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Mannitol; Hypertonic saline; Serum Na; Serum osmolality

Abbreviations

HTS: Hypertonic Saline; MA: Mannitol; GCS: Glasgow Coma Scale; LOS: Length of Stay; TBI: Traumatic Brain Injury

Review Article

Comparison of Survival and Function after Traumatic Brain Injury among Patients Exposed to Hypertonic Saline and Mannitol: A Case Control Study

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Abstract

Object: Hyperosmolar agents are used for several purposes, of which one of the most common is to diminish pressure within contained compartments. The most commonly used hyperosmolar agents include Hypertonic Saline (HTS) and Mannitol (MA). The most commonly treated compartment is the cranial vault. While both HTS and MA are known to reduce compartment pressures, there is some data suggesting that HTS may be more effective than MA. However, there is virtually no data comparing the effect of HTS and MA on survival, function, nor length of stay. The goal of this study is to compare HTS and MA according to the outcomes of survival, function, and length of stay and to compare the effect of HTS and MA on the sodium flux and osmolality.

Methods: We conducted a case-control study to compare HTS and MA according to the outcomes of survival, neurological function, and length of stay. We reviewed all patients admitted to the Neurosciences and General Systems Intensive Care Units at the University of Alberta Hospital with a diagnosis of Traumatic Brain Injury (TBI) for a one-year period from Jan 1 2018 until Dec 31, 2018.

Results: Ninety-two patients with TBI were found in the database from January 1 2018 till December 31 2018. Twenty-three patients were treated with osmotherapy, 15 patients were treated with 3% HTS and 8 patients were treated with 20% MA. Comparison between patients receiving osmotherapy and patients not receiving osmotherapy was made. Survival was no different between the HTS (x%, 95% CI) and the MA (y%, 95% CI) groups, p=. Likewise there was no difference in the hospital length of stay between groups, x +/- days versus y=/- days in the HTS and MA groups respectively, p=. The HTS group had significantly higher initial GCS presentation compared to MA group, despite that HTS failed to show improved survival or LOS compared to MA treated patients. The mean delta serum osmolality and mean delta Na were wider in the MA group, this wide delta serum osmolality and Na was not seen in the HTS group.

Conclusion: Our study challenges the multiple recent literatures favouring HTS in TBI patients. Also, our study indicates MA and HTS may not be equiosmolar and have different influence on serum electrolytes and osmolality. A large sample size multi center RCT is needed to compare between different osmotherapies and their effect on mortality and neurological outcome.

Introduction

Hyperosmolar agents are used for several purposes, of which one of the most common is to diminish pressure within contained compartments. The most commonly used hyperosmolar agents include Hypertonic Saline (HTS) and Mannitol (MA). The most commonly treated compartment is the cranial vault, and pressure may be elevated within the vault due to tumor, stroke, or trauma among other reasons. While both HTS and MA are known to reduce compartment pressures, there is some data suggesting that HTS may be more effective than MA in equimolar volumes in terms of duration of effect and in terms of minimization of sodium flux [1-7]. However, there is virtually no data comparing the effect of HTS and MA on survival, function, nor length of stay. The goal of our study is to compare HTS and MA according to the outcomes of survival, function, and length of stay. Also, to compare the effect of HTS and MA on the sodium flux and osmolality and see if this has any effect on the functional outcome.

Materials and Methods

The study was approved by the Health Research Ethics Board of the University of Alberta. We conducted a case-control study to compare HTS and MA according to the outcomes of survival, function, and length of stay. We reviewed all patients admitted to the Neurosciences and General Systems Intensive Care Units at the University of Alberta Hospital with a diagnosis of TBI for a one-year period from Jan1 2018 until Dec 31 2018. The study was approved by the local Health Research Ethics board.

We retrospectively reviewed patients with traumatic brain injury (TBI) to document and compare the following:

a) Incidence and severity of TBI

b) Exposure, dose, and frequency of HTS and MA

c) Peak, trough, and mean daily serum and urine sodium, osmolarity, and creatinine

d) Peak, trough, and mean intracranial pressure and cerebral spinal fluid volume drained

e) Peak, trough, and mean daily Glasgow Coma Scale (GCS)

f) Use of vasopressor daily (peak, trough, and mean)

g) Fluid balance daily (total input and hourly peak, trough and mean urine output)

h) Vital status at ICU discharge and hospital discharge

i) Length of stay in ICU and hospital.

Within this data set, patients exposed to HTS and MA were compared according to the variables of interest.

Inclusion criteria

i. Patients with TBI

ii. Age 18-85

iii. Severe TBI with GCS < or equal to 8

Exclusion criteria:

i. Age <18 or >85

ii. Underlying coagulopathy

iii. Use of dual antiplatelets or anticoagulation

Statistical Analysis

Categorical analyses were performed using the Chi squared test and linear comparisons were performed using student's t-test as appropriate. All statistical analyses were carried out using Microsoft Excel.

Results

92 patients with TBI were found from January 1 2018 until December 31 2018. Twenty-three patients were treated with osmotherapy, of whom15 patients were treated with HTS and 8 patients were treated with MA (Figure 1).

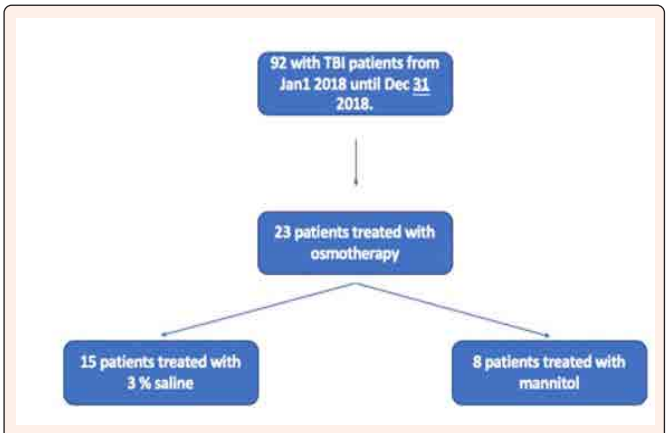

Figure 1: TBI patients included in our retrospective case control study.

Comparison between patients received osmotherapy and patients who did not receive osmotherapy was made, which showed no difference in terms of the survival or the Length of Stay (LOS), (Table 1).

Table 1: Comparison between TBI patients treated with osmotherapy vs. no osmotherapy.

	Tx with Osmotherapy (23)	No Osmotherapy (69)	p
Age	51	49	0.82
Gender	14M 9 F	49M 20F	0.9
GCS	6.7	7.9	0.28
APACHE II	20.8	18.5	0.21
ICU survival	18 A 5 D	54 A 15 D	1
Hospital survival	17 A 6 D	49A 20D	0.97
ICU LOS	7	5.4	0.54
Hospital LOS	22.5	17.2	0.26

Next, comparison was made between patients who received HTS vs patients who received MA. There was no difference in terms of the age and gender between HTS and MA groups. There was a significant difference in the baseline GCS, where mannitol group had significantly lower GCS compared to HTS group (p=0.02). The APACHE II score was not significantly different between MA and HTS groups. There was no significant difference in the mortality rate (p=1.0) and hospital LOS (p=0.26) between the two groups. The mean delta serum osmolality and Na showed higher numbers in MA group however this did not reach a significant difference when compared with HTS group. (Table 2) summarizes the comparison between MA and HTS.

Table 2: Comparison between TBI patients treated with HTS vs. MA.

	3 % Saline (15)	Mannitol (8)	p
Age	49	53	0.6
Mvs F	9 vs 6	5 vs 3	0.97
GCS	8.1	4.3	0.03
APACHE II	19.2	24.3	0.18
ICULOS	7.8	5.5	0.41
Hosp LOS	19.4	29.4	0.26
MAX Osm	326.6	311.2	0.27
MIN Osm	322	303.7	0.25
MAX Na	141.5	147.6	0.12
MIN Na	137.7	141.4	0.24
Mean Delta Osm	3.1	7.5	0.2
Mean Delta Na	3.8	6.1	0.28
ICU Alive vs Dead	12 vs 3	6 vs 2	0.95
Hosp Alive vs Dead	11 vs 4	6 vs 2	1

Discussion

Our retrospective data showed important findings in patients with TBI treated with hyperosmolar therapy. When first comparing patients treated with osmotherapy with patients who did not receive osmotherapy, the mortality rate and LOS showed no difference. It is assumed that the reason osmotherapy was not used in the latter group of patients was that they were not neurologically impaired enough to require osmotherapy. This raises the question of if the osmotherapy should be given prophylactically for TBI patients before they exhibit severe ICP manifestations and a lower GCS. This was evidenced by the fact that the group not receiving osmotherapy had no difference in hospital survival or length of stay despite having a higher GCS and lower APACHE-II at baseline. When comparing patients with severe TBI that did require osmotherapy, we did not demonstrate a survival benefit in patients receiving HTS over those receiving MA. This is aligned with previous studies and systematic reviews which have not demonstrated a clear advantage of one osmotic over the other [8]. The HTS group had a significantly higher baseline GCS presentation compared to the MA group, however, despite this, the use of HTS failed to show improved survival benefit or LOS compared to the use of MA. However, another important finding that warrants further investigations is the fact

that the mean delta serum osmolality and mean delta Na were wider in the MA group, this wide delta serum osmolality and Na was not seen in the HTS group. This suggests that MA and HTS are likely not equimolar and they deliver their effect on raised ICP through different mechanisms, those mechanisms are not well understood yet. Also, this finding could explain why MA sustained similar mortality and LOS compared to HTS despite having significantly lower initial GCS, or it could explain why HTS did not show lower mortality and LOS. These findings are challenging many recently published studies stating the superior results of HTS [4,6,7]. Also these findings emphasizes the fact that mechanisms and osmolar effects of HTS and MA are not the same and are not well understood and requires extensive further research and investigations.

Mangat [4] recently published a retrospective study comparing MA to HTS and showed superior results of HTS in reducing ICP [4]. In their comparison, their HTS subjects were significantly lower in number than those in the MA group. In addition, the number of patients included were low. Taking all these points into considerations, the results could be showing falsely superior effect of HTS, which is only going to be elucidated with higher number of samples and equal groups comparisons. Also, they compared ICP and CPP between both groups but not the LOS or mortality rate. In our review, the number of HTS patients were higher than the number of MA patients. Despite this, HTS did not show improved outcome in terms of mortality or ICU/Hospital LOS. This emphasizes the importance of conducting a large multicenter RCT to lend further clarity to this controversial topic which is limited by small sample studies. Li [6] conducted a meta analysis of patients with TBI who underwent RCT or retrospective studies [6].They included 7 studies that met their inclusion criteria, from all those studies they came with the same conclusion as Magat el al where HTS had superior results in reducing ICP. When we go through the 7 studies, they included in their meta analysis, we find small samples ranging from 10 to 29 patients per study. Also, the mortality and functional outcomes including the outcome neurological status were not discussed in those studies, focusing only on the ICP results. This meta analysis suffers from a small sample size and the use of surrogate endpoints such as ICP, rather than neurological outcome and mortality. Boone [9] also conducted a systematic review where they reviewed all articles comparing MA to HTS in severe TBI [9]. Again 7 articles met their inclusion criteria and were included in their review. In contrast to Li [6] and Mangat [3], they were not able to conclude that HTS was superior to MA. The superiority of HTS, they did have preference of HTS based on the results of their 7 articles however they recommended at the end to carefully dissect each clinical scenario and use clinical judgment and experience. The results of the review of Boone [9] clearly shows how this topic is controversial and no firm conclusion has been widely accepted regarding this topic. Interestingly, Boone [9] and Li [6] both conducted their reviews in 2015 and they included almost the same articles and despite that they came up with different results and conclusions.

A very important study published by Sokhal [10] worth including in this discussion [10]. They compared 20% MA and 3% HTS in elective patients undergoing craniotomy for supratentorial tumors. They enrolled 40 patients, they inserted subdural ICP monitor after performing craniotomies then randomizing them into either receiving MA or HTS and following the ICP and systemic hemodynamics from zero minute till 45 minutes. Interestingly, the ICP reduction was equal in both groups which really criticizes the results of the studies indicating the superior effect of HTS on ICP. Another critical point they found in their study which aligns with the findings of our study is the that MA patients had a drop in their serum Na and elevation in their serum K, while HTS patients had elevation in their serum Na and drop in their serum K. Those changes in serum electrolytes were significant enough to reach a statistical difference. This emphasizes the point that we found in our study that HTS and MA are not equiosmolar and they have different influence on serum electrolytes and serum osmolality. This study shows critical results that must be considered in this controversial topic, especially that they were able to follow the effect of HTS and MA on ICP, electrolytes, and systemic hemodynamics life from zero minute till 45 minutes after performing craniotomies. Though, the study could be criticized that it doesn't fully reflect the reality of majority of patients needing osmotherapy since the closed cranial vault was opened, still the study showed important physiological and dynamic responses to osmotherapy. Also worth mentioning, Sokhal [10] published their study 2 years after Li [6] and Boone [9] published their meta analysis and systematic review challenging their results of favouring HTS in reducing ICP.

Another important factor that must be considered in response to osmotherapy is the brain tissue oxygenation ($PbtO_2$). Oddo [5] discussed this important point when they published their study in 2009 [5]. They followed 42 patients with TBI required ICP monitors and $PbtO_2$ monitoring and treated them with 25% MA (28 patients) if their ICP is >20 or 7.5% HTS (14 patients) if ICP was not controlled with MA. They found $PbtO_2$ in HTS patients has significantly increased from baseline, while MA did not have any significant changes on $PbtO_2$. Unfortunately they did not randomize patients to either receiving HTS or MA, hence the effect of HTS on $PbtO_2$ independent of mannitol are not clear. Another important point to mention about this study is that they found HTS patients had significant increase in CPP numbers (76-78) while MA had limited increase in CPP (65-70). The finding of higher increase in CPP numbers in HTS patients is not necessarily associated with a favourable outcome since cerebral autoregulation is lost in TBI patients and hence significant increase in CPP in those patient populations could be associated with adverse events rather than benefits. This may explain the reason that multiple studies did not show improved mortality or functional outcome from HTS despite showing reduced ICP [1-3]. Patil [7] clearly elucidated this fact where they randomized 120 TBI patients to either 3% HTS, 20% MA, or 10% MA plus 10% glycerol, they found higher trend of ICP control in HTS group but did not show statistical significance in terms of the GCS and neurological outcome.

Given the limitation of observational and retrospective studies, a large sample size multi center randomized controlled trial is essential to move forward in determining which osmotic agent improves mortality or reduces ICU/hospital length of stay. An attempt was made in 2012 to conduct a double blind RCT of HTS vs MA in high ICP, however unfortunately the study was withdrawn in 2014 and no results available from this study [10]. Our study is also limited with small sample size and the fact that it is a retrospective review. Though, our study challenges the literatures favouring HTS in TBI patients. Also, our study indicates MA and HTS are not equiosmolar and have different influence on serum electrolytes and osmolality. Based on that, MA and HTS deliver their effect on ICP through different mechanisms that need further investigations and research.

Conclusion

In conclusion, over the last decade the topic of osmotherapy has gone several controversial discussions and opinions. Although majority of recent published studies favours HTS, our study along with other published literatures challenges this opinion. The topic will keep being controversial and vague with weakly designed studies and small sample sizes. Experts in this field should take ownership and responsibility in leading a large multicenter RCT to compare different osmotherapies and their effect on mortality and neurological outcome.

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