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Clinical Study

An equiosmolar study on early intracranial physiology and long term outcome in severe traumatic brain injury comparing mannitol and hypertonic saline

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ABSTRACT

The impact of hypertonic saline (HTS) on long term control of intracranial hypertension (ICH) is yet to be established. The current prospective randomized controlled study was carried out in 38 patients with severe traumatic brain injury (TBI). Over 450 episodes of refractory ICH were treated with equiosmolar boluses of 20% mannitol in 20 patients and 3.0% HTS in 18 subjects. Intracranial pressure (ICP) was monitored for 6 days. ICP and cerebral perfusion pressure (CPP) were comparable between the groups. The mannitol group had a progressive increase in the ICP over the study period ($p = 0.01$). A similar increase was not seen in the HTS group ($p = 0.1$). The percentage time for which the ICP remained below a threshold of 20 mmHg on day 6 was higher in the HTS group (63% *versus* 49%; $p = 0.3$). The duration of inotrope requirement in the HTS group was less compared to the mannitol group ($p = 0.06$). The slope of fall in ICP in response to a bolus dose at a given baseline value of ICP was higher with HTS compared to mannitol ($p = 0.0001$). In-hospital mortality tended to be lower in the HTS group (3 *versus* 10; $p = 0.07$) while mortality at 6 months was not different between the groups (6 *versus* 10; $p = 0.41$). Dichotomized Glasgow Outcome Scale scores at 6 months were comparable between the groups ($p = 0.21$). To conclude, immediate physiological advantages seen with HTS over mannitol did not translate into long term benefit on ICP/CPP control or mortality of patients with TBI.

1. Introduction

Intracranial hypertension (ICH) accounts for about half of all deaths associated with traumatic brain injury (TBI) [1]. Administration of intermittent boluses of mannitol has been a common technique of hyperosmolar therapy for the treatment of ICH [2]. Apart from its beneficial effect on cerebral edema, mannitol improves blood rheology and promotes cerebral microcirculation, but its adverse effects include hypotension, electrolyte imbalances, rebound ICH and worsening of cerebral edema [3].

Hypertonic saline (HTS) has been used for hemodynamic resuscitation in shock secondary to trauma, gastrointestinal hemorrhage, burns and sepsis [4]. HTS, used in various concentrations (1.8–30%) either alone or in combination with hyperoncotic agents, has been found to be useful in the management of ICH [5,6]. At present, for want of conclusive evidence, it is being used as a second line hyperosmolar agent [5]. Studies comparing the efficacy of HTS and mannitol, used in equiosmolar loads in TBI over several days, are very few and inconclusive [4,7–9]. In the current study, we aimed to compare the effect of equiosmolar doses of 3% HTS and 20% mannitol on the treatment of post-traumatic ICH over 6 days.

2. Methods

This study was conducted in the intensive care unit (ICU) of a tertiary neurosurgical center. Approval of the Institutional Ethics Committee and written informed consent from the next of the kin were obtained. Patients with severe TBI aged between 15 and 70 years were enrolled into the study within 24 hours of injury. Patients with a Glasgow Coma Scale (GCS) score of 3 and absent brainstem reflexes were excluded. Pregnant women and patients with spinal cord

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injury or multiple systemic injuries were also excluded from the study. Each patient was recruited into the mannitol or HTS group based on a computer generated randomization chart.

For each patient, a CT scan of the head was obtained at admission and surgically treatable lesions were immediately operated upon. An external ventricular drain catheter was placed on the more severely injured side through a frontal twist drill craniostomy. An arterial line and a central venous pressure catheter were also placed. The intracranial pressure (ICP) and the arterial pressure transducers were simultaneously zeroed to the level of tragus.

The patients were managed in the ICU according to the Brain Trauma Foundation guidelines [10,11]. Heart rate (HR), mean arterial pressure (MAP), mean ICP and mean cerebral perfusion pressure (CPP) were documented at half hourly intervals. Oxygen saturation (SpO_2) was monitored continuously. Daily fluid intake-output balance was noted. Arterial blood gases were measured twice daily. Biochemical parameters such as blood glucose, serum electrolytes, and serum osmolality were monitored at 6 hour intervals. Renal function tests were done once a day. Ventricular cerebrospinal fluid (CSF) was analyzed for evidence of infection only when suspected and the external ventricular drain tip was subjected to bacteriological culture after removal. Other body fluids (blood, urine, tracheal-bronchial secretions) were also subjected to microbiological examination on a regular basis.

All patients were sedated with morphine or fentanyl in combination with midazolam or diazepam to facilitate mechanical ventilation. The aim of mechanical ventilation was to maintain a SpO_2 of >95% and a partial pressure of carbon dioxide ($PaCO_2$) of about 35 mmHg. Glycemic levels were targeted to around 150 mg/dL by administering insulin. The head-end of the patient's bed was elevated by 15–30°. All patients received 1 mg/kg of intravenous lignocaine before tracheal suction and chest-physiotherapy.

The aim of the therapy was to maintain the ICP below 20 mmHg and CPP above 50 mmHg. Any spontaneous ICP increase to >20 mmHg qualified as an ICH episode. If an ICH episode occurred despite adequacy of sedation, ventilation and head position, CSF was drained until it stopped flowing spontaneously as a first line intervention. If the ICP remained elevated (>20 mmHg for >10 minutes) in spite of CSF drainage (until the CSF egress ceased), patients received osmotic therapy.

As per the randomization, patients received either 20% mannitol or 3% saline, in an equiosmolar dose infused as a bolus through a central venous catheter over 5 minutes. Both mannitol and HTS were administered as 2.5 ml/kg doses. If the first dose of the osmotic agent failed to decrease the ICP to below 20 mmHg, a maximum of three doses of the same drug were administered. If the ICH persisted, hyperosmolar therapy was considered a failure and thiopentone, propofol, or moderate hyperventilation ($PaCO_2$ = 30 mmHg) were instituted. As per the Brain Trauma Foundation guidelines, decompressive craniectomy was considered after exhausting general measures, CSF drainage, osmotic therapy and metabolic suppression. Hyperosmolar therapy was temporarily suspended if serum sodium increased to > 160 mmol/dL or if serum osmolality increased to >320 mosm/kg. Inotropes/vasopressors (dopamine, adrenaline and noradrenaline) were administered as and when required to maintain CPP. A CT scan of the head was repeated at 24 hours and 5 days post-trauma, and whenever the patient suffered a neurological deterioration. The ICP catheter was left *in situ* for 6 days. The catheter was removed earlier if the patient started obeying commands or the ICP was maintained <20 mmHg for 24 hours.

2.1. Data collection

Demographic and clinical details, CT scan findings, GCS scores at ICU and hospital discharge, mean ICP, MAP, CPP and HR for each day, duration of time for which the ICP was maintained at <20 mmHg in a given day, number of episodes of ICH requiring CSF release, volume of CSF drained, serum biochemical parameters and details of inotropic agents and barbiturate usage were noted. Magnitude of response to individual boluses of hyperosmolar agent was also documented. For each bolus of the hyperosmolar agent administered, the initial ICP and the lowest ICP achieved following the hyperosmolar agent, and time required to achieve ICP <20 mmHg were recorded. Duration of ICU stay, duration of hospital stay, in-hospital mortality and Glasgow Outcome Scale (GOS) scores at 6 months were also documented.

2.2. Data analysis

All data are expressed as mean ± standard deviation. GCS scores and GOS scores are expressed as median with interquartile range. Baseline characteristics of the patients in the two groups were compared by an unpaired samples t-test for continuous variables and chi-square test for non-parametric variables. The Wilcoxon rank-sum test was used to compare medians. A comparison of the physiological data at different time points and ICP/CPP changes with mannitol and HTS during the 6 days of the study was made by repeated measures analysis of variance. Significant differences within the groups were examined by *post hoc* Bonferroni testing. Outcome variables were analyzed by a one-way analysis of variance or a chi-square test. A p value < 0.05 was considered statistically significant. The statistical analysis was performed using the Statistical Package for the Social Sciences version 10 software (IBM, Armonk, NY, USA).

3. Results

3.1. Demographic profile and neurological status

Thirty-eight patients were recruited into this study with 20 patients in the mannitol group and 18 in the HTS group. Table 1 shows the demographic details and neurological condition of the patients, which were comparable between the groups. GCS scores

Table 1
Demographic and neurological condition data

	Mannitol (n = 20)	HTS (n = 18)	p value
Age, years	31 ± 13	27 ± 8	0.24
Female:male	1:9	1:8	0.91 χ^2 = 0.01
Mode of injury (n)			
Road traffic accident	12	12	0.54
Fall from height	4	4	
Others	4	2	
Injury to hospital duration, hours	4.3 ± 3.6	4.5 ± 3.2	0.88
Injury to surgery duration, hours	6.7 ± 5.2	6.1 ± 5.5	0.73
Median admission GCS score post-resuscitation	5 (4–6)	4 (4–5)	0.654
Predominant lesion on CT scan (n)			
Extradural haematoma	3	7	0.67
Subdural haematoma	15	7	χ^2 = 0.09
Contusion	2	2	
Diffuse injury	0	2	
Median GCS score (Eye + Motor) at inclusion to study (IQR)	5 (3–7)	4 (3–7)	0.317
Duration of monitoring, hours	130 ± 54	131 ± 42	0.94

Data are expressed as mean ± standard deviation or median (interquartile range) unless otherwise indicated.
GCS = Glasgow Coma Scale, HTS = hypertonic saline.