The Use of Hypertonic Saline for Treating Intracranial Hypertension After Traumatic Brain Injury

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The past decade has witnessed a resurgence of interest in the use of hypertonic saline for low-volume resuscitation after trauma. Preliminary studies suggested that benefits are limited to a subgroup of trauma patients with brain injury, but a recent study of prehospital administration of hypertonic saline to patients with traumatic brain injury failed to confirm a benefit. Animal and human studies have demonstrated that hypertonic saline has clinically desirable physiological effects on cerebral blood flow, intracranial pressure, and inflammatory responses in models of neurotrauma. There are few clinical studies in traumatic brain injury with patient survival as an end point. In this review, we examined the experimental and clinical knowledge of hypertonic saline as an osmotherapeutic agent in neurotrauma.

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Traumatic brain injury (TBI) is a major cause of mortality and morbidity in young adults (1). Cerebral edema and subsequent intracranial hypertension is an important factor influencing patient outcome, and despite considerable research, it has proven difficult to manage. Over the past 30 yr, osmotherapy has become an important tool in the management of intracranial hypertension after TBI.

The pathophysiology of intracranial hypertension is complex, and it depends on the mechanism of cerebral edema, volume of intracranial components, integrity of the blood/brain barrier (BBB), and cerebral perfusion pressure (CPP). Under physiological conditions, the BBB limits bulk flow of fluid from cerebral capillaries into brain parenchyma by forming a semipermeable membrane, which is moderately permeable to water and relatively impermeable to small solutes and proteins. The balance of Starling forces (the transcapillary hydrostatic pressure gradient that is counterbalanced by an osmotic pressure gradient) determines the magnitude of flow into the brain substance (2,3). In areas where the BBB is disrupted, this balance disappears, facilitating the flow of proteins and electrolytes across the membrane. Hydrostatic pressure becomes the dominant driving force for fluid movement from the intravascular space to brain tissue (4,5). This leads to brain swelling with an increase in intracranial pressure (ICP), a decrease in CPP, cerebral hypoxia, and secondary brain injury. Interruption of this continuing cycle of injury is the basis of treatment in TBI.

Traditionally, the salutary effects of osmotherapy on ICP were thought to result from brain shrinkage after the shift of water out of the brain substance. This has been confirmed in animal studies where osmotherapy after brain injury led to shrinkage of normal, but not injured, brain tissue (6,7). Interestingly, low ICP persists for some time after the serum concentration of the osmotic drug has decreased to less than the level considered osmotically active.

The ideal osmotic agent establishes a strong transendothelial osmotic gradient by remaining largely in the intravascular compartment. It is inert, nontoxic, and has minimal systemic side effects (4,8). Various substances, including urea, glycerol, sorbitol, mannitol, and, more recently, hypertonic saline (HTS) formulations have been investigated. Although effective, urea is associated with numerous side effects including nausea, vomiting, diarrhea, hemoglobinuria, coagulopathies, and rebound intracranial hypertension and is no longer used. Glycerol and sorbitol are only moderately successful at decreasing ICP and are associated with significant hyperglycemia. Mannitol is effective and safe and is recommended by both the Brain Trauma Foundation and the European Brain Injury Consortium as the osmotic drug of choice (9,10).

There are several mechanisms by which mannitol exerts its effects. Mannitol induces changes in blood rheology and increases cardiac output, leading to improved CPP and cerebral oxygenation. Improvements in cerebral oxygenation induce cerebral artery vasoconstriction and subsequent reduction in cerebral blood volume and ICP. Second, mild dehydration after osmotherapy is desirable and may improve cerebral edema, although severe dehydration can lead to hyperosmolality and renal failure. Finally, mannitol administration decreases cerebrospinal fluid (CSF) production by up to 50%, which, via the Monro-Kellie Doctrine, can lead to prolonged ICP decrease (11,12).

Although the predominant osmotherapeutic drug for the past four decades, mannitol has several limitations. Hyperosmolality is a common problem, and a serum osmolarity >320 mOsmol/L is associated with adverse renal and central nervous system effects (13,14). The osmotic diuresis that accompanies mannitol administration may lead to hypotension, especially in hypovolemic patients. Although controversial, accumulation of mannitol in cerebral tissue may lead to a rebound phenomenon and increased ICP. Other solutions have therefore been investigated as possible substitutes for mannitol. The most promising is HTS.

Introduction of HTS

HTS therapy after TBI was first described in 1919 by Weed and McKibben (15). Nearly 70 yr later, Worthley et al. (16) published a report of its use in two patients to manage refractory intracranial hypertension. IV administration of HTS produced a prolonged reduction in ICP and improved renal function. Subsequently, larger clinical trials have confirmed the beneficial effect of HTS administration on intracranial hypertension (17–19). However, variations in hypertonic solution preparations and dosing regimens, differing inclusion and exclusion criteria, and small numbers of patients make studies difficult to compare. The purpose of this review is to evaluate the clinical and experimental data for HTS, discuss possible complications, and suggest a protocol for HTS administration in clinical practice.

Pharmacology and Mechanisms of Action

Sodium chloride solutions are available in a range of formulations; examples are listed in Table 1.

Proposed beneficial effects of HTS in TBI may arise from several mechanisms. The permeability of the BBB to sodium is low (20). HTS administration produces an osmotic gradient between the intravascular and intracellular/interstitial compartments, leading to shrinkage of brain tissue (where BBB is intact) and therefore a reduction in ICP. The reflection coefficient

Table 1. Sodium Content and Osmolality of Solutions Administered to Patients after Neurotrauma

	Sodium concentration (mmol/L)	Osmolality[a] (mOsm/kg)
0.9% saline	154	308
Lactated Ringer's solution	130	275
20% mannitol	—	1098
1.7% saline	291	582
3% saline	513	1026
7.5% saline	1283	2566
10% saline	1712	3424
23.4% saline	4004	8008
29.2% saline	5000	10,000

* The osmolality of a solution is the number osmoles of solute per kilogram solvent. Osmolality can be measured by determining a change in the solution's colligative properties or calculated as the sum of the concentration of the solutes present in the solution.

(selectivity of the BBB to a particular substance) of NaCl is more than that of mannitol, making it potentially a more effective osmotic drug (21,22). HTS augments volume resuscitation and increases circulating blood volume, mean arterial blood pressure (MAP), and CPP (23). Other beneficial effects include restoration of the neuronal membrane potential, maintenance of the BBB integrity, and modulation of the inflammatory response by reducing adhesion of leukocytes to endothelium (24–26).

Previous Reviews and Recommendations

Several authors have reviewed the use of HTS in clinical practice and concluded that HTS may play a beneficial role in the control of intracranial hypertension. Owing to the inherent limitations of the individual studies, they also acknowledge that more trials are required before definitive recommendations can be made (4,8,27–29). Despite the enthusiasm for the use of HTS after TBI, most authors recognize that the number of human studies is limited. Less than 300 patients have been included in hospital-based clinical trials, many of which were children. Most studies were either case reports or small prospective studies. Few included a control group. Only a small number of patients have been investigated in prospective, randomized, control studies. A recent study by Cooper et al. (17), in which HTS was administered prehospital to patients with TBI, failed to demonstrate an improved outcome compared with the placebo. It is therefore clear that clinicians should use HTS with a certain amount of circumspection.

Animal Studies

TBI has been extensively studied in animals. Several different models are used to replicate the complex

pathophysiology of the injured brain, including the mechanical percussion, cryogenic injury, and balloon insufflation models (27). The type of cerebral edema (vasogenic or cytotoxic) and the degree of BBB disruption depend on the mode of injury. The forces generated by the mechanical percussive model produce contusions and subdural hemorrhages (30,31), BBB breakdown, and development of cytotoxic and vasogenic edema (32). The cryogenic model produces focal injury with rapid, focal BBB breakdown, and swelling from vasogenic edema. The compression model with balloon inflation in the extradural space induces an ischemic injury that best approximates the secondary injury of an isolated extradural or subdural hemorrhage (33). As each model has its own unique characteristics, the effects of HTS in a variety of disease states may be examined. Areas of research include the influence of HTS on cerebral water content, ICP, CPP, MAP, cerebral blood flow (CBF), and cerebral oxygenation, studies on hemorrhage and resuscitation, effects on microcirculation and metabolism, and comparisons with a variety of resuscitation solutions (6,7,34–39).

HTS Resuscitation After TBI Associated with Hemorrhagic Shock

Initial clinical trials with HTS were designed to investigate small volume resuscitation after hemorrhagic shock (36,40–43). Subgroup analysis suggested that there may be a positive therapeutic effect in those patients with associated traumatic head injury (44–47). In two separate studies, Shackford (34) investigated small volume resuscitation (4 mL/kg) comparing Ringer's lactate solution with HTS/dextran (7.5% HTS in 6% dextran) and diaspirin cross-linked hemoglobin in a porcine model of cryogenic brain injury and hemorrhagic shock followed by resuscitation. There was an improvement in MAP, CPP, ICP, and CBF in all groups compared with the Ringer's group. Battistella and Wisner (48) confirmed these findings when they compared Ringer's lactate solution with 7.5% HTS in a sheep model of hemorrhagic shock with head injury. Zornow et al. (49) compared the effects of hypertonic lactated Ringer's (469 mOsm/kg) with Ringer's lactate solution (254 mOsm/kg) in a cryogenic head injury model of New Zealand white rabbits. The hypertonic treatment group required less fluid to maintain MAP, and ICP was significantly lower. Animal experiments suggest that small volume resuscitation with HTS solution may be beneficial for increasing CPP and CBF and decreasing ICP while maintaining hemodynamic stability after hemorrhagic shock associated with TBI.

Effect On Brain Water Content.

One proposed mechanism for the ICP-decreasing action of hypertonic solutions is by means of dehydration and shrinkage of cerebral tissue. Wisner et al. (7) assessed the effects of HTS on cerebral water content after head injury in rats, comparing 6.5% HTS to lactated Ringer's solution. Brain water content was reduced in both the noninjured animals and in the uninjured hemisphere of the injured animal. Water content was increased in the injured brain to a similar extent in both groups. Similar conclusions were drawn by Shackford et al. (6) when comparing hypertonic Ringer's lactate solution (500 mOsm/L) with hypotonic Ringer's lactate solution (270 mOsm/L) in a porcine model of focal cryogenic brain injury. Ramming et al. (39) used a cryogenic porcine model of TBI to examine the relationship between fluid administration, free water, sodium, and ICP. There was a significant positive correlation between the amount of fluid administered, fluid balance, free water, and ICP and a significant negative correlation between serum osmolarity and ICP. These studies suggest the following ideas: hypertonic fluid improves intracranial compliance and CBF by dehydrating uninjured cortex, an intact BBB is required for osmotherapy to be effective, and excess free water and hypervolemia should be avoided.

Effect of HTS on Cerebral Microcirculation and Metabolism

HTS has been shown to have positive effects on CBF, oxygen consumption, and the inflammatory response at a cellular level (50,51). Heimann et al. (52) used laser Doppler to study the CBF and microcirculation in a rat cerebral ischemia model. They compared the effects of 0.9% saline with 7.5% HTS plus 10% hydroxyethyl starch. The hypertonic solution improved CBF and reduced the area of infarction. Taylor et al. (53) examined the effects of HTS in a pediatric animal model of head injury and hemorrhagic shock using a near-infrared spectrophotometer. The Ringer's lactate solution and HTS groups had similar hemodynamics, but cerebral oxygenation was more rapidly restored in the HTS group. Hartl et al. (25) provided evidence that HTS/dextran limits the local inflammatory effects in a rabbit model of TBI. After injury, intravital microscopy demonstrated an increase in cerebral vessel diameter and a decrease in endothelial adhesion of white blood cell (WBC), suggesting a dampening of the inflammatory response. The increased inflammatory response and white blood cell accumulation in brain tissue may significantly influence the development of secondary brain injury (26).

HTS Versus Mannitol

The question of whether HTS is as effective as mannitol in the management of cerebral edema has been investigated in animals. Mirski et al. (54) compared the efficacy of a single, equi-osmolar bolus dose of HTS (23.4%) and 25% mannitol for reducing increased ICP in a rodent model of acute brain injury. Animals were then treated with a single bolus of 0.9% saline (control group) or 11.0 mOsm/kg equivalents of either mannitol or HTS at the time of maximal ICP increase. HTS and mannitol reduced mean ICP, but HTS was more effective (53.9% versus 35.0% reduction in ICP; $P < 0.01$). The therapeutic effect of HTS on ICP lasted up to 500 min, whereas the mannitol treated animals' ICP returned to overshoot the baseline ICP by 10%–25% within 120 min ($P < 0.01$). Berger et al. (55) administered a single osmotic load of 7.5% HTS/10% dextran-60 or 20% mannitol to rabbits with cryogenic-induced focal brain injury. The mannitol group had lower mean arterial blood pressure (MAP), pH value, and Pao_2 and a higher $Paco_2$. Mannitol initially decreased ICP, but the effects decreased over time. HTS/dextran produced lower ICP and stable MAP but caused accumulation of water and sodium in the injured brain tissue at autopsy. Qureshi et al. (56) compared equi-osmolar doses of mannitol, 3% HTS, and 23.4% HTS in a canine model of intracerebral hemorrhage. Animals were assessed after 2 h. Initial ICP reduction was most prominent after 23.4% HTS administration; however, a sustained reduction was only found in the group that received 3% HTS. The ICP in the mannitol-treated animals exceeded the pretreatment level. The CPP was significantly higher in the 3% HTS-treated group compared with mannitol. The water content in the lesioned white matter was also smallest in the 3% HTS-treated group. These studies suggest that HTS may be more effective than mannitol in reducing ICP and has a longer duration of action. Whether this leads to improved outcome is not known.

Human Studies

There are limited human data supporting increased clinical use of HTS for resuscitation and ICP management (Table 2). Several small trials investigating HTS for the management of refractory intracranial hypertension have shown promising results. Furthermore, there is some suggestion that, in the pediatric population, outcomes may improve when HTS is used for osmotherapy. Results are difficult to compare owing to differences in study design. Protocols differ in the concentration and administration of HTS. Some make use of single-dose regimes, whereas others use multiple boluses or continuous infusions. Studies can be arbitrarily divided into those dealing with management of refractory ICP, survival studies (resuscitation and intensive care unit [ICU] phases), and pediatric trials.

HTS for Refractory ICP in Adult Patients

The definition and management of refractory intracranial hypertension varies between authors but describes an inability to decrease ICP with usual medical measures including sedation, mannitol administration, cooling, hyperventilation, paralysis, CSF drainage, and barbiturate coma. HTS seems to be effective in reducing ICP in this setting. The previously described findings by Worthley et al. (16) were confirmed by Einhaus et al. (57) who noted a 50% decrease in ICP after the administration of 7.5% HTS to a patient with refractory intracranial hypertension. Subsequent small trials have found similar results (19,58,59,64,61,68). Munar et al. (67) investigated the use of HTS as the primary osmotherapeutic drug after TBI. The acute effects of 7.2% HTS on ICP, cerebral and systemic hemodynamics, serum sodium, and osmolality were examined in 14 patients with moderate and severe TBI (Glasgow Coma Scale score ≤ 13) and increased ICP (>15 mm Hg) within the first 72 h. They demonstrated a significant decrease in ICP that correlated with an increasing serum osmolality ($r = 0.75$; $P < 0.05$). HTS, therefore, seems to effectively decrease ICP in this population. Interestingly, there was no correlation between ICP and serum sodium concentration.

Survival in ICU Adult Population

Clinical outcome studies are limited. In 1999, Qureshi et al. (65) reported a poor outcome after administration of HTS. They examined the charts of 36 patients who received IV infusion of 2% or 3% HTS/acetate compared with 46 patients who were treated with 0.9% normal saline. After adjusting for differences between groups, infusion of HTS was associated with increased inhospital mortality (odds ratio [OR], 3.1; 95% confidence interval, 1.1–10.2). Despite this, Qureshi et al. (65,69) argued for continued evaluation of HTS recognizing several deficiencies in their study. The study design was nonrandomized and retrospective. The study included a large number of penetrating brain injuries. In addition, because the effect of acetate on brain physiology has not been studied, it may have contributed to the poor outcome. In a previous study, Qureshi et al. (65,69) had reported that HTS reduced ICP and cerebral swelling but was of limited duration. They questioned the existence of a rebound phenomenon on cessation of HTS, concluding that the use of HTS in TBI was still experimental and required further study.

Table 2. Human Trials Using HTS in the Treatment of Neurotrauma

References	Patient population	Study design	Patients	Hypertonic fluid	Outcome
Worthley et al., 1988(16)	TBI with ICP resistant to conventional therapy	Case series	2	29.2% HTS (bolus)	Immediate decrease ICP
Einhaus et al., 1996(57)	TBI with ICP resistant to conventional therapy	Case report	1	7.5% HTS (bolus)	Immediate decrease ICP by more than 50%
Hartl et al., 1997(58)	TBI with ICP resistant to conventional therapy	Prospective observational	6	7.5% HTS/HHES (250 mL)	Significant decrease ICP and increase CPP at 30 min
Schatzmann et al., 1998(59)	TBI with ICIP resistant to conventional therapy	Prospective observational	6	10% HTS (100-mL/kg bolus)	42 episodes of increased ICP treated, mean ICP decreased 43% (18 mm Hg), effect lasted a mean of 93 min
Simma et al., 1998 (60)	Severely head-injured children	Propsective randomized	32	1.7% HTS maintenance versus LRS	HTS more effective than LRS for reducing ICP. Shorter ventilation, decreased ICU stay in HTS group
Horn et al., 1999 (61)	TBI and SAH and ICP resistant to conventional therapy	Prospective observational	10	7.5% HTS (2-mL/kg bolus)	HTS effective in reducing ICP
Qureshi et al., 1998(62)	Intracranial pathology and cerebral edema	Retrospective	27	3% HTS to increase serum sodium	ICP controlled in TBI group, however rebounded after 3-4 days
Shackford et al., 1998(63)	HTS versus LRS for fluid resuscitation TBI	Prospective randomized	34	1.6% HTS versus LRS for SBP <90 mm Hg	No difference in ICP, groups poorly matched
Suarez et al. 1998(64)	Increased ICP from TBI and other pathology	Retrospective	8	23.4% HTS (30 mL)	Significant decrease in ICP during first 3 hours
Qureshi et al., 1999(65)	Severe TBI	Retrospective case control	36 cases, 46 controls	2% or 3% HTS (infusion) versus 0.9% NaCl	No difference in outcome
Khanna et al., 2000(66)	Severely head-injured children with ICP resistant to conventional therapy	Prospective observational	10	3% HTS to increase serum sodium	Decrease ICP spike with hypernatremia Peak Na 187 mmol/L with 2 cases renal failure
Peterson et al., 2000(18)	Severely head-injured children	Retrospective	68	3% HTS until ICP less 20 mm Hg	Reduced ICP upon initiation of HTS therapy, no adverse effects observed only 3 deaths from uncontrolled ICP
Munar et al., 2000(67)	TBI with increased ICP	Prospective observational	14	7.2% HTS (1.5 mL/kg)	Decreased ICP associated with increased osmolality
Vailet et al, 2003(19)	TBI with ICP refractory to conventional therapy	Prospective randomized	20	7.5% HTS versus 20% mannitol 2 mL/kg	HTS more effective than mannitol for decreasing ICP
Cooper et al, 2004(17)	Prehospital resuscitation of patients with TBI	Prospective randomized	114 cases, 115 controls	7.5% HTS versus LRS (250 mL)	No difference in mortality or neurological outcome

TBI = traumatic brain injury; ICP = intracranial pressure; HTS = hypertonic saline; SAH = subarachnoid hemorrhage; CPP = cerebral perfusion pressure; LRS = lactated Ringer's solution; HES = hydroxyethyl starch; SBP = systolic blood pressure; ICU = intensive care unit.

Pediatric Studies

Recently, HTS trials have been reported in the pediatric critical care literature (23,60,66). Unlike the adult studies, hypertonic solutions are usually given as continuous infusions, and ICP, rather then serum Na concentration, is used to determine the total dose. In the recent guidelines for the management of TBI in children, HTS is proposed as an alternative to mannitol when osmotherapy is indicated (70). Simma et al. (60) performed an open, randomized, prospective study comparing maintenance HTS (sodium 268 mmol/L) with lactated Ringer's solution (sodium 131 mmol/L) in 35 pediatric patients with TBI. The study examined the correlation between ICP, CPP, and serum sodium concentration and the number of additional interventions required to keep ICP < 15 mm Hg. The HTS group required significantly fewer interventions then the control. Although survival was similar, the ICU length of stay was 8.0 ± 2.4 days in the HTS group compared with 11.6 ± 6.1 days in the controls, and there was a significant but small correlation between serum sodium concentration and ICP.

Khanna et al. (66) treated 10 severely brain-injured children refractory to conventional therapy with 3% HTS for an average of 7.6 days. They found a significant inverse correlation between sodium concentration and ICP. This study was noteworthy for several reasons. The patients were enrolled an average of 3.2 days (1–6 days) after ICU admission. Despite the length of time between injury and admission, they responded to HTS. HTS was given as an infusion rather than boluses. There was no target range for sodium because the dose was titrated to ICP. The peak serum sodium was high, averaging 170.7 mEq/L (157–187 mEq/L). This is higher than most previous studies. Although two patients developed renal failure requiring dialysis, there were no long-term complications. These patients came from a group that would be expected to do particularly poorly, but only one died, and the average Glasgow Outcome Scale score for the survivors was 4.

Current treatment guidelines for the management of pediatric patients with TBI reflect the fact that HTS is becoming more widely accepted as therapy for intracranial hypertension. The guidelines recommend a continuous infusion of 3% NaCl ranging between 0.1 and 1.0 mL·kg^{-1}·h^{-1}, administered on a sliding scale allowing serum osmolarity to reach 365 mOsm/L if required (71).

HTS for Initial Management of Traumatic Shock and Head Injury

Support for early administration of HTS solutions in brain injury came from *post-hoc* analysis of trauma data. A TBI subgroup was identified, which seemed to have better outcomes than the controls (44,46,72,73). Vasser et al. (46) performed a series of trials investigating prehospital administration of HTS. The first study looked at trauma patients undergoing helicopter transport. It was a prospective, double-blind, randomized comparison of 250 mL of 7.5% HTS/dextran compared to Ringer's lactate solution. Overall, survival was only marginally improved in the HTS arm. However, within the head injury subgroup, the HTS-treated patients had a 32% survival against 16% in the controls. In a subsequent study, Vassar et al. (72) compared different hypertonic solutions. They looked at shocked patients with multiple injuries in six trauma systems served by helicopter and compared Ringer's lactate solution, 7.5% HTS, 7.5% HTS plus 6% dextran, and 7.5% HTS plus 12% dextran 70. The mean ($\pm$ SD) change in systolic blood pressure on arrival in the emergency department was significantly higher in the HTS group (34 ± 46 versus 11 ± 49 mm Hg; $P < 0.03$). Overall survival in the four treatment groups was not statistically different. Survival to hospital discharge in patients with Glasgow Coma Scale scores of 8 or less was associated with HTS treatment (34% survival in the HTS group versus 12% lactated Ringer's group). HTS was less expensive and as effective as HTS/dextran 70.

Wade et al. (44) undertook a cohort analysis of individual patient data from previous prospective, randomized, double-blind trials. They attempted to evaluate improvements in survival after initial treatment with HTS/dextran compared with standard care (isotonic crystalloid solution) in patients suffering from TBI. All studies included comparable doses of HTS (250 mL of 7.5% HTS/6% dextran 70). Study patients came from a variety of sources, including emergency department, ambulance, and helicopter and included both blunt and penetrating trauma. The studies from Vassar et al. (46,72) were included. To assess the association of treatment and survival in the presence of potential interactions and confounding variables, a logistic regression analysis was performed. Estimation of the OR were determined for both 24-h and discharge survival. Treatment with HTS solutions led to an improved survival to discharge (OR, 2.12; $P = 0.048$). Despite the apparent benefit of HTS, confounding factors cannot be excluded as the data come from a diverse group of patients and centers, and the studies were not primarily designed to examine head injury patients.

The most recent large scale study investigating the use of HTS for the prehospital management of TBI comes from Cooper et al. (17). They compared a 250-mL bolus of 7.5% HTS with lactated Ringer's solution in 229 head-injured and hypotensive patients. Paramedics at the scene of the accident initiated allocation and treatment. Resuscitation was rapid, and

both groups were normotensive by the time they arrived at hospital. Despite a small but statistically significant difference in sodium concentration on admission (148 versus 143 mmol/L; $P < 0.001$), outcome measures were equal. The ICP and CPP in the control group compared with the interventional group were 10 mm Hg versus 15 mm Hg ($P = 0.08$) and 73 mm Hg versus 69 mm Hg ($P = 0.40$), respectively. The duration of CPP < 70 mm Hg was 9.5 h compared to 17 h ($P = 0.06$). All survival data including admission, 6 mo, and discharge from hospital were equal in both groups. They concluded that routine use of HTS in prehospital treatment of TBI has no advantage over resuscitation with Ringer's lactate solution.

The Cooper et al. (17) study seems to contradict previous reports of improved survival of HTS-treated head-injury patients. Most resuscitation studies are based on the assumption that a single dose of HTS will reduce mortality. Certainly, a single dose of a hypertonic solution will reduce ICP. In the Cooper et al. (17) study, the treatment group had lower ICP on admission and a longer period with a CPP > 70 mm Hg. However, this effect is temporary and, in most studies, repeated dosing is required (62,65). It is therefore unlikely that a single dose will make a significant difference. Further confounding these results is the influence of associated injuries on mortality. Only 14% of participants in the above study had isolated brain injury. The majority were complicated by severe multitrauma (Injury Severity Score, 38). The frequent mortality and morbidity of severe multitrauma patients makes it difficult to separate this effect from the influence of therapies for TBI. Furthermore, many patients die before ICU admission. It is often not clear whether they die from injuries related to multitrauma or TBI. Finally, some investigators use albumin solutions as part of their resuscitation regimen. Subgroup analysis from the SAFE study (74) demonstrated a possible link between the use of albumin and poor outcome after TBI. Therefore, despite the negative findings of the Cooper et al. (17) study, it remains unclear whether HTS should be initiated in the resuscitation phase of multitrauma TBI patients.

The Role of HTS in Nontraumatic Intracranial Hypertension

HTS has also demonstrated efficacy at reducing ICP in nontraumatic causes of cerebral edema including subarachnoid hemorrhage, acute liver failure, and stroke. Bentsen et al. (75) administered 7.2% saline in 6% hydroxyethyl starch to seven patients with intracranial hypertension after subarachnoid hemorrhage. ICP decreased in all patients, and the effect was still present 3 h after the infusion, with no evidence of rebound. Eighty percent of patients with Grade 4 encephalopathy after acute liver failure develop cerebral edema. In a randomized, controlled clinical trial, Murphy et al. (76) demonstrated that an infusion of HTS led to decreased ICP and less requirement for norepinephrine in the treatment group. Schwarz et al. (77) administered 10% HTS to eight patients with increased ICP after a stroke who failed to respond to mannitol. Treatment was effective in all episodes and lead to a persistent increase in CPP. Although small, these studies suggest that HTS may be effective in reducing non–trauma-related intracranial hypertension.

Relationship Between ICP and Serum Sodium

Whereas animal data have provided insights into mechanisms of ICP reduction by HTS, the basis of its benefit in humans is unclear. Furthermore, the poor correlation between serum sodium levels and ICP seems contradictory. This may be partially explained by the complex interaction between intravascular volume and serum osmolarity. After IV administration, Na is rapidly distributed throughout the extracellular compartment (approximately 1/3 of the total body water) (78,79). This volume varies among individuals according to body mass, sex, and age. Accordingly, changes in serum Na concentration after HTS administration will also vary. Whether this influences the effectiveness of HTS has not been studied. Studies differ in terms of total Na load, timing of administration, and timing of serum Na sampling. Timing of administration is important as osmoreceptors rapidly detect changes in serum osmolality and mechanisms are initiated to reestablish equilibrium. The increase in serum Na (and osmolality) stimulates antidiuretic hormone release causing absorption of free water from the kidney (80). The initial increase in serum Na and osmolarity are rapidly corrected and could be misinterpreted if measured long after dosing. Interestingly, studies of continuous HTS infusions have demonstrated a significant correlation between serum Na concentration and ICP (18,66). As with mannitol, HTS seems to exert a positive influence on ICP long after the osmotic effects have disappeared. This may be related to improvements in CPP, CBF, intracranial compliance, and autoregulation.

There is also a paucity of data on HTS and brain water in humans. Saltarini et al. (81) performed a magnetic resonance imaging (MRI) scan after the administration of 18% HTS to a patient with refractory ICP after TBI. The MRI showed a marked reduction in cerebral water content 1 h after HTS infusion. Three cerebral regions of interest were analyzed. In keeping with evidence from animal data, a reduction of 11%–23% was noted in relatively healthy brain areas but only 6% in the edematous areas surrounding the contusion. In the core of the contusion, a small increase in

signal intensity of 3% was observed, suggesting minimal response to HTS.

Complications

A number of potential adverse effects have been described with the use of HTS. These include the potential for renal failure, osmotic demyelination syndrome (ODS), a rebound increase in ICP, and various systemic complications including coagulopathies, volume overload, and electrolyte abnormalities.

Renal Failure

The link between the use of HTS and the development of renal failure is not clearly established. When using mannitol, a serum osmolarity of more than 320 mOsm/L is associated with renal failure, whereas an osmolarity of up to 365 mOsm/L seems to be well tolerated after HTS in the TBI population (9,18,66). This is not always the case. In a study of burn patients, HTS resuscitation was associated with a four-fold increase in acute renal failure (ARF) and a two-fold increase in mortality (82). Similarly, in a study of head-injured children (who received HTS), Khanna et al. (66) reported the development of ARF after HTS. This, however, was in the setting of multiorgan failure and renal function subsequently normalized. The authors concluded that multiple factors had led to ARF, and the impact of hypernatremia was unclear. Few HTS studies have reported renal failure. Peterson et al. (18) performed a retrospective chart review to determine the benefits and complications of continuous HTS infusion on ICP control in 68 children. The mean serum sodium concentration was 160 ± 10 mEq/L (range, 140–182 mEq/L). The largest recorded serum sodium concentration was 182 mEq/L. Despite this, no child developed renal failure, although a small positive correlation was noted between serum sodium and creatinine concentrations. In summary, the association between the use of HTS and the development of ARF remains tenuous.

ODS

ODS or central pontine myelinolysis was originally described in 1959 as a disease affecting alcoholics and the malnourished (83). It was only in 1976 that the link between these disorders and the rapid correction of hyponatremia was proposed and convincingly demonstrated in animal models (84). Recommendations suggest that serum Na should be increased by no more than 8–10 mmol/d in patients with chronic hyponatremia. Whether ODS occurs after rapid changes in serum Na in normonatremic patients is not known. No human studies of TBI have specifically looked at ODS after HTS administration. However, several studies have reported postmortem or MRI examinations on patients who received HTS (18,66). No evidence of ODS could be found. The study by Peterson et al. (18) failed to demonstrate ODS on MRI or postmortem examination despite maximum sodium of 182 mmol/L. It is unclear whether the reports of ODS in the setting of HTS relate to the initial sodium level, chronicity of hyponatremia, or to the rapid change in serum sodium concentration.

Rebound Increases in ICP

Continuous osmotherapy may lead to a rebound phenomenon and increased ICP when serum Na returns toward normal (3). The concentration time curves in serum and CSF suggest that in the elimination phase of an osmotic drug, a temporary reversal of the blood to brain osmotic gradient occurs (85). This is short lived, and it does not seem to be associated with an increase in ICP. The situation after long-term use is less clear. In animals, both mannitol and glycerol accumulate in CSF over time. However, it is not clear from human data whether deterioration in ICP control after prolonged use of osmotherapy is an adverse effect or whether it reflects a worsening of the underlying cerebral injury. In the context of HTS, Na has been shown to cross the BBB, but this seems to occur slowly. Prough et al. (86) demonstrated a progressive increase in ICP after HTS administration in a dog model of TBI. Qureshi et al. (69) described two patients who developed intractable intracranial hypertension after HTS. Most other studies have failed to confirm these findings. Nau (3) suggested that the risk of developing rebound ICP increases with repeated administration of HTS, the degree of damage to the BBB, and the position of the patient on the ICP-volume curve. Whether or not this phenomenon exists is still a matter of debate.

Systemic Side Effects

HTS-induced hypernatremia has been associated with other noncerebral adverse effects including coagulopathies, excessive intravascular volume, and electrolyte abnormalities. Some investigators have expressed concern that dilution of plasma coagulation factors may occur after administration of HTS (particularly large volumes). This does not seem to be an issue in the clinical setting. Certainly there were no reports of increased bleeding from any of the resuscitation studies despite the addition of 6% dextran to the HTS solutions.

Electrolyte abnormalities are common. Hyperkalemia may develop after intravascular fluid administration and natriuresis requiring judicious monitoring. HTS also tends to reduce the plasma strong ion difference, and a nonanion gap metabolic acidosis may result (87). Some physicians administer acetate in
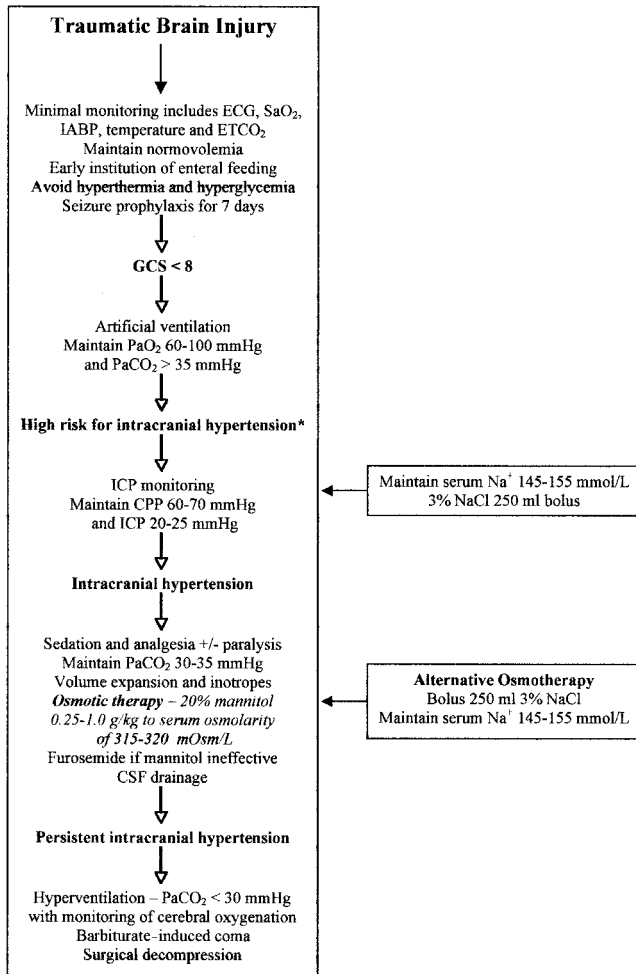
Figure 1. Suggested algorithm for cerebral resuscitation after traumatic brain injury, adapted from the Brain Trauma Foundation and the European Brain Injury Consortium Guidelines and modified to replace mannitol with hypertonic saline for osmotherapy. *Abnormal head computed tomography (CT) or normal head CT and age older than 40 yr, extensor posturing, or systolic blood pressure less than 90 mm Hg. ECG = electrocardiogram; GCS = Glasgow Coma Scale; ICP = intracranial pressure; IABP = intraarterial blood pressure; CSF = cerebrospinal fluid.

combination with HTS to prevent the acidosis from developing. Unless severe, this is unlikely to be of much clinical relevance.

Protocol

At the Princess Alexandra Hospital ICU, HTS has largely replaced mannitol as the principle osmotherapeutic drug (Fig. 1). Serum Na is maintained between 145 and 155 mmol/L in all patients with TBI. When osmotherapy is required for intracranial hypertension, a 250-mL bolus of 3% HTS is administered. Because of its propensity to cause thrombophlebitis, HTS is usually given through a central venous cannula. This dose is repeated until ICP is

controlled or a Na level of 155 mmol/L is achieved. The serum Na is maintained at this level until ICP has stabilized and then gradually allowed to normalize. If ICP control is still problematic after 3–4 days of HTS therapy, boluses of furosemide are administered in an effort to mobilize tissue Na. Serum sodium and potassium concentrations are monitored four hourly on a blood gas analyzer. Osmotherapy is only one part of a multimodal approach to the management of TBI.

Animal and human studies suggest that HTS is a potential therapeutic agent to assist with medical treatment of patients with TBI. It may have a place as osmotherapy to decreased brain size, predominately of uninjured brain, and has several potential advantages over mannitol. Animal studies support its use, but definitive human trials using mortality end points in brain trauma are lacking. Case series in pediatrics suggest that routine use as primary osmotherapy is not associated with an increased risk of complications such as ODS. HTS may be considered a therapeutic adjunct to the medical management of TBI, awaiting definitive evidence to support routine use.

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