Therapeutic Uses Of Hypertonic Saline In The Critically Ill Emergency Department Patient

Abstract

Hypertonic saline is defined as any crystalloid solution containing more than 0.9% saline. The administration of hypertonic saline has been studied alone as well as in combination with colloid solutions (most commonly dextran). Its many theoretical advantages (including small-volume resuscitation, reduction of intracranial pressure, improved hemodynamics, and improved microcirculation and immunomodulation) have prompted research into its use as a resuscitative fluid for a variety of critically ill patients. The 2 patient cohorts most frequently studied are patients with traumatic brain injury and trauma patients with hemorrhagic shock. Hypertonic saline has been shown to be safe and efficacious in decreasing intracranial pressure and improving hemodynamics with few adverse effects, but there are no prospective human trials demonstrating improved clinical outcomes for these patients. Hypertonic saline has been shown to be a valuable therapy for the treatment of severe hyponatremia in patients with signs of cerebral edema, but treatment guidelines are based mostly upon expert consensus and are not well defined. This review examines the evidence on the use of hypertonic saline for the treatment of patients with traumatic brain injury and secondary intracranial hypertension, trauma patients in hemorrhagic shock, and patients with severe hyponatremia.

CME Objectives

Upon completion of this article, you should be able to:

1. Describe the theoretical advantages of using hypertonic saline over traditional resuscitative crystalloid solutions for the treatment of traumatic brain injury.
2. Describe the practical and theoretical advantages of using hypertonic saline over traditional resuscitative crystalloid solutions for traumatic hemorrhagic shock.
3. Recognize the signs of cerebral edema secondary to severe hyponatremia.
4. Describe the use of hypertonic saline in the treatment of severe hyponatremia while avoiding or rapid correction of sodium levels.

Prior to beginning this activity, see the back page for faculty disclosures and CME accreditation information.
Case Presentations

Your shift is just beginning when you are notified that EMS is bringing in a 20-year-old male patient who was struck by a motor vehicle. As your team assesses, you notify the CT scanner and ask him to keep it open and available. When the patient arrives, you find that he has decorticate posturing, a large scalp hematoma, and multiple facial fractures. After you intubate him via RSI and complete your initial assessment, he is quickly wheeled over to CT. His head CT shows a large epidural hematoma with 10 mm of midline shift. His abdominal CT reveals a splenic laceration with active extravasation. You begin your interventions to manage the patient’s elevated intracranial pressure and arrange transport to the nearest Level 1 trauma center. As you hear the helicopter landing, you notice that the patient’s pupils have become asymmetric. You ask yourself, “Which would be better to control the patient’s intracranial hypertension: mannitol or hypertonic saline?”

A short time later, EMS wheels a first-time marathon runner into the critical care bay. She was witnessed to have collapsed at mile 22 with seizure-like activity of 1 minute duration. She is currently postictal with a normal fingerstick blood glucose. Her vital signs are as follows: heart rate of 118 beats per minute, respiratory rate of 24 breaths per minute, blood pressure of 138/90 mm Hg, rectal temperature of 38.3°C, and oxygen saturation of 98% on a nonrebreather mask. You wonder if she might have suffered a heat stroke. Her temperature is elevated — but not enough to cause a seizure. Besides her continued altered mental status, she has an otherwise normal exam. You send her off to the CT scanner to look for acute intracranial pathology. As her scan is completed and the results are confirmed by the radiologist as unremarkable, the lab calls back with a critical value: her serum sodium is 109 mEq/L. The nurse calls out to you from the scanner, “Doc, she’s seizing again!”

Introduction

Hypertonic saline (HTS), which is defined as any crystalloid solution containing more than 0.9% saline, has a potentially important role in the treatment of several life-threatening conditions seen in the emergency department (ED). With respect to the trauma patient, HTS has unique properties that may make it an ideal resuscitative fluid for the most common causes of traumatic death: central nervous system injury, exsanguination, and organ failure.1 (See Table 1.) It has been shown to reduce intracranial pressure (ICP) in patients with traumatic brain injury (TBI) and may have an immunomodulatory effect that further reduces neuronal damage and multiple-organ failure.2–7 HTS may also improve hemodynamics and microcirculation, resulting in improved resuscitation in hemorrhagic shock.8–10 Compared to traditional crystalloid solutions (normal saline or lactated Ringer’s solution), a smaller volume of HTS is required to improve hemodynamic stability in hypotensive patients.11 This has many practical advantages for the military and for other austere environments that preclude carrying a large volume of fluid for the purpose of resuscitation.12

HTS also has an important role in the treatment of severe hyponatremia. While hyponatremia in the ED is typically chronic and requires no immediate intervention, acute severe hyponatremia can cause significant morbidity and mortality. Appropriate recognition and treatment with HTS can help prevent devastating sequelae from both the hyponatremia itself and its overaggressive treatment.

This issue of EMCC examines the evidence supporting the use of HTS for the treatment of patients with TBI with elevated ICP, trauma patients in hemorrhagic shock, and patients with severe hyponatremia.

Critical Appraisal Of The Literature

A literature search was performed using Ovid MEDLINE®, PubMed, and EMBASE from 1990 to the present. The area of focus was the use of HTS in the treatment of TBI, hypovolemic shock, and severe hyponatremia. Search terms included hypertonic saline, traumatic brain injury, intracranial hypertension, shock, hypovolemic shock, hemorrhagic shock, and hyponatremia. Over 300 articles were retrieved and provided background for further literature review. The Cochrane Database of Systematic Reviews, Eastern Association for the Surgery of Trauma (EAST) Guidelines, Western Trauma Association (WEST) Guidelines, American College of Emergency Physicians Clinical Policies, National Neurotrauma Society, National Brain Trauma Foundation, Neurosurgical Society of America, Annals of Emergency Medicine’s Evidence-Based Emergency Medicine reviews, and National Guideline Clearinghouse (www.guideline.gov) were also searched. All HTS solutions were incorporated, with solutions ranging from 1.6% to 30%, including those mixed with colloids.

The literature on the use of HTS for resuscitation of trauma patients is difficult to interpret due to several confounding variables. For instance, studies

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have used varied concentrations of HTS (from 2% to 7.5%), have used varied methods of HTS administration (bolus as well as maintenance drips), and have included nontrauma patients in their study groups. In addition, the results from some clinical trials comparing HTS to mannitol can be deceiving, as they do not use equiosmolar doses of HTS. This difference may make HTS appear more effective than mannitol, where the primary effect could arguably be attributed to the higher osmotic load. Lastly, most studies only demonstrate significance in surrogate physiologic markers rather than meaningful clinical outcomes. For these reasons, current treatment guidelines for the use of HTS in trauma resuscitation are based largely upon expert opinion.

The literature on the use of HTS to treat patients with severe hyponatremia is weak and mostly comprised of retrospective studies. Few prospective studies have been done, and treatment guidelines are based mostly upon expert consensus.

**Traumatic Brain Injury**

Although the primary injury to the brain occurs at the time of impact, subsequent compromise of cerebral perfusion can extend the primary injury and create a secondary injury. Current therapy in the prehospital setting and the ED aims to minimize secondary injury by supporting systemic perfusion, reducing ICP, and optimizing cerebral perfusion pressure (CPP). The interventions to decrease intracranial hypertension that have historically been used in the ED include: head of bed elevation, supporting systolic blood pressure (SBP) > 90 mm Hg, preventing hypoxia, and ensuring normocapnic ventilation. Additionally, for patients with signs of impending herniation (such as asymmetric pupillary response, dilated and unreactive pupils, motor posturing, or rapid neurologic decline), osmotic agents (such as mannitol or HTS) should be administered.

**Intracranial Pressure Reduction**

Many trials have shown administration of HTS to be an effective method to reduce ICP for the brain-injured patient. Five case control studies have shown that HTS alone or with a colloid reduces ICP in both adult and pediatric patients with TBI. Five randomized controlled studies also compared HTS to mannitol, is isotonic crystalloid, or hypotonic crystalloid and found HTS to be effective in reducing intracranial hypertension secondary to both traumatic and nontraumatic causes. Most studies used bolus dosing rather than continuous infusion and varied the solution concentration from 1.8% to 10% with and without colloids.

**Comparison Of Hypertonic Saline To Mannitol**

Despite the lack of evidence for any mortality benefit, mannitol is currently considered to be the gold standard for osmotic therapy in the treatment of acute intracranial hypertension, and it is endorsed by the Brain Trauma Foundation’s most recent guidelines for the management of severe TBI. However, HTS is being increasingly investigated as an alternative. Several retrospective studies have suggested that HTS might be effective in reducing intracranial hypertension that is refractory to the use of mannitol. Only a few rigorous prospective studies have compared the effectiveness of HTS or HTS combined with dextran to mannitol in ICP reduction. Kamel et al performed a meta-analysis of randomized clinical trials comparing HTS and mannitol for reduction of ICP. Only studies that administered equiosmolar doses in human subjects undergoing quantitative ICP measurements were included in this meta-analysis. Five trials comprising 112 patients with 184 episodes of intracranial hypertension were included. Despite small sample sizes and mild heterogeneity (mostly due to different formulations of HTS), they found that HTS was more effective than mannitol for the treatment of intracranial hypertension. In 2007, a Cochrane review assessed the effects of mannitol therapy for acute TBI compared to other treatment regimens. Only 1 trial was found that directly compared mannitol to HTS. In this study, which was performed by Vialet et al, it was suggested that mannitol therapy for intracranial hypertension may have a detrimental effect on mortality when compared to HTS therapy (relative risk for death = 1.25; 95% confidence interval, 0.47-3.33). Unfortunately, this study was too small to make valid conclusions, as there were only 20 patients in each arm. In 2011, Cottenceau performed a multicenter prospective study on 47 severe TBI patients in intensive care units (ICUs). Patients were randomized to equiosmolar doses of 20% mannitol (4 mL/kg) or 7.5% HTS (2 mL/kg). Both treatment arms effectively reduced ICP. There was a trend toward HTS being significantly stronger and of longer duration than mannitol; however, this difference was not statistically significant. There were no reported significant adverse events or differences in neurologic outcome at 6 months between the groups. While these studies suggest that HTS is a safe and effective alternative to mannitol for treating intracranial hypertension, there is limited evidence to support any superior efficacy or improved patient outcomes, and a large randomized controlled trial comparing mannitol and HTS is needed.
Clinical Outcome

Few studies have examined how the use of HTS may affect mortality or long-term neurological disability for patients with TBI. In 2008, Bunn and colleagues performed a Cochrane review to determine whether the use of HTS decreases mortality in patients with hypovolemia with and without head injuries.\(^3\) They found only 1 trial that specifically studied whether prehospital resuscitation with intravenous (IV) HTS improves long-term neurological outcome in patients with severe TBI compared to resuscitation with crystalloid solutions.\(^3\) There was no difference in survival or neurologic outcome at 6 months between the 2 groups.

Shortly after the Cochrane review by Bunn et al, the National Institutes of Health sponsored the largest and most important study to date with respect to these outcomes. This multicenter randomized double-blind placebo-controlled trial enrolled 1331 patients from the prehospital setting.\(^3\) Patients with concomitant hypotension were excluded. Patients were randomized to receive a 250-mL prehospital bolus of 7.5% HTS, 7.5% HTS with 6% dextran, or normal saline and were followed for 6 months. The study was stopped after an interim analysis determined that HTS provided no improvement in either mortality or neurologic outcome and that enrolling new patients would not change the outcome of the study.

In 2011, Tan et al conducted a systematic literature review to investigate whether the infusion of HTS or colloid solutions results in better outcomes than standard isotonic crystalloid solutions for patients with TBI. They identified 9 randomized controlled trials and 1 cohort study that examined the effects of infusion of hypertonic solutions (with or without the addition of colloids) for prehospital volume resuscitation.\(^3\) Studies that included patients who had sustained a TBI, with and without other injuries, were included in the review. None of these trials reported better survival and functional outcomes with HTS compared to the use of standard isotonic crystalloid solutions.

In 2007, the Brain Trauma Foundation, in conjunction with the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, published guidelines regarding the use of hyperosmolar therapy for the management of severe TBI. The guideline authors only examined literature on adult human hospitalized patients. The major outcomes they reviewed included reduction in ICP, changes in CPP, changes in cerebral blood flow, and long-term morbidity and mortality. They concluded that the current evidence is not strong enough to make recommendations on the use, concentration, or method of administration of HTS in traumatic intracranial hypertension.\(^3\) Until more conclusive evidence regarding the use of HTS for ICP manage-

Traumatic Brain Injury With Concurrent Hypotension

Trauma patients with TBI often have accompanying injuries that lead to hypotension. Volume resuscitation in this patient population can be challenging, as the isotonic crystalloid solutions that are traditionally used to restore end-organ perfusion and prevent secondary anoxic brain injury could, theoretically, exacerbate cerebral edema. It would seem intuitive that these patients would be an ideal cohort to benefit from HTS. Unfortunately, there is no strong evidence to support this. One multicenter trial using 7.5% HTS with dextran suggested a mortality benefit in hypotensive patients who sustained a TBI. However, the strength of this conclusion is weak, as the improvement was in comparison with predicted survival, not a direct comparison with the control group.\(^4\) Wade et al performed a manufacturer-supported cohort analysis of 223 patients with TBI and hypotension from 6 previous prospective randomized double-blind trials. These trials compared 7.5% HTS with dextran versus a “standard-of-care isotonic crystalloid” (usually lactated Ringer’s). They showed a trend toward survival until discharge (38% vs 27%; \(P = 0.08\)).\(^5\) Cooper et al from Australia performed a double-blind randomized controlled trial focusing on the effect of prehospital resuscitation with 7.5% HTS on neurologic outcomes in patients with severe TBI and an SBP < 100 mm Hg.\(^3\) A total of 229 patients were enrolled. Though there was no significant neurologic difference between the groups at 6 months, there was a trend toward survival in the HTS group (55% for the HTS group and 47% for the control group; \(P = 0.25\)). While these studies show promise for the treatment of the hypotensive TBI patient with HTS, it is difficult to draw definitive conclusions from such small sample sizes.

Summary Of The Use Of Hypertonic Saline In Severe Traumatic Brain Injury

Although the strength of the current literature is weak, it suggests that HTS is as effective as mannitol for treating intracranial hypertension from TBI. Currently, there is no convincing evidence to suggest that osmotic therapy (whether HTS or mannitol) results in improved long-term neurologic outcome or overall mortality benefit. HTS may be an acceptable alternative to mannitol, and indications for its use by the emergency physician would include significantly deteriorating neurologic status or signs of herniation. While there is no agreement as to the dose or concentration of HTS to use, most studies administered a 250 mL bolus of 7.5% HTS with dextran.
For the trauma patient in hemorrhagic shock, the choice and amount of resuscitative fluids are issues of continued debate. Current Advanced Trauma Life Support guidelines recommend treating patients in hemorrhagic shock by infusing 2 L of isotonic or near-isotonic crystalloid solutions, followed by blood products. However, in the last decade, 2 major concepts have challenged this approach. The first is the concept of “hypotensive resuscitation” (ie, the premise that resuscitation to “normal” blood pressures may increase bleeding at a site of uncontrolled hemorrhage). The second is the use of HTS as an alternative resuscitative fluid. It is cheap, is portable, improves microcirculation, and has immunomodulatory properties. It allows “small volume” resuscitation (4 mL/kg) in austere environments and empowers a single medic to treat multiple combat casualties. The 1999 Institute of Medicine report on resuscitation of combat casualties recommended HTS with dextran as the optimal resuscitation fluid in that environment. HTS may also have practical advantages for civilian emergency medical services. Due to short transport times, restoration of mean arterial pressure (MAP) for patients with TBI is difficult with traditional crystalloid solutions. HTS with dextran administered by prehospital providers may restore MAP more quickly and reduce the potential for secondary neurologic injury in TBI patients.

In 1980, de Felippe et al reported astonishing results of survival in 11 of 12 patients with refractory hemorrhagic shock who were treated with HTS. That same year, researchers from the University of Sao Paulo published the first animal study on the use of HTS. They subjected dogs to hemorrhagic shock and reported that 7.5% sodium chloride (NaCl) infused in a volume equal to only 10% of shed blood volume rapidly restored blood pressure. These initial studies prompted several subsequent trials to evaluate the use of HTS for the treatment of hemorrhagic shock.

From 1987 to 2011, there were 10 randomized controlled trials comparing the use of HTS to isotonic crystalloid solutions in hypotensive trauma patients. Many of these trials had very low patient numbers and compared bolus therapy of 7.5% HTS with dextran to 7.5% HTS or normal saline, followed by standard resuscitation with crystalloids and blood products, if necessary. Most of the trials found that 7.5% HTS with dextran increased MAP more than a similar volume of isotonic crystalloid solution. No significant side effects were noticed. Unfortunately, no studies showed an overall mortality benefit. In post-hoc analysis, some studies showed mortality difference in certain subgroups, such as those requiring surgery or when MAP was <70 mm Hg. Vassar et al remarked that, while there was no difference in overall mortality, patients who received HTS with dextran had better survival than predicted by trauma scores.

Bunn and colleagues performed a Cochrane review to determine whether HTS decreases mortality in patients with hypovolemia from causes other than hemorrhage. Their search included randomized trials comparing isotonic and near-isotonic crystalloid solutions to HTS in patients with trauma, with burns, or who were undergoing surgery. Fourteen trials with a total of 956 participants were included in the meta-analysis. They concluded that the confidence intervals for relative risk were wide, and no conclusions could be drawn about a mortality benefit.

In 2011, a multicenter double-blind randomized controlled trial sponsored by the National Institutes of Health examined whether the effect of 7.5% HTS (with and without 6% dextran 70) compared to normal saline improved mortality in hypotensive blunt and penetrating trauma patients. This study, which included 853 patients, is the largest study to date. Patients were randomized to receive a 250-mL prehospital bolus of 7.5% HTS with dextran 70, 7.5% HTS, or normal saline. Like the previously mentioned National Institutes of Health TBI study, it was terminated early by the Data and Safety Monitoring Board after they found that patients who received HTS and did not receive blood transfusions in the first 24 hours had a higher mortality (HTS with dextran: 10%; HTS: 12.2%; normal saline: 4.8%). The authors of this study offered 2 possible explanations for this early mortality. The first is that the patients treated with HTS had a higher rate of early hemorrhage (possibly precipitated by the HTS). However, if increased bleeding was the primary mechanism for earlier mortality, one would anticipate higher mortality among penetrating rather than blunt trauma patients; the opposite effect was seen in this study. Moreover, those patients requiring emergent hemorrhage control who received hypertonic fluids did not have an increase in mortality. The other, more likely, explanation is that the administration of HTS caused a change in physician behavior that delayed the recognition of shock and subsequent transfusion. It is unclear whether any of these early deaths were preventable, as there was no overall difference in the 28-day survival between the groups.

Summary Of The Use Of Hypertonic Saline In Hypotensive Trauma Patients

HTS improves hemodynamics for trauma patients in hemorrhagic shock. Small-volume resuscitation may make HTS an ideal crystalloid solution for combat casualty situations. Most studies on the use of HTS in hypotensive trauma patients administered a 250-mL bolus of 7.5% HTS with dextran. While small trials suggest that there may be some subsets of patients who may benefit from the use of
HTS (eg, those requiring surgery or patients with SBP < 70 mm Hg), there is currently no strong evidence to support its use in hypotensive trauma patients. Further, it may worsen mortality in patients who do not receive blood transfusions in the first 24 hours, as it may delay the recognition of shock and subsequent transfusion.

**Severe Hyponatremia**

Hyponatremia (defined as a serum sodium concentration < 135 mEq/L) is one of the most common disorders of electrolytes in clinical practice, occurring in up to 30% of both acutely and chronically hospitalized patients. The majority of patients who present to the ED with hyponatremia do not require emergent management; however, patients who present with severe hyponatremia need immediate attention and an appropriate rate of correction to prevent devastating neurologic deficits or even death. Recognizing and appropriately instituting treatment is critical for this life-threatening electrolyte emergency.

**Brain Adaptation And Osmotic Demyelination Syndrome**

To understand the reasoning behind the recommended guidelines for treating severe hyponatremia (including the pitfalls of overly rapid correction), it is necessary to review how the brain adapts to hyponatremia and the time course over which this occurs. Brain adaptation to hyponatremia begins fairly quickly after an acute fall in serum sodium and is complete within 2 days. Initially, water moves from the hyposomolar extracellular compartment to the relatively hyperosmolar cells. There is a loss of interstitial sodium and water in the cerebrospinal fluid due to increased hydraulic pressure. Within hours, intracellular potassium, sodium, and organic solutes are pumped out of the cell. This adaptation helps reduce the severity of neurologic symptoms and the risk of cerebral edema. Once adaptation is complete, however, the neurons are hyposmolar and, if exposed to excess sodium (as may occur during overcorrection of the hyponatremia), are prone to suffering cellular injury; this is termed osmotic demyelination syndrome (ODS). *(See Figure 1.)*

ODS is an irreversible or only partially reversible neurologic injury that may include dysarthria, dysphagia, paraparesis or quadripleges, behavioral disturbances, lethargy, confusion, obtundation, or coma. The most important risk factors for the development of ODS include the serum sodium concentration at presentation, the duration of hyponatremia, and the rate of correction. While no rate of correction is totally protective, ODS can usually be avoided by limiting correction of chronic hyponatremia (ie, hyponatremia lasting > 48 h) to no more than 10 to 12 mEq/L in 24 hours. Certain patients may be at a particularly high risk of ODS secondary to underlying abnormalities in cerebral osmotic regulation. These include patients with alcoholism, malnutrition, hypokalemia, and burns as well as elderly women on diuretics.

**Considerations For The Treatment Of Severe Hyponatremia**

When considering whether or not to treat hyponatremia with HTS, 3 questions must first be answered:

1. Does the patient’s corrected serum sodium correspond to his clinical picture?
2. Does the patient have severe neurologic symptoms (eg, coma, seizure, focal neurologic examination) that warrant treatment with HTS?
3. Is the duration of hyponatremia acute or chronic?

The corrected serum sodium should correlate with the patient’s neurologic symptoms. Most patients with severe neurologic symptoms from hyponatremia have serum sodium levels < 115 mEq/L. If a patient’s serum sodium level does not correlate with his neurologic symptoms, consider an alternative etiology for their presentation (such as toxicological, infectious, or metabolic).

Patients who present with acute severe hyponatremia (ie, hyponatremia for < 48 h) have had little time for their brain to adapt and are more prone to cerebral edema, but they are less likely to develop ODS with rapid correction. These patients usually present with seizures, encephalopathy, or focal neurologic signs. The most common clinical scenario an emergency physician might encounter is water intoxication that is secondary to psychosis, ecstasy use, or endurance sports (such as marathon running).

Patients with chronic hyponatremia (ie, hyponatremia lasting > 48 h) have had time for their brain to adapt, are less prone to cerebral edema, and are more likely to develop ODS with rapid correction. These patients generally present with only mild neurologic symptoms (such as gait disturbances, confusion, lethargy, and nausea). Sometimes, the duration of hyponatremia is not known. In this setting, it is safest to assume that the patient has chronic hyponatremia and to treat accordingly.

Patients who have only mild symptoms of hyponatremia (eg, confusion) are unlikely to have severe neurologic sequelae from their hyponatremia, if treated conservatively. Only patients with severe neurologic symptoms such as coma, seizure, or focal neurologic signs warrant treatment with HTS.

**Treatment Of Severe Hyponatremia**

Optimal treatment strategies with HTS for severe hyponatremia are based on expert consensus and are not well defined. *(See Table 2 on page 8.)* There
The initial goal of treating hyponatremic patients with severe neurological symptoms is to reverse the cerebral edema with 3% HTS. Perhaps the easiest method of administration was developed by the Second International Exercise-Associated

| Normal state. | The extracellular fluid is in osmotic equilibrium with the intracellular fluid, including that of the brain cells, with no net movement of water across the plasma membrane. |
| Acute hyponatremia. | If the extracellular fluid suddenly becomes hypotonic relative to the intracellular fluid, water is drawn into the cells by osmosis, potentially causing cerebral edema. |
| Adaptation. | Over the ensuing few days, brain cells pump out osmoles, first potassium and sodium salts and then organic osmoles, establishing a new osmotic equilibrium across the plasma membrane and reducing the edema as water moves out of the cells. |
| Overly aggressive therapy | with hypertonic saline after adaptation has occurred raises the serum sodium level to the point that the extracellular fluid is more concentrated than the intracellular fluid, drawing more water out of the brain cells and causing the syndrome of osmotic demyelination. |

Consensus Development conference. They recommend that any athlete with severe hyponatremia and encephalopathy be treated immediately with a bolus infusion of 100 mL of 3% NaCl to acutely reduce brain edema. Two additional 100-mL boluses of 3% NaCl should be repeated at 10-minute intervals if there is no clinical improvement. This would translate to 6 mL/kg of 3% NaCl for a 50-kg woman, which is enough to raise the serum sodium concentration by 5 to 6 mEq/L. While this guideline was developed to treat those with exercise-associated hyponatremia, it is probably a reasonable regimen to extrapolate to all patients with severe hyponatremia, regardless of etiology or duration.

After the initial treatment with HTS to address the serious signs and symptoms of hyponatremia, the subsequent rate of correction should be closely monitored. The goal is not to correct the patient’s serum sodium to “normal” values. For patients with either chronic hyponatremia or hyponatremia of an unknown duration, an expert panel suggested a correction of no more than 10 to 12 mEq/L during the first 24 hours of treatment. They also suggested that, due to sometimes unexpected “autocorrection” during the course of treatment, it may be best to aim for undercorrection (more near the rate of 8 mEq/L/d). It is important to emphasize that these recommendations were derived from relatively small numbers of patients and that they only give an estimate of reasonable correction rates.

Going Deeper: How Hypertonic Saline Works

Intracranial Pressure Effects

As mentioned previously, the primary goals of managing a patient with TBI are to reduce cerebral edema, decrease ICP, and improve CPP. While mannitol has historically been considered the drug of choice for acute intracranial hypertension, it has some drawbacks. First, it is believed that the blood-brain barrier may be compromised in TBI, leading to accumulation of mannitol in already edematous tissue, which ultimately causes an increase in cerebral edema and ICP. Additionally, mannitol is an osmotic diuretic and may cause hypotension, which worsens secondary brain injury.

HTS has the theoretical potential to improve both CPP and intracranial hypertension without the deleterious effects of mannitol. The primary effect by which HTS reduces ICP is by setting up an osmotic gradient across an intact blood-brain barrier and dehydrating brain tissue in the mostly uninjured portions. It is more attractive than mannitol as a hyperosmotic therapy, as it is less permeable across an intact blood-brain barrier and has a higher osmotic gradient in the vascular compartment. Because the osmotic effect of HTS alone is transient, it is usually combined with a colloid (hydroxyethyl starch or dextran). This may prolong the clinical effect by 2 to 4 hours.

Hemodynamic And Microcirculatory Effects

Isotonic crystalloid solutions currently predominate over all other resuscitative fluids for the hypotensive trauma patient. When NaCl or lactated Ringer’s is given, it is rapidly redistributed throughout the entire extracellular space with no preference for the vascular space. Ultimately, only 10% to 20% of the infused isotonic crystalloid remains in the circulation. This can necessitate large volumes of fluid for resuscitation, potentially worsening hemorrhage and neuronal injury. (See Figure 2.)

In contrast, HTS allows for resuscitation with smaller volumes (4 mL/kg of 7.5% NaCl). The osmotic effect is immediate, and it can increase the intravascular volume by as much as 4 times the infused volume within minutes of infusion. That said, it is most likely an oversimplification to consider HTS as a potential treatment for TBI and shock solely from its actions as an osmotic agent. Fortunately, there are many rheological effects by which it may improve microcirculation, including decreasing blood viscosity, endothelial cell edema, and capillary resistance via dehydration of erythrocytes. Hypertonicity also has a direct relaxant effect on the vascular smooth muscle with resultant arteriolar vasodilation. Last but not least, the optimization of blood flow and CPP is supported by the effect of HTS on increasing the MAP.

Immunologic Effects

One of the more intriguing aspects of HTS is its potential to modulate the immune system in the trauma patient. It is well known that dysfunctional activation of the immune system after traumatic injuries and other shock states can cause subsequent tissue and organ injury. Basic science studies have confirmed that HTS has marked effects on the immune system. It has been shown to blunt
neutrophil activation, modify cytokine production,\textsuperscript{3} and augment T-cell function.\textsuperscript{4,5} In animal models, it decreases hemorrhage-induced neutrophil activation and is protective against acute lung injury.\textsuperscript{6,7} To date, no clinical studies have been conducted that demonstrate a patient-oriented benefit from these immunomodulation properties.

**Adverse Effects**

As a resuscitative fluid, HTS is cheap, does not transmit infection, and is unlikely to provoke an anaphylactic reaction. It has a strong safety record based on previous clinical trials and reported use. However, it is worthy to note that the patients at the highest risk of being harmed by HTS (such as those with heart failure, pulmonary edema, and kidney failure) were often excluded from these trials.

The largest randomized controlled trial of HTS and TBI (which included 1331 patients) did not find a statistically significant difference in the rate of adverse events between the treatment groups, although they did describe a not statistically significant trend toward a higher nosocomial infection rate in the HTS groups. Importantly, they observed no increase in progression of intracranial hemorrhage in the hypertonic fluid groups.\textsuperscript{32}

One obvious potential complication of HTS is sequelae from unintended iatrogenic-induced hypernatremia (other than ODS). A retrospective analysis of more than 600 neurointensive care unit patients examined upper threshold values of hypernatremia. Unless serum sodium values exceeded 160 mEq/L, no worse outcomes were detected. This is well beyond the value that would commonly be reached after initial treatment in the ED.\textsuperscript{62}

ODS is arguably the most-feared complication from the administration of HTS. Fortunately, it is rare and generally only associated with chronic hyponatremic patients who undergo overrapid correction. There is little evidence from the current literature to support the fear of ODS from treating patients with TBI or hemorrhagic shock with HTS. However, since ODS is a devastating condition, caution should still be exercised when using HTS in a patient who may have chronic hyponatremia (such as an alcoholic patient or a patient with congestive heart failure).

In head-injured patients whose blood-brain barrier is disrupted, the potential exists for HTS to permeate into the injured tissue, raising water content, increasing ICP, and exacerbating brain damage.\textsuperscript{11} The majority of studies do not report this

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**Figure 2. Distribution Of Crystalloid Solution Administration**

**A. Distribution of isotonic crystalloids (3000 mL isotonic solution)**

![Diagram of isotonic crystalloids distribution](image)

IV isotonic crystalloids (isotonic NaCl solution, lactated Ringer’s solution) diffuse throughout the extracellular space and do not (normally) enter the cells. Therefore, the majority of the 3000 mL of an IV isotonic NaCl solution will be distributed in the extracellular compartment, with three-quarters (2250 mL) entering the interstitial space and one-quarter (750 mL) remaining in the intravascular space. Although this intravascular volume gain is not insignificant, the majority of infused fluid enters the interstitial space, promoting edema.

**B. Distribution of hypertonic crystalloids (250 mL of 7.5% NaCl)**

![Diagram of hypertonic crystalloids distribution](image)

Hypertonic crystalloids infused into the circulation actually draw body water from the large reservoirs of the intracellular and interstitial compartments into the vessels. This shift dramatically increases blood volume by many times the actual volume infused.

Abbreviations: H\textsubscript{2}O, water; IV, intravenous; NaCl, sodium chloride.

Adverse Effects

Table 3 summarizes the adverse effects of HTS as well as its benefits.

Tools And Techniques: Practical Considerations For Hypertonic Saline

HTS for the trauma patient with TBI and/or hemorrhagic shock is most often infused as a single 250-mL IV bolus of 7.5% NaCl solution with 60% dextran 70. An alternative weight-based bolus of 4 mL/kg has also been used.

The military has examined the intraosseous route as an alternative method for infusing resuscitation fluids for the treatment of hemorrhagic shock in animals. It appears to be as effective in restoring MAP as the IV route and no short- or long-term major tissue damage was observed. Caution should still be exercised, however, as extravasated hypertonic fluid has the potential to cause tissue necrosis. This may have accounted for 1 study reporting tibial necrosis 2 days after the infusion of HTS with dextran into dehydrated pigs.

For the treatment of severe hyponatremia, 100 mL of 3% HTS saline should be given as an IV bolus. This should raise the serum sodium concentration by 2 to 3 mEq/L. Be careful, as the serum sodium may autocorrect and rise faster than expected. Some experts suggest a target increase of no more than 8 to 10 mEq/L/d.

Due to the high osmolarity of HTS, infusion through a central line is preferred to minimize phlebitis. Most studies used a 7.5% HTS solution, which has an osmolarity of 2567 mOsm/L. The usual maximum recommended osmolarity infused via a peripheral IV line is 900 mOsm/L. For this reason, when central access is not available, it is advisable to administer HTS through a large-bore peripheral IV line.

Table 3. Proposed Benefits And Adverse Effects Of Hypertonic Saline

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>• Inexpensive</td>
<td>• Theoretical risk of ODS</td>
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<tr>
<td>• Reduces ICP</td>
<td>• ‘Rebound’ increase in ICP</td>
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<tr>
<td>• Improves CPP</td>
<td>• Elevating MAP and worsening bleeding in patients with uncontrolled hemorrhage</td>
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<tr>
<td>• Improves hemodynamics and microcirculation</td>
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<td>• Immunomodulation</td>
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<td>• Vasoregulation</td>
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<td>• Small-volume resuscitation</td>
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Abbreviations: CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; ODS, osmotic demyelination syndrome.

Clinical Course In The ED

Stabilization

After an osmotic agent has been administered to a TBI patient with an asymmetric pupillary response, dilated and unreactive pupils, motor posturing, or rapid neurologic decline, the focus should be on reducing ICP and optimizing CPP. This includes head of bed elevation, supporting MAP > 90 mm Hg, preventing hypoxia, and obtaining immediate neurosurgical consultation.

For the trauma patient in shock who has stabilized after fluid resuscitation, further evaluation (including ultrasound, plain films, and computed tomography) should be used to pursue the cause for the patient’s hypotension.

For the hyponatremic patient whose neurologic symptoms have stabilized, you can reduce the risk of overrapid correction by not administering additional infusions of HTS. Careful monitoring of the serum sodium level should be performed every 2 to 3 hours.

Deterioration

The administration of an osmotic agent for severe TBI is only a temporizing measure while further diagnostic procedures or interventions are performed. If a patient continues to show signs of deterioration, efforts to reduce ICP and optimize CPP should be maximized. Immediate neurosurgical consultation is essential, as refractory intracranial hypertension may require urgent neurosurgical intervention.

For the trauma patient in refractory shock, resuscitation should continue with packed red blood cells. For patients with penetrating trauma and ongoing hemorrhage, an SBP of 80 to 90 mm Hg may be a more optimal resuscitation endpoint until definitive hemorrhage control can be achieved. Continue an aggressive search for both hemorrhagic causes (external bleeding, hemothorax, hemoperitoneum, pelvic fracture, long bone fracture) and nonhemorrhagic causes (tension pneumothorax, pericardial tamponade, myocardial contusion, spinal cord injury, coincident medical event such as gastrointestinal bleeding). Focus on etiologies that are immediately correctable in the ED (eg, tension pneumothorax), and obtain immediate consultation by a trauma surgeon.

For the hyponatremic patient whose neurologic symptoms persist or worsen, an additional 100-mL bolus of 3% HTS can be repeated 1 or 2 more times at 10-minute intervals. This will usually be effective at terminating the seizures. If seizures continue, standard anticonvulsant therapy may also be administered but should not distract the provider from treating the primary cause.
Special Circumstances

Pediatric Patients With Traumatic Brain Injury
Like many areas of pediatric critical care, the majority of evidence for using HTS to treat severe TBI in children is extrapolated from the adult literature. There have been few rigorous prospective studies examining the effect of HTS for severe TBI in children. Fisher et al performed a randomized controlled crossover study of 18 children with severe TBI and compared bolus dosing of 3% HTS with normal saline. They reported that HTS was associated with a lower ICP and a reduced need for additional interventions (thiopental and hyperventilation) to control ICP. Simma et al prospectively randomized 35 consecutive pediatric patients with severe TBI to receive either lactated Ringer’s solution or 1.7% HTS for 72 hours. All patients subsequently received ICP monitors, and their ICU courses were compared. While there was no significant difference in survival rate, patients treated with HTS had a shorter length of ICU stay and required fewer interventions to maintain ICP control. These studies suggest that HTS is promising for the treatment of severe TBI in children, but the strength of their conclusions is limited due to small sample sizes.

The pediatric section of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies published guidelines in 2012 for the treatment of the pediatric patient with severe TBI. They cited 2 pediatric studies as evidence for the use of HTS and adapted adult severe TBI guidelines. They recommended that HTS be considered for the treatment of pediatric TBI associated with elevated ICP (Level II evidence). While they recognized that there was insufficient evidence to recommend specific concentrations or doses, they recommended bolus dosing between 6.5 and 10 mL/kg of 3% HTS.

Controversies And Cutting Edge

Hypertonic Saline And Hypotensive Resuscitation
In trauma patients, restoring intravascular volume and blood pressure in an attempt to achieve normal systemic pressure may cause further blood loss, dilutional coagulopathy, and increased mortality. This has led to an increasing emphasis on the concept of hypotensive resuscitation (ie, lowering resuscitation endpoints to an SBP of 80 to 90 mm Hg until definitive hemorrhage control can be achieved). This strategy has been shown to improve mortality for patients with penetrating trauma. While it is tempting to hope for a similar benefit in blunt trauma patients, the current literature has not demonstrated this.

This begs the question: Does the use of HTS work against this new resuscitative strategy? As discussed previously, HTS has been shown to increase MAP more than a similar volume of isotonic crystalloid solution, and some animal studies of uncontrolled hemorrhage have raised concern for increased bleeding after administration of HTS. In the largest study to date evaluating HTS for trauma patients in hemorrhagic shock, the HTS group had a higher earlier mortality and lower admission hemoglobin, which might have been caused by the artificially high MAP hiding the fact that the patient has organ hypoperfusion and delaying the recognition of shock by the emergency physician (and thereby delaying subsequent transfusion).

Hypertonic Saline For Sepsis
Due to its various effects at the systemic, organ, and microcirculatory levels, HTS appears to be a promising therapy in sepsis for improving tissue oxygenation and patient outcomes. To date, there are few prospective human trials that have studied HTS as a resuscitative fluid in sepsis. Those that have been performed showed an improvement in physiologic endpoints with HTS (increased cardiac output, decreased systemic vascular resistance, and increased pulmonary capillary wedge pressure), but they did not measure clinical outcomes.

It is also theorized that, because of its immunomodulatory effects, HTS may help prevent the development of multiple organ failure in the septic patient. Thousands of patients with sepsis have been entered into various studies where different inflammatory mediators were blocked or modulated in the hope that HTS might alter outcome. Unfortunately, none of these have proven successful, and this author believes that it is doubtful that HTS will prove to have a beneficial patient effect secondary to these properties.

Disposition

Patients with a TBI requiring hyperosmolar therapy will most likely require neurosurgical specialists and transfer to either the ICU or the operating room for urgent neurosurgical intervention. Transfer from community hospitals should be performed in the most expeditious method available. (For a review of critical care transport, see Volume 2, Number 4 of EMCC: “Air Transport Of The Critically Ill Trauma Patient.”)

Trauma patients with hemorrhagic shock will likely require a surgical intervention in the operating room for definitive hemorrhage control. If a patient initially presents at a community hospital, transfer should begin as soon as the initial life threats are addressed. Transfer should not be delayed for any additional imaging.
Patients with severe hyponatremia requiring HTS administration should be admitted to an ICU.

Summary

HTS has been shown to be safe and effective for reducing ICP and improving hemodynamics for the trauma patient in hemorrhagic shock. Currently, no convincing data show any improvement in clinical outcomes. HTS is an important therapy for patients with severe hyponatremia with signs of cerebral edema. A bolus of 100 mL of 3% saline is a reasonable start and may be repeated twice over 10-minute intervals to abate neurologic symptoms. Correction of a patient’s serum sodium < 10 to 12 mEq/L in the first 24 hours is unlikely to precipitate ODS. The theoretical benefits of HTS raise the possibility of its use as a therapy for other critically ill patients; however, little data exist to make any recommendations.

Case Conclusions

You were worried about the motor vehicle accident patient’s worsening mental status and signs of herniation. Based on the available evidence indicating that HTS with dextran is as effective as mannitol to reduce ICP (and the fact that it may help support this patient’s systemic pressure and CPP during helicopter transport if his splenic laceration continues to bleed), you decided to infuse 250 mL of 7.5% HTS with dextran. Fortunately, his neurologic status did not deteriorate any further, and he was quickly transferred to the nearest Level 1 trauma center, where he underwent acute decompression for his epidural hematoma and angiography embolization for his splenic laceration.

Based on your second patient’s history and sodium level, you quickly determined that she had suffered exercise-associated hyponatremia. It was acute in onset, and, because of her seizures, you determined that she most likely had cerebral edema. After intubation, you administered 100 mL of 3% HTS. She had no continued seizures and was transferred to the ICU. Her repeat serum sodium 1 hour later had increased by 4 mEq/L. After a short stay in the ICU, she was discharged home with a normal neurologic status.

Must-Do Markers Of Quality Care

- Avoid secondary brain injury caused by hypotension and hyponatremia.
- Reduce ICP and maximize CPP by using head of bed elevation, supporting SBP > 90 mm Hg, preventing hyponatremia, and using normocapnic ventilation.
- Administer osmotic agents to patients with signs of impending herniation (asymmetric pupillary response, dilated and unreactive pupils, motor posturing, or rapid neurologic decline).
- Recognize neurologic signs of cerebral edema secondary to hyponatremia (seizures, encephalopathy, or focal neurologic signs).
- Do not try to correct the patient’s serum sodium level to “normal” values.
- Avoid overcorrection of chronic hyponatremia or undercorrection of acute symptomatic hyponatremia, as these can lead to serious neurologic injury.
- Do not increase a patient’s serum sodium by more than 10 to 12 mEq/L/d, as this may precipitate ODS.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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randomized trial; 194 patients)


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1. In regards to the evidence for the use of HTS in patients with TBI:
   a. The evidence is strongly in support of a dextran and HTS admixture over mannitol.
   b. The evidence is strongly in support of mannitol over HTS solutions.
   c. The evidence, as of yet, has not shown improved mortality outcomes with HTS.
   d. The evidence has shown that HTS clearly worsens mortality.

2. With regard to the evidence for the use of HTS in patients with TBI and concurrent hypotension:
   a. HTS is recommended for all patients with TBI and concurrent hypotension.
   b. HTS may be of use in some populations, such as combat casualty resuscitations.
   c. HTS improves mortality in patients who do not receive blood transfusions in the first 24 hours.
   d. HTS improves mortality in patients who require surgery.

3. ODS is characterized by:
   a. Cellular injury after adaptation to acute hyponatremia when the neurons are hyposmolar and are subsequently exposed to excess sodium.
   b. Cellular injury after adaptation to acute hyponatremia when the neurons are hyperosmolar and are subsequently exposed to excess sodium.
   c. Initial cerebral edema that results from acute hyponatremia.
   d. Initial cerebral edema that results from acute hypernatremia.

4. In order to reduce the risk of ODS in patients with chronic hyponatremia, the recommendation is to limit correction to:
   a. < 20 to 24 mEq/L in 24 hours
   b. < 20 to 24 mEq/L in 48 hours
   c. < 6 to 8 mEq/L in 24 hours
   d. < 10 to 12 mEq/L in 24 hours

5. Patients with severe hyponatremia for < 48 hours can present with seizures, encephalopathy, or focal neurologic signs and are:
   a. Less prone to cerebral edema but more likely to develop ODS with rapid correction.
   b. Less prone to cerebral edema and less likely to develop ODS with rapid correction.
   c. More prone to cerebral edema but less likely to develop ODS with rapid correction.
   d. More prone to cerebral edema and more likely to develop ODS with rapid correction.

6. Current recommendations are that any athlete with severe hyponatremia and encephalopathy be treated immediately with a bolus infusion of:
   a. 500 mL of 3% NaCl followed by 2 additional 100-mL boluses of 3% NaCl repeated at 10-minute intervals if there is no improvement.
   b. 100 mL of 3% NaCl followed by 2 additional 100-mL boluses of 3% NaCl repeated at 10-minute intervals if there is no improvement.
   c. 100 mL of 3% NaCl followed by 1 additional 100-mL bolus of 3% NaCl repeated after 10 minutes if there is no improvement.
   d. 100 mL of 1.5% NaCl followed by 2 additional 100-mL boluses of 1.5% NaCl repeated at 10-minute intervals if there is no improvement.

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