

Clinical outcome of paediatric patients with traumatic brain injury (TBI) receiving 3% hypertonic saline (HTS) in the emergency room of a tertiary care hospital

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Abstract

Objective: To determine the clinical outcome and mean length of hospital stay of paediatric patients with severe blunt traumatic head injury (THI) receiving 3% hypertonic saline (HTS) in the Emergency Department (ED).

Methodology: This case series study was conducted at the Department of Emergency Medicine, Aga Khan University Hospital, Karachi, from 2014 to 2015 via chart review of 105 patients. Detailed history and clinical examination of all paediatric patients aged 2-16 years was recorded which included moderate to severe head injury as classified by the Glasgow Coma Scale (GCS) by the Brain Trauma Foundation. As per routine care after admission of such a patient, for resuscitation 3% HTS was administered. GCS was recorded at 6 hours and at the time of discharge.

Results: Of the 105 patients, 76 (72.4%) were male and 29 (27.6%) were female, and the mean age was 61.6±45.9 months. Traumatic brain injury (TBI) was found moderate in 60 (57.1%) cases and severe in 45 (42.9%) of our patients as per the GCS. Six hours after resuscitation with 3% hypertonic saline, 45 (43%) patients normalised as per GCS, 39 (37%) patients had moderate TBI and 21 (20%) had severe TBI. Forty five patients had a hospital stay of 2-3 days. The GCS improved after resuscitation with 3% hypertonic saline in emergency department, with a mean length of stay of 4.6±3.9 and 12.6±10.7 days in moderate and severe head injury respectively with a P value of <0.001, and was normal in 94 (89.5%) patients at the time of discharge.

Conclusion: Paediatric patients with TBI receiving 3% hypertonic saline results in improved GCS and a decrease in the length of hospital stay.

Keywords: Hypertonic saline, Traumatic Brain Injury, Head Injury, Glasgow Coma Scale, Trauma (JPMA 69: 0000; 2019). doi: 10.5455/JPMA.296439.

Introduction

Trauma is one of the major causes of morbidity and mortality around the world and by the year 2020, it will be considered the third largest cause of the global burden of disease.¹ Despite recent advances in the field of trauma, TBI is still an area of concern for most researchers around the world, as is considered the major cause of morbidity and mortality in most developed and developing countries.² It is the leading cause of death in North America under age of 45 and stresses people financially.³ In most literature, TBI is reported as a 'silent epidemic.' It is under reported in most developing countries and estimated to affect 435,000 children. Around one third of

the deaths occurring between the ages of 1-14 years with an incidence of 679 cases per 100,000 children, projected to become 2700 deaths.^{4,5} In developed countries 200 per 100,000 people admitted in the hospitals annually are at risk of TBI.

TBI affects mostly the younger population as they are more exposed to the external environment, with a major concern of lifelong disability and a high impact on socio-economic and public health. TBI related disability has been reported to be around 5.3 M in the USA with 7.7 M having neurocognitive deficits.⁶ Asian region also has a high incidence of road traffic accidents and self-inflicted injuries, making it one of the top ten causes of mortality.⁷ India shares a significant rate of intracranial injury from road traffic accidents, falls and other injuries. While in Pakistan the incidence is 81 per 100,000 with 15% mortality

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rate.^{8,9} As a developing country, Pakistan has a mere presence of basic health needs, therefore TBI creates a significant burden on the physiological and economical aspects on the individual and the family.¹⁰

In the past few decades there is an ongoing debate on the use of hypertonic saline (HTS) for reducing intracranial pressure (ICP) after TBI. The proposed beneficial effect of the HTS is mostly believed due to its property to reduce the elevated intracranial pressure by creating an osmotic gradient between the intracellular and intravascular space, thus decreasing the intracranial pressure caused by cerebral oedema or the space occupying haematoma. Therefore HTS has shown beneficial results however the data is still lacking.

The use of HTS in lowering intracranial pressure was first done in 1919, and the effects were further investigated in animal testing showing similar results. The mechanism postulated to favour this is the creation of osmotic gradient that has been central in the aforementioned effect. The increased osmotic gradient that is created with the use of 3% hypertonic saline, causes the water to diffuse out passively across the blood brain barrier through the intravascular space and reducing it which results in the decrease of intravascular volume and eventually improving the cerebral blood flow.¹¹

While HTS proved to play a definitive role in the reduction of the ICP, Wakai et al further found hypertonic saline to be more effective in reducing the intracranial pressure as compared to mannitol.¹² However reliable data is still missing on the use of HTS, its association with the length of hospital stay and Glasgow coma scale (GCS). Recently 3% HTS has gained appreciation in the paediatric population, however no such study has been conducted in Pakistan on the use of 3% hypertonic saline in paediatric patients with traumatic brain injury. Hence our aim is to investigate clinical/GCS improvement in paediatric patients along with the mean length of hospital stay (LOS) who presented with moderate and severe traumatic head injury and were resuscitated with 3% HTS in the ED.

Methods

This case series has been conducted from 2014 to 2015 in the Emergency Department of Aga Khan University Hospital, a tertiary care level 1 trauma centre, after the approval from institutional review board. It was retrospective cross sectional study chart review, with non-probability convenient sampling. The sample size was

calculated from the study published in Anesthesia & Analgesia in 2006.¹³ In patients who used HTS, the mean length of stay was 8 days with standard deviation of 2.8, with confidence level of $(1-\alpha = 95\%)$, standard deviation ($\sigma = 2.8$) and margin of error ($d=0.5$) the calculated sample size of the study was 89. If we add 15% as non-response rate, the sample size of our study would be 102 ± 3 (105).

We included paediatric patients with blunt TBI of either gender between 1 to 16 years of age. Patients with moderate to severe traumatic brain injury diagnosed as per the operational definition were included in this study. All those patients were excluded from the study who had any pre-existing congenital or acquired central nervous system pathology, had polytrauma, more than 12 hours of TBI, patients who received any form of intravenous fluids like mannitol or dextrose from other hospitals, the ones who left against medical advice (LAMA), those who needed any neurosurgical intervention, and those who developed nosocomial infections (pneumonia, urinary tract infections and wound infections).

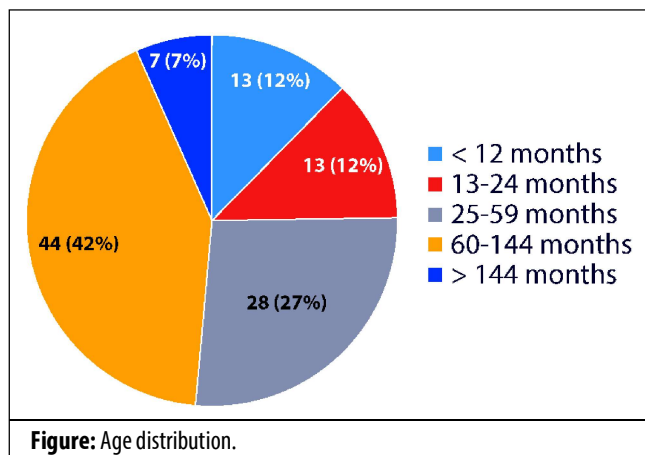
All patients enrolled were managed as per the hospital standards and policy and were observed and categorised with moderate and/or severe brain trauma on the basis of the GCS as per the Brain Trauma Foundation. Demographic variables were determined and 3% hypertonic saline was started as routine care. Six hours after resuscitation, GCS was conducted and recorded again on the questionnaire. The patients who were admitted in the hospital were followed up and the Glasgow Coma Scale was also recorded on the day of discharge.

Data was entered and analysed by using SPSS statistical package version 20. Mean and standard deviation were calculated for age groups, length of hospital stay and Glasgow Coma Scale (GCS) score. Frequency and percentages were calculated for age groups and gender. Stratification with respect to age, gender and GCS score was undertaken. Post stratification t-test was applied and p -value $< \text{or} = 0.05$ was taken as significant.

Results

Total of 105 patients were enrolled of which 76 (72%) males and 29 (28%) were female.

Mean age of the patients was 61.6 ± 45.9 months. Majority of patients were of 60-144 months while the least number of patients were above the age 144 months as shown in detail in Figure .

**Table-1:** GCS score at Triage, 6 hour after HTS and on Discharge.

GCS Score	Triage GCS	GCS after 6 hours of observation post HTS	n (%)
Severe (GCS <8)	45 (42%)	21 (20%) 12.6±10.7	8(7.5)
Moderate (GCS 9-12)	60 (57%)	39 (37%) 4.6±3.9	3(3)
Mild (GCS >12)	0	45 (43%) 2.6±1.9	94(89.5)
Total	105	105	105

Table-2: GCS score at 6 hours and Length of Hospital Stay.

GCS score at 6 hours	LOS at Hospital		p-value
	Mean ± SD	n=105	
Severe (GCS <8)	12.6±10.7	21	<0.001*
Moderate (GCS 9-12)	4.6±3.9	39	
Mild (GCS >12)	2.6±1.9	45	

Table-3: Age group and Length of Hospital Stay.

Age group	LOS at Hospital		p-value
	Mean ± SD	n=105	
< 12 months	4.3 ± 3.3	13	<0.842*
12-24 months	6.9 ± 7.9	13	
25-59 months	5.0 ± 7.3	28	
60-144 months	5.3 ± 6.6	44	
> 144 months	6.4 ± 6.2	7	

After HTS administration, GCS improved in all groups of patients with mild, moderate and severe TBI. In triage there was a reduction of 24 (22%) patients with severe TBI and after 6 hours of HTS administration, which further decreased to 8 (7.5%) patients. While 60 (57%) patients presented with moderate TBI, at the time of discharge only 3 (3%) had moderate TBI. After resuscitation with HTS, 94 (89.5%) patients were discharged with only mild TBI as described in Table 1.

Assessing the ED LOS, we found that 20 (30%) of the

patients with TBI had to stay longer than 6 hours, followed by 24 (36%) who were either discharged or transferred within 2-3 hours from ED. Only 5 (7.6%) had an ED stay of less than 1 hour.

As shown in Table 2, comparing the GCS Score at 6 hours with hospital LOS, patient with severe TBI resuscitated with 3% HTS had a mean hospital LOS of 12.6±10.7; for those with moderate TBI, mean hospital LOS was 4.6±3.9 and these with mild TBI, mean hospital LOS of 2.6±1.9 with p value of <0.001.

Table-3 compares the age groups with hospital LOS showing that 44 patients were of age group between 60-144 months with a mean and standard deviation of 5.3±6.6, followed by 28 patients of the age group 25-59 months, with a mean and standard deviation of 5.0±7.3. The smallest number of patients was 7 of the age group >144 months, with a mean and standard deviation of 6.4 ± 6.2. The p-value calculated through ANOVA was 0.842.

When comparing the gender of patients with hospital LOS using the t-test, we found 76 (72%) males with a mean and standard deviation of 5.3±6.0, followed by 29 (28%) females with a mean and standard deviation of 5.6±7.9 with a p-value of 0.830.

Discussion

In every part of the world paediatric head injury is an area of concern as it creates a critical economic burden on the family when they are faced with such an episode.¹⁴ The mechanisms of head injury are diverse and resuscitation strategies are an area of interest that are still under investigation in the developed world.¹⁴ Timely resuscitation with appropriate fluids can have significant impact on improved outcomes and the LOS.¹¹ This study is based on the use of HTS in paediatric patients with TBI and our results showed an improvement in the Glasgow coma score after 3% hypertonic saline was administered on them. Our results were very similar to studies published previously on the subject.¹⁵ Improvement of the GCS could be due to the decrease in intracranial pressure and the findings are consistent with the study by Peterson et al, that early use of HTS significantly lowers the intracranial pressure in paediatric patients with traumatic brain injury.¹⁶

One of major indications for the use of HTS as reported in literature is the head injury with raised intracranial pressure. We enrolled paediatric patients with moderate to severe head injury. These patients showed an

improvement in the GCS indicated as reduction in the score when repeated after 6 hours after resuscitation with 3% HTS. These results are very similar to recent reports that revealed an improvement after the use of the HTS.¹⁷

Majority of the patients were males, which are very similar to findings in previous studies that may be because of male children being more exposed to the outdoor environment and more prone to getting injured.¹⁸ The majority of the patients in our study were of the age 60-144 months which also explains our reasons that this is the age when a child starts walking and becomes prone to risk taking behaviours. There is a wide variation of age in our study but mostly the age corresponds to the walking stage of children.

Several studies have enumerated the beneficial effects of the hypertonic saline treatment for elevated intracranial pressure.^(5,9) We also expect similar beneficial effects of HTS on the intracranial pressure in our patients as we see improvements in the Glasgow Coma Score (GCS) 6 hours after resuscitation. Although in few patients GCS remained the same, but majority of the patients in our study benefitted from the resuscitation with the HTS. Most patients who showed an improved GCS were in minor (mild) TBI range. The findings were again very similar to the studies that have shown an unusually high survival rate of 94% for patients who were given hypertonic saline.¹⁹ Only 7% of the patients with severe TBI were discharged because of their vegetative state which developed with static or worsening GCS.²⁰

In 33% of our TBI patient population, the duration of ED stay was between 2-3 hours after there was a decrease in the intracranial pressure that HTS exerted in our patients, as demonstrated by the improvement in the GCS.

Though central venous line is a better option for HTS infusion, especially for larger amount or with higher concentration, however we use 3% HTS, and more importantly during the course of acute management. Achieving central line is time consuming and may not be available or managed during transport, hence it may delay the implementation of a potentially beneficial treatment. Although literature does not favour the use of HTS via a peripheral catheter because of the extravasation risk and subsequent local tissue damage,²¹ however we used large peripheral route for the administration of the HTS and we did not document any extravasations at an infusion site. Our study demonstrates the administration of HTS safer

through the peripheral route that is in accordance with studies published previously.^{20,21} We still recommend central line administration as the preferred route of delivery, if available for the 3% hypertonic saline as continuous infusion.

While observing the hospital LOS in our patients, a significant number of the patients with GCS between 9-12, had a mean LOS of 4 days, which is very short compared to the studies published in the past. The reason for this could be due to shifting patients efficiently and prompt allotment of the beds which have a pivotal role in the ED. Also we believe that the moderate brain injury patients have short LOS, but severe and mild head injury patients have a quite similar length of hospital stay as well, as shown in the studies. We also believe that the reason for such short stays may be due to minimal complications such as renal failure, pneumonia etc. that we did not observe in our setting. The studies reported in the past did not present these complications and are considered as harbinger for the prolonged length of hospital stay.^{9,14,15,22}

We did not find any adverse effects that could be linked to the administration of 3% HTS, which has only shown improved outcomes in all categories of TBI patients when assessed in with GCS during discharge. GCS after 6 hours of resuscitation with the HTS has shown beneficial effects.

The literature does not prove any optimal concentrations that are necessary for reducing the ICP pressure, and all concentrations have an equal effect on reducing ICP.²⁰ The end point of resuscitation is the serum sodium concentration.²⁰ The serum sodium concentration is done prior to the start of HTS and repeated after every 2 hours till level of 150meq/L is achieved.²⁰

On the contrary, a large scale study by Cooper et al negates any beneficial effects of hypertonic saline in blunt head trauma, making it unclear, whether to use it in the initial resuscitation phase of TBI.²³ Review by Mortazavi et al also reported no clear benefit from hypertonic saline, compared to mannitol in regard to neurological outcome, even though there was a small positive trend for the hypertonic saline.²⁴ However reducing the cerebral oedema and the intracranial pressure are the major concerns of an emergency physician that have favourable outcome on to the functionality of patients with TBI.^{23,24}

Hypertonic saline also improves the mean arterial pressure, resulting in an increase in the circulating blood volume

without the delayed hypotensive effect that is observed with mannitol use.²¹

There are no appropriate guidelines for the use of hypertonic saline and most physicians and specialties are administering it as per the literature.¹⁹⁻²¹ This study opens the debate for the use of hypertonic saline as per guidelines that are yet to be developed that will include the appropriate dosage and timing of its administration which are of critical importance. Also, there is a need to compare the efficacy of different concentrations of hypertonic saline to the concentration used in our hospital. The use of 3% HTS in patients with traumatic brain injury deserves more attention and those studies that are well designed and have a good sample size.

Our findings have demonstrated that most of the paediatric patients who presented with severe or moderate head injury had improved at the time of discharge and had a reduced length of stay in ED. Those paediatric patients whose GCS did not improve, could be due to delay at presentation at the hospital.

Conclusion

We concluded that resuscitation of patients after administering 3% hypertonic saline has good results in improving the Glasgow coma scale and decreasing the length of stay at the hospital. As our study was a case series there is a further need of a controlled trial to clarify the effects of resuscitation by hypertonic saline on patient outcome.

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References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; 367: 1747-57.
2. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008; 7: 728-41.
3. Eric W, Abigail C, Mark K, Laurel O, Pak Shan L. Complement inhibition mitigates secondary effects of traumatic brain injury (TBI). *Critical Care Medicine*. 2018;46(1):401.
4. Philip S, Udomphorn Y, Kirkham FJ, Vavilala MS. Cerebrovascular pathophysiology in pediatric traumatic brain injury. *J Trauma* 2009; 67: S128-34.
5. Walker PA, Harting MT, Baumgartner JE, Fletcher S, Strobel N, Cox CS Jr. Modern approaches to pediatric brain injury therapy. *J Trauma* 2009; 67: S120-7.
6. Statistics NCFH. Advance Report of Final Mortality Statistics 1985. Washington DC: US Government Printing Office: 1987.
7. Raja IA, Vohra AH, Ahmed M. Neurotrauma in Pakistan. *World J Surg* 2001; 25: 1230-7.
8. Teasdale G, Jennett B. Assessment of coma and impaired consciousness, A practical scale. *Lancet* 1974; 2: 81-4.
9. Ghani E, Nadeem M, Bano A, Irshad S, Zaidi GI, Khaleeq-uz-Zaman. Road traffic accidents as a major contributor to neurosurgical mortality in adults. *J Coll Physicians Surg Pak* 2003; 13: 143-5.
10. Abughazaleh RD, Jancik JT, Paredes-Andrade E, Solid CA, Rockswold GL. Safety of intravenous hypertonic saline administration in severe traumatic brain injury. *Ann Pharmacother* 2012; 46: 1441-2.
11. Gerberding JL, Binder S. Steps to prevent a serious public health problem. Centers for Disease Control and Prevention; 2003.
12. Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev* 2013; 8: CD001049.
13. White H, Cook D, Venkatesh B. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. *Anesth Analg* 2006; 102: 1836-46.
14. Fuhrman BP, Zimmerman JJ. Pediatric Critical Care: Expert Consult Premium. Elsevier Health Sciences; 2011.
15. Adelson PD, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, et al. American Association for Surgery of Trauma; Child Neurology Society; International Society for Pediatric Neurosurgery; International Trauma Anesthesia and Critical Care Society; Society of Critical Care Medicine; World Federation of Pediatric Intensive and Critical Care Societies. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents Chapter 15. Surgical treatment of pediatric intracranial hypertension. *Pediatr Crit Care Med* 2003; 4(3 Suppl): S56-9.
16. Langlois JA, Rutland-Brown W, Thomas KE. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2006.
17. Qureshi AI, Suarez JL. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Crit Care Med* 2000; 28: 3301-13.
18. Kamel H, Navi BB, Nakagawa K, Hemphill JC 3rd, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. *Crit Care Med* 2011; 39: 554-9.
19. Harmon KG, Drezner JA, Gammons M, Guskiewicz KM, Halstead M, Herring SA, et al. American Medical Society for Sports Medicine position statement: concussion in sport. *Br J Sports Med* 2013; 47: 15-26.
20. Chu Z, Wilde EA, Hunter JV, McCauley SR, Bigler ED, Troyanskaya M, et al. Voxel-based analysis of diffusion tensor imaging in mild traumatic brain injury in adolescents. *AJNR Am J Neuroradiol* 2010; 31: 340-6.
21. Vavilala MS, Lee LA, Boddu K, Visco E, Newell DW, Zimmerman JJ, et al. Cerebral autoregulation in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2004; 5: 257-63.
22. Dubick MA, Shek P, Wade CE. ROC trials update on prehospital hypertonic saline resuscitation in the aftermath of the US-Canadian trials. *Clinics (Sao Paulo)*. 2013; 68: 883-6.
23. Cooper DJ, Myles PS, McDermott FT, Murray LJ, Laidlaw J, Cooper G, et al; HTS Study Investigators. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. *JAMA* 2004; 291: 1350-7.
24. Mortazavi MM, Romeo AK, Deep A, Griessenauer CJ, Shoja MM, Tubbs RS, et al. Hypertonic saline for treating raised intracranial pressure: literature review with meta-analysis. *J Neurosurg* 2012; 116: 210-21.