

CLINICAL ISSUES

Hypertonic Solutions: An Update

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Learning Objectives: After reading this article, the reader will be able to

1. Understand the mechanisms of action of hypertonic solutions.
2. Appreciate the current clinical and possible future applications of hypertonic solutions.
3. Understand the possible adverse effects of hypertonic solutions.

History and Background

In the military setting, where longer transport times and logistical concerns present more difficult problems than in the civilian setting, smaller-volume resuscitation fluids are a necessity.¹ In the past two decades, the answer to this requirement has been the administration of hypertonic saline (HS) solutions with and without the addition of colloids. In 1999, the Committee on Fluid Resuscitation for Combat Casualties for the US Army recommended the use of HS for the treatment of combat casualties.² However, the concepts behind this treatment strategy are by no means novel.

Clinical use of hypertonic solutions dates back to 1926, when Silbert³ used 5% saline to treat Burger's disease. Moderately hypertonic solutions of 1.5% to 3% have been used to treat patients with burn shock and hypovolemia since the 1970s.⁴ Renewed interest in these solutions was not widespread, however, until 1980, when researchers in São Paulo, Brazil, reported using 2400 mOsm HS to treat severe hemorrhagic shock successfully.^{5,6} Numerous studies over the past two decades have established that HS infusions promote diuresis/natriuresis, augment cardiac output, increase cardiac contractility, and directly vasodilate the peripheral vasculature. Adding a colloid can transiently (depending on type added) expand plasma volume and can be used safely for resuscitation of patients with hypovolemia.⁷ Several experimental and clinical studies have investigated the efficacy, dosages, and infusion rates of different hyperosmotic solutions—primarily 7.5% HS administered solely or in combination with dextran or hetastarch.⁸⁻¹⁰ The focus now is on 7.5% HS, 7.5% HS/6% dextran 70 (HSD), and 7.2% or 7.5% HS/6% hetastarch (HHS). Although originally developed for hypovolemic resuscitation in the prehospital setting, these solutions have also been used to treat burns, sepsis, nontraumatic hemorrhages, and vascular

and cerebral injuries. This article reviews the mechanisms of action and clinical indications for the use of hypertonic solutions.

Mechanisms of Action of Hypertonic Solutions

Volume Expansion. One of the most striking features of infusing hypertonic solutions is the rapid onset of plasma volume expansion.¹¹ This is accomplished by mobilization of fluid from the extravascular space into the vascular space because of the concentration difference created by the infusion of the hypertonic solution.^{7, 12} An analysis of transcapillary driving forces shows a nearly immediate vascular expansion after HS infusion. Several reasons for the instant volume expansion have been suggested. One theory postulating a vagus-mediated pulmonary reflex that dilates peripheral resistance vessels while constricting venous capacitance vessels¹³ has been ruled out.¹⁴ Instead, some investigators have suggested that the instant volume expansion is, at least in part, centrally mediated.¹⁵ A more recent explanation is that the rapid onset of cardiovascular response to HS infusion is explained by the mobilization of endothelial cell water, the reduction of hydraulic resistance, and the restoration of the sodium/potassium pump, which in turn restores intracellular pH, ATP, and Ca²⁺ levels.⁷ Nevertheless, the key feature of HS infusion remains the rapid increase of plasma volume caused by the mobilization of endogenous fluid along osmotic gradients across membranes.¹⁶ On the basis of field studies of resuscitation with hypertonic solutions, it was estimated that administration of 250 mL HSD to a 70-kg patient who has suffered a 2-L blood loss would result in plasma volume expansion of at least 700 mL (or, in other words, a 3- to 4-fold increase). To achieve equivalent plasma volume expansion with lactated Ringer's it was estimated that nearly 3 L would be necessary.¹⁷ Recent kinetic studies have further shown that the volume effect, or "efficiency," is about four times as high for HS and seven times as high for HSD compared with the equivalent amount of 0.9% saline.¹⁸⁻²⁰

Cardiac and Vascular Effects. Cardiac output is increased in response to hypertonic solutions. The intravascular expansion results in a raised preload together with a decrease in peripheral vascular resistance. Both heart rate and the contractility are also raised. Early in the course of hypovolemia and shock, the lumen of the capillaries becomes narrower as a result of swelling of hypoxic endothelial cells²¹ and adhesion of activated polymorphonuclear leukocytes to the endothelium of postcapillary venules,²² which may block local flow. This is followed by the release of vasoactive mediators and free radicals that promote macromolecular leakage, interstitial edema, and redistribution of tissue perfusion, which in turn results in compromised oxygen transport to tissues. When administering hypertonic solutions, endogenous fluid is mobilized first from the microvascular endothelium and the red blood cells, with the most pronounced effect taking place

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in those capillaries that have a swollen endothelium.²¹ Increasing concentrations of sodium thus have a positive inotropic effect²³ at an osmolality range of 240 to 320 mOsm, whereas concentrations higher than 320 mOsm have a negative effect. This could explain why too rapid infusion of HS could lead to a decrease in blood pressure.

Renal Effects. Renal physiologists have infused 5% to 10% salt solutions to determine how the kidneys handle an acute salt load and increased serum osmolality.²⁴ Administration of hypertonic solutions is associated with an increased urine output, which in turn is associated with a natriuresis, to which, in hypovolemic conditions, rectification of renal blood flow and glomerular filtration are contributing factors.^{25, 26} The improvement in diuresis, which occurs even during hypovolemia, is the result of an osmotic diuresis.

Coagulation Effects. The administration of hypertonic solutions affects coagulation by the extent of hemodilution.²⁷ The slight effect of prolongation of prothrombin and decreased human platelet aggregation when diluting human blood with HSD is attributed to the HS component.²⁸ Since dextran 70 is a part of HSD, there have been concerns about combined causes of impaired hemostasis.²⁹ In fact, the doses of dextran needed to impair hemostasis must be much higher,³⁰ and there is no interaction between the HS component and the dextran component. Furthermore, there are no effects on typing or cross-matching when using clinical doses of HSD.³¹

Immunologic Effects. The physiologic responses to trauma and hemorrhage are manifestations of complex cellular and molecular events. Inflammatory cells, including macrophages, polymorphonuclear cells, and lymphocytes, are recruited to the site of injury and secrete inflammatory mediators. The inflammatory response to injury involves an interplay between hormones (e.g., catecholamines, adrenocorticotropic hormone, cortisol, and glucagon), cytokines (e.g., tumor necrosis factor- α), interleukins (e.g., IL-6, IL-8, IL-10, IL-1- β), and other cellular products such as proteases, free radicals, eicosanoids, acute-phase reactants, and growth factors.³²⁻³⁵

Posttraumatic immunosuppression is thus a well-documented phenomenon that has been implicated in the pathogenesis of posttraumatic complications such as acute respiratory distress syndrome, sepsis, and multiple organ failure. Therapeutic approaches to counter these threats have been the focus of numerous investigations for many years. Traditional therapies have concentrated on antibiotics, mechanical ventilation, and fluid therapy toward endpoints such as blood pressure and urine output.³⁶ Current fluid regimens use large volumes of both crystalloids and colloids.³⁶ Recent research has shown that lactated Ringer's solution has inflammatory properties.^{33, 37}

Efforts to use hypertonic solutions in animal models as a volume expander have shown some promising results (i.e., less volume used, improved cardiac support).^{38, 39} In addition, HS has been shown to enhance T-cell function *in vitro* and cell-mediated immune function *in vivo*.³⁸ It has been suggested that these capabilities of HS are the result of the ability of the fluid's hypertonicity to co-stimulate the T cells in proliferation. Thus, HS replaces the abundant signal pathway for activating T cells

in immune-compromised patients^{38, 39}—a concept that researchers have suggested might protect patients from septic challenge,³⁹ improve intestinal mucosal blood flow,⁴⁰ and reduce the onset of late complications in trauma patients.¹ As in the prehospital scenario,⁴¹ investigations have shown that HS should be given as early as possible to a patient if it is to be used to enhance that patient's immune response.^{1, 42, 43} It has also been shown that hypertonic solutions are associated with the attenuation of the neuroendocrine response to surgery and hemorrhage.^{41, 44} Infusion of HS was associated with attenuation of the cortisol, aldosterone, and angiotensin II responses to surgery.

Clinical Use

Prehospital Use. Effective resuscitation of the patient suffering from hemorrhagic hypotension is an attractive proposition to both military and civilian health care professionals. In warfare, wounds from bullets and shrapnel cause bleeding, hypotension, and ultimately hemorrhagic shock.⁴⁵ More often than not, the battlefield setting is plagued by long transport times and difficult logistics. Added to these problems is the fact that medics can carry only a limited amount of fluids. From the civilian perspective, conditions are quite different. Typically, transport times are much shorter and logistical preparations allow ambulances and rescue personnel to carry substantial amounts of fluids.

The types of trauma encountered in each setting also differ. While military medical personnel most often have to deal with penetrating trauma, civilian health care professionals encounter both penetrating and blunt trauma. The importance of early intervention has been debated,⁴⁵⁻⁵¹ but there is now widespread consensus to initially stabilize a traumatized victim by securing the airway, stabilizing the neck, and stopping external bleeding. When it comes to intravenous infusion therapy, the mainstay of prehospital management of postinjury hypotension has been to immediately replace the lost intravascular volume.⁵² This concept originates from animal studies performed during the 1950s and 1960s, which formed the basis for treatment of wounded soldiers in the Vietnam War. This treatment eventually was transferred to the streets of the United States in the 1970s. With the advent of rapid transportation systems and trauma centers, however, the type, volume, time of initiation, and even the value of prehospital fluid resuscitation have been challenged in the past 20 years.^{49, 50, 53, 54} The reluctance of certain providers to start intravenous fluid therapy in the field has been associated primarily with the lack of sufficient education among rescue personnel, the risk of rebleeding,^{53, 55} and the delay of transportation to definitive care sites.⁵³ Since the development of these new technologies, no consensus has been reached as to how to initially treat trauma patients, and different trauma protocols have been launched depending on the different types of trauma and the different settings in which they occur.

Although promising, clinical trials have not provided definitive data as to the efficacy of hypertonic solutions.^{56, 57} This has been in part due to the limited numbers of enrolled patients and the diversity of the underlying trauma responsible for the injuries. Wade et al⁵⁶ in 1997 conducted an extensive meta-analysis of all randomized prospective clinical trials using hypertonic 7.5% saline solutions to determine whether

hypertonic solutions improved survival in patients with hypotension associated with traumatic injury. They separated the analysis into the effects of a 250-mL bolus of HS alone and/or in combination with HSD. The two hypertonic groups were compared with matched groups receiving a 250-mL bolus of isotonic solution. In all cases, additional isotonic solution was administered to continue the hypertonic solution started. After a meticulous search for available studies, the authors found six eligible studies using HS and eight studies using HSD. A total of 615 patients were treated with HSD and 340 patients were treated with HS. All individual studies were randomized, included a control group, and had as endpoints survival at discharge or after 30 days. In the meta-analysis for studies using HS, no difference in outcome was found. In the HSD group, all studies^{1,58-64} except one showed an improvement in survival, but again, differences reached statistical significance in only one of the individual studies⁶² and only in specific subpopulations—patients with head injuries and those with penetrating injuries requiring surgery.¹ The mean difference of survival calculated for all studies favoring treatment with HSD over controls was 3.5% ($P=0.07$, one-tailed). The conclusion was that HSD might be beneficial in improving survival in patients with hypotension associated with traumatic injury. Subsequently, a meta-analysis using *individual data* from six of the eight studies containing data with HSD was performed,⁶⁵ which showed a significantly lowered mortality for HSD in patients for whom HSD was infused as the first fluid (in contrast to isotonic therapy).

The lesson to be learned from these studies is that the number of patients in individual trauma trials generally has been insufficient to establish statistically significantly improved survival and that aggregate data from these same trials are encouraging but not fully significant. Moreover, meta-analysis studies can be criticized⁶⁶ because there are difficulties associated with comparing the underlying studies. Since meta-analyses are not generally considered sufficient evidence for regulatory approval, HSD has not been approved for use in the United States. Interestingly, no other intravenous fluid or volume expander has been required to improve survival in order to be used in the clinical setting. Current fluids are used mainly because they have shown volume-expansion properties. When established rules of obtaining consent for participating in clinical studies in the United States appeared in the first half of the 1990s, prehospital studies became difficult to perform. This development, coupled with concerns raised among surgeons when Bickell et al⁵³ reported that conventional fluid therapy might be inferior to delayed prehospital fluid resuscitation in hypotensive and penetrating trauma patients, resulted in a general reduction of interest in prehospital resuscitation with hypertonic solutions in the United States.

In Europe, however, the situation is different. In Austria, HS colloid solution has been in use since 1991. Austria and Brazil were the first countries in which this type of solution was used routinely for resuscitation from severe trauma and shock. In Austria, HS is mixed with hetastarch (Osmohes—7.2% sodium chloride + 10% hetastarch 200/0.5—is now replaced by Hyperhes—7.2% sodium chloride + 6% hydroxyethyl starch 200/0.62). In the past decade, more than 50,000 units have been administered safely. Sweden was the first country to register Rescueflow® (7.5% sodium chloride + 6% dextran 70), in 1998.⁶⁷ Now this solution is registered in 14 countries in

Europe. Finally, Germany in 2000 approved HyperHAES (7.2% sodium chloride + 6% hetastarch 200/0.5). In the majority of these cases, the standard amount of hypertonic solutions given was 250 ml.

Head Trauma. Closed head injury is a common feature of severe blunt trauma. The outcome from closed head injury is determined primarily by the severity of the injury and the age of the patient. Additional important factors are the presence of hypoxia and hypotension,⁶⁸ making the brain vulnerable to secondary brain injury. This condition, however, can be reversed. Prehospital care of patients should therefore focus on minimizing the effects of secondary insults to the brain.⁶⁹ Many patients with severe head injury have hypoxemia upon arrival at hospital, with PaO₂ values <60 mmHg or pulse oximeter saturation readings <90%.^{70,71} Hypoxemia may be caused by direct injuries to the brain, as occurs when a driver's head hits the windshield of a car during a crash, or by associated injuries to the chest or major hemorrhage. Studies have highlighted the importance of maintaining the cerebral perfusion pressure (CPP),⁷⁰ which is defined as a function of the mean arterial pressure (MAP) and the intracranial pressure (ICP):

$$CPP = MAP - ICP$$

Mean arterial pressure can be measured fairly accurately in the field by using noninvasive devices, but it is not possible to measure ICP. However, when the Glasgow Coma Scale score is 8 or less, the prehospital rescue team should be able to assume that ICP is elevated unless there is substantial evidence to suspect that the low level of consciousness is related to reasons other than trauma or hypoxemia.⁷² To reach a perfusion higher than the necessary 70 mmHg, the MAP would need to be maintained in the range of 90 to 105 mmHg (assuming an ICP of 20 to 25 mmHg).⁷³ Traditional fluid therapy for head trauma patients or multiply injured patients with head trauma has consisted of using crystalloids or a combination of crystalloids and colloids.^{74,75} Early fluid resuscitation with crystalloid solutions after head injury worsens cerebral hemodynamics.⁷⁶ Despite some conflicting evidence in animal models with regard to improved perfusion pressure but worsened oxygen delivery because of hemodilution caused by using hypertonic solutions,⁷⁷⁻⁷⁹ there is much clinical evidence that HS or HS in combination with colloids is the fluid of choice for head trauma patients.^{56,60,69,72,80}

Clinical Recommendations—Prehospital Use.⁶⁷ The following protocols were all designed for the use of HSD (Rescueflow®).

1. For head trauma patients with a Glasgow Coma Scale score ≤ 8 or for multiply injured patients in severe shock with or without head trauma:
 - Give 250 ml of hypertonic solution over the course of 5 to 10 minutes.
2. For other types of trauma, if prehospital time (from arrival at scene to admittance to emergency department) is ≥ 30 minutes and systolic blood pressure ≤ 90 mmHg:
 - Give 250 ml of hypertonic solution over the course of 5

to 10 minutes. Do not start intravenous fluid earlier than 15 minutes after trauma.

3. For other types of trauma, if prehospital time is ≤ 30 minutes:
 - Give no fluid.

In all these scenarios, one should continue treatment with the standard fluid of care (crystalloids or colloids as needed) after the administration of the hypertonic solution. If HSD is given, hapten dextran (Promit) to prevent immune complex formation when dextran 70 is given is not recommended as necessary in the trauma setting.⁶⁷ If the patient deteriorates, one should suspect rebleeding, stop infusion of the hypertonic solution, and give a slow crystalloid infusion (1000 ml over the course of 30 minutes).⁸¹

Adverse Effects

Dose and Rate of Administration. Hypertonic solutions were originally developed for prehospital use and designed to replace larger volumes of isotonic solutions. The reasons for using a standard dose of 4 ml/kg or 250 ml of HS, HSD, or HHS seem to be based more on practicality rather than on any true physiologic concept. Although it may be reasonable even in the prehospital area to titrate the solutions toward an endpoint,⁸² there is still support among some clinicians for using a standard dose for reasons of simplicity. The rate of infusion should be rapid in order to establish the desired effects. The greatest concern regarding rate of infusion has been derived from the hypothesis that fluid resuscitation of prehospital trauma can exacerbate uncontrolled internal hemorrhage.^{55, 81, 83, 84} A controlled bleed (< 1 L) is normally treated adequately by the internal redistribution of fluids and thus does not need intravenous fluid support. Controlled bleeding > 1 L implies a situation in which fluids need to be given, but if intravenous line insertion will be difficult and transport time will be short, it is probably better to go to the hospital immediately. In the scenario in which major penetrating injury to the heart or large vessels has created an uncontrolled bleed that has not stopped, immediate transport to the proper surgical center is the only thing that will save the patient.

Uncontrolled bleeding that has stopped is seen in some victims of penetrating trauma but also at times in cases of blunt trauma.⁸⁵ In such cases, an increased risk of rebleeding should be considered. Since hypertonic solutions tend to increase blood pressure more than isotonic solutions, this could be a potential risk. Consequently, decreasing the rate of infusion and reducing the infused volume to patients with presumptive "uncontrolled bleeding" is recommended.⁸² However, this recommendation is disputed, since the clinical data do not show that the administration of hypertonic solutions increases mortality in the clinical setting.⁶³ The results of experimental studies suggesting that administration of HS exacerbates bleeding from injured vessels and leads to early death in anesthetized animals with lacerations in the aorta or cut tails are probably not relevant to the clinical setting in most patients.^{60, 63} Nevertheless, since the beneficial properties of hypertonic solutions are obtained anyway, it seems reasonable to slow the dose from the recommended 2 to 5 minutes to 5 to

10 minutes. Furthermore, the timing of the infusion must be considered. In an urban setting with short transport times, it is most likely best to transfer the patient to an emergency department immediately. In a longer transport scenario, it is unlikely that any intravenous infusion will be started earlier than 15 minutes after trauma, when the risk of rebleeding is less likely.

Hypernatremia. Hypernatremia is common with the infusion of hypertonic solutions. Levels of hypernatremia in excess of 165 mmol/L have been reported without any adverse effects.¹ The levels of sodium and raised osmolality usually go up 9 to 12 mmol/L and return to baseline within 4 to 6 hours. The infusion of hypertonic solutions causes an increased diuresis, increased natriuresis, and subsequent kaluresis. As a result, it is recommended that clinicians monitor electrolytes closely.

Anaphylaxis. It has been suggested that HSD can cause anaphylactic reactions because of the dextran contained in the solution. Patients with hypersensitivity have high plasma titers of dextran-reactive antibodies, particularly of the IgG-class. Infusion of dextran in a patient with such antibodies may cause the formation of large immune complexes with ensuing activation of plasma enzyme cascades and an anaphylactic reaction. HSD contains a small amount of dextran; nevertheless, only a few drops of dextran can cause an adverse reaction and pretreatment with hapten dextran (Promit) is normally necessary. Trauma patients, however, seem to be protected in a way that is different from other patients. This may be because of large amounts of circulating catecholamines. Hapten dextran was not given in any of the prehospital studies mentioned in this review.^{1, 59-61, 63, 64} There were no anaphylactic reactions in any of these clinical studies. The Swedish Physician's Desk Reference (FASS) makes no recommendation for using hapten dextran for trauma patients.

As for dextran, previous exposure to hetastarch can trigger reactive antibodies that cause anaphylactoid or anaphylactic reactions. There is, in contrast to dextran, no existing pretreatment, but again this seems not necessary for trauma patients.⁹

Conclusion


Perhaps what can most easily be ascertained from the voluminous amount of work on hypertonic solutions is that it seems to be very safe to give them. In 35 clinical trials, more than 1,400 patients have received HS, HSD, or HSS without any complications.^{9, 86} Furthermore, in the prehospital scenario, patients suffering from severe head trauma seem to be the group that benefits most from receiving hypertonic solutions.

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Blunt Abdominal Aortic Transection in an Abused Child: A Case Report and a Literature Review

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Learning Objectives: 1) To identify the indicators of abdominal aortic injury in children after blunt trauma, 2) to review diagnostic options for pediatric patients with blunt abdominal trauma, and 3) to appreciate the advantages/disadvantages of clamp-and-sew versus intraoperative bypass techniques.

Abstract

Blunt abdominal aortic trauma is most frequently caused by motor vehicle crashes. We report the second successful management, to our knowledge, of a case of pediatric abdominal aortic trauma caused by known child abuse and resulting in almost complete transection of the abdominal aorta.

Case Report

A 2 1/2-year-old girl (16 kg, 65 cm) was brought to the emergency department by paramedics, who stated that she had reportedly been thrown against a couch by her mother's boyfriend. The child was lethargic at the scene with bleeding from a scalp laceration and had not lost consciousness.

Upon arrival in the trauma emergency department, the child was lethargic with a Glasgow Coma Scale (GSC) score of 6 (E4, M1, V1). She was not crying; slow movement of the upper extremities and no movement of the lower extremities were observed. She presented with the following vital signs: blood pressure, 67/41 mmHg; heart rate, 120/150 beats/min; respiratory rate, 20 to 32 breaths/min; and temperature, 33°C; O₂ saturation was 90%. Physical examination revealed a distended, tense abdomen, with no bowel sounds. The lower extremities were bluish and cold with no palpable pulses below the femoral vessels. Two intravenous lines (18 gauge) were placed in the upper extremities. A blood sample was sent for type and crossmatch. The patient was intubated with a 4.5 endotracheal tube and was resuscitated using fluids. Radiographs of the chest, pelvis, and C-spine were normal with no sign of fractures. Hemoglobin concentration was 6.0 g/dL.