COMPARISON OF THE EFFECTS OF MANNITOL AND HYDROXY ETHYL STARCH vs HYPERTONIC SALINE AND HYDROXY ETHYL STARCH ON BLOOD COAGULATION AND PLATELET FUNCTION IN NEURO SURGICAL PATIENTS PRESENTING FOR ELECTIVE CRANIOTOMY.

Thesis submitted for the partial fulfillment for the requirement of
The degree of DM (Neuroanesthesiology)
of
SCTIMST

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DECLARATION

I hereby declare that this thesis entitled **"Comparison of the effects of mannitol and Hydroxy Ethyl Starch versus Hypertonic saline and Hydroxy Ethyl Starch on blood coagulation and platelet function in neuro-surgical patients presenting for elective craniotomy"**, has been prepared by me under the capable supervision and guidance of Dr. P. Gayatri, Additional Professor, Department of Anesthesiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

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CERTIFICATE

This is to certify that this thesis titled **"Comparison of the effects of mannitol and Hydroxy Ethyl Starch (HES) versus Hypertonic saline (HS) and Hydroxy Ethyl Starch (HES) on blood coagulation and platelet function in neuro-surgical patients presenting for elective craniotomy"**, is a bonafide work of Dr Vidhu Bhatnagar, DM Neuroanesthesia Resident, and has been done under my direct guidance and supervision at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. She has shown keen interest in preparing this project.

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CERTIFICATE

This is to certify that this thesis titled **"Comparison of the effects of mannitol and Hydroxy Ethyl Starch versus Hypertonic saline and Hydroxy Ethyl Starch on blood coagulation and platelet function in neuro-surgical patients presenting for elective craniotomy"**, has been prepared by Dr. Vidhu Bhatnagar, DM Neuroanesthesia Resident, under the guidance of Dr. P Gayatri, Additional Professor, Department of Anesthesiology at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. She has shown keen interest in preparing this project.

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Contents

INTRODUCTION

One of the important goals of anesthetic management for patients undergoing craniotomy is to provide a relaxed brain for the surgeon to operate on. This allows easy surgical manipulations and causes less damage to the normal brain tissue. This in turn, results in less secondary injury to the brain, which improves the patient's neurologic outcome. Therefore, elective neurosurgical procedures often require the use of osmotic agents such as mannitol or Hypertonic saline (HS) to reduce intracranial pressure by reducing the brain bulk[1]. Mannitol is a white, crystalline polyhydric alcohol with chemical formula $C_6H_8(OH)_6$. It is derived by hydrogenation of fructose with a molecular weight of 182.17g/mol and density of 1.52g/ml. Mannitol is infused intravenously in doses of 0.25 to 1 gm/kg. Being hyperosmolar (osmolality more than that of blood), mannitol facilitates the shift of water from the brain into the vasculature[2]. This facilitates the surgeon in gaining access to deep structures by reducing the retraction pressure on the brain. The use of hypertonic saline solution in the treatment of cerebral edema and elevated intra cranial pressure (ICP) in the clinical setting is largely based on an extension of laboratory-based research, a few prospective studies in humans, and anecdotal case reports. A variety of formulations of hypertonic saline solutions (2, 3, 7.5, 10, and 23%) are used in clinical practice for the treatment of cerebral edema with or without elevations in ICP. Hypertonic saline solutions of 2, 3, or 7.5% contain equal amounts of sodium chloride and sodium acetate (50:50) to avoid hyperchloremic acidosis[3,4].

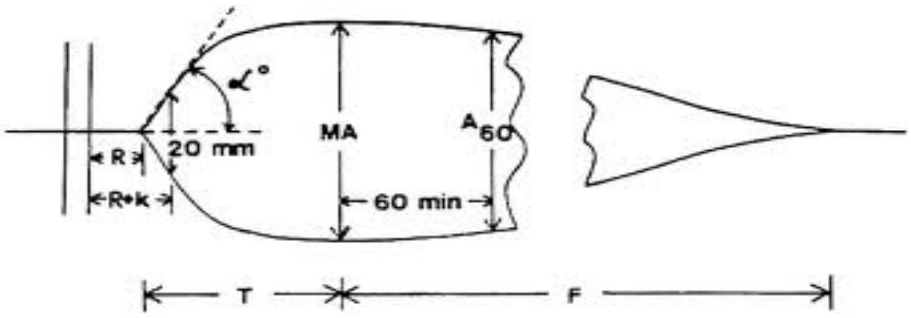
Some tumors in the brain such as meningiomas can result in considerable blood loss during surgery due to their high vascularity. Intravascular volume resuscitation in

these situations is done with the help of crystalloids and colloids. Therefore in a patient who had received mannitol or hypertonic saline in the beginning of surgery often receives colloids such as Hydroxy ethyl starch during the time of bleeding. Colloids, such as Hydroxy ethyl starch, interfere with coagulation of blood and are known to cause defects in coagulation by decreasing F VIII concentration and interfering with fibrin polymerization thereby decreasing clot strength[5-10]. A few in-vitro studies have shown the interference in coagulation with 7.2 % hypertonic saline and hydoxyethyl starch[11]. However to our knowledge, in vivo effects of these agents on coagulation have not been studied. No study till date has compared the effect of combination therapy (mannitol + HES vs Hypertonic saline + HES). Therefore we designed this study to compare the effects of administration of either mannitol or HS as well as when these two agents are combined with hydroxyl ethyl starch on in vivo blood coagulation and platelet function in patients undergoing elective neurosurgical procedures.

Brief Review of Thromboelastography

Platelet function is a complex series of interactions of the endothelium with whole blood that provides platelets and coagulation factors for haemostasis. The gold standard measure of platelet function is platelet aggregometry using platelet-rich plasma. The thromboelastograph (TEG), invented in 1948, is another test of the visco-elastic properties of blood that examines the time of initiation through acceleration, control, and eventual lysis[12]. Initially used for coagulation monitoring during liver transplantation, the TEG has found applications in cardiovascular surgery, obstetric anaesthesia, and trauma anaesthesia[13-15]. A small amount of blood (0.36 ml) is placed in an oscillating cup or cuvette and a piston is lowered into the blood sample. As the

blood begins to clot, the elastic force exerted on the piston is translated to a signature tracing that reveals information about fibrin formation, platelet–fibrin interactions, platelet clot strength, and fibrinolysis. With the current disposables, an activator is needed because the onset to coagulation varies, and the time to clot formation can conveniently be accelerated so that the test is useful. Celite, kaolin, or tissue factor have all been used to activate the TEG.[12,16] There are five parameters to the TEG tracing that measure different stages of clot development: *R*, *K*, alpha (α) angle, maximum amplitude (MA), and maximum amplitude at 60 minutes (MA60). In addition, clot lysis indices are measured at 30 and 60 minutes after MA (LY30 and LY60). Normal values vary depending on the type of activator used. The *R* value is a measure of clotting time (CT) which is the period of time from the start of the test to the initial fibrin formation. The *K* value is the clot kinetics measurement of the speed to reach a specific level of clot strength: the time from beginning of clot formation (the end of *R* time) until the amplitude reaches 20 mm. The alpha (α) angle is the angle between the horizontal line in the middle of the TEG tracing and the line tangential to the developing 'body' of the TEG tracing at 2 mm amplitude. The alpha angle represents the acceleration (kinetics) of fibrin build up and cross-linking (clot strengthening). The MA reflects the ultimate strength of the clot which depends on the number and function of platelets and their interaction with fibrin. The MA is the parameter most frequently measured because it correlates with platelet dysfunction in cardiac surgery. The MA is used as a marker for platelet function and has thus been incorporated into transfusion algorithms used to reduce platelet and other transfusions given to patients after CPB. LY30, or the lysis index at 30 min after MA, is increased with fibrinolysis. Thus, we decided to measure alpha angle and MA as the parameters for platelet function in our study.[12,16]



R: The *R* value is a measure of clotting time (CT) which is the period of time from the start of the test to the initial fibrin formation.

K: The *K* value is the clot kinetics measurement of the speed to reach a specific level of clot strength: the time from beginning of clot formation (the end of *R* time) until the amplitude reaches 20 mm.

Alpha angle: The alpha (α) angle is the angle between the horizontal line in the middle of the TEG tracing and the line tangential to the developing 'body' of the TEG tracing at 2 mm amplitude. The alpha angle represents the acceleration (kinetics) of fibrin build up and cross-linking (clot strengthening).

MA: The MA reflects the ultimate strength of the clot which depends on the number and function of platelets and their interaction with fibrin.

AIMS AND OBJECTIVES

1. The aim of this study is to compare the effect of administration of either mannitol or Hypertonic saline as well as when combined with hydroxyl ethyl starch on in vivo coagulation and platelet function in patients undergoing elective craniotomy.

2. The objective of this study is to be able to choose between mannitol and hypertonic saline, keeping in mind their effects on coagulation and platelet function in vivo, so as to reduce brain bulk in a patient in whom bleeding and hence the use of Hydroxy ethyl starch is anticipated during surgery**.**

REVIEW OF LITERATURE

Osmotherapy can be defined broadly as the use of osmotically active solutions to reduce the volume of the intracranial contents. The first description of the principles of osmotherapy as applied to the central nervous system (CNS) is often attributed to Weed and McKibben in 1919[17]. Their interpretation has formed the foundation of the concept of "osmotherapy" as it may be applied to treatment of space-occupying intracranial pathology.

In 1927, Fremont-Smith and Forbes[18]formalized the intravenous delivery of osmotic agents for clinical practice, first making the use of concentrated urea.

Hughes et al[19]were the first to demonstrate that concentrated solutions of human plasma proteins could effectively reduce raised intracranial pressure (ICP). However, concerns about allergic reactions and the cost of preparation of concentrated human plasma limited early interest in "oncotic therapy."

Wise and Chater[20]clearly demonstrated that the carbohydrate mannitol was a more practically useful agent. Unlike urea, mannitol was easy to prepare, chemically stable in solution, and did not produce vein irritation when infused, among other desirable properties that are discussed later. Intravenous mannitol infusions subsequently became a central modality in controlling of intracranial hypertension.

In the 1970s, the work of Little[21], Sundt[22], and Crowell and Olsson[23] identified the potentially beneficial rheologic effects of mannitol and other osmotic agents in the management of cerebral ischemia.

More recently, several investigators, most notably Rosner and Coley[24]and Muizelaaret al[25], have challenged the nostrum that osmotherapy is based on direct osmotic action and "shrinkage" of the brain parenchyma. Alternative theories that emphasize dynamic changes in cerebral blood volume (CBV) and cerbrospinal fluid (CSF) circulation have been put forth[26]. In general, these theories reflect a more differentiated view of the volume dynamics of the intracranial space.

Rosner[27] has opined that in general, the ideal agent for use in osmotherapy is a rapidly excreted diuretic that establishes strong trans-endothelial osmotic gradients. Mannitol comes as close to this ideal as any agent currently available. An additional advantage of mannitol, which is typically administered as a rapid intravenous infusion, is the potentially beneficial hemodynamic effects resulting from the bolus itself[28].

As per Nikkiet al[29] the effect of a mannitol bolus on systemic arterial pressure is variable. A slight increase in pulse pressure and mean arterial blood pressure is most commonly observed, but transient decreases in blood pressure secondary to decreases in systemic vascular resistance are not uncommon and have been described definitively in the literature.

Findlay et al have tried to explain the mechanisms of vasodilatory effects of mannitol. As per their opinion the acute vasodilatory effect of mannitol is not well understood and has been related to mechanisms as diverse as decreases in plasma pH, release of atrial natriuretic factor, histamine release from basophils, and direct impairment of the contractile properties of vascular smooth muscle[30].

Barry et al have looked at systematically administered mannitol boluses to patients with reduced left or right ventricular function[28]. Presumably because of the

rapid clearance of mannitol from the plasma, signs and symptoms of congestive heart failure were not observed in this series. According to them special care of course must be taken in the case of patients with impaired renal clearance[31]. If osmotherapy is used at all in this population, the dose and dosing interval should be decreased and increased, respectively. In addition, monitoring of pertinent hemodynamic variables that may guide the course of therapy should be considered.

Richard et al[32] have emphasized that an important practical point being the ratio of the volume of fluid diuresed to the volume of mannitol administered, which may be appreciably high, approaching five for a 25% solution of mannitol (the approximate ratio of the osmolality of mannitol to normal plasma osmolality). As per them, this fact readily explains the extent to which marked dehydration of the body can result from administration of osmotic diuretics. Hyperosmolar dehydration can be insidious. Unlike hemorrhage or relatively isotonic volume losses, which cause early clinical signs of impending hemodynamic instability, gradual hypertonic dehydration occurs in the presence of mounting osmotic and oncotic gradients favouring movement of fluid from the tissues into the vascular space. These forces tend to preserve circulating volume. Clinical signs of hemodynamic compromise therefore may not develop until quite late, when extravascular dehydration is severe.

Knapp has stated that intravenous bolus administration of mannitol lowers the ICP in 1 to 5 minutes, with a peak effect at 20 to 60 minutes. The effect of mannitol on ICP lasts 1.5 to 6 hours, depending on the clinical condition[1].

Muizelaar et al[33] have shown that because of mannitol having rheologic and osmotic effects, infusion of mannitol is immediately followed by an expansion of

plasma volume and a reduction in hematocrit and blood viscosity, which may increase cerebral blood flow (CBF). The osmotic effect of mannitol increases serum tonicity and draws edema fluid from cerebral parenchyma. This process takes 15 to 30 minutes, until gradients are established.

Nikki et al has shown the hemodynamic changes in response to a single dose of mannitol using non invasive cardiac output monitor, in patients undergoing craniotomy[29].They have measured blood pressure by non invasive means and cardiac output by bioimpedanceplethysmography. They have shown that all post mannitol systolic blood pressure values were significantly lower than pre mannitol values, whereas stroke volume increased significantly for 15 minutes after the infusion of mannitol, but at 45 minutes it was significantly lower than that from 1 to 30 minutes. Cardiac index also showed similar changes. The rate of urine output was higher during first 10 minutes than during rest of the study period.

The conventional osmotic agent mannitol, when administered at a dose of 0.25 to 1.5 g/kg by intravenous bolus injection, usually lowers ICP, with maximal effects observed 20 to 40 minutes following its administration. Repeated dosing of mannitol may be instituted every 6 hours and should be guided by serum osmolality to a recommended target value of approximately 320 mOsm/L; higher values result in renal tubular damage. This therapeutic goal is based on limited evidence, however, and higher values can be targeted provided that the patient is not volume depleted.Safety concerns with mannitol include hypotension, hemolysis, hyperkalemia, renal insufficiency, and pulmonary edema.[31-35]

Mannitol has been used extensively, and various clinical and experimental studies have demonstrated that single doses of mannitol—at least transiently—reduce increased ICP.[25-26,28-29] Though, mannitol has been the agent of choice in traumatic braininjury (TBI) when osmotherapy has been needed to decreaseICP, the long-term beneficial effects of mannitol are still controversial, and there is some evidence that repeated doses of mannitol may even aggravate brain edema[32]. Furthermore, mannitol is not effective in some patients. Therefore, alternative therapies for increased ICP were warranted.Alfred and colleagues have shown that although osmotic agents are among the most fundamental tools to control ICP, prospective data to establish clear guidelines on their use are lacking [36].

The use of hypertonic saline solution in the treatment of cerebral edema and elevated ICP in the clinical setting is largely based on an extension of laboratory-based research, a few prospective studies in humans, and anecdotal case reports. The first report to demonstrate the efficacy of hypertonic saline in patients with TBI[37] involved two patients with elevated ICP refractory to mannitol who were treated successfully with a single intravenous bolus of 30% saline, after which ICP decreased and systemic perfusionimproved.Few studies have made direct comparisons between mannitol and hypertonic saline[38]. In a prospective, randomized comparison of 2.5 ml/kg of either 20% mannitol (1400 mOsm/kg) or 7.5% hypertonic saline (2560 mOsm/ kg) in patients undergoing elective supratentorial procedures, ICP and intraoperative clinical assessment of brain swelling were similar in both treatment groups[39-40]. In a prospective, randomized trial of hypertonic saline with hydroxyethyl starch (for more prolonged action), hypertonic saline was shown to be more effective than equiosmolar doses of mannitol in lowering elevated ICP and augmenting cerebral perfusion

pressures (CPP) in patients with ischemic stroke[41]. In a small prospective study, isovolemic intravenous infusion of 7.5% hypertonic saline was more effective in the control of ICP following TBI, compared with mannitol treatment[42]. In summary, the literature supports the use of hypertonic saline as a therapy to decrease ICP in patients following TBI and stroke and to optimize intravascular fluid status in patients with sub arachnoid hemorrhage (SAH)induced vasospasm[43-46].A variety of formulations of hypertonic saline solutions (2, 3, 7.5, 10, and 23%) are used in clinical practice for the treatment of cerebral edema with or without elevations in ICP[43].The goal in using hypertonic saline is to increase serum sodium concentration to a range of 145 to 155 mEq/L (serum osmolality approximately 300–320 mOsm/L), but higher levels can be targeted cautiously. This level of serum sodium is maintained for 48 to 72 hours until patients demonstrate clinical improvement or there is a lack of response despite achieving the serum sodium target. During withdrawal of therapy, special caution is emphasized due to the possibility of rebound hyponatremia leading to exacerbation of cerebral edema. Serum sodium and potassium are monitored every 4 to 6 hours, during both institution and withdrawal of therapy, and other serum electrolytes are monitored daily (particularly calcium and magnesium). Chest radiographs are obtained at least once every day to try and find evidence of pulmonary edema from congestive heart failure, especially in elderly patients with poor cardiovascular reserve. Intravenous bolus injections (30 ml) of 23.4% hypertonic saline have been used in cases of intracranial hypertension refractory to conventional ICPlowering therapies; repeated injections of 30 ml boluses of 23.4% saline may be given if needed to lower ICP[43]. Thus far, no Phase 1 trials have been conducted to investigate the safety of hypertonic saline solutions; however, clinical experience suggests that the side-effect profile of

hypertonic saline is superior to mannitol, but some theoretical complications that are possible with hypertonic saline therapy are notable. Myelinolysis, the most serious complication of hypertonic saline therapy, typically occurs when rapid corrections in serum sodium arise from a chronic hyponatremic state to a normonatremic or hypernatremic state. Experimental studies suggest that for myelin injury to occur, the degree of rapid change in serum sodium is much greater from a normonatremic to a hypernatremic state (change of approximately 40 mEq/L), but further study with neuro imaging techniques is required[47].Hypertonic saline solutions (1.8, 23.4%) have been investigatedin various clinical settings. As a replacementfluid, it is cheaper, free of risk of infection or allergicreactions compared with colloids[48].Hypertonic saline is effective in the initial resuscitationof patients with burns or hemorrhagic shock[49-50]. It canbe used in combination with other plasma expanders suchas 6% dextran 70 and hydroxyethyl starch. Comparedwith standard crystalloid resuscitation fluids, a smallervolume (4–5 ml/kg) of hypertonic saline is required torestore mean arterial pressure and cardiac output. Thehemodynamic response is thought to be due to volumeexpansion from transcellular fluid shifts secondary toincreased plasma osmolarity[34]. In 1988, Worthleyet al[35]reported two patients withtraumatic cerebral edema and elevated intracranial pressurein which the continued administration of intravenousmannitol and furosemide resulted in progressivelyworsening intracranial hypertension and prerenal failure.The subsequent administration of a hypertonic salinesolution resulted in a sustained reduction in intracranialpressure and improvement in renal function. Severalother clinical studies confirmed the effectiveness of hypertonicsaline for treatment of raised intracranial pressure[43-46,48].Earlierstudies suggest that hypertonic saline is equally effective or even betterthan mannitol in reducing brain swelling in

patientsundergoing craniotomy[38]. However, due to variablestudy protocols, e.g., regarding osmolarity and administeredvolumes, definite conclusions about differences inphysiological responses or occurrence of untoward effects cannot be drawn.An in vitro study by Reed on normal humanplasma demonstrated significant increases in prothrombintimes (PT), activated partial thromboplastin times(APTT) and platelet aggregation studies when 10% ormore of normal plasma was replaced by hypertonicsaline[51]. Previous in vitro studies have demonstrated that bothmannitol and hypertonic saline interfere negatively with various componentsof blood coagulation[52]. Mannitol (15%)alone interferes with blood coagulation by reducing clotstrength[28]. Mannitol (15%) when combined withhydroxyethyl starch causes a disturbance in fibrin formationand, consequently, in blood coagulation in 10 and20 vol% dilution[53]. Hypertonic saline in different concentrations (3–7.5%)disturbs both fibrin formation and platelet function in thecoagulation process[52-54].

Colloids are used more often for resuscitation in setting of hypovolemia due to bleeding or in the intensive care unit than crystalloids. The choice of colloid varies noticeably between countries, but worldwide hydroxyethyl starch is most commonly used and thus more used than, for example, human albumin and gelatin. Hydroxyethyl starch (HES) is a nonionic starchderivative. It is one of the most frequently used volume expanders under the trade names Hespan by B. Braun Medical Inc. and Voluven or Volulyte by Fresenius Kabi.HES is a general term and can be sub-classified according to average molecular weight, molar substitution, concentration and Maximum Daily Dose[9].

Different types of hydroxyethyl starches are typically described by their average molecular weight, typically around 130 to 200 kDa (bearing in mind that there will be a range of different-sized molecules in any given solution); and their degree of molar substitution (what proportion of the glucose units on the starch molecule have been replaced by hydroxyethyl units), typically around 0.35 to 0.5[55]. A solution of hydroxyethyl starch may further be described by its concentration in % (i.e. grams per 100ml). So for example, one commercially available hydroxyethyl starch (Voluven) is described as 6% HES 130 / 0.4.

The elimination depends on molar substitution degree. Molecules smaller than the renal threshold (60–70 kDa) are readily excreted in the urine while the larger ones are metabolized by plasma alpha–amylase before the degradation products are renally excreted.

The use of hydroxyethyl starch is controversial as the former higher molecular weight hydroxyethyl starch 200/0.5-0.6 caused acute kidney injury in two randomised clinical trials of patients with sepsis. The newer starches with molecular weights of 130 kDa and substitution ratios ranging from 0.38 to 0.45 have been claimed to be safer, but the data to support this are insufficient[56].

Adverse events noted are Anaphylactoid reactions: hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm and non-cardiogenic pulmonary edema. Caution should be observed before administering Voluven® (hydroxyethyl starch in sodium chloride injection) to patients with severe liver diseaseor severe bleeding disorders (e.g., severe cases of von Willebrands'

disease)[57].Elevated serumamylase levels may be observed temporarily following administration of the product and can interfere with the diagnosis of pancreatitis.

At high dosages the dilutional effects may result in decreased levels of coagulation factors and other plasmaproteins and a decrease in hematocrit.Decrease in hematocrit and disturbances in coagulation have been noted. One litre of 6% solution (Hespan) reduces factor VIII level by 50% and will prolong APTT[58].

Hydroxyethyl starch has recently become the subject of renewed interest because of the introduction of a new specification, hydroxyethyl starch 130/0.4, as well as the clinical availability of a solution using a previous hydroxyethyl starch type (hydroxyethyl starch 670/0.75) with a carrier other than 0.9% saline. Various types of hydroxyethyl starch show different pharmacokinetic behaviour[55]. Since hydroxyethyl starch is a polydisperse solution acting as a colloid, pharmacodynamic action depends on the number of oncotically active molecules, not on the plasma concentration alone; therefore, solutions with a lower in vivo molecular weight contain more molecules at similar plasma concentrations. On the other hand, high plasma concentrations as well as high in vivo molecular weight can affect blood coagulation, especially factor VIII and von Willebrand factor[57-58]. Hydroxyethyl starch types with a molar substitution >0.4 accumulate in plasma after repetitive administration, most pronounced with hetastarch (hydroxyethyl starch 670/0.75). Correspondingly, tissue storage as measured by (14)C tracer studies in animals showed significantly higher values for hydroxyethyl starch 200/0.5 compared with hydroxyethyl starch 130/0.4 (about 4-fold at the latest timepoint after the last administration), and considerably higher values for hetastarch compared with both hydroxyethyl starch 130/0.4 and 200/0.5. Hydroxyethyl starch 130/0.4 does

not accumulate in plasma after single-dose and multiple-dose administration in contrast to all other available hydroxyethyl starch specifications. Plasma clearance of hydroxyethyl starch 130/0.4 is at least 20-fold higher than that for hetastarch, and considerably higher than for pentastarch. In patients with renal insufficiency, pharmacokinetic data are only available for hydroxyethyl starch 130/0.4. Cumulative urinary excretion, even in the presence of severe non-anuric renal failure, is higher for hydroxyethyl starch 130/0.4 than values published for older hydroxyethyl starch specifications. Hydroxyethyl starch 130/0.4 may be given to patients with severe renal impairment as long as urine flow is preserved. The pharmacodynamics with respect to the volume effect does not directly mirror pharmacokinetics in the case of hydroxyethyl starch solutions. Equivalent volume efficacy has been proven for hydroxyethyl starch 130/0.4 compared with 200/0.5. Prolonged persistence of hydroxyethyl starch in plasma and tissues can be avoided by using rapidly metabolisablehydroxyethyl starch types with molar substitution <0.5. Influence on coagulation is minimal with hydroxyethyl starch 130/0.4, and no adverse effects on kidney function have been observed even with large repetitive doses when used according to the product information[56].

Not many studies have been conducted to study the effect of Mannitol and HES or HS and HES on coagulation parameters. Lindroos AC et al[59] in their study "Effect of the combination of mannitol and Ringer Acetate or HES on whole blood coagulation in vitro" analyzed blood samples by modified Thromboelastometry and concluded that "mannitol in combination with HES 130/0.4 impairs clot propagation and clot strength in vitro. Fibrin clot strength impairment is more pronounced when mannitol is combined with HES than Ringer acetate."Their findings indicate that HES in

combination with mannitol should be avoided whenever a disturbance in hemostasis is suspected during craniotomy.

A study conducted by Hanke AA et al[11] regarding in vitro impairment of whole blood coagulation and platelet function by HS and HES concluded that when both HS and HES were used together during in vitro dilution lead to impaired platelet function which was significant after 10% dilution or more. The effect was pinpointed to the platelet function impairing HS component and to a lesser extent to fibrin polymerization inhibition by the HES or the dilution effects. Thus it was concluded that repeated administration and overdosage should be avoided.

There are several earlier clinical studies comparing the use of mannitol and HS in neurosurgical patients both in the intraoperative setting and in the neurointensive care.However, none of these studies have compared the effects of mannitol and HS on whole blood coagulation. Instead,the focus has been on what effect these two solutions haveon ICP, hemodynamics, and acid base balance[38-40]. Theresults of these studies have been difficult to interpret, andonly in one study the osmolarity and the volume have beenthe same for both solutions. In that particular study,Rozet and coworkers concluded that 20% mannitol and 3%saline had similar effect on brain relaxation during craniotomy[38].Both solutions caused a similar increase in bloodosmolarity lasting for 6 h. Other studies, where either theosmolarity or the volume of the study solutions have beendifferent, have shown that HS is equally effective or evenbetter in reducing ICP or brain swelling. There have been few studies comparing the effects of mannitol with HES and HS with HES on the coagulation parameters and most of them have been conducted as in vitro studies[59-60].As normal blood coagulation is essential in

neurosurgery,any treatment method that could impair coagulationshould be avoided. Thus, this pilot study was planned so as to find out which anti-edema therapy will be better in neurosurgical patients expected to have massive blood loss.

The purpose of the present study was to compare theeffect of equimolar and equivolemic solutions of 3%HS and20% mannitol on blood coagulation in vivo. Our hypothesis wasthat HS with low concentrations of sodium chloride wouldimpair blood coagulation more than 20% mannitol.

Clotting is a dynamic process and conventional coagulationtests on human plasma (PT, APTT, platelet countand fibrinogen concentration) provide little or noinformation about the quality of the clot or the dynamicsof its formation. Thus, Thromboelastography was selected for conducting the study to find out about the effects of mannitol and HES vs HS and HES on coagulation.

Thromboelastography enables a globalassessment of haemostatic function to be made from asingle blood sample[12]. Conventional coagulation testsend with the formation of fibrin strands, whereasthromboelastography begins at this point. Thromboelastographyis a more sensitive test of fibrinolytic activitythan conventional measurements of fibrin degradation products[12,16]. It is useful in liver transplantation,pre-eclampsia, trauma and after cardiopulmonary bypass[13-15]. Contrary to traditional laboratory coagulation test,thromboelastometry is a method allowing dynamic evaluationof coagulation process[16].In classical thrombelastography, a small sample of blood (typically 0.36 ml) is placed into a cuvette (cup) which is rotated gently through 4º 45´ (cycle time 6/min) to imitate sluggish venous flowand activate coagulation. When a sensor shaft is inserted into the sample a clot forms between the

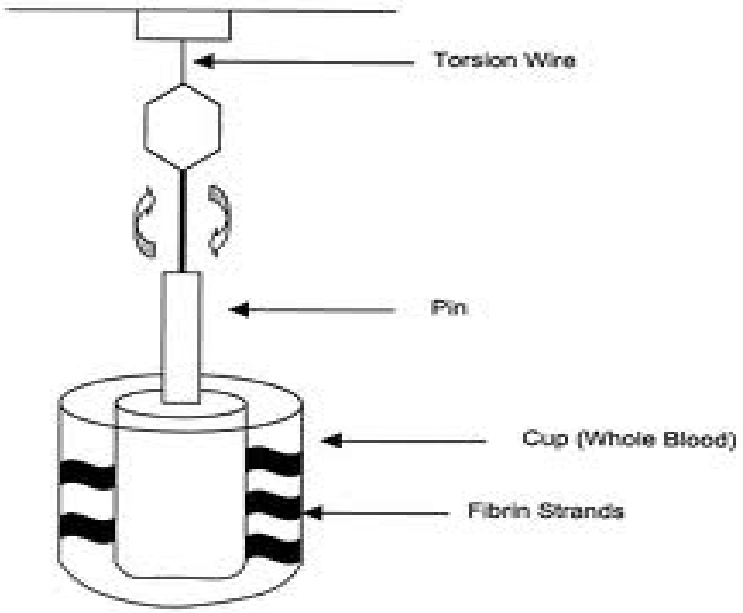
cup and the sensor. The speed and strength of clot formation is measured in various ways (now usually by computer), and depends on the activity of the plasmatic coagulation system, platelet function, fibrinolysisand other factors which can be affected by illness, environment and medications. If there is suspicion that the blood will have difficulty clotting (either through medication or disease) then the blood may be exposed to a thrombosis-inducing agent (such as kaolin) immediately prior to the start of the test.

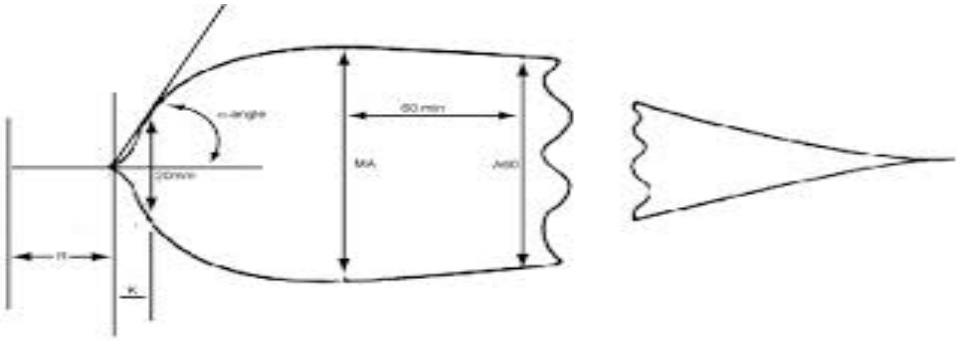
The patterns of changes in strength and elasticity in the clot provide information about how well the blood can perform hemostasis (the halting of blood flow), and how well or poorly different factors are contributing to clot formation.

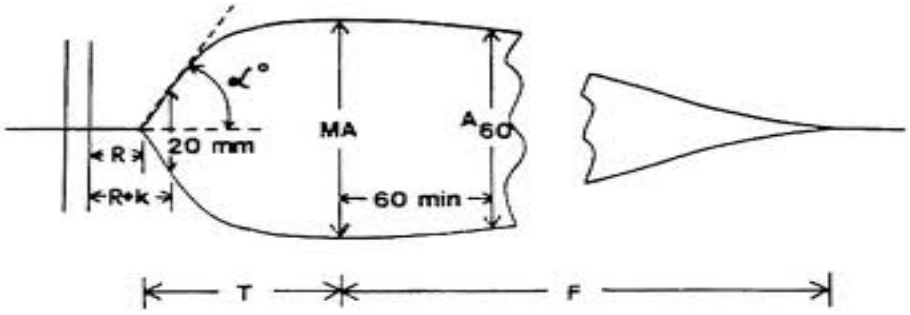
Four values that represent clot formation are determined by this test: the R value (or reaction time), the K value, the angle and the MA (maximum amplitude). The R value represents the time until the first evidence of a clot is detected. The K value is the time from the end of R until the clot reaches 20mm and this represents the speed of clot formation. The angle is the tangent of the curve made as the K is reached and offers similar information to K. The MA is a reflection of clot strength. A mathematical formula determined by the manufacturer can be used to determine a Coagulation Index (CI) (or overall assessment of coagulability) which takes into account the relative contribution of each of these 4 values into 1 equation[12].

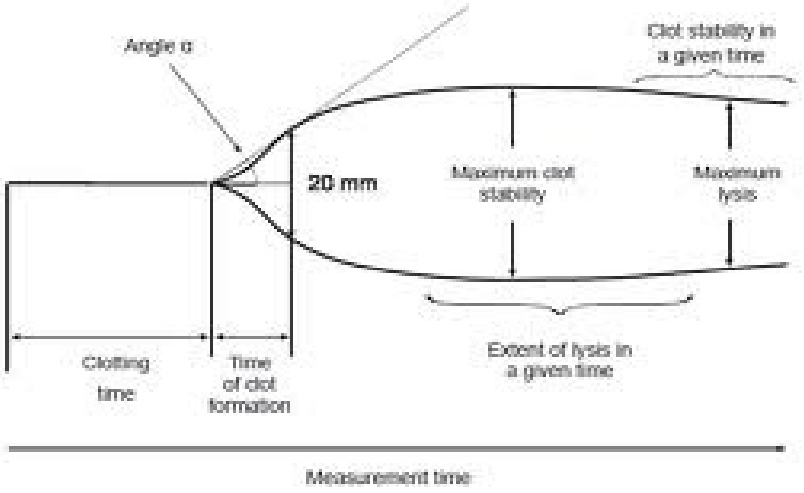
Rotational thromboelastometry or ROTEM(the name is a trademark of Tem Innovations GmbH, Munich) is another version in which it is the sensor shaft rather than the cup which rotates. Blood (300 µl, anticoagulated with citrate) is placed into the disposable cuvette using an electronic pipette. A disposable pin is attached to a shaft

which is connected with a thin spring (the equivalent to Hartert's torsion wire in thrombelastography) and slowly oscillates back and forth. The signal of the pin suspended in the blood sample is transmitted via an optical detector system. The test is started by adding appropriate reagents. The instrument measures and graphically displays the changes in elasticity at all stages of the developing and resolving clot. The typical test temperature is 37°C, but different temperatures can be selected, e.g. for patients with hypothermia. In contrast to thrombelastography with its pendulum-like principle, the design of the TEM viscoelastic detection system (figure 1) makes it quite robust and insensitive against mechanical shocks or vibrations, making the transportation and installation of the instrument very simple.






α°
MA
A60
R
20 mm
R+k
60 min
T
F


Angle α
Clot stability in a given time
20 mm
Maximum clot stability
Maximum lysis
Extent of lysis in a given time
Clotting time
Time of clot formation
Measurement time

R: The *R* value is a measure of clotting time (CT) which is the period of time from the start of the test to the initial fibrin formation.

K: The *K* value is the clot kinetics measurement of the speed to reach a specific level of clot strength: the time from beginning of clot formation (the end of *R* time) until the amplitude reaches 20 mm.

Alpha angle: The alpha (α) angle is the angle between the horizontal line in the middle of the TEG tracing and the line tangential to the developing 'body' of the TEG tracing at 2 mm amplitude. The alpha angle represents the acceleration (kinetics) of fibrin build up and cross-linking (clot strengthening).

MA: The MA reflects the ultimate strength of the clot which depends on the number and function of platelets and their interaction with fibrin.

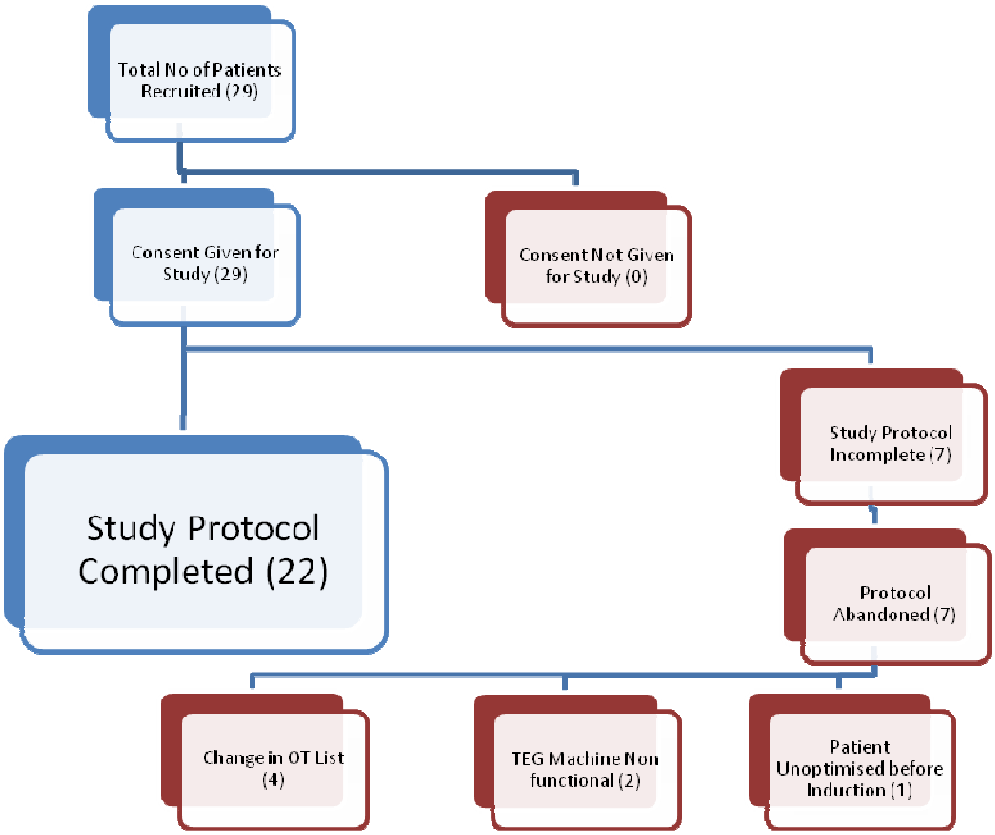
MATERIALS AND METHODS

METHODOLOGY:

A prospective, randomised, pilot study in neurosurgical patients undergoing craniotomy and requiring mannitol or hypertonic saline (HS) for intraoperative brain relaxation. Sample size calculation was not performed as this was only a pilot study. Patients were recruited from the elective surgery list of Neurosurgery Department. Patients were randomized by the Principal investigator with help of picking folded chits labeled as mannitol or HS from a box. This was a single blinded study. Randomization was done before patients were taken up for surgery in the operation theatre. Screening for large numbers was not required. Consort flow chart is as under.

"Comparison of the effects of mannitol and Hydroxy Ethyl Starch (HES) versus Hypertonic saline (HS) and Hydroxy Ethyl Starch (HES) on blood coagulation and platelet function in neuro-surgical patients presenting for elective craniotomy".

Flow diagram for Recruitment of patients in the study



METHODOLOGY

22 patients, divided into 2 groups (10 studied in HS group and 12 studied in mannitol group), subjected to elective Decompression/ resection of tumors were recruited in the study. Adult males or females in ASA I or II (patients with no co morbid illness or with well controlled co morbid illnesses) were recruited. Pregnant women, pediatric or geriatric age group patients, persons incompetent to give informed consent or prisoners were not recruited for the study.

INCLUSION CRITERIA:

- Patients categorized as American society of Anesthesiology (ASA) class I and II.
- Age 18-65 years.
- Elective Decompression/Resection of tumors.
- Preoperative Glasgow coma scale (GCS) 15.

EXCLUSION CRITERIA:

- ASA class 3 and above
- Age less than 18 years and more than 65 years.
- Preoperative GCS<15
- Known allergy to Mannitol or Hypertonic Saline or HES
- Patient with CAD, LV dysfunction

- Pregnant or Nursing woman.
- Participation in another drug study during the preceding 1 month period.
- Patient refusal to participate in the study
- Later, patients suffering from Diabetes Mellitus and patients who had history of prolonged Anti Epileptic Drug (AED) ingestion were also excluded, on account of the effects of AEDs and prolonged deranged glycemic control on the platelet functions.

Patients were grouped into 2:-

- One group received 20% mannitol, on beginning of craniotomy, followed by administration of HES. The other group received 3% hypertonic saline, on beginning of craniotomy, followed by administration of HES.
- Upon arrival into the OR, standard monitors like, Pulse Oximeter, ECG, NIBP and later arterial blood pressure monitoring were placed.
- Patients, in both the groups, received standard anesthesia care. The patients were induced with Propofol, fentanyl was used for analgesia. Vecuronium was administered in dosage of 0.15mg/kg for muscle relaxation and facilitation of endotracheal intubation.
- Patient were maintained on O2 (50%)/ Air (50%)/ Isoflurane/ Sevoflurane (MAC 0.6-0.8) and bolus doses of Fentanyl as and when required were administered.

- Baseline investigations such as Hemoglobin (Hb), platelet count, PT, APTT and platelet function test (by Thromboelastograph coagulation analyser (TEG^R 5000 Thromboelastograph^R Hemostasis Analyzer System, Haemonetics)) were done in all patients before the start of surgery. As soon as the craniotomy was initiated, in the first group, 20% mannitol was administered intravenously (iv) in the dose of 5ml/kg. In the second group of patients, 3% hypertonic saline was administered intravenously, in dosage of 5ml/kg. A second set of similar investigations namely Hb, platelet count, PT, APTT and platelet function test (by TEG) were performed after administration of mannitol or hypertonic saline.

- Then both groups of patients received 20ml/kg of HES (Voluven-6% HES 130/0.4; Fresenius Kabi). Next set of similar investigations Hb, platelet count, PT, APTT and platelet function test (by TEG) were repeated after administration of HES in both the groups.

The observations and samples were collected by Principal Investigator (PI) or Co Principal Investigator (CO PI) (1), in Neurosugery Operation Theatre.

Primary end points studied were:

Hemoglobin, PT, APTT, Platelet function test assessed by TEG and platelet count (thrice) - Baseline before surgery, after mannitol or hypertonic saline and finally after HES in both groups.

Secondary end points noted were:

Total amounts of crystalloid, colloid, bleeding, urine output and blood and blood products used during surgery.

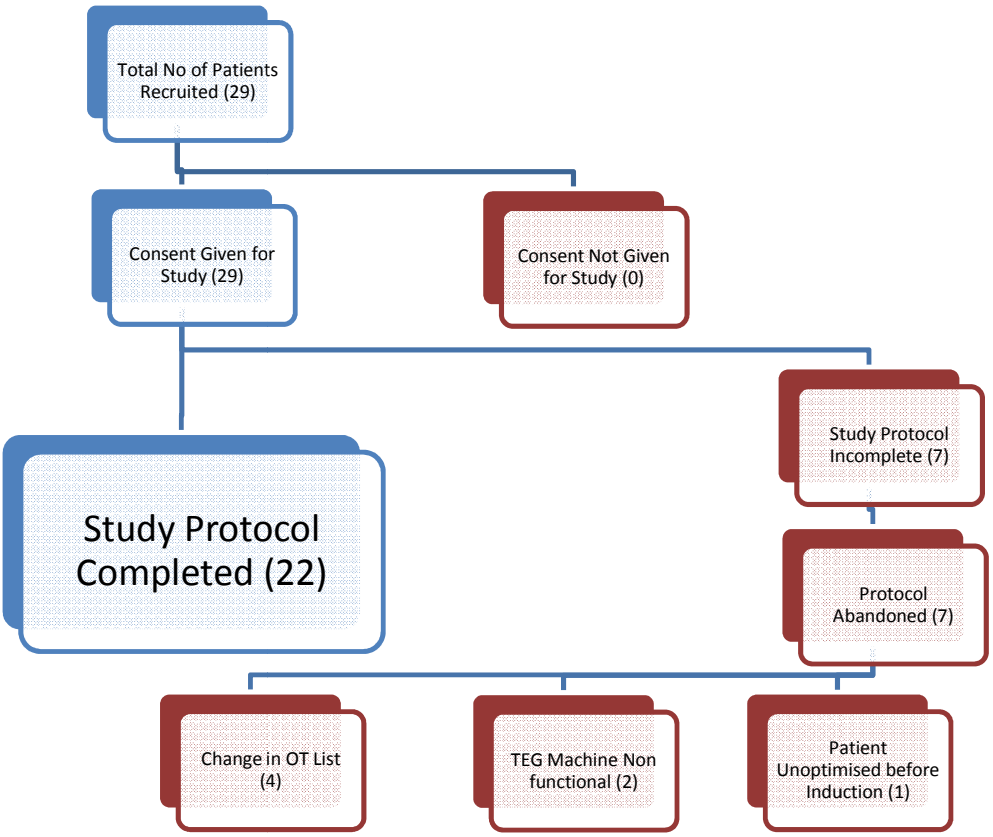
STATISTICAL ANALYSIS:

Manual data entry was done into the study chart by PI or Co PI (1). Data was not analyzed to understand caste, creed, ethnicity, race differences. Data was analyzed using SPSS software. Two way repeated measure Annova was utilized to find out any significant difference between different time points. If a statistical difference was found then post hoc analysis applying Bonferroni test was done to know which time points differed statistically. Continuous data was compared with independent t test between the two groups.

RESULT

"Comparison of the effects of mannitol and Hydroxy Ethyl Starch (HES) versus Hypertonic saline (HS) and Hydroxy Ethyl Starch (HES) on blood coagulation and platelet function in neuro-surgical patients presenting for elective craniotomy".

Flow diagram for Recruitment of patients in the study



Patient Selection

The age of both the HS and the Mannitol groups were comparable with mean age being 45 (±9.7) and 40.8 (±11.4) years respectively. Males and Females were equally distributed in both the groups being 50% each. The distribution of age and sex is not significantly different between the two treatment groups.

Haematological parameters

Haemoglobin (Hb) (in gm%) was comparable in both the groups at baseline. Within group comparison Hb showed a statistically and clinically significant decline. The mean Hb in HS group fell from 12.8 gm% to 11.6 gm% after HS and to 8.9 gm% after HES. Similarly, the mean Hb in Mannitol group fell from 12.2 gm% to 11.0 gm% after Mannitol and to 8.1 gm% after HES. However, these differences were similar in both the groups.

Packed Cell Volume (PCV) was comparable in both the groups at baseline. Within group comparison PCV showed a statistically and clinically significant decline. The mean PCV in HS group fell from 37.1% to 33.7 % after HS and to 25 % after HES. Similarly, the mean PCV in Mannitol group fell from 38.8 % to 35.6 % after Mannitol and to 27.8 % after HES. However, these differences were similar in both the groups.

International normalized Ratio (INR) was comparable in both the groups at baseline. It increased in both groups from baseline to the delivery of mannitol or HS and after HES. The mean INR in HS group rose from 1.0 to 1.1 after HS and to 1.2 after HES. Similarly, the mean INR in Mannitol group remained static at 1.0 till Mannitol administration and subsequently rose to 1.2 after HES. The differences noted

were similar in both the groups.However, INR was maintained well within normal limits in both the groups.

Prothrombin Time (PT) was comparable in both the groups at baseline. It increased in both groups from baseline to the delivery of mannitol or HS and after HES. The change in PT was statistically significant when compared within group between baseline and after administration of HES. However, these differences were similar in both the groups across different time points and PT was maintained well within normal limits at all times.

Activated Pro Thrombin Time (APTT) was comparable in both the groups at baseline. The mean APTT in HS group rose from 29.6 s to 29.8 s after HS and to 34.9 s after HES. Similarly, the mean APTT in Mannitol group rose from 30.9 s to 31.7 s after Mannitol and to 35.8 s after HES. The change in APTT was statistically significant when compared within group between baseline and after administration of HES. However, these differences were similar in both the groups across different time points and APTT was maintained well within normal limits at all times.

Platelet Count was comparable in both the groups at baseline. It decreased in both groups from baseline to the delivery of mannitol or HS and after HES. The mean Platelet Count in HS group fell from 2,80,000/mm^3 to 2,50,000/mm^3 after HS to 2,00,000/mm^3 after HES. Similarly, the mean Platelet Count in Mannitol group fell from 2,70,000/mm3 to 2,50,000/mm^3 after Mannitol to 2,10,000/mm^3 after HES. The Platelet Count did not fall to subnormal levels in any patient in any group. The change in platelet count was statistically significant when compared between groups between

baseline and after administration of HES. However, these differences were similar in both the groups across different time points.

Thromboelastography (TEG) parameters

The TEG parameters that were observed in both the groups were: - R, K, MA and Alpha angle.

R value denotes the clotting time and the normal value is 3-8 minutes in the blood sample utilizing Kaolin as activator inhibitor. The R value was comparable in both the groups at baseline. It decreased in both groups from baseline to the delivery of mannitol or HS and improved thereafter. The mean R in HS group fell from 4.9 to 4.2 minutes after HS to 4.8 minutes after HES. Similarly, the mean R in Mannitol group fell from 5.7 to 3.8 minutes after Mannitol and subsequently increased to 5.4 minutes after HES. The change in R value was not statistically significant, both within as well as between group comparison.

K value denotes clot kinetics and the normal value is 1-4 minutes in the blood sample utilizing Kaolin as activator inhibitor. The K value was comparable in both the groups at baseline. It decreased in both groups from baseline to the delivery of mannitol or HS and improved thereafter. The mean K in HS group fell from 4.3 to 3.4 after HS to 4.6 after HES. Similarly, the mean K in Mannitol group fell from 4.7 to 4.1 after drug (i.eMannitol) and subsequently increased to 4.7 after HES. The change in K value was not statistically significant, both within as well as between group comparison.

Alpha angle denotes the clot strengthening and is the slope between the R and K. The normal value is in the range of 55-70 degree in the blood sample utilizing Kaolin as activator inhibitor. The Alpha (α) angle was comparable in both the groups at baseline. The mean alpha angle in HS group increased from 45.3 to 55.3 after HS, which was statistically significant and then decreased to 43.7 after HES. Similarly, the mean alpha angle in Mannitol group increased from 42.2 to 48.1 after Mannitoland subsequently decreased to 42.6 after HES. The changes in the alpha angle were similar in both the groups and were maintained within normal limits at all times.

The Maximum Amplitude (MA) denotes the maximum strength of the clot and the normal value is in the range of 51-69 mm in the blood sample utilizing Kaolin as activator inhibitor. MA was comparable in both the groups at baseline. The mean MA in HS group decreased from 51.4 to 46.9 after HS and then further decreased to 45.9 after HES. The mean MA in Mannitol group increased from 47.1 to 50.5 after Mannitol and subsequently decreased to 38.8 after HES. The change in MA value was not statistically significant both, within as well as between group comparison.

Blood products consumed

Various blood products were consumed during the intra operative period to maintain hemodynamic and coagulation parameters. These are a useful adjunct in correlating the magnitude of coagulation derangement, if any, among the two study groups. The findings are as follows:-

The mean intra operative consumption of crystalloids was 2535 ml (±1562.1 ml) in the HS group whereas it was 3318.2 ml (±1209.8 ml) in the Mannitol group. The p value for this distribution was 0.219.

The mean intraoperative consumption of colloids was 1050 ml (±158.1 ml) in the HS group whereas it was 1218 ml (±252.3 ml) in the Mannitol group. The p value for this distribution was 0.086.

The mean intraoperative consumption of Fresh Frozen Plasma (FFP) was 0.3 Units (±0.7 Units) in the HS group whereas it was 0.36 Units (±1.2 Units) in the Mannitol group. The p value for this distribution was 0.885.

The mean intraoperative consumption of Packed Red Blood Cells (PRBC) was 0.9 Units (±1.5 Units) in the HS group whereas it was 1.36 Units (±1.9 Units) in the Mannitol group. The p value for this distribution was 0.535.

The mean intraoperative consumption of Ringer Lactate (RL) was 245 ml (±160.8ml) in the HS group whereas it was 227.1 ml (±160.8 ml) in the Mannitol group. The p value for this distribution was 0.792.

Other intraoperative parameters

The intraoperative mean urine output was 520 ml (±349.5 ml) in the HS group and 1029.2 ml (±515.4 ml) in the mannitol group. The p value of this distribution was 0.008. This difference is statistically significant and the reason is that mannitol has an osmotic diuretic effect.

The mean Total blood loss was 790 ml (±316.9 ml) in the HS group and 1077 ml (±628.3 ml) in the mannitol group. The p value of this distribution was 0.199.

Table.1

Patient details

	Sex		
	male	**female**	**Total**
mannitol	**6**	**6**	**12**
HTS	**5**	**5**	**10**

	Age			
	mean(age)	**sd(age)**	**min(age)**	**max(age)**
mannitol	**40.8**	**11.4**	**28**	**57**
HTS	**45.0**	**9.7**	**31**	**63**

	Weight			
	mean(wt)	**sd(wt)**	**min(wt)**	**max(wt)**
mannitol	**40.8**	**11.4**	**28**	**57**
HTS	**45.0**	**9.7**	**31**	**63**

Nb: The distribution of age, sex and weight is not significantly different between the two treatment groups.

Table.2
Mean and SD of blood coagulation and platelet function parameters by treatment groups

Variables	group	Time point 0 mean	(sd)	Time point 1 mean	(sd)	Time point 2 mean	(sd)
Hb*	**mannitol**	**12.81**	**(1.5)**	**11.62**	**(1.3)**	**8.92**	**(1.6)**
	HS	**12.15**	**(1.6)**	**11.03**	**(1.4)**	**8.12**	**(0.9)**
PCV*	**mannitol**	**38.78**	**(4.7)**	**35.59**	**(4.7)**	**27.78**	**(6.1)**
	HS	**37.06**	**(4.7)**	**33.68**	**(3.6)**	**25.02**	**(2.9)**
INR*	**mannitol**	**0.97**	**(0.1)**	**1.01**	**(0.1)**	**1.2**	**(0.1)**
	HS	**1.01**	**(0.1)**	**1.08**	**(0.1)**	**1.25**	**(0.1)**
APTT1*	**mannitol**	**30.87**	**(3.7)**	**31.7**	**(5.0)**	**35.78**	**(5.1)**
	HS	**29.61**	**(4.3)**	**29.76**	**(4.0)**	**34.94**	**(5.3)**
PLT COUNT*	**mannitol**	**2.74**	**(0.6)**	**2.46**	**(0.5)**	**2.1**	**(0.5)**
	HS	**2.8**	**(0.6)**	**2.46**	**(0.5)**	**1.98**	**(0.3)**
R**	**mannitol**	**5.75**	**(1.8)**	**3.84**	**(2.4)**	**5.37**	**(2.5)**
	HS	**4.94**	**(6.0)**	**4.23**	**(1.9)**	**4.8**	**(2.4)**
K**	**mannitol**	**4.66**	**(2.7)**	**4.08**	**(1.8)**	**4.65**	**(2.1)**
	HS	**4.28**	**(2.4)**	**3.39**	**(2.9)**	**4.59**	**(2.9)**
MA**	**mannitol**	**47.11**	**(13.51)**	**50.45**	**(12.2)**	**37.99**	**(17.44)**
	HS	**51.89**	**(17.7)**	**48.1**	**(8.8)**	**45.92**	**(21.9)**
Alpha angle*	**mannitol**	**42.2**	**(14.17)**	**48.06**	**(12.7)**	**41.36**	**(14.52)**
	HS	**47.77**	**(10.17)**	**58.98**	**(7.62)**	**43.7**	**(17.0)**

Two way- repeated measure anova has been done and the results show that there is a significant difference in means between different time points (* for Hb, PCV, INR, APTT1, Platelet count and Alpha angle) in both treatment groups. And, those differences between time points are similar in both treatment groups. (i.e., the two treatment groups are not statistically different in their performance. Or the variation between time points is not associated with treatment groups)
However, the variables R, K and MA (**) do not show any significant differences. I.e. no significant difference can be seen between time points in both treatment groups, and the two treatment groups are not statistically different in their performance.

Results of posthoc analysis.

Group1 (Mannitol)

Hb: all combinations are significant.
PCV: all combinations are significant.
INR: all combinations are significant.
APTT1:T1 and T3 are significantly different, T2 and T3 marginal significance (0.05) t1 and t2 are not significant.
Platelet Count: T1 and T2, T1 and T3 are significant, but T2 and T3 is not significant.
Alpha angle: no combinations are significant.

Group2 (HS)

Hb: all combinations are significant.
PCV: all combinations are significant.
INR: all combinations are significant.
APTT: T1 and T3 are significantly different, T2 and T3 are also significant, but T1 and T2 are not significant.
Platelet Count: T1 and T2, T1 and T3, and T2 and T3are significant
Alpha angle: T1 and T2 are significant. Other combinations are not significant.

Table.3
Between group comparison of Means

Variables	Group	Mean	(SD)	P-value
Crystalloid(ml)	**mannitol**	**3318.2**	**(1209.8)**	
	HS	**2535**	**(1562.1)**	**0.219**
Colloid(ml)	**mannitol**	**1218.2**	**(252.3)**	
	HS	**1050**	**(158.1)**	**0.086**
FFP	**mannitol**	**0.36**	**(1.2)**	
	HS	**0.3**	**(0.7)**	**0.885**
PBRC	**mannitol**	**1.36**	**(1.9)**	
	HS	**0.9**	**(1.5)**	**0.535**
RL	**mannitol**	**227.1**	**(160.8)**	
	HS	**245**	**(151.8)**	**0.792**
Urine output	**mannitol**	**1029.2**	**(515.4)**	
	HS	**520**	**(349.5)**	**0.008**
Bleeding	**mannitol**	**216.7**	**(173.6)**	
	HS	**130**	**(25.8)**	**0.115**
Total blood loss	**mannitol**	**1077**	**(628.3)**	
	HS	**790**	**(316.9)**	**0.199**

Independent T test (Unpaired) used to compare means.

Socio Demographic Profile

Table 1. Distribution according to sex

Sex	Mannitol		HS	
	Count	Percent	Count	Percent
Male	6	50.0	5	50.0
Female	6	50.0	5	50.0

(^{2}= 0.00, p= 1.000

Table 2. Within group comparison of Hb

		Mean	SD	N	Pair	Mean Difference	p**
Mannitol	Base line (A)	12.8	1.4	12	A & B	1.2	0.000
	After Mannitol (B)	11.6	1.3	12	A & C	3.9	0.000
	After HES (C)	8.9	1.6	12	B & C	2.7	0.000
HS	Base line (A)	12.2	1.6	10	A & B	1.1	0.000
	After HS (B)	11.0	1.4	10	A & C	4.0	0.000
	After HES (C)	8.1	0.9	10	B & C	2.9	0.000

**: - Significant at 0.01 level

Table3. Between group comparison of Hb

		Mean	SD	N	p
Base line	Mannitol	12.8	1.4	12	0.323
	HS	12.2	1.6	10	
After Mannitol or HS	Mannitol	11.6	1.3	12	0.324
	HS	11.0	1.4	10	
After HES	Mannitol	8.9	1.6	12	0.180
	HS	8.1	0.9	10	

Table4. Within group comparison of PCV

		Mean	SD	N	Pair	Mean Difference	p**
Mannitol	Base line (A)	38.8	4.7	12	A & B	3.2	0.000
	After Mannitol (B)	35.6	4.7	12	A & C	11.0	0.000
	After HES (C)	27.8	6.1	12	B & C	7.8	0.000
HS	Base line (A)	37.1	4.7	10	A & B	3.4	0.001
	After HS (B)	33.7	3.6	10	A & C	12.0	0.000
	After HES (C)	25.0	2.9	10	B & C	8.7	0.000

**: - Significant at 0.01 level

Table5. Between group comparison of PCV

		Mean	SD	N	p
Base line	Mannitol	38.8	4.7	12	0.404
	HS	37.1	4.7	10	
After Mannitol or HS	Mannitol	35.6	4.7	12	0.303
	HS	33.7	3.6	10	
After HES	Mannitol	27.8	6.1	12	0.206
	HS	25.0	2.9	10	

Table 6 Within Group comparison of PT

		Mean	SD	N	Pair	Mean Difference	p*
Mannitol	Base line (A)	13.0	4.2	12	A & B	1.7	0.194
	After Mannitol (B)	14.8	0.9	12	A & C	4.1	0.008
	After HES (C)	17.1	1.4	12	B & C	2.4	0.000
HS	Base line (A)	14.0	0.9	10	A & B	0.8	0.016
	After HS (B)	14.8	0.9	10	A & C	2.6	0.000
	After HES (C)	16.6	0.9	10	B & C	1.8	0.000

*: - Significant at 0.05 level

Table 7 Between Group comparison of PT

		Mean	SD	N	p*
Base line	Mannitol	13.0	4.2	12	0.482
	HS	14.0	0.9	10	
After Drug	Mannitol	14.8	0.9	12	0.940
	HS	14.8	0.9	10	
After HES	Mannitol	17.1	1.4	12	0.276
	HS	16.6	0.9	10	

: - Significant at 0.05 level

Table 8. Within Group comparison of APTT

		Mean	SD	N	Pair	Mean Difference	p*
Mannitol	Base line (A)	30.9	3.7	12	A & B	0.8	0.428
	After Mannitol (B)	31.7	5.0	12	A & C	4.9	0.001
	After HES (C)	35.8	5.1	12	B & C	4.1	0.017
HS	Base line (A)	29.6	4.3	10	A & B	0.2	0.867
	After HS (B)	29.8	4.0	10	A & C	5.3	0.011
	After HES (C)	34.9	5.3	10	B & C	5.2	0.005

*: - Significant at 0.05 level

Table 9. Between group comparison of APTT

		Mean	SD	N	p
Base line	Mannitol	30.9	3.7	12	0.472
	HS	29.6	4.3	10	
After Mannitol or HS	Mannitol	31.7	5.0	12	0.335
	HS	29.8	4.0	10	
After HES	Mannitol	35.8	5.1	12	0.711
	HS	34.9	5.3	10	

Table10. Within group comparison of Platelet Count.

		Mean	SD	N	Pair	Mean Difference	p*
Mannitol	Base line (A)	2.7	0.6	12	A & B	0.3	0.001
	After Mannitol (B)	2.5	0.5	12	A & C	0.6	0.000
	After HES (C)	2.1	0.5	12	B & C	0.4	0.019
HS	Base line (A)	2.8	0.6	10	A & B	0.3	0.004
	After HS (B)	2.5	0.5	10	A & C	0.8	0.000
	After HES (C)	2.0	0.3	10	B & C	0.5	0.000

*: - Significant at 0.05 level

Table 11. Between group comparison of Platelet Count.

		Mean	SD	N	p
Base line	Mannitol	2.7	0.6	12	0.824
	HS	2.8	0.6	10	
After Mannitol or HS	Mannitol	2.5	0.5	12	0.993
	HS	2.5	0.5	10	
After HES	Mannitol	2.1	0.5	12	0.527
	HS	2.0	0.3	10	

Table 12. Between Group comparison of MA value.

		Mean	SD	N	p
Base line	Mannitol	46.5	13.0	12	0.457
	HS	51.4	16.8	10	
After Mannitol or HS	Mannitol	50.5	12.2	11	0.465
	HS	46.9	9.1	10	
After HES	Mannitol	38.8	16.9	12	0.409
	HS	45.9	22.0	9	

Table 13. Within Group comparison of MA value.

		Mean	SD	N	p
Base line	Mannitol	46.5	13.0	12	0.457
	HS	51.4	16.8	10	
After Mannitol or HS	Mannitol	50.5	12.2	11	0.465
	HS	46.9	9.1	10	
After HES	Mannitol	38.8	16.9	12	0.409
	HS	45.9	22.0	9	

Table 14. Within Group comparison of alpha angle values

		Mean	SD	N	Pair	Mean Difference	p*
Mannitol	Base line (A)	42.2	14.2	11	A & B	5.9	0.254
	After Mannitol(B)	48.1	12.7	11	A & C	1.2	0.828
	After HES (C)	42.6	14.5	12	B & C	6.7	0.135
HS	Base line (A)	45.3	12.4	10	A & B	10.0	0.014
	After HS (B)	55.3	13.6	10	A & C	4.1	0.509
	After HES (C)	43.7	17.0	9	B & C	15.3	0.026

*: - Significant at 0.05 level

Table 15. Between group comparison of alpha angle values

		Mean	SD	N	p
Base line	Mannitol	41.4	13.8	12	0.496
	HS	45.3	12.4	10	
After Mannitol or HS	Mannitol	48.1	12.7	11	0.222
	HS	55.3	13.6	10	
After HES	Mannitol	42.6	14.5	12	0.869
	HS	43.7	17.0	9	

Table 16. Within group comparison of R values

		Mean	SD	N	Pair	Mean Difference	p
Mannitol	Base line (A)	5.7	1.8	11	A & B	1.9	0.065
	After Mannitol (B)	3.8	2.4	11	A & C	0.4	0.658
	After HES (C)	5.4	2.5	10	B & C	1.5	0.190
HS	Base line (A)	4.9	6.0	8	A & B	0.7	0.661
	After HS (B)	4.2	1.9	8	A & C	2.0	0.104
	After HES (C)	4.8	2.4	7	B & C	1.2	0.332

Table 17. Between group comparison of R values

		Mean	SD	N	p
Base line	Mannitol	5.7	1.8	11	0.677
	HS	4.9	6.0	8	
After Mannitol or HS	Mannitol	3.8	2.4	11	0.710
	HS	4.2	1.9	8	
After HES	Mannitol	5.4	2.5	10	0.642
	HS	4.8	2.4	7	

Table 18. Within group comparison of K values

		Mean	SD	N	Pair	Mean Difference	p*
Mannitol	Base line (A)	4.7	2.7	11	A & B	0.6	0.509
	After Mannitol (B)	4.1	1.8	11	A & C	0.1	0.900
	After HES (C)	4.7	2.1	10	B & C	0.6	0.515
HS	Base line (A)	4.3	2.4	8	A & B	0.9	0.042
	After HS (B)	3.4	2.9	8	A & C	1.1	0.346
	After HES (C)	4.6	2.9	7	B & C	2.2	0.114

*: - Significant at 0.05 level

Table 19. Between group comparison of K values

		Mean	SD	N	p
Base line	Mannitol	4.7	2.7	11	0.749
	HS	4.3	2.4	8	
After Mannitol or HS	Mannitol	4.1	1.8	11	0.530
	HS	3.4	2.9	8	
After HES	Mannitol	4.7	2.1	10	0.959
	HS	4.6	2.9	7	

Comparison of other variables based on group

Table 20. Comparison of other variables based on group

		Mean	SD	N	p
RL	Mannitol	227.1	160.8	12	0.792
	HS	245.0	151.7	10	
Urine output	Mannitol	1029.2	515.4	12	0.009
	HS	520.0	238.3	10	
Bleeding	Mannitol	216.7	173.6	12	0.135
	HS	130.0	25.8	10	
Total Blood Loss	Mannitol	1077.3	628.2	11	0.209
	HS	790.0	316.9	10	
Total Crystalloid	Mannitol	3318.2	1209.8	11	0.212
	HS	2535.0	1562.1	10	
Total Colloid	Mannitol	1218.2	252.3	11	0.086
	HS	1050.0	158.1	10	
PRBC	Mannitol	1.4	1.9	11	0.534
	HS	0.9	1.4	10	
FFP	Mannitol	0.4	1.2	11	0.885
	HS	0.3	0.7	10	

Comparison of other variables based on group

Table 21. Distribution according to PRBC

PRBC	Mannitol		HS	
	Count	Percent	Count	Percent
Not given	6	54.5	6	60.0
Given	5	45.5	4	40.0

(^{2}= 0.06, p= 0.801)

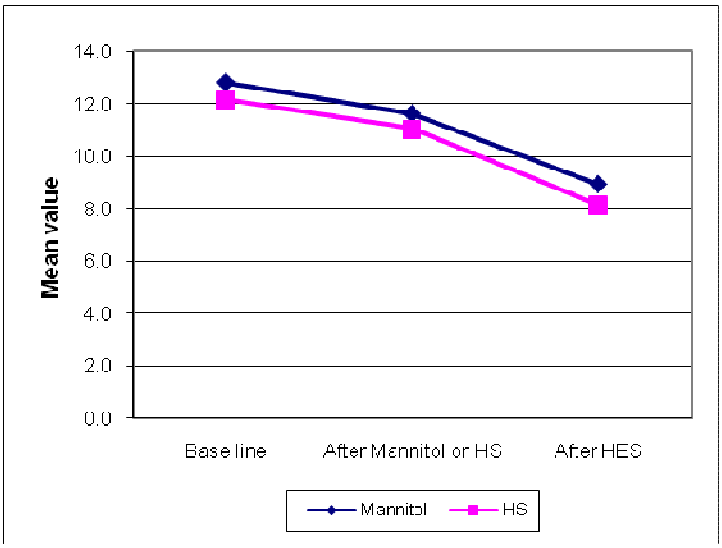
Table 22. Distribution according to FFP

FFP	Mannitol		HS	
	Count	Percent	Count	Percent
Not given	10	90.9	8	80.0
Given	1	9.1	2	20.0

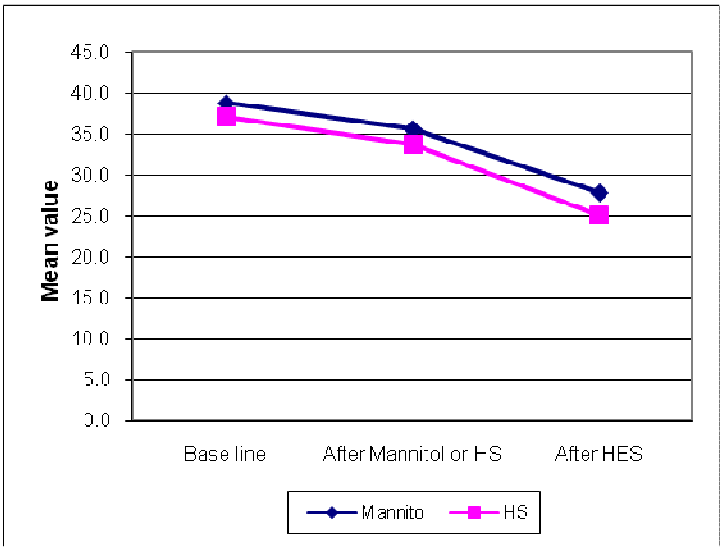
(^{2}= 0.06, p= 0.801)

Comparison of Mannitol and HS on various coagulation and TEG parameters

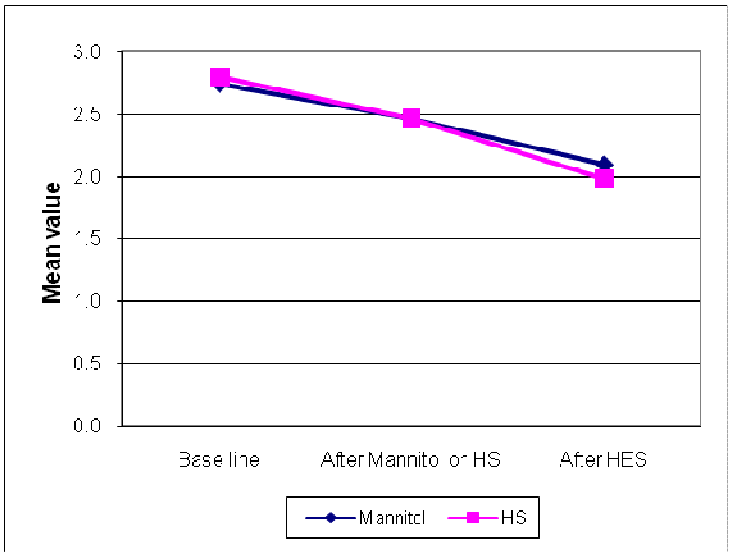
Graph 1. **Comparison of Mannitol and HS on Hb**



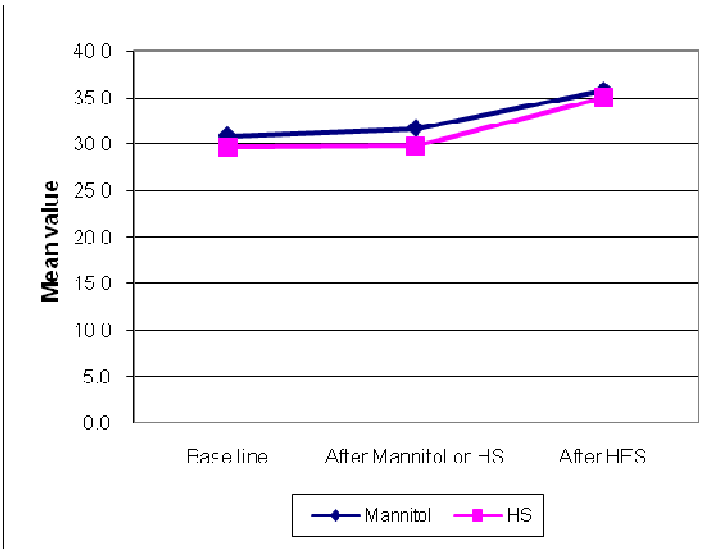
Graph 2. **Comparison of Mannitol and HS on PCV**



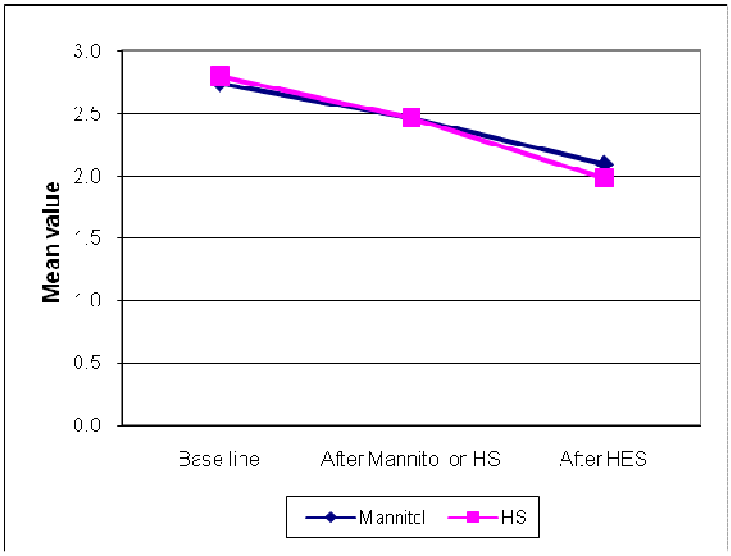
Graph 3. **Comparison of Mannitol and HS on PT**



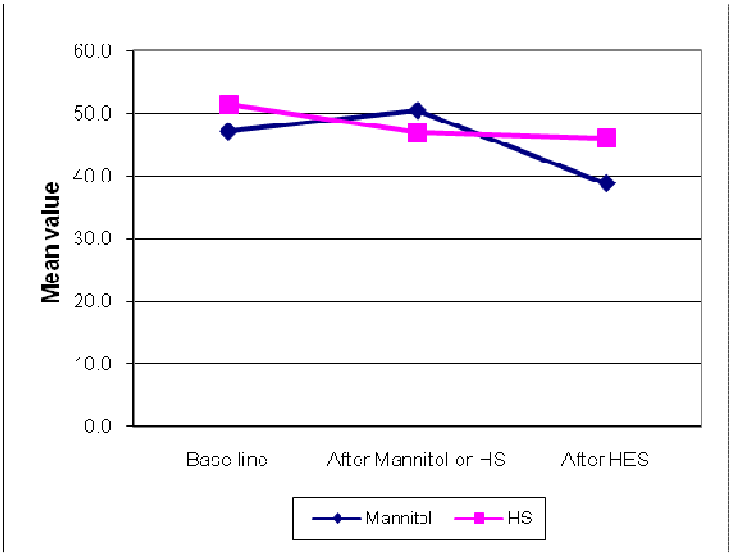
Graph 4. **Comparison of Mannitol and HS on APTT**



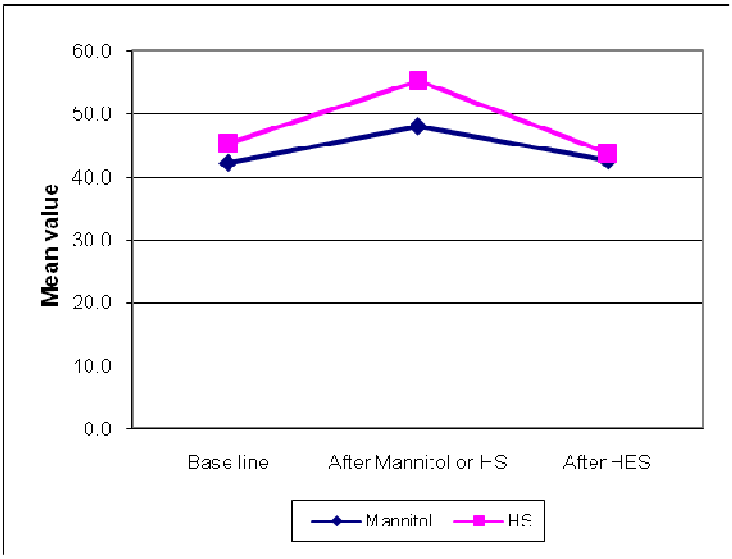
Graph 5. **Comparison of Mannitol and HS on Plt Count**



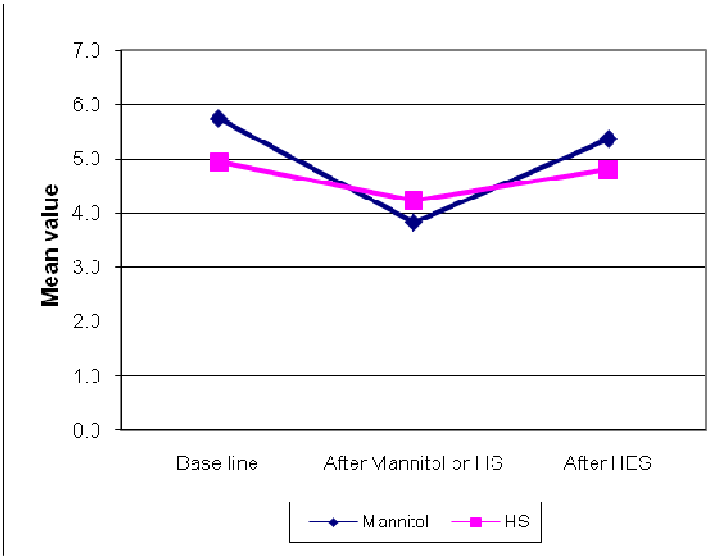
Graph 6. **Comparison of Mannitol and HS on MA**



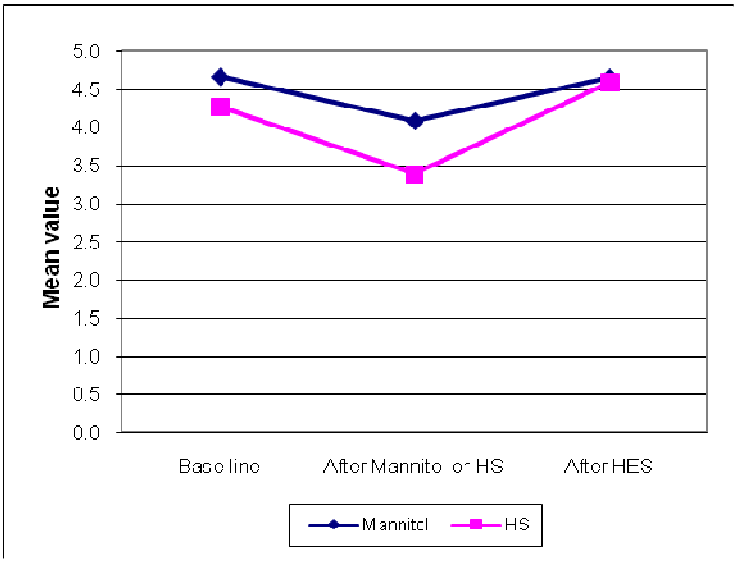
Graph 7. **Comparison of Mannitol and HS on Alpha angle**



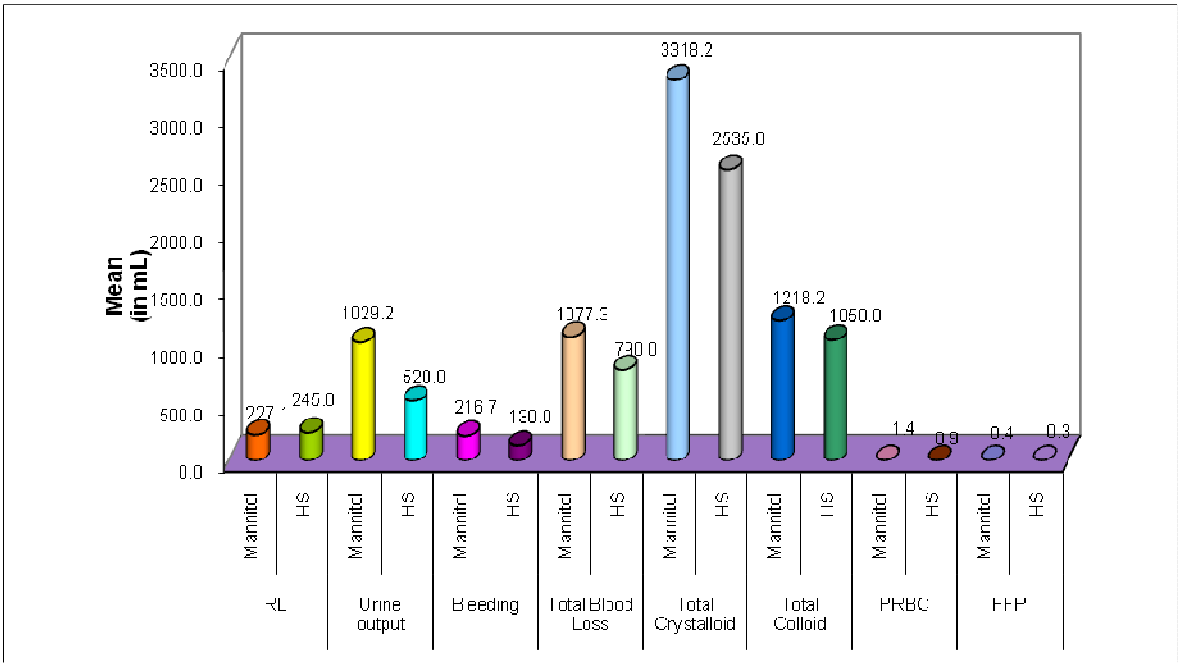
Graph 8. **Comparison of Mannitol and HS on R**



Graph 9. **Comparison of Mannitol and HS on K**



Graph 10. Comparison of others variables based on group



DISCUSSION

In this prospective study to understand the effects of combining mannitol or HS with HES on coagulation, we did not observe any statistically significant changes between the two groups. We also analyzed coagulation changes within the same group (within group analysis) as compared to baseline. We did not observe any clinically and statistically significant changes in TEG parameters.

Mannitol or HS are administered in the setting of neurosurgery for providing a relaxed brain[38,39]. This study was conducted to objectively delineate the effects of Mannitol and HS on blood coagulation when used along with HES in patients undergoing elective craniotomy, by Thromboelastography.

Effect of Mannitol on coagulation

Mannitol, a six carbon sugar, with a molecular weight of 182, is the most commonly used hyperosmolar solution, administered during craniotomy to reduce brain bulk. The dose of mannitol is 0.5 to 2 gm/kg (commonly used at 1gm/kg), and generally administered over 15 minutes. Action of mannitol begins within 4-5 minutes of administration and peaks at about 30-45 minutes. Classic mechanism of action of mannitol is the movement of intracellular water into intravascular compartment along the osmotic gradient across an intact blood brain barrier (BBB)[20-21,24].

In various in vitro studies, mannitol has been found to alter the coagulation parameters such as, clotting time, clot formation time, and maximum clot firmness (MCF)[53]. In an in-vitro study by Loustarinen et al, comparing the effects of 15%

mannitol with that of 0.9%, 2.5% and 3.5% HS has shown that blood coagulation is disturbed more by 15% mannitol than by equiosmolar 2.5% saline. This disturbance seems to be attributed not only to overall clot formation and strength but also to pure fibrin clot firmness[53].

However, in the in vivo study by Singh GP, comparison of TEG parameters in patients who received mannitol and HES with that of mannitol and saline did not show major alterations in clotting parameters as assessed by TEG. The MCF though, differed in both the groups, were still within normal range and hence the authors have concluded that mannitol can be safely administered in patients undergoing craniotomy for supratentorial tumors, without clinically significant changes in coagulation parameters as measured by rotational TEG[61]. Our results are also consistent with these findings.

In our study the mean R and mean K values in Mannitol group did not change significantly as compared to the baseline values. The mean α angle and mean MA also showed variation which was not statistically significant. The findings of our study are different may be due to minimal change in blood volume and utilization of lesser dosage of mannitol (average mannitol used was 200ml).

Effect of hypertonic saline on coagulation

Hypertonic solution (HS) is available in various concentrations. Hypertonic saline solutions are used in cerebral edema, acutely increased intracranial pressure, symptomatic hyponatremic seizures, small volume resuscitation for shock and as a renoprotetive agent in the prevention of radiocontrast and cytotoxic nephropathy, and rhabdomyolysis induced renal failure. Intravenous hypertonic saline (HS) induces a

shift of fluid from the intracellular to the extracellular space across the osmotic gradient it generates. It therefore reduces brain water, increases blood volume and increases plasma sodium. It has been shown that hypertonic saline alters plasma clotting times and platelet aggregation[51].

TS Tan et al studied the studied the effects of hypertonic (7.5%) and normal saline on coagulation and fibrinolysis in an in vitro model using thromboelastography of human whole blood. Reaction times increased and alpha angles decreased with hypertonic saline replacement at 7.5% blood volume compared with similar dilution with normal saline. At 10% blood volume replacement with hypertonic saline, reaction and coagulation times were significantly increased and alpha angles were decreased. Clot lysis at 30 min was also significantly reduced. The study confirmed that 7.5% hypertonic saline does affect the coagulation system in vitro[52].

In our study the mean R (reaction time) in HS group fell from 4.9 to 4.2 minutes after HS. The mean α angle in HS group increased from 45.3 to 55.3 after HS. The mean MA in HS group decreased from 51.4 to 46.9 after HS. These changes were not statistically significant and the values of all parameters remained within clinically accepted range.

Effect of HES on coagulation

Hydroxyethyl starch solutions (HES) are plasma volume expanders which affect hemostasis. Infusion of HES is shown to interfere with coagulation by decreasing Factor VIII plasma concentration and by interference with fibrin polymerization and thus decreasing clot strength [10,57,58].

Newer HES 130/0.4 is said to be safer[56]. In a systematic review on the effect of newer HES on coagulation, nineteen studies have shown significant hypocoagulatory effect of HES 130/0.4 on clot formation, while three studies have shown non-significant effects.

Goluza Eleonora et al conducted a pilot study to evaluate influence of the HES 130/0.4 solution on coagulation parameters in patients with benign prostatic hyperplasia (BPH) undergoing transurethral resection (TURP) in spinal anaesthesia. They found that Coagulation time (CT) and clot formation time (CFT) increased significantly and Maximum clot firmness (MCF) decreased and alpha angle (a) decreased significantly in postoperative period in TEG. Despite significant changes of TEG parameters, they were still within normal clinical range[62].

I Topcu et al[63] evaluated hemostatic changes using thromboelastography after crystalloid or colloid fluid administration during major orthopedic surgery. TEG parameters changed from normal values in all patients. In HES group, R and K times increased, however, the alpha angle and MA decreased ($P < 0.05$).

Effect of combination of mannitol and HES on coagulation

Lindroos AC et al[59] in a study on in vitro effect of the combination of mannitol and ringer acetate or hydroxyethyl starch on whole blood coagulation by using TEG, found that Clot formation time was prolonged in all dilutions compared with control. The MCF decreased in all dilutions compared with control. MCF in 20 vol% dilution of mannitol with HES was lower than MCF in the corresponding dilution with Ringer acetate. Fibrinogen-dependent MCF in 10 vol% dilution of mannitol with HES was lower than MCF in the corresponding dilution with Ringer acetate. They concluded that

mannitol in combination with HES 130/0.4 impairs clot propagation and clot strength in vitro. Fibrin clot strength impairment is more pronounced when mannitol is combined with HES than Ringer acetate. Their findings indicate that HES in combination with mannitol should be avoided whenever a disturbance in hemostasis is suspected during craniotomy. However, in our study we did not find any statistically and clinically significant changes in R, K and MA values after administration of mannitol and HES as compared to baseline values. The possible reason could be that the study we conducted is an in vivo study.

In the in vivo study by Singh GP et al[61], comparison of TEG parameters in patients who received mannitol and HES with that of mannitol and saline did not show major alterations in clotting parameters as assessed by TEG. The MCF (though differed in both the groups) was within normal range. Hence the authors have concluded that mannitol can be safely administered in patients undergoing craniotomy for supratentorial tumors, without clinically significant changes in coagulation parameters as measured by rotational TEG. Our findings are consistent with this study.

Effect of Hypertonic saline and HES on coagulation

In a study that looked at the alteration of coagulation after infusion of hypertonic saline-hydroxyl ethyl starch it was shown that Hypertonic saline - HES impaired platelet function during in vitro dilution at 5% dilution[60]. Impairment of whole blood coagulation is significant after 10% dilution or more. This effect can be pinpointed to the platelet function impairing hypertonic saline component and to a lesser extend to fibrin polymerization inhibition by the colloid component or dilution effects. Nevertheless, in a porcine model of hemorrhagic shock and resuscitation, in

general, the least effects on coagulation were observed following small volume resuscitation by administration of hypertonic saline - hydroxyethyl starch for resuscitation[64].

Our results showed that the TEG parameters were within normal limits at both baseline as well as at after delivery of HES and HS. Our study showed that there was a statistically significant prolongation of PT and APTT and reduction in Platelet count, hemoglobin and PCV after administration of either mannitol or HS and later with HES, as compared with baseline within the groups. However, these changes were similar in both the groups. This denotes that these changes are due to the effect of hemodilution per se and not related to administration of any particular solution, such as mannitol and HS or HES.

Limitations of the present study? Does our methodology limit the application of the results to only a limited set of patients or clinical conditions?

There are some limitations of this study. This is a pilot study with only 22 subjects. We used only a single bolus dose of either mannitol or HS. The dose of HES was also limited to 20ml/kg body weight. The results are limited to a subset of patients who were not suffering from Diabetes Mellitus nor had a long standing exposure to Antiepileptic drugs. We excluded patients with Diabetes Mellitus and patients on long standing Antiepileptic treatment from our study protocol because both the conditions are related to some alteration in platelet function.

Diabetes Mellitus is considered to be prothrombotic state, with chronic platelet activation, activation of coagulation system and decreased fibrinolytic potential[65]. On

account of platelet dysfunction due to Diabetes Mellitus all those patients with this comorbidity were excluded from the study protocol.

Antiepileptic drugs (AED) on chronic use also lead to various abnormalities in platelet quantity and quality. Leukopenia, thrombocytopenia and various anemias have been reported in isolated cases with the all the AED[66,67], except gabapentin and lamotrigine. A dose-dependent thrombocytopenia and/or platelet dysfunction (due to inhibition of platelet aggregation) has been reported infrequently in patients on valproic acid.[68, 69] Hence patients on chronic antiepileptic medication were also excluded from the study protocol. Further studies including large number of patients is required to confirm the results of our study.

To conclude, the results of this study shows that combining a single dose of either mannitol or hypertonic saline and with hydroxyl ethyl starch does not appear to affect in vivo coagulation as measured by TEG. However further studies involving a large number of patients are required to confirm this finding.

CONCLUSION

The results of this study show that combining a single dose of either mannitol or hypertonic saline with hydroxyl ethyl starch does not appear to affect in vivo coagulation as measured by Thromboelastography. However further studies involving a large number of patients are required to confirm this finding.

CONSENT FORM

Title of the Project: Comparison of the effects of mannitol and Hydroxy Ethyl Starch (HES) versus Hypertonic saline (HTS) and Hydroxy Ethyl Starch (HES) on blood coagulation and platelet function in neuro-surgical patients undergoing elective surgery.

Name of the Investigators: Dr. P. Gayatri, Dr. Vidhu Bhatnagar, Dr. Suresh Nair

I am explained that this study, which I will be participating in, involves the testing of my blood for research purposes so as to know the function of blood clotting in response to the infusion of brain relaxation medication either mannitol or 3% hypertonic saline and HES infusion during surgery. I have been explained that the use of brain relaxation medication as well as HES is a routine for any major surgery done on the brain.

I am explained that the duration of my participation in this study corresponds to the duration of the surgery as the blood investigations required will be collected intraoperatively, while I'm undergoing the surgery.

I confirm that I have been explained that these blood investigations are routinely used in major neurosurgical procedures especially in the presence of increased bleeding and the procedure requires collection of my blood (15-20ml) by the intra-venous/intra-arterial lines already in situ for monitoring. The use of this blood testing improves patient safety during anesthesia and surgery. I understand that laboratory results collected during the study will be used by the doctors' team for research, as well as for my care and treatment wherever required

I have been explained that there are no risks or discomforts involved during the procedure because I will be under the effects of anaesthesia. I have also been explained that I will be notified in a timely manner if in course of the research some new findings develop which may affect my willingness for participation in the above said study.

I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily in a language understandable to me. I understand that my participation 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.

I have also been explained that my identity will not be disclosed and all essential precautions will be taken by the investigators, so as to maintain confidentiality. I give permission for these individuals to have access to my records and present in scientific journals and meetings. I understand that that the results of this study may help in performing surgery safer in the future years.

I have been provided with the contact numbers of the principle investigator in case I want to know more about the study and participants rights. I agree to take part in the above research study.

Signature part of informed consent form for Subjects participating in a clinical trial.

Informed Consent form to participate in a clinical trial Study Title: Comparison of the effects of mannitol and Hydroxy Ethyl Starch (HES) versus Hypertonic saline (HTS) and Hydroxy Ethyl Starch (HES) on blood coagulation and platelet function in neuro-surgical patients undergoing elective surgery.

Study Number:

Subject's Initials: _____

Subject's Name (*if needed*): _____

Date of Birth /Age:_____

Please initial box (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 Sponsor of the clinical trial, others working on the

Sponsor's 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 Representative:_____ Date: _____/_____/_____ Signatory's Name:_____

Signature of the Investigator: _____ Date: _____/_____/_____

Study Investigator's Name: Dr. Vidhu Bhatnagar, Dr. P Gayatri

Signature of the Witness (If needed): _____

Name of the witness (if needed):_____

പഠനത്തിന്റെ പേര് : തലച്ചോറിലെ രോഗങ്ങൾക്ക് ശാസ്ത്രക്രിയ വേണ്ടി വരുന്ന രോഗികളുടെ രക്തം കട്ടപിടിക്കുന്നതിൽ മാനിറ്റോൾ (manitol)+ ഹൈഡ്രോക്സി ഈഥൈൽ സ്റ്റാർച്ച്(HES)/ ഹൈപ്പർടോണിക് സലൈൻ (Hypertonic saline)+ HES എന്നി മരുന്നുകൾ ഉണ്ടാകുന്ന വ്യതിയാനത്തെക്കുറിച്ചുള്ള താരതമ്യ പഠനം.

ഗവേഷകരുടെ പേര് : ഡോ. പി ഗായത്രി . ഡോ. വിധുഭട്നാഗർ, ഡോ. സുരേഷ് നായർ

തലച്ചോറിന്റെ ശാസ്ത്രക്രിയാവേളയിൽ തലച്ചോറ് ചുരുട്ടേണ്ടതുണ്ട്. അതിനായി മാനിറ്റോൾ അല്ലെങ്കിൽ ഹൈപ്പർടോണിക് സലൈൻ എന്നി മരുന്നുകൾ ഉപയോഗിക്കുന്നു. ഹൈഡ്രോക്സി സലൈൻ എന്നി മരുന്നുകൾ ഉപയോഗിക്കുന്നു. ഹൈഡ്രോക്സി ഈഥൈൻ സ്റ്റാർച്ച് എന്ന മരുന്നു സാധാരണയായി ഇത്തരം വലിയ ശാസത്രക്രിയകളിൽ ഉപയോഗിക്കാറുണ്ട് എന്ന് എനിക്ക് പറഞ്ഞുതന്നിട്ടുണ്ട്. ഈ മരുന്നുകൾ നൽകുമ്പോൾ എന്റെ രക്തം കട്ടപിടിക്കുന്ന പ്രക്രിയയിൽ എന്തെങ്കിലും വ്യതിയാനം വരുന്നുണ്ടോ എന്ന് അറിയാനാണ് ഈ പഠനം എന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. ഈ പഠനം നടക്കുന്നത് ശാസ്ത്രക്രിയാവേളയിലാണ്. അതിനാൽ എന്റെ സഹകരണം ഈ സമയത്ത് മാത്രമേ വേണ്ടുള്ളു എന്ന് എനിക്ക് പറഞ്ഞുതന്നിട്ടുണ്ട്. ഈ പഠനത്തിനായി 5-10 മില്ലി രക്തം ശേഖരിക്കുന്നതാണ്. ഈ രക്തം ശാസ്ത്രക്രിയ നടത്തുന്നതിനായി എന്റെ രക്തധമനിയിൽ ഇട്ടിട്ടുള്ള സൂചി വഴിയാണ് എടുക്കുക. പരിശോധനകൾക്കായി ഇങ്ങനെ രക്തം ശേഖരിക്കുക ശാസ്ത്രക്രിയാവേളയിൽ സാധാരണയാണ്. ഇങ്ങനെയുള്ള പരിശോധനകൾ എനിക്ക് ശാസ്ത്രക്രിയാവേളയിൽ സുരക്ഷിതത്വം നൽകും എന്നും ഈ പരിശോധന വഴി ഡോക്ടർക്ക് എന്റെ രക്തം കട്ടപിടിക്കുന്ന പ്രക്രിയയെക്കറിച്ച് അധികമായ വിവരം ലഭിക്കുമെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. ഈ വിവരം ശാസ്ത്രക്രിയാവേളയിലെ എന്റെ ചികിത്സയിൽ ഉപയോഗപ്പെടും. ഈ പഠനത്തിലൂടെ തലച്ചോറ് ചുരുങ്ങാനായി ഉപ

യോഗിക്കുന്ന മരുന്നുകളെക്കുറിച്ച് കൂടുതലായുള്ള വിവരങ്ങൾശേഖരിക്കാനും അതിലൂടെ രോഗികളുടെ സുരക്ഷ ഉറപ്പാക്കാനും സാധിക്കും.

ഈ പഠനവേളയിൽ ഞാൻ മയക്കത്തിൽ ആകുന്നതുമൂലം എനിക്ക് യാതൊരു ബുദ്ധിമുട്ടും ഉണ്ടാകില്ല എന്ന് എനിക്ക് പറഞ്ഞു തന്നിട്ടുണ്ട്.

ഈ പഠനത്തിലൂടെ പുറത്തുവരുന്ന വിവരങ്ങൾ എന്നെ സമയാസമയം ധരിപ്പിക്കുന്നതാണ്. ഈ പഠനത്തെക്കുറിച്ച് എനിക്ക് മന-സ്സിലാകുന്ന ഭാഷയിൽ വിശദമായി പറഞ്ഞുതരുകയും എന്റെ സംശയങ്ങൾ ദൂരികരിക്കുകയും ചെയ്തിട്ടുണ്ട്.

എനിക്ക് സ്വമേധയാ ഈ പഠനത്തിൽ നിന്നും എപ്പോൾ വേണമെങ്കിലും പ്രത്യേകിച്ച് കാരണം പറയാതെ തന്നെ പിൻമാറാമെന്നും അതു മൂലം എന്റെ ചികിത്സയിലോ നിയമപരമായ അവകാശങ്ങളിലോ യാതൊരുവിധ തടസ്സങ്ങളും ഉണ്ടാവുകയില്ലെന്നും മനസ്സിലാക്കികൊണ്ട് ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ ഞാൻ സ്വമേധയാ സമ്മതിക്കുന്നു.

എന്റെ വിവരങ്ങൾ രഹസ്യമായി സൂക്ഷിക്കുന്നതിനായി ഡോക്ടർ പരമാവധി ശ്രമിക്കുമെന്ന് എനിക്ക് ഉറപ്പ് നൽകിയിട്ടുണ്ട്. അതേ സമയം ഈ പഠനത്തിലൂടെ ശേഖരിക്കുന്ന വിവരങ്ങൾ ഡോക്ടർക്ക് പ്രബന്ധരൂപത്തിൽ പ്രസിദ്ധീകരിക്കുന്നതിനായി ഞാൻ സമ്മതം നൽകുന്നു.

ഡോക്ടറിനെ ബന്ധപ്പെടാനുള്ള നമ്പർ :

പഠനത്തെക്കുറിച്ച് കൂടുതൽ അറിയേണ്ടതുണ്ടെങ്കിൽ അന്വേഷിക്കുന്നതിനായി ഗവേഷകന്റെ ഫോൺ നമ്പരും എനിക്കു തന്നിട്ടുണ്ട്.

എല്ലാ വിവരങ്ങളും മനസ്സിലാക്കികൊണ്ട് ഈ പഠനത്തിൽ പങ്കെടുക്കുവാൻ പൂർണ്ണസമ്മതമാണ്.

രോഗിയുടെ പേര് : തീയ്യതി : ഒപ്പ് :

ഡോക്ടറിന്റെ പേര് : തീയ്യതി : ഒപ്പ് :

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S No	Hosp IP	Age	Sex M1F2	Wt	Diagnosis	Surgery	Group Mannitol1 HTS2	Hb1 in gms	PCV1 %	INR1	APTT1 in seconds	Plt Count1 in lacs	MA1 in cm	Alpha angle 1 in degrees	Hb2 in gms	PCV2	INR2	APTT2 in seconds	Plt Count2 in lacs	MA2 in cm	Alpha angle2 in degrees
1	344784	29	2	72	Rt prepontine epidermoid lesion	Rt RMSO C&E	1	11.7	36	1.07	34	3.93	72.5	67.8	9.6	29.7	1.1	34.8	3.15	67.3	69.5
2	348552	56	1	65	Rt Temporal Glioma	C&D	1	14.5	45	0.94	27	3	59.6	59.6	12.5	39	0.99	27.8	2.58	38.3	52
3	349741	42	2	65	Rt VS	Rt RMSO C&E	2	10.1	31	1.04	32	3.44	58.3	56.6	8.8	28.4	1.13	33	3.23	56.3	73.8
4	350498	34	1	50	Craniopharyngioma	Rt Pterional C&E	2	12	38	1.06	30.6	2.19	46.5	22.9	11.4	33	1.03	35	2.15	36.2	22.4
5	348777	48	2	56	Rt VS	Rt RMSO C&E	2	14.2	45.1	0.93	32	2.79	39.6	44.2	12.5	37	1.1	27	2.37	49.9	58
6	350289	29	1	75	Rt Parietal HGG	C&D	1	14	42.1	0.88	23.9	2.63	57.1	53	12.4	39.4	0.93	24.7	2.39	47.8	37.7
7	350886	52	1	58	Lt VS	Lt RMSO C&E	1	15.7	46	1.07	29	2.56	52.5	51	14	44	1.07	31.4	2.71	49.1	36.7
8	351404	55	2	56	Lt anterior falcine meningioma	Bifrontal C&E	2	12.7	39	1.08	32.5	3.14	82.6	42.7	11.5	36	1.07	33.7	2.66	60.1	55.8
9	351182	50	1	51	Pituitary Macroadenoma	Pterional C & E	2	11.1	35	1.06	29.8	2.4	42.8	40.8	10.3	33	1.13	30	2.16	47	57.1
10	351239	47	1	55	Clivus Hemangiopericytoma	C&E through Lat Approach	1	13.6	45	0.98	29.5	3.58	45.1	23.4	12.5	40	1.05	29.3	3.22	32.3	38.5
11	349688	45	1	70	Lt V S	Lt RMSO C&E	1	11.7	35.3	0.93	32.8	2.25	40.2	32.1	10.7	32	1	30	1.85		
12	352171	49	2	60	Parasagittal meningioma	C&D	1	11.2	32.9	0.91	31.4	1.73	41.3	40.5	10.5	31.3	0.95	31.5	1.66	60.7	63
13	352216	57	2	65	B/L V S	Lt RMSO C&E	1	10.8	33	0.98	27.8	2.79	43.7	28.2	9.8	29.6	1	29.8	2.64	68.7	55.1
14	351866	40	2	58	Rt V S	Rt RMSO C&E	2	12.5	36.6	1.05	22.3	4.16	75.7	47.7	11	32.7	1.12	22.3	3.25	52.6	62.1
15	353465	31	1	75	Rt Ant Third Falcine Meningioma	C&E	2	14.9	43.8	0.86	32.1	2.62	26.8	50.7	13.6	40.1	0.96	29.9	2.49	49.4	57.3
16	352968	31	2	60	Lt V S	Lt RMSO C&E	1	13	39.2	0.98	35.6	2.37	42.7	26.8	12.3	36.3	0.95	31.5	2.04	59.4	48
17	353737	29	2	71	Lt V S	Lt RMSO C&E	1	12.9	36.5	0.98	35.2	2.38	49.8	40.4	12.4	34.9	1	45.3	2.21	41.7	32.3
18	353287	48	2	75	Tuberculam Sella Meningioma	Pterional C & E	2	9.8	30.5	1.13	35.5	2.28	44.2	30.7	9.4	29.7	1.2	33.1	2.27	48.8	58.8
19	354520	63	1	60	Lt frontal convexity meningioma	Pterional C & E	2	12	35.6	0.93	23	2.27	50.8	66.7	10.4	30.9	1.08	26	1.89	32.4	63.1
20	352813	28	1	60	Craniopharyngioma	Pterional C & E	1	12.1	35.7	0.9	34.8	3.2	25.1	38	10.9	32.2	0.94	33.2	2.96	39	60
21	356490	38	2	55	Lt CP angle tumour	Lt RMSO C&E	1	12.5	38.7	1.04	29.4	2.48	28.8	35.5	11.8	38.7	1.08	31.1	2.12	50.7	35.9
22	357687	39	1	48	Lt Insular glioma	C&D	2	12.2	36	0.93	26.3	2.72	46.2	49.8	11.4	36	0.98	27.6	2.12	36.4	44.8

S No	Hosp IP	INR3	APTT3 in seconds	Plt Count3 in lacs	MA3 in cm	Alpha angle3 in degrees	RL till 3 sample	Urine output till 3 sample	Bleeding till 3 sample	total blood loss	Temp1	Temp2	Temp3	R1 in minutes	K1 in minutes	R2 in minutes	K2 in minutes	R3 in minutes	K3 in minutes	Total Crystalloid used in m	total colloid used in ml	PRBC used in units	FFP used in units	PT 1	PT 2	PT 3
1	344784	1.27	40	3.23	57.9	62.4	200	750	100	500				4.6	1.7	5.3	1.4	6.2	1.8	3500	1000	0	0	15.1	15.5	17.4
2	348552	1.13	30.1	2.28	46.9	49.6	500	800	100	400				4.3	2.3	0.3	4	3.7	3.6	2000	1000	0	0	13.6	14.2	15.9
3	349741	1.25	31	2.28	89.4	74.6	400	800	150	600				0.8	2.7	3.3	1.2	2	1.9	3350	1000	1	0	14.6	15.9	17
4	350498	1.16	38	1.97			50	700	100	750				19.6	10	8.5	10.2			2500	1000	0	0	15	14.8	16
5	348777	1.15	26	1.94	32.8	25.1	50	250	150	800				3.8	3.2	2.8	2.5	5.8	9.6	2500	1000	0	0	13.4	15.5	16
6	350289	1.18	28.4	1.8	44.4	51.5	100	400	150	800				3.8	2.1	6.2	5	2.8	3.5	3000	1000	0	0	12.8	13.5	16.4
7	350886	1.23	37.1	2.12	5.9	8.4	200	900	500	1200				5.7	3.2	6	5.5	10.9	5.8	1500	1500	0	0	15.1	15.1	17
8	351404	1.17	37.1	2.24	58.9	62.1	100	500	100	400				2.5	4.2	5.2	2.8	4.1	1.5	1500	1000	0	0	15.2	15.1	16.3
9	351182	1.23	39.1	1.73	59.4	35.1	150	750	150	600				4.2	4.3	4.1	2.4	3.2	5.8	1500	1000	0	0	15	15.9	17.2
10	351239	1.15	36.2	2.88	40.6	40.2	100	1300	100	2200				9.4	9.3	0.7	6.7	5.8	5.4	5000	1500	3	0	14.1	14.9	16.1
11	349688	1.1	34.8	1.99	47.5	55.7	200	950	150															13.5	14.3	15.5
12	352171	1.45	45.7	1.56	24.9	31.9	150	550	100	1500				3.8	2.7	1.5	2.3	7.9	8.1	3000	1000	5	0	13.1	13.6	19.2
13	352216	1.2	29.8	1.59	63	46.4	100	750	100	1400				7.2	8.3	3.2	3.7	3.8	1.9	4500	1500	2	0	14.1	14.3	16.7
14	351866	1.25	28.5	2.52	41.6	47	350	450	150	1000				3.2	2.2	2.8	1.8	6.7	3.4	2500	1000	0	0	14.9	15.7	17.3
15	353465	1.27	41	1.97	41.9	32	450	750	150	1500				1.8	4	3	1.9	8.8	6.7	5500	1000	4	2	12.6	13.8	17.5
16	352968	1.13	40	2.13	17.6	48.7	150	750	100	2000	34.8	34.8	34.8	7	3.4	3.7	4.2	4.2		5000	1500	4	4	14	13.6	15.8
17	353737	1.13	39.5	2.08	33.4	40	75	2000	500	750	35.8	35.8	35.8	7.5	5	7.9	7	4.8	5.2	4000	1400	0	0	14	14.3	15.8
18	353287	1.54	41.3	1.98	41.3	29.4	250	150	100	500	35.9	35.9	35.9							500	1500	0	0	15.9	16.7	20
19	354520	1.33	35.5	1.5	9.3	32.9	400	250	100	750	35.9	35.9	35.9							1000	1000	1	0	13.5	15.3	18.2
20	352813	1.16	32.5	1.61	31	48.3	450	2000	500	500	35.9	35.8	35.6	5	6.8	3.6	2.5		3.8	2000	1000	0	0	13.1	13.6	16.2
21	356490	1.31	35.2	1.87	52.3	27.6	500	1200	200	600	35.9	35.9	35.8	4.9	6.5	3.8	2.6	3.6	7.4	3000	1000	1	0	15.1	15.2	17.9
22	357687	1.12	31.9	1.63	38.7	55.2	250	600	150	1000	37	36.8	37	3.6	3.6	4.1	4.3	3	3.2	4500	1000	3	1	13.5	14	15.8