmannitol hemogram. Neurosurgery. 1987 Aug;21(2):147–56.

19. Dziedzic T, Szczudlik A, Klimkowicz A, Rog TM, Slowik A. Is mannitol safe for patients with intracerebral hemorrhages? Renal considerations. Clin Neurol Neurosurg. 2003 Apr;105(2):87–9.

20. García-Morales EJ, Cariappa R, Parvin CA, Scott MG, Diringer MN. Osmole gap in neurologic-neurosurgical intensive care unit: Its normal value, calculation, and relationship with mannitol serum concentrations. Crit Care Med. 2004 Apr;32(4):986–91.

21. Rabetoy GM, Fredericks MR, Hostettler CF. Where the kidney is concerned, how much mannitol is too much? Ann Pharmacother. 1993 Jan;27(1):25–8.

22. Osmotic nephrosis with mannitol: review article: Renal Failure: Vol 36, No 7 [Internet]. [cited 2017 Sep 28]. Available from: http://www.tandfonline.com/doi/full/10.3109/0886022X.2014.926758?src=recsys&

23. Chen C-H, Toung TJK, Sapirstein A, Bhardwaj A. Effect of duration of osmotherapy on blood-brain barrier disruption and regional cerebral edema after experimental stroke. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 2006 Jul;26(7):951–8.

24. Oddo M, Levine JM, Frangos S, Carrera E, Maloney-Wilensky E, Pascual JL, et al. Effect of mannitol and hypertonic saline on cerebral oxygenation in

patients with severe traumatic brain injury and refractory intracranial hypertension. J Neurol Neurosurg Psychiatry. 2009 Aug;80(8):916–20.

25. Bhardwaj A. Osmotherapy in neurocritical care. Curr Neurol Neurosci Rep. 2007 Nov 1;7(6):513–21.

26. Zakaria ER, Tsakadze NL, Garrison RN. Hypertonic saline resuscitation improves intestinal microcirculation in a rat model of hemorrhagic shock. Surgery. 2006 Oct;140(4):579–88.

27. Kumasaka K, Marks JA, Eisenstadt R, Murcy MA, Samadi D, Li S, et al. In vivo leukocyte-mediated brain microcirculatory inflammation: a comparison of osmotherapies and progesterone in severe traumatic brain injury. Am J Surg. 2014 Dec;208(6):961–8; discussion 967–8.

28. Rizoli SB, Rhind SG, Shek PN, Inaba K, Filips D, Tien H, et al. The immunomodulatory effects of hypertonic saline resuscitation in patients sustaining traumatic hemorrhagic shock: a randomized, controlled, double-blinded trial. Ann Surg. 2006 Jan;243(1):47–57.

29. Pascual JL, Khwaja KA, Chaudhury P, Christou NV. Hypertonic saline and the microcirculation. J Trauma. 2003 May;54(5 Suppl):S133–40.

30. Lazar RM, Fitzsimmons B-F, Marshall RS, Berman MF, Bustillo MA, Young WL, et al. Reemergence of stroke deficits with midazolam challenge. Stroke. 2002 Jan;33(1):283–5.

31. Ornstein E, Matteo RS, Schwartz AE, Silverberg PA, Young WL, Diaz J. The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. Anesthesiology. 1987 Aug;67(2):191–6.

32. Yeh JS, Dhir JS, Green AL, Bodiwala D, Brydon HL. Changes in plasma phenytoin level following craniotomy. Br J Neurosurg. 2006 Dec;20(6):403–6.

33. Albin MS, Carroll RG, Maroon JC. Clinical considerations concerning detection of venous air embolism. Neurosurgery. 1978 Dec;3(3):380–4.

34. McGirt MJ, Woodworth GF, Brooke BS, Coon AL, Jain S, Buck D, et al. Hyperglycemia independently increases the risk of perioperative stroke, myocardial infarction, and death after carotid endarterectomy. Neurosurgery. 2006 Jun;58(6):1066–73; discussion 1066–73.

35. Prognostic Significance of Hyperglycemia in Acute Intracerebral Hemorrhage | Stroke [Internet]. [cited 2017 Sep 20]. Available from: http://stroke.ahajournals.org/content/47/3/682

36. Lanier WL, Stangland KJ, Scheithauer BW, Milde JH, Michenfelder JD. The effects of dextrose infusion and head position on neurologic outcome after

complete cerebral ischemia in primates: examination of a model. Anesthesiology. 1987 Jan;66(1):39–48.

37. Beleña JM, Núñez M, Vidal A, Anta D. Randomized double-blind comparison of remifentanil and alfentanil in patients undergoing laparoscopic cholecystectomy using total intravenous anesthesia. J Anaesthesiol Clin Pharmacol. 2016;32(4):487–91.

38. Other Stimuli Add to Effect of Remifentanil on BIS - Journals - NCBI [Internet]. [cited 2017 Sep 20]. Available from: https://www.ncbi.nlm.nih.gov/labs/articles/12538234/

39. Pharmacokinetics, pharmacodynamics, and rational opioid selection. - PubMed - NCBI [Internet]. [cited 2017 Sep 20]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/1824743

40. Excitatory Amino Acid Antagonists - Neuroanaesthesia [Internet]. [cited 2017 Sep 20]. Available from: https://www.mitchmedical.us/neuroanaesthesia/excitatory-amino-acid-antagonists.html

41. Arshad A, Shamim MS, Waqas M, Enam H, Enam SA. How effective is the local anesthetic infiltration of pin sites prior to application of head clamps: A prospective observational cohort study of hemodynamic response in patients undergoing elective craniotomy. Surg Neurol Int [Internet]. 2013 Jul 18 [cited

2017 Sep 20];4. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3740611/

42. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, et al. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. J Neurotrauma. 2007;24 Suppl 1:S14–20.

43. Wakai A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD001049.

44. Llorente G, de Mejia MCN. Mannitol versus hypertonic saline solution in neuroanaesthesia. Colomb J Anesthesiol. 2015 Jan 1;43(Supplement 1):29–39.

45. Rudehill A, Gordon E, Ohman G, Lindqvist C, Andersson P. Pharmacokinetics and effects of mannitol on hemodynamics, blood and cerebrospinal fluid electrolytes, and osmolality during intracranial surgery. J Neurosurg Anesthesiol. 1993 Jan;5(1):4–12.

46. James HE. Methodology for the control of intracranial pressure with hypertonic mannitol. Acta Neurochir (Wien). 1980;51(3-4):161–72.

47. Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ, Lee LA, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on

intraoperative brain relaxation and electrolyte balance. J Am Soc Anesthesiol. 2007;107(5):697–704.

48. Wu C-T, Chen L-C, Kuo C-P, Ju D-T, Borel CO, Cherng C-H, et al. A comparison of 3% hypertonic saline and mannitol for brain relaxation during elective supratentorial brain tumor surgery. Anesth Analg. 2010 Mar 1;110(3):903–7.

49. Qureshi AI, Wilson DA, Traystman RJ. Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: comparison between mannitol and hypertonic saline. Neurosurgery. 1999;44(5):1055–63.

50. Harutjunyan L, Holz C, Rieger A, Menzel M, Grond S, Soukup J. Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients – a randomized clinical trial [ISRCTN62699180]. Crit Care. 2005;9(5):R530–40.

51. Mirski AM, Denchev ID, Schnitzer SM, Hanley FD. Comparison between hypertonic saline and mannitol in the reduction of elevated intracranial pressure in a rodent model of acute cerebral injury. J Neurosurg Anesthesiol. 2000 Oct;12(4):334–44.

52. Shackford SR, Zhuang J, Schmoker J. Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. J Neurosurg. 1992 Jan;76(1):91–8.

53. Shackford SR. Effect of small-volume resuscitation on intracranial pressure and related cerebral variables. J Trauma. 1997 May;42(5 Suppl):S48–53.

54. Vialet R, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med. 2003 Jun;31(6):1683–7.

55. Battison C, Andrews PJD, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. Crit Care Med. 2005 Jan;33(1):196–202; discussion 257–8.

56. Horn P, Münch E, Vajkoczy P, Herrmann P, Quintel M, Schilling L, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. Neurol Res. 1999 Dec;21(8):758–64.

57. Treatment of Elevated Intracranial Pressure by Infusions of 10% Saline in Severely Head Injured Patients | SpringerLink [Internet]. [cited 2017 Sep 30].

Available from: https://link.springer.com/chapter/10.1007/978-3-7091-6475-4_9

58. Mortazavi MM, Romeo AK, Deep A, Griessenauer CJ, Shoja MM, Tubbs RS, et al. Hypertonic saline for treating raised intracranial pressure: literature review with meta-analysis. J Neurosurg. 2012 Jan;116(1):210–21.

59. Mannitol versus hypertonic saline for intraoperative brain relaxation in patients undergoing surgery for brain tumour - National Library of Medicine - PubMed Health [Internet]. [cited 2017 Sep 20]. Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0066082/

60. Gayatri P, Misra S, Menon G, Arulvelan A, Thulaseedharan JV. Transesophageal echocardiographic evaluation of left ventricular systolic and diastolic function in response to 20% mannitol and 3% hypertonic saline infusion in neurosurgical patients undergoing craniotomy. J Neurosurg Anesthesiol. 2014 Jul;26(3):187–91.

61. White H, Cook D, Venkatesh B. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. Anesth Analg. 2006 Jun;102(6):1836–46.

APPENDIX

Table of Figures

Table of Tables

LIST OF ABBREVIATIONS

HR: HEART RATE.

SBP: SYSTOLIC BLOOD PRESSURE.

DBP: DIASTOLIC BLOOD PRESSURE.

MAP: MEAN ARTERIAL PRESSURE.

ICP:INTRACRANIAL PRESSURE.

$PACO_2$: PARTIAL PRESSURE OF OXYGEN IN ARTERIES.

$PAO_{2:}$ PARTIAL PRESSURE OF OXYGEN IN ARTERIES.

CBF: CEREBRAL BLOOD FLOW.

$CMRO_2$: CEREBRAL METABOLIC REQUIREMENT OF OXYGEN.

CSF: CEREBROSPINAL FLUID.

$ETCO_{2:}$ ENDTIDAL CARBONDIOXIDE.

CPP: CEREBRAL PERFUSION PRESSURE.

PVI: PRESSURE VOLUME INDEX.

ATP: ADENOSINE TRIPHOSPHATE.

CVP: CENTRAL VENOUS PRESSURE.

BIS: BISPECTRAL INDEX.

BMI: BODY MASS INDEX.

PATIENT INFORMATION SHEET

TITLE OF RESEARCH: A comparison of equiosmolar concentrations of combination of mannitol and hypertonic saline vs. mannitol alone to assess brain relaxation, hemodynamic profile and electrolyte changes in patients undergoing elective supratentorial craniotomy-a randomised control trial"

Dear sir/madam,

You are requested to participate in a study to determine the brain relaxation and hemodynamic profile during supratentorial craniotomy .All patients undergoing supratentorial craniotomy receive hypertonic agents to reduce intracranial pressure. In our institute we routinely use mannitol as part of management of craniotomies. By this study we aim to compare mannitol with combination of mannitol and hypertonic saline and determine whether brain relaxation is same and we will compare hemodynamic profile in both group.

1) Why have I been invited to participate in this study?

You are eligible to participate in this study as you are diagnosed with intracranial tumor and planned for craniotomy and removal of tumor.

2) IF U TAKE PART, WHAT WILL U HAVE TO DO?

If u agree to take part in this study, you will be divided into two groups based on computer generated randomization. As per the group allocated, you will receive either of drugs during surgery. Your hemodynamics will be monitored and around 10-15ml of blood will be collected from existing lines and will be sent to laboratory. We will also record amount of brain relaxation during surgery and if we felt it's inadequate another dose of drug will be administered.

3) CAN U WITHDRAW FROM THE STUDY AFTER IT STARTS?

Your participation in the study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you so, this will not affect your treatment at this hospital in any way.

4) WILL U BE SUBJECTED TO INVASIVE PROCEDURES UNDER THIS STUDY?

As you are undergoing neurosurgery, all patients require placement of invasive arterial access and intravenous access as a part of your routine management. This routine access will be used to monitor your hemodynamic variables and to collect blood for arterial blood gas analysis and other biochemical tests. No new invasive procedures will be done for this study.

5) WHAT WILL HAPPEN IF YOU DEVELOP ANY STUDY RELATED INJURY?

We do not expect any injury related to study as study involves of administration of drugs, which are routinely, used in practice and collection blood samples.

6) WILL YOU HAVE TO PAY FOR ADDITIONAL BLOOD TESTS?

No.the additional tests done as part of study will be done free of cost to the study participants.

7) Are there risks to me in taking part in this study?

No extra risk is associated with the study other than the due risk associated with surgery.

8)Will I benefit from the study?

This study aims to further medical knowledge and may improve future treatment of craniotomy and tumor excision.

9) Will taking part in this study cost me anything, and will I be paid

Participation in this study will not cost you anything.

10) WILL YOUR PERSONAL DETAILS BE KEPT CONFIDENTIAL?

If you agree to participate in this study, you will be allotted a specific study number. The name and other personal details of the study participants will be available only with the primary investigator, kept securely. The results of this study will be published in a medical journal 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.

IF YOU HAVE ANY FURTHER QUESTIONS, PLEASE FEEL FREE TO CONTACT:
DR.SNEHA.E-MOBILE NUMBER: +919655535271
EMAIL ID: snehaeda@gmail.com

Data collection sheeth

Serial no: _ _ _ _ Date:

PREOPERATIVE DATA:

Name : Age(yrs):
Sex:M/F

Hospital number:

Weight (kg): Height(cm): BMI:

Diagnosis:

Proposed surgery:

ASA:

Other comorbidities:

GCS:E _/4 M _/6 V _/5 (_ _ _/15)

Preoperative midline shift of more than 0.5mm:YES/NO

Preoperative edema: YES/NO

Patients on steroids and antiedema measure: YES/NO

If yes drug ,dose and duration:

INTRAOPERATIVE DATA:

Drug: a/b

Amount of drug administered:

Time of starting administration:

Vitals

time	Pr(bpm)	Sbp(mm hg)	Dbp(mm hg)	Map(mm hg)	Ppv(mm hg)	Etco2(%)	Cvp
baseline							
0 min							
5 min							
10 mins							
15 mins							
30 mins							
60 mins							
2hrs							

Vasopressors support started before administering study drug:yes/no
If yes any increase in the dose;yes/no
Vasopressor used:noradrenaline/others
Dose:

Urine input/output:

time	Input(ml)	Output(ml)
0		
1hr		
2hr		
3hr		
4hr		
5hr		
6hr		

Total fluid intake(ml):

Total urine outpu(ml)t:

Biochemical values:

time	Sodium (meq/l)	Potassium (meq/l)	Chloride (meq/l)	lactate	Anion gap(meq/l)	Serum osmolality (mosm/l)	Glucose (grbs)
0 mins							
1 hour							

Surgeons assessment of brain relaxation at opening of dura: 4/3/2/1
4:Bulging
3:Firm brain
2:Satisfactorily relaxed
1:Perfectly relaxed.

Additional dose of hyperosmotic agents required:yes/no

Total amount of drug administerd:

Informed Consent form to participate in a research study

Study Title: A COMPARISON OF EQUIOSMOLAR CONCENTRATIONS OF COMBINATION OF MANNITOL AND HYPERTONIC SALINE VS MANNITOL ALONE TO ASSESS BRAIN RELAXATION,HEMODYNAMIC PROFILE AND ELECTROLYTE CHANGES IN PATIENTS UNDERGOING ELECTIVE SUPRATENTORIAL CRANIOTOMY-A RANDOMISED CONTROL TRIAL"

1.

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the investigators of the clinical trial, others working on the Investigators behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or

Represe

Date: ___

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

_____

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
1	slno	date	age	drugname	sex	weight	Height	bmi	diagnosis	propsur	asa	othcomor	E	M	V	GCS	midline	edema	steroids	drugdose	drugdur	prbase	sbpbase	dbpbase	mapbase	pr0m
2	1	03-Apr-2017	47	1	1	84	166	30.50	"right frontal convexity meningioma"	"right frontoparietal craniotomy and tumo	2	"seizure"	4	6	5	15	1	1	1	41		100	144	90	111	79
3	2	13-Apr-2017	36	2	2	55	150	24.60	"left optic nerve sheath meningioma"	"left frontoorbital craniotomy and tumour	2	"nil"	4	6	5	15	2	2	2			78	126	86	99	80
4	3	06-Apr-2017	37	2	1	70	166	25.10	"right insular glioma"	"right pteranial craniotomy and tumour ex-	2	"nil"	4	6	5	15	2	1	1	4		65	151	76	105	90
5	4	13-Apr-2017	36	1	1	59	150	26.60	"right anterior falcine meningioma"	"craniotomy and tumour excision"	2	"nil"	4	6	5	15	2	2	1	4		98	127	60	73	101
6	5	17-Apr-2017	33	1	2	57	147	26.40	"left parietal parasagittal meningoma"	"left parietal craniotomy and tumour excis	2	"hypothyroidism"	4	6	5	15	1	1	1	4	14.00	49	137	68	85	60
7	6	17-Apr-2017	48	2	2	52	147	24.00	"left clinoidal meningioma"	"left frontotemporal craniotomy "	2	""	4	6	5	15	2	2	1	4		88	129	75	88	88
8	7	19-Apr-2017	59	2	1	90	170	31.00	"right temporoparietal glioma"	"right temporoparietal craniotomy and exc	2	"hypertension"	4	6	5	15	2	1	1	4		95	135	72	91	92
9	9	20-Apr-2017	52	1	1	71	170	24.60	"left parietal convexity meningioma"	"left frontoparietal craniotomy and excisio	2	"diabetes and hypertension"	4	6	5	15	2	1	1	4		78	150	64	82	58
10	10	20-Apr-2017	47	1	1	86	168	30.00	"left frontal glioma"	"left frontal craniotomy"	2	""	4	6	5	15	2	1	1	4		92	127	78	94	93
11	11	24-Apr-2017	41	2	2	65	150	28.90	"olfactory groove meningioma"	"bilateral frontal craniotomy and tumour e	2	"diabetes mellitus"	4	6	5	15	2	1	1	44		85	150	75	98	81
12	12	########	44	2	2	63	148	28.80	"right parasagittal meningioma"	"right parietal craniotomy and tumour exci	2	"hypothyroidism"	4	6	5	15	2	2	1	4		120	142	78	103	105
13	13	########	47	2	2	50	156	20.50	"parietal meningioma"	"parietal craniotomy and tumour excision"	2	"hypothyroidism"	4	6	5	15	2	1	1	4		50	135	90	104	48
14	14	########	27	1	2	67	150	29.80	"left angular gyrus glioma"	"left parietal craniotomy and tumour excis	2	""	4	6	5	15	2	1	1	4		100	133	78	89	97
15	15	10-May-2017	28	2	1	84	172	29.10	"sphenoid wing meningioma"	"right temporal craniotomy nd tumour exci	2	""	4	6	5	15	2	1	1	4		78	133	110	117	77
16	16	11-May-2017	49	1	1	55	168	19.50	"parasagittal meningioma"	"craniotomy and excision"	2	""	4	6	5	15	1	1	1	4		82	129	72	89	84
17	19	19-May-2017	42	2	1	54	164	20.00	"frontal glioma"	"frontal craniotomy and tumour excision"	2	""	4	6	5	15	2	2	1			90	140	64	84	117
18	20	########	19	1	1	61	165	22.40	"right middle 1/3 falcine meningioma"	"right parietal craniotomy and tumour exci	2	""	4	6	5	15	2	1	1	4		115	135	89	102	93
19	21	########	46	2	1	80	169	28.90	"left lateral sphenoid wing mass"	"left pteranial craniotomy and tumour exci	2	"hypertension"	4	6	5	15	1	1	1	4		95	110	77	84	101
20	22	########	43	1	2	64	156	26.30	"right temporal glioma"	"temporal craniotomy and excision"	2	""	4	6	5	15	2	2	1	4		58	132	78	104	65
21	23	########	40	1	2	51	158	21.60	"right lateral sphenoid wing meningioma"	"right pteranial craniotomy and tumour ex-	2	""	4	6	5	15	2	1	1	4		105	126	73	90	91
22	24	########	24	2	1	82	159	32.40	"pituitary adenoma"	"right frontal craniotomy and tumour excis	2	"panhypopituitarism"	4	6	5	15	2	1	1	4		90	125	70	90	75
23	25	########	44	1	1	66	168	23.40	"recurrent left anterior temporal meningio	"temporal cranitomy and excision"	2	"diabetes mellitus and hypertension"	4	6	5	15	1	1	1	4		105	176	94	114	107
24	26	########	38	2	1	47	175	15.30	"right frontal convexity meningioma"	"right frontal craniotomy"	2	""	4	6	5	15	2	1	1	4		80	99	56	68	81
25	27	########	43	2	2	35	143	17.10	"olfactiry groove meningioma"	"craniotomy and tumour excision"	2	"diabetes mellitis"	4	6	5	15	1	1	1	4		98	115	60	87	100
26	28	########	26	1	2	55	159	21.80	"temporal glioma"	"temporal craniotomy and tumour excision	2	""	4	6	5	15	1	1	1	4		74	120	70	86	68
27	29	31-May-2017	26	1	1	65	165	23.90	"suprasellar meningioma"	"craniotomy and tumour excision"	2	""	4	6	5	15	1	1	1	4		96	109	60	72	94
28	30	31-May-2017	37	2	1	36	160	14.30	"suprasellar meningioma"	"craniotomy and excision"	2	""	4	6	5	15	1	1	1	4		92	110	80	70	76
29	31	02-Jun-2017	21	2	2	63	163	23.70	"left frontal glioma"	"left frontal craniotomy and tumour excisi	2	""	4	6	5	15	2	1	1	4		80	100	60	70	81
30	32	06-Jun-2017	56	1	2	51	155	21.20	"suprasellar craniopharyngoma"	"craniotomy and excision"	2	"psychiatric illness"	4	6	5	15	2	1	1	4		107	110	75	82	93
31	33	13-Jun-2017	27	1	2	60	168	21.30	"sellar mass"	"right frontal craniotomy and excision"	2	""	4	6	5	15	2	1	1	4		68	122	62	76	67
32	34	14-Jun-2017	44	2	2	69	160	28.00	"left fronto parietal convexity meningiom	"excision of tumour"	2	"hypertension an calcium channel blockers	4	6	5	15	1	2	1	4		100	130	70	93	98
33	35	14-Jun-2017	47	1	1	74	163	27.90	"left motor cortex cavernoma"	"left frontoparietal craniotomy and excisio	2	""	4	6	5	15	2	2	1	4		96	134	77	99	95
34	36	14-Jun-2017	18	2	1	621	154	26.10	"left frontal epidermoid"	"left frontal craniotomy and excision"	2	"diabetes and seizures"	4	6	5	15	2	1	1	4		58	134	75	96	59
35	37	14-Jun-2017	44	2	2	53	158	27.50	"left frontal glioma"	"left frontal excision"	2	""	4	6	5	15	2	1	1	4		114	117	60	84	110
36	41	23-Jun-2017	28	2	1	71	162	27.10	"right frontal glioma"	"right frontal craniotomy and tumour excis	2	""	4	6	5	15	1	1	1	4		78	141	71	96	75
37	42	27-Jun-2017	35	2	2	75	154	31.60	"left parietal meningioma"	"left parietal craniotomy and tumour excis	2	"obesity"	4	6	5	15	1	1	1	4		110	127	86	98	102
38	44	27-Jun-2017	36	1	1	74	174	24.50	"temporal meningioma"	"temporal craniaomy and tumour excision"	2	""	4	6	5	15	1	1	1	4		85	134	55	72	84
39	45	30-Jun-2017	21	2	2	65	151	25.80	"left thalamic cavernoma"	"left temporal craniaomy and tumour excis	2	""	4	6	5	15	1	1	1	4		89	120	79	89	63
40	46	30-Jun-2017	18	1	1	64	164	23.80	"temporal glioma"	"temporal craniotomy and tumour excision	2	""	4	6	5	15	1	1	1	4		64	124	64	84	60
41	47	26-Jul-2017	37	1	2	55	155	22.90	"left frontal lobe glioma"	"frontal craniotomy and tumour excision"	2	"hypothyroid"	4	6	5	15	1	1	1	4		85	125	62	81	82
42	49	23-Aug-2017	25	1	1	83	182	25.00	"craniopharyngoma"	"right frontal craniotomy and tumour excis	2	""	4	6	5	15	2	2	1	4		75	122	84	97	90
43	51	24-Aug-2017	33	2	2	70	152	30.30	"right frontal glioma "	"right frontal craniotomy and tumour excis	2	""	4	6	5	15	1	1	1	4		132	137	100	108	112
44	50	22-Aug-2017	50	1	1	73	167	26.20	"left parietal menigioma"	"left parietal cranitomy and tumour excisio	2	""	4	6	5	15	2	1	1	4		95	145	82	98	76
45	52	25-Aug-2017	38	2	1	57	160	22.30	"right parietal glioma"	"right parietal craniotomy and tumour exci	2	"diabetes mellitus and hypertension"	4	6	5	15	1	1	1	4		106	116	76	84	104
46	55	26-Aug-2017	35	1	1	53	156	21.80	"left atrial mass"	"left temporal craniotomy and tumour exci	2	""	4	6	5	15	2	1	1	4		107	136	77	96	105
47	56	04-Sep-2017	22	1	2	48	158	19.20	"intersphenoid epidermoid"	"left parietal craniotomy and tumour excis	2	""	4	6	5	15	2	1	1	4		90	119	79	88	90
48	57	04-Sep-2017	60	1	2	60	157	24.30	"bilateral falcine meningioma"	"left frontal craniotomy and tumour excisi	2	""	4	6	5	15	2	1	1	4		88	94	50	65	99
49	58	06-Sep-2017	31	2	2	58	161	22.40	"right parietal astrocytoma"	"right parietal craniotomy and tumour exci	2	""	4	6	5	15	2	1	1	4		80	118	61	83	83
50	59	06-Sep-2017	45	2	1	78	168	27.60	"left parietal meningioma"	"left parietal cranotomy and tumour excisi	2	"hypertension"	4	6	5	15	2	2	1	4		95	154	86	111	112
51	60	07-Sep-2017	58	1	1	56	163	21.10	"cystic schwannoma trigeminal nerve"	"left temporal craniotomy and tumour exci	2	"seizures disorders on antiepileptics"	4	6	5	15	2	1	1	4		72	171	72	102	64
52	17	15-May-2017	18	1	2	45	158	18.00	"Â Intraventricular Mass"	"Left frontal Craniotomy and excision"	2	""	4	6	5	15	1	1	1	4		93	152	84	109	110
53	15	18-May-2017	42	2	1	54	164	20.10	"Left frontal massÂ "	"left frontal craniotomy and tumour excisi	2	""	4	6	5	15	2	1	1	4		72	155	73	98	64
54	38	26-Jun-2017	50	1	1	60	154	25.30	"LEFT MIDPARIETAL CONVEXITY MENINGIO	"LEFT PARIETAL CRANIOTOMY AND EXCIS	2	""	4	6	5	15	1	1	1	4		98	142	88	109	77
55	39	28-Jul-2017	36	2	1	65	170	22.50	"Left parietal meningiomaÂ "	"left parietal craniotomy and tumour excis	2	""	4	6	5	15	2	1	1	4		68	154	79	108	93
56	40	28-Jun-2017	62	1	1	76	165	27.90	"right temporal mass"	"Right temporal craniotomy and excisionÂ	2	"diabetes mellitus"	4	6	5	15	1	1	1	4		90	130	76	90	90
57	43	23-Aug-2017	57	1	2	155	68	28.30	"Â Right tempolar and insular glioma"	"Right temporal craniotomy and excisionÂ	2	""	4	6	5	15	1	1	1	4		98	112	78	86	104
58	48	24-Aug-2017	50	2	1	73	167	26.20	"Left parietal glioma"	"left parietal craniotomy and tumour excis	2	""	4	6	5	15	1	1	1	4		95	166	84	104	97
59	54	07-Sep-2017	48	2	1	55	157	22.30	"right frontal glioma"	"frontotemporal craniotomy and tumour e:	2	""	4	6	5	15	2	1	1	4		83	106	58	70	104

	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP	AQ
1	sbp0m	dbp0m	map0m	pr5m	sbp5m	dbp5m	map5m	pr10m	sbp10m	dbp10m	map10m	pr15m	sbp15m	dpb15m	map15m	pr30m	sbp30m
2	90	44	60	80	91	48	63	75	84	43	58	71	88	45	60	81	121
3	118	68	85	85	122	74	90	82	100	58	72	72	108	54	72	74	118
4	183	93	122	74	131	66	91	68	95	51	67	69	97	52	68	85	142
5	108	70	79	91	107	86	92	91	100	86	92	88	103	65	74	89	97
6	105	52	73	61	121	59	83	67	99	48	68	66	99	48	68	75	103
7	112	65	86	60	138	73	97	76	98	53	72	72	105	51	73	86	103
8	131	72	92	85	116	73	73	92	120	56	90	91	130	72	88	90	105
9	109	57	70	58	103	55	71	59	103	54	70	60	106	51	72	59	138
10	138	86	103	931	368	0	99	93	117	65	82	95	111	63	77	96	97
11	162	90	100	85	130	75	94	81	127	74	89	84	137	89	98	86	125
12	110	64	72	98	101	58	70	104	116	68	83	96	103	60	75	101	103
13	122	69	91	51	130	70	88	93	162	96	120	93	100	65	78	79	125
14	132	62	84	90	124	58	79	87	129	63	85	80	130	64	86	69	133
15	103	60	73	77	111	62	78	67	113	62	76	66	106	54	68	111	167
16	125	63	85	88	112	56	77	86	109	58	77	82	111	59	79	89	131
17	148	76	98	97	132	64	82	101	126	66	87	99	124	64	88	94	121
18	118	66	83	86	116	65	82	94	111	55	72	95	106	53	69	102	122
19	125	81	98	94	112	76	88	95	110	75	87	99	99	70	79	102	101
20	133	78	104	65	125	56	78	72	128	73	93	69	110	59	76	63	105
21	113	61	82	106	108	58	77	105	104	54	72	104	108	56	74	96	103
22	125	61	80	85	126	65	83	89	118	66	82	82	119	62	81	80	115
23	140	73	93	109	160	83	107	109	151	77	100	107	166	83	109	105	143
24	117	65	80	113	96	64	72	93	82	50	59	77	93	53	66	73	94
25	140	65	95	125	156	77	109	125	143	69	98	124	124	61	84	123	131
26	126	72	94	74	136	88	108	62	92	50	68	76	142	91	112	74	132
27	100	58	71	96	87	49	61	104	94	54	66	108	105	51	67	104	102
28	90	56	72	65	100	63	79	66	113	74	92	68	117	59	86	79	86
29	103	61	71	78	95	52	67	76	98	56	71	65	109	597	76	59	108
30	117	72	80	105	85	51	64	109	95	55	71	93	116	79	79	67	108
31	118	49	64	58	113	57	68	57	97	58	69	54	116	58	69	85	131
32	127	69	92	95	117	65	84	85	120	64	85	91	116	66	83	82	119
33	132	75	90	95	106	65	78	103	159	90	118	100	141	78	103	901	124
34	135	77	98	60	128	69	88	57	125	67	86	77	134	78	99	62	117
35	109	61	79	112	114	60	82	105	103	59	71	103	105	62	74	108	109
36	105	48	66	73	98	40	56	68	114	50	69	76	129	48	75	89	120
37	121	50	66	98	110	57	76	96	107	54	71	93	105	53	71	91	115
38	132	51	69	83	141	62	76	85	127	48	67	85	113	61	80	83	107
39	104	52	72	62	105	53	72	83	128	77	98	55	115	60	82	67	120
40	117	59	76	60	112	60	76	60	113	60	76	59	119	62	80	57	121
41	121	63	82	75	106	46	63	72	110	62	80	81	120	60	78	90	95
42	126	84	96	120	134	88	103	116	130	86	107	114	150	90	117	116	122
43	145	74	91	109	117	66	78	106	114	70	79	104	116	65	76	113	114
44	128	82	102	63	122	74	94	79	131	83	104	77	117	71	89	88	107
45	111	73	82	98	107	74	82	97	107	68	83	99	134	79	102	96	97
46	112	63	79	108	107	62	77	106	111	65	82	97	107	59	76	89	111
47	96	52	68	79	102	59	75	78	111	63	80	75	112	67	84	90	114
48	106	62	78	97	99	54	70	97	99	54	70	82	91	47	62	90	131
49	116	55	80	72	97	45	65	69	102	47	68	89	101	47	68	100	109
50	180	98	127	96	122	68	85	96	116	67	84	99	138	81	100	105	153
51	123	64	82	61	107	58	72	61	105	64	72	59	107	59	75	60	118
52	186	951	128	95	115	67	88	95	127	68	89	98	135	86	97	99	136
53	123	64	82	61	107	58	72	61	106	64	72	59	107	59	75	60	118
54	88	42	58	78	88	46	62	74	82	42	56	69	82	42	58	79	119
55	190	98	125	76	134	68	94	72	100	58	70	72	100	55	70	88	145
56	114	68	88	62	140	75	99	78	100	55	74	74	110	55	75	88	106
57	126	83	100	96	114	78	90	98	112	78	89	100	100	74	81	104	103
58	130	63	83	99	150	73	97	99	141	67	90	97	156	73	90	95	133
59	124	87	100	97	129	87	101	90	106	77	88	88	131	82	94	84	100

	AR	AS	AT	AU	AV	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH
1	dbp30m	dpb30m	pr60m	sbp60m	dbp60m	map60m	pr2h	sbp2h	dbp2h	map2h	varapres	varadrug	varaused	varadose	input0	output0	input1hr
2	57	78	77	134	67	90	73	113	66	85	2		1	280	100	700	1,300
3	64	82	78	116	68	84					2				500	100	1,200
4	73	98	78	142	75	100	78	119	60	81	2				500	150	1,000
5	54	73	83	124	77	98	80	115	70	90	2				1,000	300	750
6	48	68	75	116	64	84	72	106	56	76	2				100	600	1,000
7	53	74	90	105	56	76	88	110	68	88	2				500	150	800
8	78	89	106	125	70	91	106	120	83	95	2				800	400	600
9	73	97	55	128	66	88	62	99	86	93	2		2	100	800	100	1,200
10	53	66	95	98	55	68	94	98	54	70	2				500	100	1,300
11	72	90	90	106	55	71					1	1	1	320	700	150	500
12	59	76	106	105	57	74	98	100	60	70	2				250	100	500
13	79	98	70	100	60	72	64	104	60	74	2				500	300	500
14	70	93	731	116	56	76					2		2	100	500	200	900
15	90	124	102	120	72	86	101	94	78	86	2		1	450	300	300	500
16	63	88	92	143	67	94					2	2					600
17	65	86	89	115	64	83					2				500	50	1,000
18	65	83	85	128	70	86	95	118	65	81					1,000	600	500
19	76	85	111	150	100	111	97	108	71	84	2				500	50	1,500
20	56	73	71	138	60	83	72	100	51	66	2				250	100	700
21	55	72	84	122	71	94					2		2		750	200	750
22	61	77	83	113	58	72					2				100	100	150
23	74	94	106	142	75	95	104	115	60	76	2	2	2		1,000	500	500
24	56	70	77	105	52	71	64	106	49	70	1	1	1	300	500	100	1,500
25	62	87	109	132	59	84									600	200	700
26	81	103	79	120	61	83	80	106	60	76	2						1,000
27	54	67									2				100	100	1,000
28	44	61	72	111	65	84	67	120	77	96	2				750	50	500
29	60	78	71	91	46	60	60	102	56	73	2				700	250	500
30	71	87	76	128	80	100	89	99	66	76	2				700	600	400
31	65	79	92	129	56	72	107	112	61	77	2				100	150	1,000
32	69	87	96	118	68	86	85	120	67	86	2	2			500	600	1,000
33	68	89	92	95	50	64	85	91	63	74	2				700	100	300
34	58	77	60	125	60	80	59	134	75	95	2						700
35	64	76	113	108	63	75	110	113	61	77	2						300
36	55	75	83	110	49	66					2		2		500	600	1,200
37	57	77	91	127	65	86					2				1,000	600	500
38	56	73	81	127	68	87					2				1,000	400	500
39	63	87	82	124	65	87	74	124	70	89	2						800
40	62	80	91	147	68	91					2				1,000	400	1,000
41	68	79	100	115	60	81	100	110	73	85	1	1	1	100	500	150	500
42	86	98	110	124	84	97					2				1,000	50	1,200
43	58	78	101	124	63	83	88	95	46	62	1	2	2		500	100	1,000
44	57	74	89	119	69	85	92	106	66	81	2				500	100	1,000
45	48	63	92	99	55	70					2				500	600	550
46	47	68	116	115	53	71					2				1,500	500	500
47	52	71	78	111	58	76	70	110	59	77	2				100	50	500
48	67	91	82	117	69	88	76	83	52	65	2				500	50	600
49	53	70									2				500	250	500
50	83	105	104	109	64	76					1	2	1	200	500	200	1,500
51	65	65	76	118	70	68					2				1,200	600	300
52	84	100	107	110	65	78					1	2	1	200	500	200	2,000
53	65	65	76	118	65	65					2				500	600	500
54	54	76	74	130	64	86	70	110	65	84	2				500	700	800
55	75	100	80	143	78	102	80	120	64	84	2				500	150	1,100
56	55	78	94	108	58	78	90	110	68	88	2				500	400	1,000
57	78	88	111	147	98	110	100	110	74	85	2				500	50	1,500
58	64	84	96	132	65	85	94	105	50	66	2				800	300	300
59	60	75															

1	output1h	input2hr	output2hr	input3hr	output3hr	input4hr	output4hr	input5hr	output5hr	input6hr	output6hr	totfluid	toturine	sodium0m	potass0m	chlor0m	grbs0m	sodium1hr	potass1hr	chlor1hr	grbs1hr	surgeons	adddays	totdrug
2	300	1,000	400	1,000	450	500	600					3,800	2,450	137.00	3.60	4.70	131.00	133.00	4.70	4.10	151.00	2	2	
3	700	500	600	800	200							3,000	1,600	128.00	4.30	1.50	145.00	134.00	3.60	2.90	156.00	1	2	
4	500	400	450	300	250	600	200					2,800	1,550	138.00	3.20	1.40	117.00	133.00	4.00	1.20	154.00	3	1	
5	700	1,250	200	1,500	400	1,000	600					4,500	2,300	136.00	3.40	1.00	122.00	140.00	4.00	1.00	145.00	1	2	
6	550	500	300									1,500	1,450	139.00	3.30	3.20	110.00	140.00	3.70	5.90	111.00	2	2	
7	350	200	250	1,000	400							2,500	1,150	140.00	3.50	3.80	153.00	137.00	3.60	4.90	153.00	1	2	
8	600	700	400	600	300							2,700	1,700	135.00	3.80	3.00	115.00	136.00	3.90	3.20	130.00	4	1	
9	300	1,500	200	2,000	100							3,000	800	141.00	3.50	1.90	186.00	138.00	4.10	1.90	171.00	2	2	
10	500	500	100									2,300	700	136.00	4.10	2.20	197.00	136.00	5.10	2.20	202.00	3	2	
11	200	500	300	600	300	500	350	250	350			2,500	1,000	138.00	3.50	1.20	82.00	132.00	4.10	1.20	138.00	2	2	
12	350	750	300	500	100	250	200	100	150			2,350	1,100	139.00	3.70	3.90	150.00	134.00	4.60	5.30	145.00	1	2	
13	1,050	500	350	1,000	650	500	400					3,000	2,750	130.00	3.60	1.80	110.00	127.00	3.60	4.20	113.00	2	2	
14	450	600	400									2,000	1,050	135.00	3.90	3.10	131.00	137.00	4.40	2.40	128.00	4	2	
15	600	300	200	700	700	200	300					4,500	2,200	136.00	3.90	1.60	137.00	132.00	4.20	2.00	157.00	4	1	
16	500	500	500	700	300	500	250					2,300	1,550	135.00	4.00	1.20	135.00	135.00	4.10	2.00	162.00	3	1	
17	100	1,000	100									2,500	250	135.00	3.30	4.50	150.00	131.00	3.80	6.60	135.00	2	2	
18	700	500	400	300	200							2,300	1,900	138.00	3.60	1.90	121.00	137.00	3.90	2.30	121.00	2	2	
19	300	500	300	200	200	500	200	1,000	300	500	200	4,700	1,550	133.00	3.70	1.90	98.00	127.00	4.00	1.90	94.00	3	2	
20	350	250	450	300	250	500	250					2,000	1,350	137.00	3.20	1.90	97.00	136.00	3.50	4.50	100.00	2	2	
21	100	300	250									1,800	550	140.00	3.30	1.10	168.00	138.00	4.80	2.70	170.00	2	2	
22	500	500	300	350	350	800	300	900	1,060	1,000	300	9,999	2,600	135.00	5.20	2.00	170.00	129.00	5.60	2.80	192.00	2	2	
23	600	500	450	500	700							3,000	1,250	134.00	3.70	3.00	191.00	133.00	4.00	2.60	175.00	2	2	2
24	150	350	100	350	100	500	100					3,200	550	135.00	3.60	0.90	105.00	132.00	3.80	1.10	100.00	3	1	1
25	200											1,300	400	134.00	3.60	2.80	140.00	136.00	3.70	3.80	193.00	2	2	
26	150	500	200	500	100	400	100	600	100			3,000	750	138.00	3.40	2.10	99.00	141.00	3.90	2.70	124.00	2	2	
27	300	500	300									1,600	700	140.00	3.30	2.60	117.00	137.00	4.50	2.90	125.00	3	1	
28	150	250	100	500	150	500	150	500	150	500		3,200	475	135.00	3.20	1.40	97.00	135.00	3.20	1.80	110.00	1	2	
29	250											2,000	1,200	139.00	3.30	0.80	86.00	135.00	3.30	1.20	117.00	1	2	
30	250	300	100	300	100							1,700	1,050	146.00	3.60	2.40	166.00	147.00	4.30	2.50	192.00	2	2	
31	220	700	380									1,800	700	141.00	3.60	1.50	119.00	141.00	3.40	3.50	134.00	3	2	
32	700	400	200									1,900	1,500	140.00	3.10	2.10	95.00	133.00	3.20	2.50	101.00	2	2	
33	250	400	200									1,400	550	140.00	5.70	1.70	122.00	139.00	3.80	1.80	130.00	2	2	
34	300	300	300	200	200							1,200	800	137.00	3.90	3.40	188.00	131.00	4.10	4.40	178.00	1	2	
35	200	200	300									500	500	136.00	3.30	1.30	101.00	129.00	3.40	1.10	98.00	2	1	
36	700	500	500									2,200	1,800	134.00	3.60	4.10	132.00	133.00	4.00	5.40	148.00	2	2	
37	200											1,500	800	136.00	3.50	2.30	160.00	133.00	3.80	1.90	148.00	2	2	
38	800											1,500	1,200	139.00	3.50	3.30	105.00	132.00	3.60	3.20	136.00	3	1	
39	400	800	300									1,600	700	138.00	3.00	2.30	108.00	130.00	3.90	2.90	123.00	2	2	
40	200											2,000	600	139.00	3.50	3.30	105.00	137.00	4.00	4.50	119.00	1	2	
41	100	500	150	500	200							2,000	500	138.00	3.10	1.00	105.00	139.00	4.20	1.20	120.00	1	2	
42	950	800	450	500	200	500	150					4,000	1,800	136.00	3.70	2.80	137.00	130.00	5.00	3.30	144.00	3	2	
43	400	1,000	200	500	300	500	300					3,500	1,300	140.00	3.80	1.60	157.00	134.00	3.40	1.80	153.00	1	2	
44	350	500	300									2,000	750	136.00	3.40	3.40	126.00	136.00	3.80	2.00	119.00	2	2	
45	300	500	400									1,550	1,300	135.00	3.80	2.50	202.00	128.00	4.70	1.80	219.00	2	2	
46	900											2,000	1,400	135.00	3.90	2.40	121.00	132.00	4.20	3.30	126.00	4	1	
47	400	500	200	100	150	400	400					1,600	1,200	134.00	2.80	2.50	120.00	137.00	3.20	2.10	115.00	1	2	
48	750	400	600	500	600	200	400					2,200	2,380	134.00	3.60	2.00	88.00	136.00	3.80	2.90	93.00	1	2	
49	550	200	200									1,200	1,000	137.00	3.30	1.80	126.00	135.00	3.80	1.30	142.00	4	2	
50	400	500	200	1,000	200							3,500	1,000	132.00	3.60	3.40	161.00	134.00	3.70	2.20	177.00	4	1	
51	90	500	100	1,000	450							3,000	1,240	137.00	3.80	1.40	118.00	135.00	4.80	2.30	132.00	2	2	
52	400	500	200	1,000	200							4,000	1,000	134.00	3.50	3.50	156.00	136.00	3.60	2.30	177.00	3	1	
53	190	1,000	450									2,500	1,240	137.00	3.80	1.40	118.00	135.00	4.80	2.30	132.00	2	2	
54	300	1,000	400	1,000	450	500	600					3,800	2,450	137.00	3.60	4.70	131.00	133.00	4.70	4.10	151.00	2	2	
55	500	400	450	300	250	600	200					2,800	1,550	138.00	3.20	1.40	117.00	133.00	4.00	1.20	154.00	3	1	
56	350	1,000	400									2,500	1,050	138.00	4.00	3.40	164.00	135.00	4.10	4.50	164.00	1	2	
57	300	500	300									2,000	650	137.00	4.00	2.00	100.00	132.00	4.50	2.00	100.00	3	2	
58	300	500	450	500	500							2,100	1,550	132.00	3.70	3.00	156.00	131.00	3.80	2.60	144.00	2	2	
59												3,000	700	130.00	3.50	1.40	122.00	132.00	3.90	1.40	122.00	3	1	
60																								