Comparison between Hypertonic Saline and Isotonic Saline in Resuscitating Hypotensive Patients with Severe Traumatic Brain Injury; a Prospective Randomized Study

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Abstract: Introduction: The use of hypertonic saline in resuscitation of patients with traumatic brain injury (TBI) has been studied several times in the literatures. According to the knowledge of the authors, it was not compared to normal saline in resuscitation of such patient group in a head to head study. Hypothesis: To evaluate the efficacy of the use of a bolus 3% HTS against isotonic crystalloids in the resuscitation of hypotension associated with severe TBI. As regards early hemodynamic parameters, survival and neurological =outcome after 3 months. Methods: 40 patients presented with hypotension (systolic blood pressure <100 mmHg) and severe TBI (GCS <9) were randomly classified into; GroupI: received 250 mL of 3% HTS as the primary resuscitation solution, GroupII (Control group): received 250 mL of normal saline, Then fluid resuscitation was continued as the condition of each patient dictates. Results: HTS group had statistically significant higher blood pressure (after one hour of resuscitation; p value = 0.003) than the control group though they received less amount of fluids (p value=0.0001). Regarding Glasgow outcome scale (GOS) at 3 months, there was a trend towards better outcome in the HTS group but that was not statistically significant. In the HTS group, the patients who survived were more, less patients with persistent vegetative state and more patients with good recovery or moderate disability than the control group. The mean of the GOS was higher in the HTS group but again with no statistically significant difference. In a subgroup analysis, HTS did not have any statistically significant difference on survival between the groups regarding the time interval between trauma and admission. Moreover, the use of HTS did not show statistically significant difference in the survival of patients having isolated head injury than those with associated injuries. Most importantly, there was no added beneficial effect on different degrees of severity of head trauma classified according to either GCS at admission or Marshall's classification of CT brain findings. Conclusions: HTS is effective in elevation of blood pressure in severe TBI patients while less fluid is required. Although not statistically significant, there was a trend towards improved outcome in severe TBI patients who received HTS.

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1. Introduction:

Head trauma is injury to the scalp, skull or brain. This can range from a minor bump to the skull to a devastating brain injury. Head injury, which encounters the basis of some of the most frequent and serious neurogenic disorders, poses many problems to the practicing physician. Severe traumatic head injury (defined as the Glasgow Coma Scale of 3 to 8 and inability to follow commands) is the leading cause of morbidity and mortality in the age group between 10 and 45 years. (1-2)

There are two types of head injuries. Primary head injury that occurs at the time of the impact may involve neural or vascular elements of the brain. On the other hand, secondary brain injury (hours or days from the traumatic incident) is a major determinant of the patient's ultimate neurologic outcome. Goal of emergency and critical care management of patients with severe traumatic brain injury is to enhance cerebral perfusion as well as to avoid therapy that may cause cerebral ischemia, thus avoiding secondary brain injury. Most common preventable causes of cerebral ischemia are hypotension, hypoxia and intracranial hypertension. (3)

Severe traumatic brain injury is usually a part of multiple traumas, in which hypotension (most commonly due to hypovolemia) is usually encountered. Rapid fluid resuscitation and restoration of the normal blood pressure is of crucial importance because hypotension has been associated with doubling of the mortality rate in severe traumatic brain injury. (3)

Crystalloids have been conventionally used in fluid resuscitation. These isotonic fluids diffuse freely from the intra vascular compartment to the interstitial compartment, and to some extent, to the

intracellular compartment causing tissue edema and impaired oxygen perfusion. Moreover, large quantities must be infused to adequately restore plasma volume. (4)

Hypertonic saline is any sodium chloride solution more concentrated than normal saline. Solutions of 3.0% to 7.5% are used. Hypertonic saline has received attention as a resuscitative fluid since the 1970s. (5-7) Its value in the resuscitation of burn victims is well documented. (8-9) It has been suggested that its use in brain edema and intracranial hypertension is comparable to Mannitol solution. (10) It also has some immunomodulating effects that may be helpful in the post resuscitative phase. (1) Research suggests that these fluids decrease the activation of neutrophils, (11) so they may offer an advantage in preventing multiple organ dysfunction syndrome. (12)

High concentrations of sodium chloride in the vascular system favor the flux of water from the interstitial space and from the cells to augment the blood volume. This results in a rapid restoration of intravascular volume. Once fluid is drawn into the vascular space, the sodium chloride is diluted, so it then equilibrates across the fluid spaces of the body. As this happens, the effect of the hypertonic saline is gradually lost. This occurs over a longer period of time than for standard crystalloid solutions, but it eventually occurs. Infusions of small amounts of these solutions lead to hemodynamic responses equivalent to much larger volumes of crystalloid solutions. This is advantageous due to the rapidity of the response. Although some rapid and transient hypernatremia seems to be tolerated, caution in administration and careful monitoring of sodium levels are important in the safe use of these solutions. (13-15)

Hypothesis:

The aim of this work is to compare the use of hypertonic saline to normal saline in the early resuscitation of hypotension in severe traumatic brain injury patients, as regards neurological outcome and survival.

2. Patients and Methods:

Patients

This study was carried out on 40 patients with severe traumatic brain injury and hypotension on admission to Alexandria Main University Hospital. The *inclusion criteria* included: Age group 15 -50 years or body weight >50 kg, history of blunt trauma to the head, systolic blood pressure <100 mmHg and a GCS < 9. The *exclusion criteria* included: Patients with previous history of any medical illnesses e.g.; hypertension, diabetes mellitus, cardiac, renal or hepatic disease, history of neurological diseases or spinal cord injuries, known or suspected pregnancy, administration of >2 L of crystalloids, any colloids or blood products before admission, severe hypothermia (Temperature<28^{o}C), drowning or asphyxia, burns of total body surface area (TBSA)> 20%, isolated penetrating injury to the head and time of the onset of trauma to study intervention >4 hours.

METHODS:

The study is a prospective randomized double-blinded controlled pilot study. The study was conducted on forty patients admitted to the Alexandria Main University Hospital after approval of the ethical committee of the Faculty of Medicine, University of Alexandria. An informed consent was signed by a relative of patients participated in the study. All the patients were managed according to the following lines: *History included:* Biosocial data (name, age sex, occupation …etc.), medical illnesses e.g. Hypertension, Diabetes mellitus, cardiac, renal or hepatic troubles, type, mechanism and time of the injury and interval of time between the onset of the trauma and the start of the management. *Clinical assessment:* Full physical examination included Vital signs (blood pressure, pulse, temperature and respiratory rate), admission Glasgow Coma Scale (GCS), and type of the injury (closed or penetrating) and assessment of associated injuries if present. *Radiological and Laboratory assessment:* Computed Tomography on the brain. Findings were classified according to Marshall classification(16) of CT brain in head injury (table 2), routine investigations e.g. random blood sugar (RBS), complete blood count (CBC), blood urea nitrogen (BUN) and serum creatinine (S Cr), arterial blood gases (ABG), serum electrolytes (Na and K). *Management:* Patient were managed according to their conditions: A. Primary management: Airway support, maintaining Oxygenation and Ventilation. B. *Circulatory support*: Patients were randomized into two groups of 20 patients each. The first group received 250 ml of 3% hypertonic saline (HTS) and the second control group received 250 ml normal saline (NS). After that, volume resuscitation was continued as required guided by blood pressure measurement. Double blinded randomization was ascertained. Forty bottles (20 bottles of 3% saline and 20 of normal saline) each of 250 ml were prepared. The labels of these were removed from the bottles and placed in sealed envelopes. Each envelope was assigned to a serial number referring to a correspondent patient. Accordingly, the treating physician did not know in advance the type of solution given for each patient. *C. Definitive management:* Either operative (according to the condition) or medical (e.g.

measures for brain edema and intra cranial hypertension) was accomplished as the condition of the patient dictates. *D. Follow up and Outcome:* Comparison between both groups as regards duration of use of vaso-active drugs if any, duration of intubation, duration of mechanical ventilation (17), duration of hospital stay, Glasgow outcome scale(18) and survival. *D. Statistic analysis:* Collected data and statistical analysis was done using SPSS-14 (Statistical package for Social Sciences version 14).

3. Results:

Baseline characteristics are illustrated in table (1). It shows homogeneity of both groups without a significant difference between both groups regarding all variables on admission.

Table (1): Baseline characteristics of the two study groups.

	HTS Group (I) N=20	Control group (II) N=20	Significance (p value)
Age mean ±SD (Years)	28.60 ±9.040	28.80 ±13.18	0.956
Sex Males no. (%) Females no. (%)	14(70.0%) 6 (30.0%)	18(90.0%) 2(10.0%)	0.114
Mechanism of trauma no (%)			
Road traffic accidents (RTA)	15 (75.0%)	15 (75.0%)	
Falling from a height (FFH)	2 (10.0%)	4 (20.0%)	0.435
Blunt trauma	3 (15.0%)	1 (5.0%)	
Time interval between trauma and admission (minutes) (mean±SD)	34.75 ±22.564	51.25 ±53.702	0.213
Blood Pressure on admission (mmHg)			
Systolic BP (mean ±SD)	81.05 ±11.002	80.56 ±11.618	0.894
Diastolic BP (mean ±SD)	51.58 ±13.850	52.22 ±10.603	0.875
Mean BP (mean ±SD)	61.40 ±11.932	61.67 ±10.556	0.944
Glasgow Coma Score			
Total (mean ±SD)	5.15 ±1.531	5.60 ±1.667	0.380
Motor (mean ±SD)	2.95 ±1.276	3.35 ±1.599	0.387
Heart Rate (mean ±SD)	114.35 ±26.158	109.50 ±21.758	0.528
Respiratory Rate (mean ±SD)	18.10 ±5.360	17.95 ±4.310	0.923
Temperature (mean ±SD)	36.475±.6172	36.300 ±.6366	0.383
Associated injuries no (%)			
Chest	4 20.0%	6 30.0%	0.465
Abdomen	4 20.0%	8 40.0%	0.168
Pelvis	4 20.0%	1 5.0%	0.151
Upper limbs	1 5.0%	5 25.0%	0.077
Lower limbs	4 20.0%	4 20.0%	1.000
Laboratory Investigations: Arterial Blood Gases (Mean±SD) pH	7.322 ±.1039	7.313 ±.1323	0.812
PaO_2 (mmHg)	99.68 ±60.853	69.40 ±16.119	0.038
$PaCO_2$ (mmHg)	29.30 ±10.770	29.35 ±9.331	0.988
HCO_3 (mmHg)	17.05 ±3.686	17.61 ±4.751	0.682
SaO_2 (%)	93.30 ±4.635	92.25 ±3.754	0.436
Hemoglobin g/dL (mean ±SD)	9.02 ±2.221	12.36 ±14.983	0.343
White blood Count ($x10^3$/dL) (mean ±SD)	15.925 ±5.035	15.930 ±5.9793	0.998
Sodium (mean ±SD) mg/dL	141.10 ±3.582	140.30 ±3.785	0.497
Potassium (mean ±SD) mg/dL	4.020 ±.4708	3.900 ±.4690	0.424
Random Blood glucose level (mean ±SD) mg/dL	176.15 ±35.74	191.6 ±25.05	0.109

CT brain Findings:

CT brain findings (classified according to Marshall's classification) were compared between the two groups (after resuscitation and surgical intervention if any) and presented in table 2. In general, there was no statistically significant difference in CT brain findings in the two groups (p value 0.505). The most common CT finding among the two groups was diffuse injury II (13 patients, 6 in group I and 7 in group II). Diffuse injury III and IV each was presented by 7 patients. The rate of operations for a mass lesion was slightly commoner in the HTS group (4 patients) than the control group (only 2 patients) and the number of patients with non evacuated mass lesion was evenly distributed (3 patients each).

Table 2: CT brain findings in the study groups according to Marshall's classification.

CT brain (Marshall's classification)	HTS Group N=20	Control group N=20	Significance (p value)
Diffuse injury I	0 0%	1 5.0%	0.505
Diffuse injury II	6 30.0%	7 35.0%	
Diffuse injury III (swelling)	5 25.0%	2 10.0%	
Diffuse injury IV (shift)	2 10.0%	5 25.0%	
Evacuated mass lesion	4 20.0%	2 10.0%	
Non evacuated mass lesion	3 15.0%	3 15.0%	

HTS= Hypertonic saline

Follow up and outcome (table 3)

There has been a highly significant difference (p value 0.0001) between the two groups regarding the Total Fluids used in the resuscitation of hypotension (at one hour) in the two groups. The mean of the fluids taken in group I was 1225 ±72.9. This was much less than the fluids used in the control group with a mean ±SD = 2087.5 ±481.7.

Most importantly, Blood Pressure (systolic, diastolic and mean arterial blood pressure) measurement after one hour of resuscitation had increased in both groups. However, blood pressure measurements were significantly higher in the group of patients that received HTS as the initial resuscitation solution, the mean of the three parameters (systolic, mean and diastolic) calculated 111.25, 74.25 and 86.4 respectively while in group II the mean was calculated 98.42, 62.37 and 72.8 respectively. The p values calculated were (0.008, 0.003 and 0.003) respectively.

On the other hand, Serum Na measured after one hour was significantly higher in the HTS group compared to the control group (p value 0.0001). In the group of patients that received 3% hypertonic saline, the mean was 146.35 mg/dL (was 141.1 mg/dL at admission) while the mean in the control group was 141.84 mg/dL (was 140.3 mg/dL at admission). However, it did not exceed the normal range (135 to 150 mg/dL).

Regarding survival of the patients in both groups for the first 24 hours, only 3 patients in each group could not survive the 1st 24 hrs.

The durations of intubation, mechanical ventilation, use of vasoactive drugs and hospital stay were compared in the two groups. Although they were more in the control group, this was not statistically significant. Though not statistically significant (p value = 0.19), patients who survived (assessed at 3 months) were higher in the group of patients who received HTS (11 out of 20) than in the control group (8 out of 20).

The GOS assessed at 3 months was compared between the two groups; the mean was higher in group I (2.5) than the control group II (1.8). However, this was statistically insignificant (p=0.121). The five components of GOS (Death, Vegetative state, Severe disability, Moderate disability and Good recovery) were compared between the two groups and the number of the non survivors was higher in the control group I (12 vs. 9) as well as the number of persistent vegetative state (3 vs. 1). Furthermore, those who had good recovery and moderate disability were higher in the HTS group (both 3 vs. 1). However, all these results were statistically insignificant.

Table 3: Follow up and outcome

	HTS group N=20	Control group N=20	Significance (p value)
Total fluids at 1 hr. (mean ± SD)	1225.0±572.9	2087.5±481.7	0.0001*
Blood Pressure (BP) after 1 hour			
Systolic BP mmHg (mean± SD)	111.25 ±10.745	98.42 ±17.083	0.008
Diastolic BP mmHg (mean± SD)	74.25 ±8.156	62.37 ±14.754	0.003
Mean BP mmHg (mean± SD)	86.4±8.2	72.8±15.9	0.002*
Sodium after 1 hour (mean ±SD) mEq/L	146.35 ±2.390	141.84 ±3.253	0.0001*
First 24 hours survival (patients no. and %)	17(85%)	17(85%)	0.99
Intubation duration (days) mean ±SD (including Tracheostomy days)	24.05 ±31.842	27.30 ±34.556	0.759
Mechanical ventilation duration (days) mean ±SD	3.4 ±2.761	5.25 ±3.354	0.07
Vasoactive drugs (days used) mean ±SD	0.70 ±0.923	1.10 ±1.373	0.286
Hospital stay (days) mean ±SD	28.63 ±32.803	31.05 ±35.214	0.826
Patients survived (no.)	11 (55%)	8 (40%)	0.19
GOS mean ± SD	2.5 ±1.57	1.8 ±1.1	0.121

GOS= Glasgow Outcome Scale

Subgroups analysis (table 4)

Patients were divided into different subgroups according to biosocial data, clinical findings and investigations to compare outcome between the two groups and to test if the use of HTS as the initial resuscitation solution in hypotensive patients with severe traumatic brain injury could benefit any of these subgroups.

Patients were classified into different age groups (15 to 30 years, 30 to 40 years and 40 to 50 years). There was no statistically significant difference regarding survival in different age groups. The worst outcome was among the older age group where 6 out 7 patients (in both groups) did not survive. A relatively better outcome was observed among the younger age group where eight out of 11could survive in the HTS group versus seven out of 12 in the control group. All the three patients in the control that were between 30 and 40 years old could not survive while three out of seven patients survived in the HTS group in the corresponding age group.

Regarding the sex, there was no significant effect by the use of HTS as regards survival at 3 months in the different genders. However, HTS had a relatively better effect on males as 10 survived out of 18 male patients while 5 only out of 14 male patients could survive in the control group (p=0.62). On the other hand, 50% of females survived in both groups.

The interval of time between trauma and admission did not have impact on survival in both groups. However a relatively insignificant better outcome was obtained by the use of HTS in the longer time interval where three among five patients survived while all the five patients who arrived late in the control group did not survive (p=0.46).

The mechanism of trauma did not have effect on survivors in both groups. Moreover, the use of HTS did not have effect on survival of patients having associated injuries other than head injury (p=.11).

GCS was categorized into 3 groups milder (7 or 8), moderate (5 or 6) and more severe (3 or 4). HTS couldn't prove any benefit of use in the three categories. However, the p value (0.088) is approaching significance in those who had better score with GCS assessed at admission either 7 or 8 indicating that HTS could have a fairly better outcome on the patients that had higher GCS (7 or 8) on admission. Similarly, all patients with worse GCS (3 or 4) that didn't receive HTS died, While two out of eight patients survived among those who received HTS (p value 0.09).

CT brain findings (according to Marshall's classification; (Table 5) were compared against outcome in the two groups and there was no statistically significant difference in any of the 6 categories indicating that HTS had no added benefit on different degrees of intracranial pathology in the present study.

Similar outcome was noticed in different categories of CT brain findings in the two groups. All the patients that had diffuse injury IV (5 in the control group and 2 in the HTS group) or non evacuated mass lesion (3 in both groups) could not survive. All the patients that had undergone surgical evacuation for a mass lesion had survived.

Table 4: Subgroups analysis

	HTS Group N=20		Control Group N=20		p
	Non survivors N=9	Survivors N=11	Non survivors N=12	Survivors N=8	
Age (Years) n (%) 15-30 years	3 (33.3%)	8 (72.7%)	5 (41.7%)	7 (87.5%)	0.16
30-40 years	4 (44.4%)	3 (27.3%)	3 (25.0%)	0 (0.0%)	0.12
40-50 years	2 (22.2%)	0 (0.0%)	4 (33.3%)	1 (12.5%)	0.42
Sex n (%) Males	8 (88.9%)	10 (90.9%)	9 (75.0%)	5 (62.5%)	0.62
Females	1 (11.1%)	1 (9.1%)	3 (25.0%)	3 (37.5%)	0.11
Time interval between trauma and admission: < 30 min.	3 (33.3%)	6 (54.5%)	2 (16.7%)	4 (50.0%)	0.42
30 - 60 min.	4 (44.4%)	2 (18.2%)	5 (41.7%)	4 (50.0%)	0.39
> 60 min.	2 (22.2%)	3 (27.3%)	5 (41.7%)	0 (0.0%)	0.46
Mechanism of trauma Road Traffic Accident no. (%)	6 (66.7%)	9 (81.8%)	8 (66.7%)	7 (87.5%)	0.68
Fall From a Height no. (%)	2 (22.2%)	0 (0.0%)	3 (25.0%)	1 (12.5%)	0.22
Blunt trauma no. (%)	1 (11.1%)	2 (18.2%)	1 (8.3%)	0 (0.0%	0.82
Associated injuries no.	9	4	7	3	0.42
Chest no. (%)	2 (22.2%)	2 (18.2%)	4 (33.3%)	2 (25.0%)	0.36
Abdomen no. (%)	3 (33.3%)	1 (9.1%)	6 (50.0%)	2 (25.0%)	0.25
Pelvis no. (%)	4 (44.4%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0.041*
Upper Limbs no. (%)	0 (0.0%)	1 (9.1%)	2 (16.7%)	3 (37.5%)	0.21
Lower Limbs no. (%)	3 (33.3%)	1 (9.1%)	2 (16.7%)	2 (25.0%)	0.13

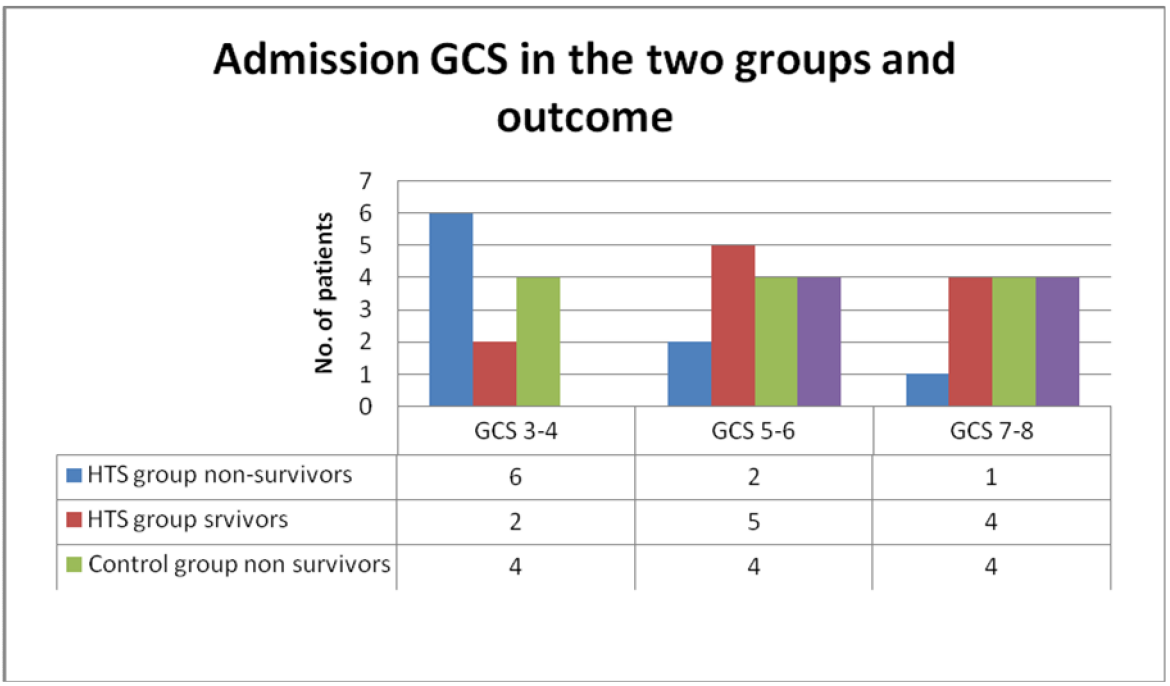

Figure 1: Admission GCS grouped into milder (GCS 7, 8), moderate (GCS 5, 6) and more severe (GCS 3, 4) and compared to outcome in the HTS and the control groups.

Table 5: CT brain Marshall's score versus outcome in each group

CT brain		HTS group		Control group		p value
		Died	Survived	Died	Survived	
1 Diffuse Injury I	No.	0	0	0	1	-
	%	0.0	0.0	.0%	12.5%	
2 Diffuse Injury II	No.	1	5	2	5	0.61
	%	11.1%	45.5%	16.7%	62.5%	
3 Diffuse Injury III	No.	3	2	2	0	0.11
	%	33.3%	18.2%	16.7%	.0%	
4 Diffuse Injury IV	No.	2	0	5	0	0.09
	%	22.2%	.0%	41.7%	.0%	
5 Evacuated Mass Lesion	No.	0	4	0	2	0.19
	%	.0%	36.4%	.0%	25.0%	
6 Non evacuated mass lesion	No.	3	0	3	0	0.99
	%	33.3%	.0%	25.0%	.0%	
Total	No.	9	11	12	8	0.13
	%	100.0%	100.0%	100.0%	100.0%	

4. Discussion:

HTS has been suggested for use in severe TBI since 1919. (19) However, few patients have been studied using a prospective, randomized, control study design. Complicating the interpretation of these findings is a variation in protocols regarding HTS concentration and administration when used in patients who have experienced TBI. In the present study, the baseline characteristics of the two groups were similar without a significant difference between both groups. In the present study, the patients who received HTS had significantly higher blood pressure (after one hour of resuscitation) than the control group although they received much less amount of fluids during the same period. The serum Na assessed after resuscitation was significantly higher but it did not exceed the normal range. First 24 hours survival was identical (85%) between the two groups. Although not statistically significant, the number of patients who survived (after 3 months) was higher as well as the number of persistent vegetative state was less. Furthermore, those who had good recovery and moderate disability were higher in the HTS group. However, the mean of the GOS (assessed at 3 months) was compared between the two groups and there was no statistically significant difference.

In a subgroup analysis, patients were divided into different subgroups according to biosocial data, clinical findings and investigations to compare outcome between the two groups in order to test if the use of HTS as the initial resuscitation solution in hypotensive patients with severe traumatic brain injury could affect survival after 3 months in any of these subgroups. In the present study, there was no significant difference regarding the use of HTS in different age groups as well as in different sexes. Twenty Four hours survival was the same in the two groups. HTS did not have any statistically significant effect on survival between the shorter, intermediate or longer interval of time between trauma and admission. Moreover, the use of HTS did not differ in the survival of patients having isolated head injury or those who have associated injuries other than head injury. Most importantly, there was no added beneficial effect on different degrees of severity of head trauma classified according to either GCS at admission or Marshall's classification of CT brain findings.

Many animal studies tested the use of hypertonic saline vs. isotonic fluids to control hemorrhagic shock and the largest series of experiments used various animal models of TBI with hemorrhage to examine the effects of HTS on intracranial pressure (ICP). For example, Gunnar et al. (20) used a dog model of epidural balloon inflation and hemorrhagic shock and observed a decrease in ICP and cerebral water content and a decline in the incidence of herniation with HTS versus normal saline (NS) or dextran which showed increase in the ICP and less mean arterial pressure (MAP) and cerebral perfusion pressure (CPP). Interestingly, they used Evans blue solution to

evaluate blood-brain barrier integrity and found an increase in staining with HTS, which they speculated was a result of enhanced perfusion to injured areas. Two studies evaluated the efficacy of HTS as both a resuscitation fluid and a maintenance fluid. Walsh et al. (21) used a swine model of cryogenic injury and hemorrhage to examine the efficacy of HTS versus LR . Animals were randomized to receive an initial bolus of LR versus 7.5% HTS and were again randomized to undergo continuous infusion with either fluid, making this one of the first studies to use HTS as both a resuscitation fluid and a maintenance fluid. They found that an initial HTS bolus prevented the ICP increase observed with isotonic fluid resuscitation. An increase in cerebral blood flow (CBF) and a lower cortical water content was observed in animals receiving HTS as both bolus and maintenance therapy. In addition, a continuous infusion of HTS was able to maintain ICP near normal, whereas animals receiving Lactated Ringer's (LR) maintenance experienced a slow rise in ICP. Shackford et al. [(22)] also used a swine model of cryogenic injury and hemorrhage to compare LR and HTS for both resuscitation and maintenance. Animals resuscitated with HTS had improved MAP, higher CBF, and lower ICP values; the effect on ICP lasted up to 6 hours, even when LR was used for maintenance. Only those animals given HTS both as initial bolus and as maintenance had ICP measurements below 20 mm Hg at 24 hours; this same group also had the highest CPP. There were no significant differences between groups with regard to cerebral water content.

Vassar et al. (23) were among the first investigators (as a clinical trial) to evaluate HTS as a prehospital resuscitation fluid. Dextran was added to HTS on the basis of its potential to augment the favorable hemodynamic effects of HTS. They reported 20 trauma patients transported by helicopter who were randomized to receive either 7.5% HTS/4.2% dextran (250 mL) or Lactated Ringer's (LR) 250 mL followed by supplemental LR as needed to maintain systolic blood pressure (SBP) of 100 mm Hg or greater. They observed a statistically significant increase in SBP and overall survival in patients receiving HTS. The study was significantly limited by its small sample size; furthermore, the LR group had higher incidence of severe TBI as defined by lower GCS scores, making the improved survival observed in the HTS group difficult to interpret. Nevertheless, this was one of the first studies that demonstrated the efficacy of HTS to increase SBP in the clinical setting.

The same group then prospectively studied 166 trauma patients during their transport by helicopter using the same protocol. The HTS group had smaller fluid requirements for hemodynamic stabilization and a higher SBP. (24) The improvement in survival to discharge with HTS did not reach statistical significance for the entire population but was statistically significant for the subgroup of patients with severe traumatic brain injury. There were no significant differences between groups regard to the injury severity as reflected by GCS score, Injury Severity Score, or Revised Trauma Score.

The same group (25) then performed a multicenter trial to compare 7.5% HTS, 7.5% HTS/6% dextran, 7.5% HTS/12% dextran, and LR (250mL of each in hypotensive trauma patients, and again observed improvements in SBP with HTS [(]. No differences in overall survival were observed; however, survival was significantly higher than predicted in patients receiving HTS but not LR. In addition, subgroup analysis of patients with an initial GCS score of 8 or less revealed significant improvements in survival to hospital discharge with use of HTS. Again, dextran appeared to confer no additional benefit over HTS alone.

Wade et al. (13) performed a meta-analysis using these studies to evaluate the effect of HTS/dextran on patients with TBI and SBP of 90 mm Hg or less. Primary outcome measures included 24-hour survival and survival to hospital discharge, both of which were higher in patients receiving HTS/dextran (38 vs27%, odds ratio 2:1, p=0.048). After adjusting for confounding variables (e.g. Severity of head trauma and presence of associated injuries) the survival benefit with HTS/dextran reached statistical significance.

Shackford et al. (26)enrolled 34 patients with severe head injury and used ICP monitoring in a prospective randomized controlled trial. They used 1.6% HTS vs. Ringer's lactate to treat episodes of hemodynamic stability during initial resuscitation. The study showed no significant difference regarding the ICP measured between the two groups and there was no significant differences regarding Glasgow outcome score at discharge. However, limitations of this study include the use of low concentration of HTS; the HTS group had more severe injuries and the few number of patients.

Simma et al. (15) enrolled 32 children with severe head injury and also used ICP monitoring. 1.6% HTS was compared to Ringer's lactate as the only IV fluid for 3 days following injury. They found no significant difference as regard survival though hospital and ICU stay were significantly less. However, study limitations include small number of sample, the use of the same low concentration of HTS.

In a large double blind, prospective randomized controlled study, Cooper et al. [27]enrolled 229 patients who had severe head injury (GCS<9) and were hypotensive (BP <100mmHg) between the years 1998 and 2002 in Melbourne, Australia. Patients were randomly assigned to receive a rapid intravenous infusion of either 250 mL of 7.5% saline (n=114) or 250 mL of LR solution (n=115; controls) in addition to conventional intravenous fluid and resuscitation protocols administered by paramedics during the pre-hospital period. Significantly, there was no difference in total resuscitation IV fluids (1,250 ml) and SBP on arrival unlike other studies. A higher serum Na and Chloride (26) were noted with HTS on admission, which lasted approximately for12 hours. No difference was seen in ICP, cerebral perfusion pressure (CPP), duration of CPP <70, gas exchange, duration of mechanical ventilation or duration of inotropic support between the groups. Although the number of patients who survived was more in the HTS group, this did not reach statistic significance. Furthermore, there was no statistically significant difference as regards extended Glasgow outcome score assessed at 3 and 6 months period. However, the survival was better in both groups than predicted by trauma and injury severity score (TRISS), and the LR group may have benefited from an excellent prehospital resuscitation protocol to maintain an adequate CPP that obviates the need for HTS. Also, this was a limited trial, which did not address HTS only or HTS/dextran resuscitation, and did not use HTS during the hospitalization, which may also affect outcomes.

Therefore, it may be that adequate volume and hemodynamic resuscitation is in fact the critical factor in improving neurological outcome. Additionally, the beneficial effects of HTS resuscitation improving cardiovascular parameters while still limiting the amount of fluid may have been obviated in this study. Also, there may be a need to have a sustained hyperosmolar state. Thus, the initial HTS resuscitation may not have prevented the usual cascade of cerebral edema, increased ICP and secondary brain injury. This can be evaluated by using a protocol that titrates resuscitation fluid administration tightly to cardiovascular parameters, although this may be difficult in the prehospital setting.

5. Conclusion:

HTS is effective in elevation of blood pressure in severe TBI patients while less fluid is required. Although not statistically significant, there was a trend towards improved outcome in severe TBI patients that received HTS.

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