

Efficacy comparison of mannitol and hypertonic saline for Traumatic Brain Injury (TBI) treatment

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Efficacy comparison of mannitol and hypertonic saline for Traumatic Brain Injury (TBI) treatment

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ABSTRACT

Traumatic Brain Injury (TBI) case is commonly found in the emergency room. TBI accompanied by increased intracranial pressure (ICP) is a neurological emergency that requires prompt and appropriate management. Hyperosmolar fluid is the main treatment in the initial management of increased ICP. Mannitol and hypertonic saline are hyperosmolar fluids which are generally used. There is no specific

recommendation regarding the choice between the two fluids. From the current studies indicate that both fluids are equally effective in reducing ICP. Regarding the superiority between the two fluids, it is difficult to determine because of the heterogeneity of the studies that exist. Therefore, clinicians should choose between hyperosmolar fluids based on indications and contraindications exist in TBI patients.

Keywords: Traumatic brain injury, increased intracranial pressure, comparison, Mannitol, hypertonic saline

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INTRODUCTION

Traumatic Brain Injury (TBI) is a case that is commonly found in the emergency room (ER) and an important global public health issue. According to data in United States, an average of 1.7 million TBI cases occur each year, and 235,000 of the total patients are hospitalized, and 50,000 are dead.¹ The data obtained from several hospitals in Indonesia such as dr. Soetomo Hospital, Surabaya, showed total number of 17,254 patients with brain injury from January 2002 until December 2013,² while Hasan Sadikin Hospital, Bandung, found the TBI incidence rate as many as 3,578 patients.³ In moderate and severe head injury, abnormalities are frequently found on CT scans either in the form of diffuse lesions or focal lesions such as epidural hematoma (EDH), subdural hematoma (SDH), subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH).

The existence of such lesions may increase intracranial pressure (ICP).⁴ Some signs of the increased ICP can be headache, vomiting, loss of consciousness, papilledema, paralysis of Abducens (VI) nerve and Oculomotor (III) nerve, Cushing's response which characterized with irregular breathing pattern and hypertension accompanied by bradycardia.⁵ The neglected increased ICP may lead to nerve damage, seizures, and death.⁵ Therefore the initial treatment of the increased ICP is needed. One of the main therapy for lowering ICP is by using the hyperosmolar fluids.^{1,2,5,6} There are two fluids that commonly used which are mannitol and hypertonic saline. There is still controversy about the superiority between the two fluids until now. In the Emergency, Neurological Life Support (ENLS) and Advanced Trauma Life

Support (ATLS) guidelines concerning TBI, there is no specific recommendation regarding the ultimate choice between the two fluids.^{1,6} In this review, we will discuss the comparison between the two fluids with recent evidences.

Pathophysiology of Increased Intracranial Pressure in Traumatic Brain Injury

ICP normally ranges from 50 to 200 mm H₂O or 3-15 mmHg.⁷ ICP depend on cerebral blood flow (CBF) and maintained at constant pressure between mean arterial pressures (MAP) of 60-160 mmHg. Inside close space of cranial cavity, there are fixed volume (total 1400 to 1700 ml) of several substances namely blood (10 percent ~150 ml), cerebrospinal fluid (CSF) (10 percent ~150 ml), and brain tissue (80 percent ~1400 ml). In case of TBI, there will be increased volume of blood and CSF which cause increase in ICP. When autoregulatory mechanism of CBF fail, the CBF will depend entirely on systolic blood pressure (SBP) and slightly change in SBP is able to bring catastrophic consequences on brain tissue.⁸

Several mechanisms are responsible in increasing ICP after TBI (Figure 1).⁹ Disruption of blood brain barrier leads to hemorrhage or exudation of plasma into brain tissue that increases plasma portion of cranial tissue. In addition, inflammatory process causes by injured tissue also aggravate the exudation process by inducing vasodilatation. Injured brain parenchyma itself also contributes to increase ICP. Injured cells tend to have dysfunctional transport mechanism within plasma membrane. This leads to sodium and calcium accumulation in cytoplasm that eventually lead to cellular edema.⁹

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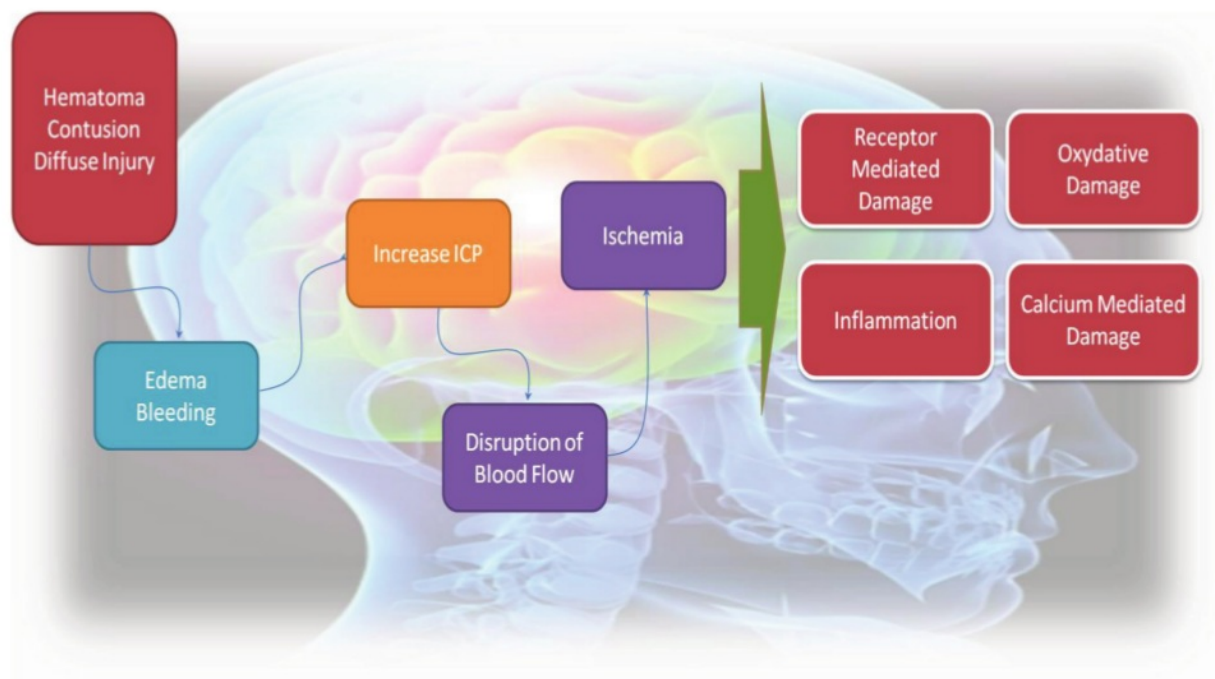


Figure 1 Diagrammatic illustration of pathophysiology of increased intracranial pressure in traumatic brain injury⁹

Severe and persistent increase in ICP caused by primary injury will lead to secondary injury within brain parenchyma. Inflammation induced by tissue damage not only induce vasodilatation that will further increases ICP, but also damage nearby tissue by means of oxidative damage and proteolytic enzyme secreted by macrophage and neutrophile. Oxidative damage also originated from poor tissue perfusion that lead to mitochondrial oxidative dysfunction and increase ROS production. Calcium accumulation within damaged cell also induces further damage primarily by inducing apoptosis of affected cell. Meanwhile, damaged neuronal cells itself also secrete glutamate neurotransmitter, a potential inducer of neurotransmitter induced cytotoxicity within brain tissue. All of these secondary damages eventually will aggravate the edema even further and create vicious cycle of pressure-damage within traumatic brain.^{8,9}

Treatment of Increased Intracranial Pressure in Traumatic Brain Injury

In the case of increased ICP, fast and precise management to reduce ICP should be done immediately.¹⁰ Decreasing ICP can be achieved in two ways: conservative and operative.¹⁰ In most intracranial hemorrhagic case, operation is definitive therapy in reducing ICP by evacuating hematoma.¹¹ Indication of operation depend on the cause of TBI and patient's condition particularly from neurological status,

radiological status and the measurement of ICP.¹² Indication of operation in EDH is if the volume >30 cc regardless of the GCS score.¹³ Whereas, an EDH with volume less than 30 cc and with less than a 15-mm thickness or with less than a 5-mm midline shift (MLS) in patients with a GCS score greater than 8 without focal deficit can be managed non-operatively with close neurological observation.¹³ Meanwhile, indication of operation in subdural hematoma (SDH) is an acute SDH with a thickness greater than 10 mm or a midline shift greater than 5 mm on computed tomographic (CT) scan should be surgically evacuated, regardless of the patient's GCS score.¹⁴ For intracranial hematoma (ICH) the indication is if the patients develop sign of progressive neurological deterioration referable to the lesion, medically refractory intracranial hypertension, or signs of mass effect on computed tomographic (CT) scan.¹⁵ Patients with GCS scores of 6 to 8 with frontal or temporal contusions greater than 20 cc in volume with midline shift of at least 5 mm and/or cisternal compression on CT scan, and patients with any lesion greater than 50 cc in volume should also be treated operatively.¹⁵

Conservative treatment (Figure 2) can be carried out immediately prior to the operative procedure or if the operative procedure cannot be conducted.¹ Conservative treatment such as the 30° head-up position, hyperventilation,¹³ othermia, and the use of hyperosmolar fluid.¹² Head up position have beneficial effects on intracranial pressure (ICP) by

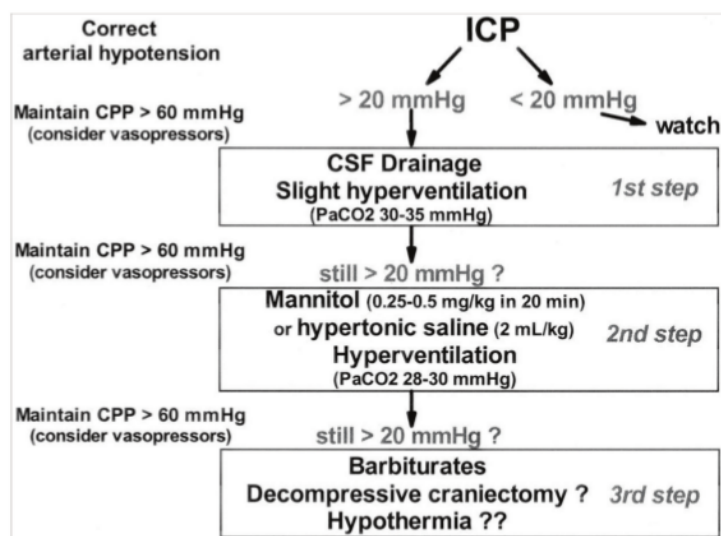


Figure 2 Schematic diagram of conservative management of elevated intracranial pressure^{8,9}

improving mean arterial pressure (MAP), airway pressure, central venous pressure and cerebro-spinal fluid displacement.¹⁶ Other approach in conservative therapy include mild induced hypothermia (MIH) defined as the maintenance of body temperature at 32-35°C. MIH is intended to lower metabolic rate especially within intracranial tissue which exerts significant neuroprotection and attenuates secondary cerebral damage after TBI.^{17,18} In addition to MIH, prophylactic hyperventilation can be delivered to patient with TBI. Hyperventilation lowers intracranial pressure (ICP) by the induction of cerebral vasoconstriction with a subsequent decrease in cerebral blood volume.²⁰ The target prophylactic hyperventilation is to reach PaCO₂ levels of 25 to 28.¹⁹

In order to reduce intracranial pressure more effectively, hyperosmolar fluid is often used. The principle of this treatment follow diffusion law in which the edematous fluid will be absorbed into intravascular compartment due to higher osmolarity caused by hyperosmolar fluid administration.⁸ However, because of its potential to cause brain atrophy, close monitoring during administration period is mandatory. The principle use of hyperosmolar fluids is in osmotic pressure difference between the intravascular to the interstitial. Two types of hyperosmolar fluids commonly used are mannitol and hypertonic saline.¹

Mannitol

Mannitol, 1,2,3,4,5,6-hexanehexol (C₆H₈ (OH)₆), is a natural polyol (sugar alcohol) which is used primarily for the osmotic diuretic properties.²¹ Because of its inability to pass through endothelial

layer, mannitol lowers ICP increasing intravascular osmotic pressure that will attract extracellular fluid into intravascular compartment. Initially, mannitol lowers blood viscosity through increased plasma volume which resulting increased microvascular flow and tissue oxygenation. Increased tissue perfusion lead to vasoconstriction reflex that limit blood supply to brain tissue and hence, decrease ICP. Meanwhile, because of its large size and inability to diffuse through endothelial layer, mannitol cause increase in intravascular osmotic pressure, widening the osmotic gradient between intravascular and extra vascular compartment. Eventually, the edematous fluid will be drawn into blood vessel and greatly contribute to lowering ICP.

Clinical mannitol preparations are sterile solution of 10% and 20%.²¹ Usual dose of mannitol (0.5-1 g/kg) was given over 5-15 minutes and could be repeated in every 4-6 hours.²² The decrease in ICP occurred within 30 to 45 minutes after the administration of mannitol and it lasted for 6 hours.²³ The administration of mannitol is contradicted in patients who experienced hypotension and renal failure because the working mechanism as a diuretic and excretion pathway through kidney.²³ Repeated administration of mannitol may cause rebound phenomena, an increased in ICP because of the accumulation of mannitol in extracellular fluid.²¹ Because of these side effects, the discontinuation process is conducted gradually by tapering off the dosage.²¹

Hypertonic Saline

Hypertonic saline is a saline solution containing 1% to up to 23.4% sodium chloride.²⁴ Hypertonic saline which is commonly used is 3%, 5%, 7.5%, and 23.4%.²² The mechanism of action of this solution is principally the same as mannitol infusion that is by increasing intravascular osmotic pressure. The advantage of hypertonic saline is the fluid can be administered for hypotensive patients with increased ICP.²² It is because hypertonic saline do have diuresis effects as mannitol.²² In addition, hypertonic saline can inhibit the inflammatory cascade mechanism which prevent secondary brain injury and also improve the neurotransmitters as well as restore electrolyte levels in brain tissue.^{26,27} However, the use of hypertonic saline needs to be considered in patients with a chronic state of hypernatremia and hyponatremia because it may cause the demyelination syndrome.²² Therefore, the periodical electrolyte serum evaluation may be needed to avoid the side effects. Rebound phenomenon is less common in hypertonic saline administration compared to mannitol. It is because of the coefficient to penetrate the brain barrier in hypertonic Saline is higher than mannitol.⁹

Comparison of the Effectiveness between Hypertonic Saline and Mannitol

When no contraindications were present, clinicians are faced with the problem choosing between hypertonic saline and mannitol to reduce ICP on the TBI. Viallet et al conducted a randomized prospective study in 20 patients with severe TBI (Glasgow Coma Scale [GCS] ≤ 8).²⁸ The patients were randomized and divided into two groups: the group receiving 7.5% hypertonic Saline (361 mOsm) and the one receiving 20% mannitol (175 mOsm) in the same amount which was 2 ml/kg. The study found that the mannitol group experienced total and duration of longer daily episodes of ICP > 25 mmHg and required more drainage of cerebrospinal fluid compared to hypertonic saline. This study also got number of treatment failure by 70% in the mannitol group compared to 10% treatment failure in the hypertonic saline group. There was no significant difference in death or neurological improvement in 90 days. Notes should be given that although the amount of fluid used was the same, but this study used two fluids with different osmolarity.²⁸

In 2005, Battison et al conducted a prospective cross-over randomized controlled study that compared the efficacy of hypertonic saline and dextran mixture with 20% mannitol to reduce the increase of ICP.²⁹ This study included nine patients, consisting of six patients with TBI and three patients with SAH. The fluids that being used are 200 mL of 20% mannitol (249 mOsm) and mixture of 100 mL of Saline 7.5% and 6% dextran-70 (250 mOsm), which infused over 5 minutes. The study found that both mannitol and hypertonic saline significantly reduced ICP, but hypertonic saline decreased ICP more significantly and had longer duration effect than mannitol. The main strength of this study is the use of same osmolarity between the two fluids.²⁹ In 2009, Oddo et al conducted a prospective, nonrandomized, and cross-over study in 12 patients with severe TBI who experienced episodes of intracranial hypertension (ICP > 20 mmHg for more than 10 minutes) by comparing the effects of oxygen pressure in the brain tissue (PbtO₂) on the administration of mannitol and hypertonic saline.³⁰ All patients were infused with 25% mannitol (412 mOsm) over 20 minutes with dose of 0.75 gr/kg. If the ICP was not decreased or the patient experienced recurrent increased ICP, 250 ml of 7.5% hypertonic saline (641 mOsm) will be given. This study found 42 episodes of intracranial hypertension which 28 episodes were treated with mannitol and 14 boluses of hypertonic saline were given for recurrent intracranial hypertension episodes. The study found that the administration of hypertonic saline produced lower ICP and cerebral perfusion

pressure (CPP) and also improved brain tissue oxygenation compared to mannitol.³⁰

Cottenceau et al in 2011 conducted a prospective, randomized controlled trial (RCT) which included 47 patients with severe TBI and ICP > 15 mmHg. The patients were randomized and divided into two groups: the group receiving 4 ml/kg dose of 20% mannitol (n=25) and the group receiving 2 ml/kg of 7.5% hypertonic saline (n=22). The two fluids had similar osmolarity. The results of the study showed that both fluids were equally effective in lowering ICP, but stronger and longer duration of ICP reduction effect was shown in hypertonic saline group. There was no significant difference in neurological outcome between groups for 6 months using the Glasgow Outcome Score (GOS).³¹

Sakellariadis et al, in 2011 conducted a prospective study to compare the effectiveness of mannitol and hypertonic saline in dose with same osmolarity. Twenty-nine patients with severe TBI and suffering continuous intracranial hypertension (> 20 mmHg for 5 minutes) were treated with either 20% mannitol (2 ml/kg) or 15% hypertonic saline (0.42 ml/kg).³² The study found that there was no significant difference both in decreasing ICP and duration of the action of the two fluids.³²

Mangat et al, 2015 conducted a retrospective cohort study in patients with severe TBI using The Brain Trauma Foundation TBI—trac New York State database. They found 35 patients who received hypertonic saline only and 477 patients who received mannitol only. The authors were conducting analysis by matching the patients between the groups. After the pairing, they included 25 patients in 20% mannitol group and 25 patients in hypertonic saline (3% hypertonic Saline n = 24; 23.4% hypertonic Saline, n = 1) with similar characteristics. The study found that the number of days and the number of hours per days where a patient had ICP > 25 mmHg was lower in hypertonic saline group compared to mannitol group. The authors also found that patient in hypertonic saline group were hospitalized in ICU for shorter period.³³

Systematic review in 2015 by Burgess et al, found that there was no significant difference between mannitol and hypertonic saline in reducing mortality, ICP, and the neurological output in the patients with severe TBI.³⁴ This review involved seven well-publicized trials until November 2015. The failure rate of ICP-lowering therapy was less found in the hypertonic saline group. This systematic review wrote that the data which were currently used were still limited due to the high heterogeneity of each study.³⁴ A review by Boone et al, also found that because of the heterogeneity among studies, the superiority between hypertonic saline and mannitol in reducing ICP in patients TBI could

Table 1 Studies regarding comparison of effectivity of mannitol and hypertonic saline for Traumatic Brain Injury

Study	Study design	Sample	Solution used	Result
Vialet et al. (2003)	RCT	20 patients with severe TBI	7.5% Saline hypertonic solution (2400 mOsm/kg/H(2)O) or 20% mannitol (1160 mOsm/kg/H(2)O), a number of 2 ml/kg body weight.	There was no difference in mortality and neurological improvement, but the total and duration in hypertonic saline group ICP were > 25 mmHg lower than that in mannitol group.
Battison et al. (2005)	Prospective, cross-over, controlled	9 TBI patients (n=6) and SAH (n=3)	200 mL 20% mannitol (249 mOsm) or 100 mL of 7.5% Saline and 6% dextran-70 (250 mOsm)	Hypertonic saline gave more significant reduction in ICP and longer duration effect than mannitol.
Oddo et al. (2009)	Prospective, nonrandomized, cross-over	12 patients with severe TBI	25% Mannitol, 0.75 g / kg, 412 mOsmol / dose vs 7.5% Hypertonic Saline, 250 mL, 641 mOsmol / dose	Hypertonic saline had effects in decreasing ICP, increasing CPP, and brain tissue oxygenation which was better than mannitol.
Cottenceau et al. (2011)	Prospective, Randomized Controlled Trial (RCT)	47 patients with severe TBI	20% Mannitol (4 mL/kg; n=25 patients) or 7.5% Saline hypertonic (2 mL/kg; n=22 patients)	Hypertonic saline provided more powerful effect on the improvement of CPP. There was no difference in neurological outcome in both groups.
Sakellarindis et al. (2011)	Prospective	29 patients with severe COT	20% Mannitol, 2 ml/kg vs 15% Hypertonic saline, 0.42 mL/kg	There was no significant difference either in decreasing ICP and duration of the action of the two solutions.
Mangat et al. (2015)	Retrospective cohort	50 patients with severe TBI	Hypertonic Saline (3% hypertonic saline, n = 24; 23.4% hypertonic saline, n = 1) vs. 20% mannitol (n = 25)	Hypertonic saline provided lower daily and cumulative increased ICP and shorter period of ICU hospitalization than mannitol.

not be concluded.³⁵ Studies regarding comparison of effectivity of mannitol and hypertonic saline in lowering intracranial pressure for TBI patient were summarized in Table 1.

CONCLUSION

Traumatic brain injury (TBI) with increased ICP is a neurological emergency that is commonly found and may cause death. Early treatment which is quick and effective should be given. Hyperosmolar fluid administration, such as mannitol or hypertonic saline, has been proven to be effective in reducing ICP. While some studies favored hypertonic saline over mannitol, however it is still difficult to prove the superiority between the two fluids because of the heterogeneity of the studies. Therefore, until there are more evidences, mannitol and hypertonic saline should be given in accordance with the indications and contraindications of the administration.

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