

# Hypertonic saline dextran. A review of current literature

Dominic Richardson<sup>1</sup>, Charles D. Deakin<sup>1</sup>

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## Correspondence

Dr Charles D. Deakin

Shackleton Department of Anaesthetics  
Southampton University Hospital NHS Trust  
Tremona Road, Southampton SO16 6YD U.K.  
E-mail: charlesdeakin@doctors.org.uk

<sup>1</sup> Shackleton Department of Anaesthetics,  
Southampton University Hospital

## ABSTRACT:

The optimal resuscitation fluid has long been sought. The concept of small volume resuscitation, 4ml/kg 7.5% hypertonic saline with or without dextran, has been proposed for over 20 years. Initially devised for the pre-hospital management of trauma patients its use is now commonplace in many hospitals.

This review aims to explore the mechanisms of action of hypertonic saline dextran (HSD) and how it differs from conventional crystalloid/colloid resuscitation. Its role in a number of different clinical situations is then evaluated and the potential disadvantages/side effects explored.

HSD has been shown to be a safe alternative to conventional fluid resuscitation. It is an effective volume expander and improves cardiovascular haemodynamics by increasing blood pressure and cardiac output. It improves micro-circulatory flow by drawing fluid from oedematous endothelium into the intravascular space. Its use in penetrating trauma and head injury associated with systemic hypotension improves survival.

The use of HSD is established in the management of trauma victims however its immunomodulatory effects and potential benefits in the perioperative period have yet to be fully elucidated.

## Introduction

The effective management of haemorrhage involves the arrest of bleeding and the replacement of lost volume (1). The ideal agent to replace this loss has long been the issue of debate. The use of crystalloids originated during the First World War and colloids were introduced during World War II. Resuscitation using hypertonic saline (HS) has been proposed for over two decades. It has been shown to significantly improve cardiovascular parameters and reduce crystalloid and blood requirements in both animal models and adult hypovolaemic shock (2, 3). Addition of Dextran 70 has been shown to enhance the effects of hypertonic saline and this combination is now in regular clinical use in some areas (4). Though primarily indicated in hypovolaemic shock, its use has been proposed for head injury, burns, sepsis, multiple organ dysfunction syndrome (MODS) and cardiac surgery. This review critically assesses the current literature for this novel intravenous fluid therapy.

## Physiology of intravenous fluids

Intravenous fluids cause an initial expansion of the vascular compartment. The extent and duration of this expansion depends on the ability of the fluid to freely cross the vascular endothelium. Intravenous normal (0.9%) saline is isotonic and will transit the vascular endothelium relatively rapidly. Dextrose solutions are rapidly metabolised, leaving only water, which lowers the plasma osmolality and accelerates osmotic loss from the vascular compartment.

Hypertonic saline causes an osmotic gradient from the intravascular to extravascular compartment, resulting in recruitment of water from the interstitial and intracellular fluid compartments. The hydrophilic dextran component in hypertonic saline dextran (HSD) prolongs the osmotic effect by binding free water molecules.

## Circulatory effects of HSD

Hypertonic saline increases the plasma volume by 2-3 times the volume infused as opposed to just 1/3 for isotonic solutions. Hence 500mls of hypertonic saline has a volume effect equivalent to approx 3000ml 0.9% saline. In haemorrhagic animal models, a bolus of 4ml/kg HSD increased mean arterial pressure (MAP) and renal blood flow to approx. 80% of baseline and restored cardiac output and glomerular filtration rates (GFR) to levels similar to controls (5).

## Endothelial effects

During periods of shock/hypoperfusion, ischaemic endothelium becomes oedematous and physically restricts blood flow. Administration of HSD to unanaesthetised hypovolaemic swine produced significantly higher blood flows to the myocardium, kidneys, liver and gut (5, 6). A proposed mechanism is that HSD mobilises water from endothelium, thus increasing capillary luminal diameter by shrinking endothelial cells and improving microcirculatory flow (Figure 2) (7).

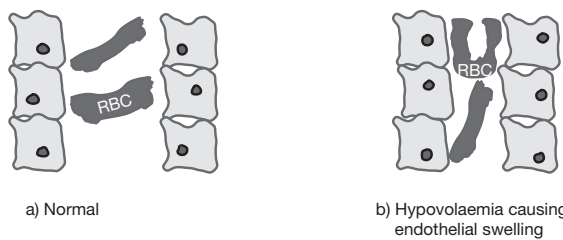


Fig. 2. Hypertonic saline dextran reverses endothelial swelling, restoring blood flow to near normal levels.

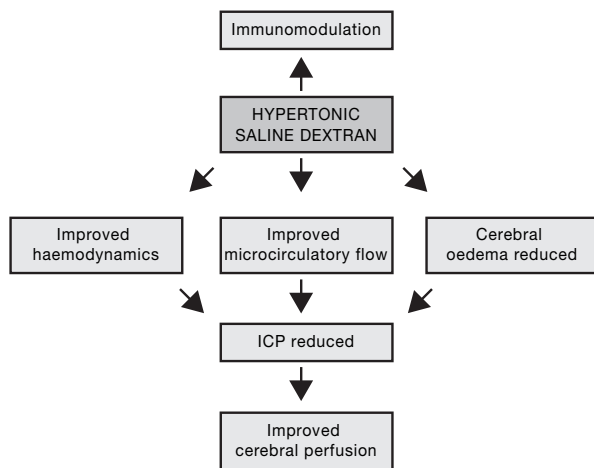


Fig. 3. Potential benefits of hypertonic saline dextran in treating traumatic brain injury.

### Other microcirculatory effects

In a dog model, HS induces a muscular cutaneous precapillary constriction, which aids the shunting of blood to the visceral compartments (8). This is thought to be a response initiated by pulmonary osmoreceptors and mediated by the vagal, sympathetic and renin-angiotensin axis.

### Clinical studies

#### Hypovolaemic shock

Rapid restoration of blood volume and subsequently cardiovascular function are vital in the management of acute hypovolaemia. In the preclinical scenario, administration of large volumes of crystalloid is often not appropriate and small volume resuscitation using HSD was developed as a way of improving haemodynamics without delaying transfer. Its use may also prevent some of the complications of large volume crystalloid infusion. Furthermore the use of HSD becomes more attractive when taking into account its endothelial and microcirculatory effects.

A recent multicentre trial compared the use of HSD in a pre-clinical setting with standard (Randomised Control) care crystalloid therapy. Patients with a systolic blood pressure of 90mmHg or less following blunt or penetrating trauma were randomised to an initial therapy of 250ml HSD or 250ml Ringer's lactate followed by conventional therapy. In the first 24 hours there was no significant difference in survival between the two groups. However for those requiring surgery and those with penetrating injuries survival was significantly increased in the HSD group,  $p = 0.02$  and  $0.01$  respectively (9). This study has been criticised for retrospective analysis of

sub-group data.

In a previous study of pre-clinical use of HSD its administration again has been shown to improve BP more effectively than Ringer's lactate (RL), with a trend towards improved survival, which did not reach statistical significance (10).

HSD use within hospital has been shown to be feasible and safe. In 1992, 70 patients with hypovolaemic shock (systolic BP < 80mmHg) were randomised to receive HSD or isotonic saline with further resuscitation continuing using crystalloids or blood. HSD significantly improved MAP and reduced the volume of blood and crystalloids needed, though with no difference in survival (3).

In an attempt to integrate the current evidence on HSD, Wade et al performed a meta analysis of the current individual studies. A total of 604 patients were identified from 8 trials using the following inclusion criteria.

- (i) Prospective double blinded trials
- (ii) Traumatic injuries with systolic BP < 90mmHg
- (iii) 250ml HSD or 250ml isotonic saline as initial therapy.

This study found that initial treatment with HSD enhanced survival for all injuries with an odds ratio of 1.47. For those requiring surgery for penetrating injuries, the benefits were greater, with an odds ratio of 1.97 (11).

### Traumatic brain injury

Traumatic brain injury remains a major cause of mortality and morbidity in all groups. In major trauma, haematoma, vasogenic oedema and disruption of cerebral capillary endothelial integrity lead to an increase in the volume of the skull contents. This rise in intra-cranial pressure (ICP) reduces cerebral perfusion pressure, worsening oxygenation and causing vasodilatation and further increases in ICP.

The management of traumatic brain injury centres on preventing secondary damage, namely the avoidance of hypoxia and hypotension, which have been well documented to worsen neurological outcome (12, 13).

The potential benefits of HSD in treating traumatic brain injury rely on its haemodynamic effects, its ability to reduce ICP, vasoregulatory effects and possibly immunomodulatory effects. (Figure 3).

The increase in mean arterial pressure (MAP) that occurs following HSD infusion translates directly to an increase in cerebral perfusion pressure (CPP). Although hypertonic saline and Ringer's lactate both improve CBF, hypertonic saline has the benefit of reducing ICP (14). Restoration of MAP using large volume crystalloid infusions may eventually reduce CPP by exacerbating cerebral oedema and increasing ICP (15). HTS and mannitol both exerts their effects on ICP by osmotically withdrawing water from brain tissue (16). Mannitol however may cause significant hypotension through its diuretic action and ultimately reduce CPP. Clinical studies comparing HTS

with mannitol are limited and most are accounts of HTS use when patients have known intracranial hypertension refractory to mannitol. One small study prospectively examined 48 episodes of raised ICP in 10 patients with traumatic sub-arachnoid haemorrhage, where ICP was refractory to mannitol. Bolus doses of 7.5% HTS decreased ICP from 33 to 19 mmHg with an increase in CPP. This effect lasted approx 3 hours and further doses were effective (17).

As discussed, the beneficial circulatory effects of HSD are partly due to its effect on the endothelium. Following shock or trauma, endothelial oedema impairs cerebral oxygen delivery and contributes to cerebral ischaemia. In a swine haemorrhagic shock model, hypertonic saline reduced cortical water content and improved cerebral oxygen delivery and cerebral blood flow for 24 hours post resuscitation (18).

Wade et al. performed a meta-analysis of prospective randomised trials of patients with head injury and hypotension receiving HSD. Primary outcome measures were survival to discharge and 24 hour survival. Those who received HSD were twice as likely to survive than those who did not (19).

#### **Burns**

Following severe burns, extravasation of intravascular fluid leads to volume depletion and cardiovascular dysfunction. Resuscitation using standard crystalloid solution improves cardiac parameters and renal function but can worsen oedema and impairment of gas exchange. Hypertonic fluids have the theoretical appeal of reducing the volume of fluids needed and drawing water back into the intravascular compartment.

Animal studies have shown that HSD helps improve post-burn cardiac function and reduce fluid requirements. Unfortunately these improvements are only seen if hypertonic saline is given within the first four hours of injury and the benefits are not maintained past eight hours (20, 21). Evidence in human trials is scarce. A study of 18 burned patients receiving 4ml/kg HSD or RL showed no significant difference in fluid requirements (22). In contrast, a small study of 65 burned patients recruited to receive hypertonic saline were found to be twice as likely to die and four times more likely to develop renal failure as 39 others receiving RL although pre-hospital care and initial resuscitation differed (23).

These studies are small and not without fault and it seems further work looking at the post resuscitation fluid management in order to prolong the initial benefits of HS is needed.

#### **Immunomodulatory effects**

The effect of HSD on post-traumatic immunological function is arousing much interest. Severe trauma is well known to activate a systemic inflammatory response. In animal models of sepsis administering HTS reduces the albumin leak rate when compared to colloid, Ringers lactate and saline (24). HSD has also been shown to reduce leucocyte activation and

endothelial interaction that occurs during the inflammatory cascade. These studies have yet to be translated into human studies though hold promise for future investigation.

#### **Adverse effects**

##### **Demyelination**

Osmotic demyelination syndrome (ODS) occurs following a rapid rise in plasma sodium, and has been one of the primary concerns when infusing hypertonic saline. In a study of 52 patients who died following administration of HS for traumatic hypotension, none showed evidence of central pontine myelinosis and seven of these had extreme hyperosmolality (osmolality > 350) (25). Hyponatraemia above 160 meq/l occurred in 2 of 55 patients with no neurological symptoms.

##### **Metabolic effects – transient hyperchloraemic acidosis**

Infusion of HSD during haemorrhagic shock in swine results in an immediate hyperchloraemia and corresponding reduction in pH. By 120 min, acid base and electrolytes were normalising in the HSD group and worsening in those animals treated with normal saline (26). An initial hyperchloraemic acidosis has been reported in human trials, though this effect is rapidly spontaneously reversed, with little apparent detriment (25, 10).

##### **Acute renal failure**

Renal insufficiency has been reported with the use of HS. A fourfold increase in the incidence of renal failure has been observed in a small study of patients with severe burn injuries resuscitated using HS (23). However most animal and human studies have shown improved haemodynamics and improved renal blood flow (6, 8, 5)

##### **Use in dehydration**

There are concerns that administering HSD to dehydrated patients in haemorrhagic shock will draw fluid from an already depleted extravascular and intracellular space. The mild hypernatraemia seen in dehydration may also cause an exacerbation of hypernatraemia following HS administration. Currently animal studies have shown that HSD therapy in dehydrated haemorrhage is effective and safe, though currently there are no human studies examining HSD use in dehydrated patients (27, 28, 29).

##### **Exacerbation of bleeding**

The benefits and potential problems of restoring blood pressure before definitive surgical haemostasis has long been debated. However clinical studies of HSD use have not been shown to exacerbate bleeding when compared with isotonic fluid resuscitation, even though the HSD groups have had significantly higher systolic blood pressures (10, 30)

##### **Haematological**

The addition of dextran to hypertonic saline raises concerns regarding problems with bleeding and typing and cross

matching of blood. In vitro studies using 1:5 dilutions of HSD to blood show a slight prolongation of prothrombin time and reduction of platelet aggregation. These effects were also observed using just the hypertonic saline component (31) Similar effects have been observed with isotonic crystalloids and there are no reports of HSD associated coagulopathy.

There have been no reports of the Dextran 70 component of HSD interfering with the cross matching of blood.

### Anaphylaxis

The risk of allergy to dextran exists though in the clinical trials of HSD use, there have been no reports of anaphylactoid-like reactions.

### Extravasation

HSD may cause significant tissue damage if infused inadvertently into peri-venous tissue. Care must be taken to ensure that the peripheral infusion is flowing well, particularly in the prehospital environment.

### Summary and conclusions

Fluid resuscitation using hypertonic saline dextran (approx 4ml/kg) is associated with improved haemodynamics and rapid correction of blood pressure. Importantly, it enhances microcirculatory flow by drawing fluid from oedematous endothelium, improving perfusion. Its use in trauma patients has been shown to improve survival, especially in cases of penetrating trauma and those with hypotension and head injury. Though safe and effective, the results of some studies need to be viewed with caution. Management of trauma patients differs in Europe to the U.S. None of the studies compared HSD use against resuscitation with crystalloid/colloid as occurs in many European countries. A recent Cochran review states that there is still not yet enough data to say whether hypertonic solutions are better than isotonic crystalloid for the resuscitation of patients with trauma, burns or undergoing surgery (32). There are also the concerns regarding tissue extravasation.

Further clinical studies will hopefully further clarify its role in trauma, as well as its use in other conditions such as MODS and sepsis.

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