Urinary Sodium Loss following Hypertonic Saline Administration Curtails its Superior Osmolar Effect in Comparison to Mannitol in Severe Traumatic Brain Injury: A Secondary Analysis of a Randomized Controlled Trial

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Abstract

Background Mannitol and hypertonic saline (HTS) are used as boluses during episodes of raised intracranial pressure (ICP) in severe traumatic brain injury (TBI). We recently demonstrated that ICP reduction and neurological outcomes are similar with mannitol and HTS in TBI. In the current post hoc analysis, we hypothesized that this lack of difference between mannitol and HTS is due to increased urinary sodium losses after HTS.

Methods In this post hoc analysis of our earlier randomized controlled trial, we analyzed serum and urine osmolarity and sodium levels in 38 patients with severe TBI over 6 days. Equiosmolar boluses of mannitol and HTS were administered whenever ICP increased above 20 mm Hg. Seven hundred sixty samples each of serum sodium, urine sodium, serum osmolarity, and urine osmolarity were analyzed during this period.

Results Three hundred and one and 187 boluses of mannitol and HTS, respectively, were required to maintain ICP below 20 mm Hg. The urinary osmolarity was similar between mannitol and HTS groups (p = 0.63). The urinary sodium excretion was significantly higher in HTS group compared with mannitol group (p = 0.002). Serum sodium and osmolarity values were similar between mannitol and HTS groups (p = 0.16 and 0.31, respectively). There was no difference in the mean ICP between the groups (p = 0.31).

Conclusion Increased urinary sodium loss after HTS contributes to its lack of superiority over mannitol in controlling raised ICP.

Keywords
- traumatic brain injury
- mannitol
- hypertonic saline
- urine sodium

Introduction

Hypertonic saline (HTS) is increasingly being used as an alternative to mannitol for osmotherapy in patients with traumatic brain injury (TBI). However, studies have not been able to convincingly demonstrate that HTS is superior to mannitol in controlling the intracranial pressure (ICP) or improving the outcome.[1–4] The lack of expected benefit can probably be answered by examining the effect of both the osmotic agents on serum and urine osmolarity and sodium.

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Our earlier randomized trial in patients with severe TBI demonstrated that when administered in equiosmolar doses during episodes of intracranial hypertension (ICH), ICP control over the 6-day-period and clinical outcomes were similar.[2] We hypothesized that the similar osmolar state achieved by HTS and mannitol is largely due the increased urinary losses, thus bringing about similar osmolar effects. The primary objective of this study was to compare the urinary sodium and osmolarity in patients receiving equiosmolar doses of HTS and mannitol.

Methods

This is a post hoc analysis of the data of a prospective randomized controlled trial conducted following the approval of the institute ethics committee. The detailed methods are published earlier.[2] Briefly, 38 patients with severe TBI (Glasgow coma scale [GCS] score ≤ 8) were randomized to mannitol and HTS groups. Their ICP, cerebral perfusion pressure (CPP), serum, and urinary biochemistry (sodium and osmolarity) were monitored over a period of 6 days. Patients were treated as per the 2007 Brain Trauma Foundation guidelines. Serum and urine electrolytes and serum and urine osmolarity were monitored at 6-hour intervals every day for the study period. The serum and urine osmolarities were measured using depression of freezing point method. We aimed to maintain ICP ≤ 20 mm Hg and CPP ≥ 50 mm Hg. ICP was monitored using an intraventricular catheter and connected to a pressure transducer to display ICP values and waveform on the multi-parameter patient monitor. If ICP increased to > 20 mm Hg, cerebrospinal fluid (CSF) was drained first by opening the three-way connector until it stopped flowing or ICP reduced to below 20 mm Hg. Despite above measures, if the ICP remained > 20 mm Hg for 10 minutes, equiosmolar doses (2.5 mL/kg) of either 20% mannitol or 3% HTS were administered. If this bolus dose failed to reduce the ICP to < 20 mm Hg, up to two additional boluses of the same hyperosmolar agent were repeated. If ICH persisted despite CSF removal and osmotherapy, barbiturate coma was instituted.

Statistical Analysis

All data are expressed as mean ± standard deviation [SD] or median and interquartile range (IQR) depending on the normality of distribution of our data. The biochemical and ICP data within and between mannitol and HTS groups over the 6-day-period were compared using mixed design analysis of variance model. A p-value < 0.05 was considered statistically significant. The statistical analysis was performed using SPSS for Windows, version 16 software.

Results

Twenty patients received mannitol, and 18 patients received HTS. There were no differences in the demographic variables (age [31 ± 13 vs. 27 ± 8 years; $p = 0.24$]) and preoperative neurological status at recruitment (median GCS score [eye + motor] at inclusion to study IQR (5 [3–7] vs. 4 [3–7]; $p = 0.32$) between the mannitol and HTS groups. The boluses of mannitol and HTS administered during the 6 days were 301 and 187, respectively. Seven hundred sixty samples each of serum sodium, urine sodium, serum osmolarity, and urine osmolarity were analyzed. No patient had serum osmolarity > 320 mOsm/kg or serum sodium > 160 mmol/dL to withhold osmotherapy. The changes in ICP and serum sodium in both mannitol and HTS groups over 6 days are depicted in (►**Fig. 1**). The ICP was not significantly different between the groups ($p = 0.32$).

There was no difference in mean serum sodium levels between the groups ($p = 0.16$). The changes in serum osmolarity in the groups and the ICP changes between the two study groups are shown in (►**Fig. 2**). Mean serum osmolarity was comparable between the groups ($p = 0.31$). The urinary excretion of sodium in the HTS group increased from the second day, peaked at day 4, and remained elevated till the end of the study period, while remaining largely unchanged in the mannitol group. The difference in the urinary sodium levels

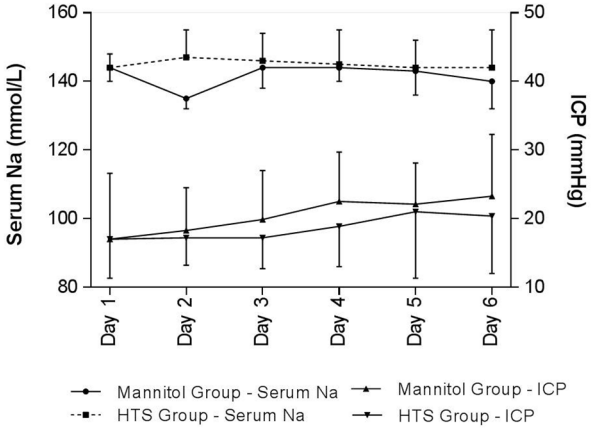

Fig. 1 Changes in ICP and serum sodium in mannitol and HTS groups over 6 days. HTS, hypertonic saline; ICP, intracranial pressure.

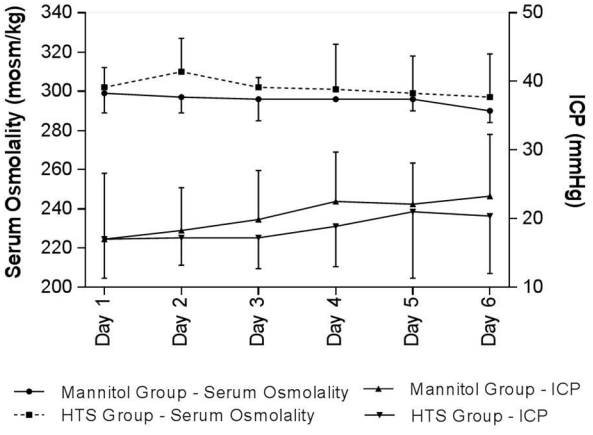

Fig. 2 Changes in ICP and serum osmolarity in mannitol and HTS groups over 6 days. HTS, hypertonic saline; ICP, intracranial pressure.

between the two groups was significant ($p = 0.002$) (►**Fig. 3**). The urinary osmolarity remained stable within each group during the study period ($p = 0.31$ and $p = 0.82$, respectively, for mannitol and HTS) and was comparable between the two groups ($p = 0.63$) (►**Table 1**).

Discussion

In our study, comparing equiosmolar boluses of mannitol and HTS as osmotherapeutic agents for ICP management in TBI, we observed a significantly higher urinary sodium excretion in the HTS group than in the mannitol group. Even though the trend in serum osmolarity in HTS group was higher than in the mannitol group over the 6-day-period, it was not statistically significant, thus resulting in similar ICP values with the both agents. The mechanism of augmented sodium excretion following HTS involves an increased glomerular filtration and renal tubular excretion of sodium.[5–7] Interventions designed to retain the serum sodium, therefore maintain better osmolarity.[8] An earlier study has shown that continuous infusion of HTS resulted consistently in higher natremia and lower ICP.[9] Median serum sodium level was however only 146 mmol/L (IQR: 142–147 mmol/L) in those patients who developed hypernatremia (65% of the cohort) when continuous HTS was administered.[10]

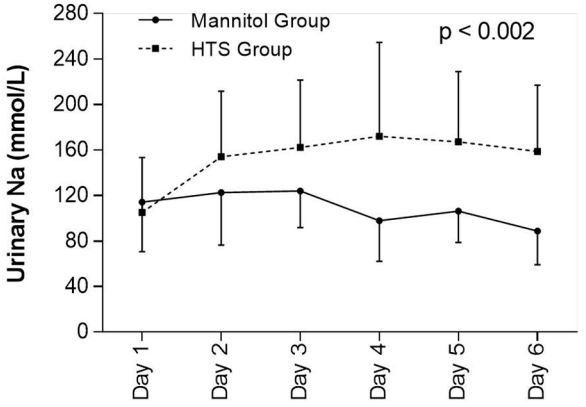

Fig. 3 Urinary sodium excretion during the first 6 days after traumatic brain injury. HTS, hypertonic saline.

Vaptans, such as tolvaptan and conivaptan, are selective and competitive arginine vasopressin receptor-2 antagonists. They induce aquaresis, increase serum sodium concentration and osmolarity in patients with hyponatremia, and have shown promise in reducing ICP in patients with TBI.[11] Fludrocortisone, a corticosteroid, has significant mineralocorticoid potency. It increases serum sodium concentration and also intravascular blood volume by its sodium and water retention property.[12] Whether judicious use of a vaptan with adequate maintenance of intravascular volume or fludrocortisone will help sustain a higher serum hyperosmolar state in these patients needs to be studied in future.

Strengths and Limitations

The strength of the current study lies in the fact that we performed serum and urine biochemical assessments four times daily for 6 days after acute TBI, thus evaluating 760 samples each of serum and urine sodium and osmolarity. We found that urinary sodium loss after HTS is more compared with mannitol. Unfortunately, despite this being considered a familiar understanding, the data regarding direction and magnitude of urinary sodium losses after HTS administration compared with mannitol in TBI were lacking which this study addresses. The major limitation of this study is that it is a post hoc analysis of another randomized controlled study. A prospective trial specifically designed to test this hypothesis is likely to result in greater confidence in our results. Second, this study was based on the premise that the therapeutic benefits of osmotherapy are largely due to hyperosmolar state achieved after osmotherapy. However, literature shows that there are mechanisms other than hyperosmolarity too that bring about therapeutic effects of osmotherapy on ICP, which this study has not taken into account.

The findings of this study imply that unless methods of sustaining intravascular hyperosmolarity are identified and implemented, results of osmotherapy with HTS would continue to be similar to that of mannitol.

Conclusions

Administration of mannitol and HTS results in similar intravascular hyperosmolar state and both agents are equally effective in reducing ICP. Increased urinary sodium loss after HTS may have contributed to its lack of superiority over

Table 1 Mean urinary osmolarity in mannitol and hypertonic saline groups over 6 days

Day after injury	Mannitol (mmol/L) $N = 20$	Hypertonic saline (mmol/L) $N = 18$	Significance between the groups
1	513.8 ± 155.4	515.9 ± 173.0	$p = 0.628$
2	531.1 ± 127.3	418.7 ± 98.9	
3	465.2 ± 60.7	481.0 ± 208.5	
4	426.2 ± 119.3	481.4 ± 172.0	
5	446.0 ± 127.0	384.4 ± 133.2	
6	477.2 ± 147.5	473.5 ± 177.2	
Significance within the groups	$p = 0.309$	$p = 0.822$	

mannitol in controlling raised ICP. Future studies should examine if prevention of urinary sodium loss by administering HTS as a continuous infusion or by using adjuvants such as vaptans or mineralocorticoids to the osmotherapeutic regimen result in sustenance of higher intravascular osmolarity.

Conflict of Interest
None.

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