

## REGULAR REVIEW

### Hypertonic Saline

J E Smith, M J Hall

#### ABSTRACT

**The optimal fluid for the resuscitation of critically ill and injured patients remains the subject of considerable controversy. Hypertonic crystalloid solutions such as hypertonic saline provide rapid volume expansion, have an acceptable safety profile, and are easy to store and transport. Recent meta-analyses suggest a trend toward increased survival in patients given hypertonic saline, and it has been suggested that they may have particular benefit in certain groups of patients such as hypovolaemic head injury patients. This short review examines the physiological and experimental evidence supporting the use of hypertonic saline in fluid resuscitation.**

#### Introduction

The recognised approach to treating trauma patients that are hypotensive as a result of obvious or presumed haemorrhage has been to initiate fluid resuscitation in an attempt to restore normal systemic arterial blood pressure and maintain adequate end organ perfusion. The ongoing debate about the optimum fluid for the resuscitation of shocked patients would suggest that the ideal has not yet been found. This would be effective in supporting end organ perfusion and maintaining oxygenation of vital organs while having little or no adverse effect on the patient. Two recent meta-analyses comparing resuscitation with crystalloid and colloid solutions have suggested that mortality may be reduced when crystalloid is used compared to colloid (1,2).

Hypertonic solutions of crystalloid may offer benefits over isotonic solutions such as normal (physiological, 0.9%) saline or Ringer's lactate, and there is increasing literature focusing on the physiological effects of hyperosmotic solutions that maximise volume expansion with minimal fluid infusion (3).

Large volumes of isotonic solutions used in resuscitation have been implicated in fluid overload, interstitial oedema and the development of multiple organ failure. They also may contribute to the cascade of activation of various cellular mediators including activation of neutrophils that

subsequently contribute to the systemic inflammatory response to trauma. Using smaller volumes of hypertonic solutions reduces the total amount of fluid necessary in resuscitation, and reduces neutrophil activation (4). Clinical trials have shown that there are improved physiological responses in humans, and a trend towards increased survival. This review examines the current evidence to establish possible uses of hypertonic saline in the resuscitation of critically ill or injured patients in the UK. Solutions made up of combinations of hypertonic saline and colloid are not included in this review.

#### Theory

The average 70kg man contains about 42 litres of water, divided into intracellular (26-28l), interstitial (7-8l) and intravascular (5-6l) compartments. Isotonic crystalloid solutions move freely between these compartments resulting in expansion of all compartments when given intravenously. In studies using healthy volunteers who had venesection of between 600-800mls of blood, it was found that for every litre of isotonic crystalloid given, intravascular volume expansion equated to about 100-150mls (5-7).

When a hypertonic solution is given, the subsequent increase in osmotic pressure within the intravascular compartment draws fluid into the circulation from the interstitial space causing further expansion of the intravascular compartment. Numerous different hypertonic concentrations of sodium chloride have been tested in experiments over the last few years, but perhaps the most widely used is 7.5% sodium chloride (osmolarity 2,400mOsm/l) in a dose of 4mls/kg. This results in an initial plasma volume expansion of 3-4 times the volume of fluid infused, but the effect is relatively short-lived (3,8). Once the osmotic equilibrium is re-established between the fluid compartments, it has been estimated that there is a 750ml volume expansion for every litre given. As a result, the administration of hypertonic saline solutions causes an increase in systemic blood pressure, cardiac output and peripheral tissue perfusion (5-7).

Other effects of hypertonic saline may include cellular modulation, in particular of cells within the vascular endothelium. As a

Surg Lt Cdr J E Smith  
MBBS MSc MRCP  
FFAEM RN  
Specialist Registrar in  
Emergency Medicine  
Defence Medical  
Services  
Email: jasonsmith@doctors.org.uk

M J Hall  
BSc (Hons) MBChB  
Senior House Officer,  
Surgical Rotation

Derriford Hospital  
Plymouth  
PL6 8DH  
United Kingdom  
Email: matthall50@yahoo.com

result of trauma, the vascular endothelium becomes more permeable, and the individual endothelial cells swell and become activated, releasing cellular mediators that contribute to the systemic inflammatory response. Hypertonic saline appears to reduce this cellular activation and swelling, normalising the state of the vascular endothelium and reducing the amount of cellular interactions between leucocytes, platelets and endothelial cells following resuscitation (9-11).

### Head injury patients

Traumatic brain injury accounts for a significant proportion of deaths in all age groups, and is a factor in around 60% of trauma related deaths in the United States (12). The cornerstone of management of traumatic brain injury is the maintenance of an adequate cerebral perfusion pressure, defined as the difference between systemic mean arterial pressure and intracranial pressure. The traumatised brain becomes susceptible to further injury by secondary ischaemia, either resulting from systemic hypotension or from a reduced cerebral perfusion pressure as a consequence of raised intracranial pressure. The maintenance of a cerebral perfusion pressure above 50mmHg was the most important prognostic factor and predictor of survival in a series of 320 paediatric patients with traumatic brain injury (13). The aim of fluid resuscitation in these patients is to provide adequate intravascular volume to maintain mean arterial pressure without precipitating a rise in intracranial pressure due to fluid overload.

Hypertonic saline may have benefits over other forms of fluid resuscitation in this group of patients. With an intact blood brain barrier, infusion of hypertonic saline establishes an osmotic gradient between the intravascular compartment and cerebral tissue, drawing fluid from the cerebral intracellular and interstitial compartments into the intravascular space. The effects of hypertonic saline on intracranial pressure are similar to the effects of mannitol, but may not last as long (14). Both mannitol and sodium exhibit low penetration of the blood brain barrier, helping to sustain the osmotic gradient between the brain tissue and intravascular space. In a prospective, randomised comparison of these two agents in patients with traumatic intracranial

hypertension, it was shown that hypertonic saline resulted in significantly fewer and shorter episodes of intracranial hypertension compared to mannitol, although there was no demonstrable difference in long term outcome (15). The cerebral protective properties of hypertonic saline may also include local vasodilatation, counteracting the vasospasm that occurs secondary to traumatic brain injury (16). In addition to the effects on intracranial pressure, hypertonic saline produces a rise in mean arterial pressure which goes further to maintain adequate cerebral perfusion pressure.

As a result, the use of hypertonic saline has been supported in recent guidelines on the treatment of severe paediatric traumatic brain injury issued by several international organisations including the American Association for Surgery of Trauma and the Society of Critical Care Medicine (17).

### Clinical evidence

As well as the theoretical benefits there is now an abundance of experimental evidence describing the haemodynamic and microvascular properties of hypertonic saline (5-7, 18-22). However, a recent Cochrane review has highlighted the lack of robust clinical evidence to support the routine use of hypertonic saline as a resuscitation fluid (23). This looked at randomised trials comparing hypertonic to isotonic crystalloid in the resuscitation of patients sustaining trauma, burns, or undergoing surgery, with mortality as the primary outcome. It found 17 trials including 6 trauma (24-29), 4 burns (30-33) and 7 surgery (34-40), but only 5 were deemed to be methodologically adequate (24-28). The pooled relative risks (RR) for death in each group of patients from the studies are shown in Table 1. Only one randomised trial looked specifically at head injury patients (24), involving paediatric patients admitted to an intensive care unit (ICU) following severe head injury (Glasgow Coma Score <8 at scene). Patients were randomised to receive either hypertonic saline or lactated Ringer's solution in addition to routine care. It found that there was a statistical relationship between serum sodium concentrations and intracranial pressure in these children, and a reduction in the amount of interventions necessary to keep intracranial pressure within normal limits in the hypertonic saline

Table 1. Pooled relative risks of death with use of hypertonic saline compared to isotonic crystalloid.

Patient group	Relative risk of death	95% confidence interval
Trauma	0.84	0.61 - 1.16
Burns	1.49	0.56 - 3.95
Surgery	0.62	0.08 - 4.57

group. There was also a reduction in length of ICU stay, but no reduction in mortality or duration of hospital stay.

Another trial not included in the meta-analysis randomised 34 head injury patients to receive either 1.6% sodium chloride or Ringer's lactate, but used 0.45% sodium chloride as the maintenance fluid in the Ringer's lactate group, adding a further variable to the melting pot (41). This trial found no benefit in using this concentration of hypertonic saline over Ringer's lactate.

Looking through the clinical trials comparing hypertonic to isotonic solutions there are several pitfalls in the methodologies that become apparent. Most trials use surrogate physiological markers of outcome rather than mortality which, while sometimes persuasive, are less clinically meaningful than defined morbidity or mortality data. Many of the trials are small and few describe power or sample size calculations prior to the study. Because the standard of care in resuscitation differs by country (and sometimes hospital) and has evolved over the last 20 years, many of the trials comparing hypertonic saline to a standard protocol have inherently different variables other than the use of a hypertonic solution.

Despite these caveats, when the data are pooled from these trials there would appear to be a trend toward improved survival in trauma and surgery patients, without statistical significance. Although the confidence intervals are wide, a clinically significant difference in survival cannot be ruled out. There is still a requirement for a large, well designed, prospective randomised controlled trial comparing the use of hypertonic saline to isotonic crystalloid in the resuscitation of seriously ill or injured patients.

**Potential for military use**

Military units often operate in austere environments where resources are limited by how much equipment can be carried. Often evacuation to a definitive care facility is delayed for operational reasons. As smaller volumes are needed to expand intravascular volume when using hypertonic saline, there are potential

benefits to its use as a resuscitation fluid on the battlefield, as discussed in a recent review article by Dubick and Atkins (42). These include ease of carriage and administration, and maintenance of blood pressure, cardiac output and peripheral tissue perfusion following injury.

**Adverse effects**

Compared to other fluids used in resuscitation, hypertonic saline is cheap, does not transmit infection, and is unlikely to provoke an anaphylactic reaction. However, the possibility that the use of hypertonic saline may worsen outcome in some patients should not be discounted. Theoretically, in patients with uncontrolled bleeding it may cause continuing haemorrhage by increasing blood pressure to a point where formation of a blood clot is inhibited or disrupted. It may have a direct effect on coagulation, as shown in a recent *in vitro* study using thromboelastography to examine the formation of blood clots following administration of hypertonic saline (43). This demonstrated that following the administration of hypertonic saline the formation of clot may be delayed, although the quality of the clot once formed was not affected. How this relates to coagulation *in vivo* in the trauma patient is unclear.

In head injury patients whose blood brain barrier is disrupted the leak of hypertonic saline into the brain tissue may draw water with it, worsening cerebral oedema and increasing intracranial pressure (44). With a rapid rise in plasma sodium concentration there is a theoretical risk of central pontine myelinolysis, although to date there have been no reported cases, and no post mortem evidence of its occurrence (45). Sodium concentrations may rise up to 170mmol, but usually return to within normal limits within 24 to 48 hours with no apparent adverse effect (46,47). The trials using hypertonic saline to date have not demonstrated a high incidence of adverse events, and it has been suggested that the theoretical disadvantages may not in practice be clinically relevant (25). However, with the small numbers of patients in these trials it would be prudent to wait until larger numbers have been

Table 2. Potential advantages and disadvantages of hypertonic saline.

Advantages	Disadvantages
Rapid and effective volume expansion. Reduction in intracranial pressure. Small overall volumes reduce risk of fluid overload. Lightweight and small volume means ideal for pre-hospital and military use. Low incidence of adverse effects.	Volume expansion short lived. Theoretical problems of hyperchloraemia, hypernatraemia, risk of central pontine myelinolysis. Clinical benefit remains unproven.

exposed to the treatment before coming to any firm conclusions.

## Conclusion

Many questions remain regarding the use of hypertonic saline. It would appear from the trend of results from recent trials that certain subgroups of patients do indeed benefit from the administration of hypertonic saline, although statistical significance has not been demonstrated. In hypotensive head injury patients hypertonic saline is effective in maintaining blood pressure while lowering intracranial pressure although effects on mortality remain undefined. The potential logistical advantages of small volume resuscitation in pre-hospital and military environments should ensure further investigation into its use. Further work is clearly needed before any firm conclusions about its use can be drawn.

## References

- Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999; **27**: 200-10.
- Scierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised controlled trials. *BMJ* 1998; **316**: 961-4.
- Kramer GC. Hypertonic resuscitation: physiologic mechanisms and recommendations for trauma care. *J Trauma* 2003; **54**: S89-99.
- Rotstein OD. Novel strategies for immunomodulation after trauma: revisiting hypertonic saline as a resuscitation strategy for haemorrhagic shock. *J Trauma* 2000; **49**: 580-3.
- Svenson C, Hahn RG. Volume kinetics of Ringer solution, dextran 70, and hypertonic saline in male volunteers. *Anesthesiology* 1997; **87**(2): 204-212.
- Drobin D, Hahn RG. Volume kinetics of Ringer's solution in hypovolemic volunteers. *Anesthesiology* 1999; **90**(1):81-91.
- Tollofsrud S, Tonnessen T, Skraastad O, Noddeland H. Hypertonic saline and dextran in normovolaemic and hypovolaemic healthy volunteers increases interstitial and intravascular fluid volumes. *Acta Anaesthesiol Scand* 1998; **42**: 145-153.
- Jarvela K, Koskinen M, Koobi T. Effects of hypertonic saline (7.5%) on extracellular fluid volumes in healthy volunteers. *Anaesthesia* 2003; **58**(9): 878-81.
- Pascual JL, Khwaja KA, Chaudhury P, Christou NV. Hypertonic saline and the microcirculation. *J Trauma* 2003; **54**(5 Suppl): S133-40.
- Junger WG, Coimbra R, Liu FC, et al. Hypertonic saline resuscitation: a tool to modulate immune function in trauma patients? *Shock* 1997; **8**: 235-241.
- Deitch EA, Shi HP, Feketeova E, Hauser CJ, Xu DZ. Hypertonic saline resuscitation limits neutrophil activation after trauma-hemorrhagic shock. *Shock* 2003; **19**(4): 328-33.
- Doyle JA, Davis DP, Hoyt DB. The use of hypertonic saline in the treatment of traumatic brain injury. *J Trauma* 2001; **50**(2): 367-83.
- Hackbarth RM, Rzeszutko KM, Sturm G, Donders J, Kuldane AS, Sanfilippo DJ. Survival and functional outcome in pediatric traumatic brain injury: a retrospective review and analysis of predictive factors. *Crit Care Med* 2002; **30**(7): 1630-5.
- Qureshi AI, Suarez JJ. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Crit Care Med* 2000; **28**(9): 3301-13.
- Vialet R, Albanese J, Thomachot L, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 ml/kg 7.5% saline is more effective than 2 ml/kg 20% mannitol. *Crit Care Med* 2003; **31**(6): 1683-7.
- Shackford SR, Schmoker JD, Zhuang J. The effect of hypertonic resuscitation on pial arteriolar tone after brain injury and shock. *J Trauma* 1994; **37**(6): 899-908.
- Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 11. Use of hyperosmolar therapy in the management of severe pediatric traumatic brain injury. *Pediatr Crit Care Med* 2003; **4**(3 Suppl): S40-44.
- Walsh JC, Zhuang J, Shackford SR. A comparison of hypertonic to isotonic fluid in the resuscitation of brain injury and hemorrhagic shock. *J Surg Res* 1991; **50**(3): 284-92.
- Ogata H, Luo XX. Effects of hypertonic saline solution (20%) on cardiodynamics during hemorrhagic shock. *Circ Shock* 1993; **41**(2): 113-8.
- Holcroft JW, Vassar MJ, Turner JE, Derlet RW, Kramer GC. 3% NaCl and 7.5% NaCl/dextran 70 in the resuscitation of severely injured patients. *Ann Surg* 1987; **206**(3): 279-88.
- Velasco IT, Pontieri V, Rocha e Silva M, et al. Hyperosmotic NaCl and severe hemorrhagic shock. *Am J Physiol* 1980; **239**: H664-H673.
- de Felipe J Jr, Timoner J, Velasco IT, Lopes OU, Rocha-e-Silva M Jr. Treatment of refractory hypovolaemic shock by 7.5% sodium chloride injections. *Lancet* 1980; **2**(8202): 1002-4.
- Bunn F, Roberts I, Tasker R, Akpa E. Hypertonic versus isotonic crystalloid for fluid resuscitation in critically ill patients (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.
- Simma B, Burger R, Falk M, Sacher P, Fanconi S. A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. *Crit Care Med* 1998; **26**(7): 1265-70.
- Vassar MJ, Perry CA, Holcroft JW. Analysis of potential risks associated with 7.5% sodium chloride resuscitation of traumatic shock. *Arch Surg* 1990; **125**(10): 1309-15.
- Vassar MJ, Perry CA, Holcroft JW. Prehospital resuscitation of hypotensive trauma patients with 7.5% NaCl versus 7.5% NaCl with added dextran: a controlled trial. *J Trauma* 1993; **34**(5): 622-32.
- Vassar MJ, Fischer RP, O'Brien PE, et al. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. The effect of added dextran 70. *Arch Surg* 1993; **128**(9): 1003-11.
- Younes RN, Aun F, Accioly CQ, Casale LP, Szajnbok I, Birolini D. Hypertonic solutions in the treatment of hypovolemic shock: a prospective, randomized study in patients admitted to the emergency room. *Surgery* 1992; **111**(4): 380-5.
- Younes RN, Aun F, Birolini D, et al. (Initial treatment of patients with hypovolemic shock: use of a 7.5% hypertonic solution of NaCl.) *Rev Hosp Clin Fac Med Sao Paulo* 1988; **43**(3): 138-41.
- Bortolani A, Governa M, Barisoni D. Fluid replacement in burned patients. *Acta Chir Plast* 1996; **38**(4): 132-6.
- Caldwell FT, Bowser BH. Critical evaluation of hypertonic and hypotonic solutions to resuscitate severely burned children: a prospective study. *Ann Surg* 1979; **189**(5): 546-52.
- Gunn ML, Hansbrough JF, Davis JW, Furst SR, Field TO. Prospective, randomized trial of hypertonic sodium lactate versus lactated Ringer's solution for burn shock resuscitation. *J Trauma* 1989; **29**(9): 1261-7.

33. Jelenko C, Wheeler ML, Callaway BD, Divilio LT, Bucklen KR, Holdredge TD. Shock and resuscitation. II: Volume repletion with minimal edema using the "HALFD" (Hypertonic Albuminated Fluid Demand) regimen. *JACEP* 1978; **7(9)**: 326-33.
34. Croft D, Dion YM, Dumont M, Langlois D. Cardiac compliance and effects of hypertonic saline. *Can J Surg* 1992; **35(2)**: 139-44.
35. Cross JS, Gruber DP, Burchard KW, Singh AK, Moran JM, Gann DS. Hypertonic saline fluid therapy following surgery: a prospective study. *J Trauma* 1989; **29(6)**: 817-25.
36. Jarvela K, Koskinen M, Kaukinen S, Koobi T. Effects of hypertonic saline (7.5%) on extracellular fluid volumes compared with normal saline (0.9%) and 6% hydroxyethyl starch after aortocoronary bypass graft surgery. *J Cardiothorac Vasc Anesth* 2001; **15(2)**: 210-5.
37. McGough EK, Kirby RR. Hypertonic saline for intraoperative fluid therapy. *Crit Care Med* 1990; **18(4)**: 5193.
38. Shackford SR, Sise MJ, Fridlund PH, et al. Hypertonic sodium lactate versus lactated ringer's solution for intravenous fluid therapy in operations on the abdominal aorta. *Surgery* 1983; **94(1)**: 41-51.
39. Shackford SR, Fortlage DA, Peters RM, Hollingsworth-Fridlund P, Sise MJ. Serum osmolar and electrolyte changes associated with large infusions of hypertonic sodium lactate for intravascular volume expansion of patients undergoing aortic reconstruction. *Surg Gynecol Obstet* 1987; **164(2)**: 127-36.
40. Younes RN, Bechara MJ, Langer B, et al. (Use of a hypertonic solution of 7.5% NaCl in preventing post-declamping hypotension of the abdominal aorta) *AMB Rev Assoc Med Bras* 1988; **34(5)**: 150-4.
41. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. *J Trauma* 1998; **44(1)**: 50-8.
42. Dubick MA, Atkins JL. Small-volume fluid resuscitation for the far-forward combat environment: current concepts. *J Trauma* 2003; **54(5 Suppl)**: S43-5.
43. Tan TS, Tan KH, Ng HP, Loh MW. The effects of hypertonic saline solution (7.5%) on coagulation and fibrinolysis: an in vitro assessment using thromboelastography. *Anaesthesia* 2002; **57(7)**: 644-8.
44. Krausz MM. Controversies in shock research: hypertonic resuscitation - pros and cons. *Shock* 1995; **3(1)**: 69-72.
45. Wade CE, Kramer GC, Grady JJ, et al. Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. *Surgery* 1997; **122**: 609-616.
46. Dubick MA, Wade CE. A review of the efficacy and safety of 7.5% NaCl/6% Dextran in experimental animals and in humans. *J Trauma* 1994; **36**: 323-330.
47. Mattox KL, Maningas PA, Moore EE, et al. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. *Ann Surg* 1991; **213(5)**: 482-9.