

## Effect of Three Different Mannitol 20% Doses on Cerebral Edema and Consciousness Levels in Traumatic Brain Injury

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**Abstract:** Diffuse Axonal Injury (DAI) is the most common type of head injury among head trauma types. Mannitol 20% has an important role in the treatment of decreasing intracranial pressure (ICP) as hyperosmolar agent. The aim of the present study was to evaluate three doses of 20% mannitol on brain edema reduction level and consciousness increase in patients with brain edema and diffuse axonal lesions associated with cerebral edema and shift of more than 5 mm. Thirty DAI patients admitted with GCS $\leq$ 8 and cerebral edema and midline shift >5mm were randomly studied in three groups (10 patients in each group): groups I, II, and III received mannitol with doses of 0.5g/kg, 1g/kg and 1.5g/kg, respectively. GCS and the shift midline change were compared and analyzed during hospitalization and 48 hours after admission. GCS was increased at 48h after admission in all three groups, but the difference was not significant (P=0.08). Cerebral edema and brain shift between first and second group and first and third groups was significant (P<0.001). However, this difference was not significant between groups II and III (P=0.99). Our study demonstrated that in DAI increasing dose of mannitol from 0.5g/kg to 1.5g/kg did not significantly increase consciousness during 48h after hospitalization. By increasing dose of mannitol from 0.5g/kg to 1g/kg and 1.5g/kg, the level of edema decreased significantly.

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### 1. Introduction

Nowadays traumatic brain injuries are a common cause of death in people less than 44 years. Totally head trauma by title of Traumatic Brain Injury (TBI) is divided into two categories: focal and diffuse. Diffuse brain injury is the most common type of head injury which clinically comprises a broad spectrum from mild trauma to diffuse axonal injury (DAI). DAI is responsible for most cases of severe brain injury in the absence of extensive parenchymal lesions, laceration or hematoma (Barzó et al., 1997; Li and Feng, 2009). Diffuse brain injury characterizes by multiple small lesions in the white matter tracts. Patients with DAI usually have a deep coma as a result of injury and outcomes of treatment are poor. DAI pathophysiology includes a major force in angular and rotational as acceleration and deceleration that induces rupturing forces with tension over tension axons (Smith et al., 2003). Histopathologic findings include tearing and swelling of axons, retraction balls (terminal proximal axons severely injured and swollen), bleeding spots on pons, midbrain, and the corpus callosum (Kallakuri et al., 2012). Some of these abnormalities show no axonal damage and after hours and days the brain

damage will occur (Alves and Bullock, 2003; Barzó et al., 1997). DAI often occurs with stretch hemorrhage on regions with maximum pressure of acceleration in trauma like the corpus callosum, the elements of the third ventricle (hypothalamus, columns of fornix, anterior interface), internal capsules, the core base, dorsolateral of brainstem and upper peduncle cerebellum.

Neuronal damage occurs in two shapes: primary and secondary. Primary injuries occur during neural cell wall damage in a small percentage of neurons after traumatic injury due to the compressive and tensile forces. The main resection arises due to secondary injury after trauma. A series of chemical and biochemical reactions starts immediately after the trauma on trauma site that final product of this reaction is the deleterious effects on brain tissue (Raghupathi, 2004; Barzó et al., 1997; Shakeri et al., 2008; Shoja et al., 2008; Shoja et al., 2011; Taheraghdam et al., 2013). Wide range of secondary injury including intracranial hematoma, edema, hypoxemia, ischemia, elevated intracranial pressure (ICP), and vasospasm is considered. Brain edema can be vasogenic (secondary to blood-brain barrier opening) or cellular. Sudden increase in post-

traumatic cerebral edema is due to vasogenic edema and its gradual increase a few days after trauma is a cellular type edema.

Using mannitol as a therapeutic agent is common in hyperosmolar patients with intracranial hypertension. A small amount of intravenous mannitol within 1-5 min reduces ICP that affect maximum 20 to 60 minutes with residual effect until 1.5 to 6 hours. Mannitol causes a rapid expansion of the plasma hematocrit and blood viscosity that led to increased cerebral blood flow and better delivery of oxygen. The decrease in ICP occurs within a few minutes, especially when cerebral perfusion pressure <70. Mannitol increases serum tonicity that reduces parenchymal edema that effect of mannitol is created within 15-30 minutes. Mannitol improves the microcirculation of blood by improving blood sensitivity. In addition, it seems that mannitol scavenges free radicals (Myburgh and Lewis, 2000; Morley and Zehtabchi, 2008; Lin et al., 2008; Schrot and Muizelaar, 2002; Ghabili et al., 2009; Ghabili et al., 2008). Cerebral edema and increased ICP are associated with high mortality and poor outcome. The aim of the present study was to evaluate three doses of 20% mannitol on brain edema reduction level and consciousness increase in patients with brain edema and diffuse axonal lesions associated with cerebral edema and shift of more than 5 mm.

## 2. Material and Methods

In a single blind randomized clinical trial, 30 patients older than 18 years were studied in three groups (each group 10 patients) from April 2011 to March 2013. Study was conducted on patients with Glasgow Coma Scale (GCS)  $\leq 8$  in trauma ward or ICU in Tabriz Imam Reza Hospital, Tabriz, Iran. Inclusion criteria were age between 15 to 60, informed consent, DAI patients with GCS  $\leq 8$  and cerebral edema and midline shift >5mm. Exclusion criteria were patients with renal failure, severe electrolyte disorders, death during treatment, severe midline shift due to surgical decompression craniotomy patients, and patients with hemodynamic instability.

Randomized parallel group design by random allocate was used for randomizing 30 patients into three groups. Written informed consent was taken from the patients. For the measurement of midline shift, first CT scan and 48 hours after arrival were used according to the formula (Middle shift = biparietal diameter - 2SP; SP = The distance from inner table to septum placidum on the side of shift). Basal cistern closing was used for the study of brain edema on CT scan. Results were divided into three groups based on the basal cistern: (A) open, (B) partially close, and (C) completely close. The first group

received 20% mannitol as 0.5g/kg and group II as 1g/kg and group III as 1.5g/kg initially by bolus dose and then intravenous infusion dose were administered every 6 hours for 15 minutes after. GCS, midline shift decrease, and brain edema decline in CT scan control (48 h) was measured based on the improvement.

Electrolyte checking was performed due to the adverse effects of mannitol including hypovolemia, electrolyte disorders, renal failure and hyperosmolarity in all patients. Laboratory evaluation including electrolytes, complete blood count, blood sugar and urine lactate was measured in all patients. Hemodynamics, temperature, urine output and intake were measured during the treatment (Hosseinzadeh et al., 2012; Ghabili et al., 2013; Soleimanpour et al., 2013; Hosseinzadeh et al., 2013).

Data were presented as mean  $\pm$  SD. Statistical analysis was performed with SPSS for Windows version 15.0 (Chicago, IL) using one-way ANOVA, Mann-Whitney U test, chi-square Test or Fisher's Exact test, wherever appropriate. A *P* value less than 0.05 was considered to be statistically significant.

## 3. Results

In this study, 30 patients were recruited in three groups (each group 10 patients). Treatment by mannitol 20% was administered as 0.5g/kg in group I, 1g/kg in group II, and 1.5g/kg in group III. The mean age of patients was 28.1  $\pm$  11.04 years in group I, 31.1  $\pm$  11.2 years in group II, and 33.5  $\pm$  10.9 years in group III (*P*=0.8). The age of the patients in this study had no effect on the rate of recovery (*P*=1). No statistically significant differences were observed in GCS between groups (*P*=0.86). GCS was slowly increased during the treatment in all groups. GCS increase after 48h of admission in all groups was not significantly different (*P*=0.08). In group I, two patients (2%), in group II one patient (1%), and in group III three patients (3%) died.

The mean middle cerebral shift was in 0.54  $\pm$  0.25, 1.63  $\pm$  0.51, and 1.64  $\pm$  0.53 in groups I, II, and III, respectively (*P*<0.001). The mean difference between the first and second group, and the first and third groups in reduction of brain edema was significantly different (*P*<0.001). However, this difference was not statistically significant between the second and third group (*P*=0.99).

## 4. Discussion

This study showed that in patients with DAI increasing doses of intravenous mannitol from 0.5g/kg to 1 mg/kg or 1.5g/kg had no significant effect on increasing consciousness 48 hours after admission. However, intravenous mannitol increased

from 0.5 to 1 and 1.5g/kg caused significant edema reduction.

Traumatic injury and particularly the TBI is an inevitable clinical entity in different hazardous situations (Golzari and Ghabili, 2012; Golzari and Ghabili, 2012; Golzari et al., 2013; Golzari et al., 2013; Ghabili et al., 2012; Khanli et al., 2013; Golzari et al., 2013; Golzari et al., 2012). One of the most important treatments of TBI is preventing or minimizing secondary damage after brain trauma. The main mechanism of secondary injury includes hypoxia-ischemia, cerebral edema excitotoxicity, calcium dysregulation criteria, apoptosis, cytoskeletal proteolysis, metabolic and mitochondrial disarrangement, oxidative stress and inflammation (Barzó et al., 1997; Li and Feng, 2009; Hashemzadeh et al., 2012; Somi et al., 2011). The main objective of neuroprotection is starting treatment before damage with the aim of minimizing the severity of the injury and the treatment effects on the nervous system by causing immediate interruption of the pathways and harmful waterfalls of biochemical reactions. The classical concept of DAI is mechanical disconnection of incompatible axons with stops at re-generation. Neuronal axons can rebuild their building. Patient can recover by using new neurocortical cares. In vitro studies have shown that 48 hours is needed for completion of the DAI process, then it can be very useful for therapeutic intervention (Smith et al., 1997). Osmotic diuretic medication has major role in reducing ICP and 20% mannitol is most commonly used in cases of increased ICP (Lin et al., 2008; Schrot and Muizelaar, 2002). Initial dose is 1g/kg that continues 0.25-0.5 g/kg. In case of emergency when decrease in ICP is needed, high doses of mannitol are used (2g/kg). Hypertonic saline is used in patients if treatment by mannitol is unsuccessful (Shawkat et al., 2013).

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