

REGULAR REVIEW

Hypertonic Saline- Hydroxyethyl Starch In Trauma Resuscitation

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INTRODUCTION

Hypertonic saline hydroxyethyl starch (HS-HES) is one of a number of hypertonic hyperoncotic solutions which have been investigated for the management of hypovolaemic shock. This article examines the mechanism of action of HS-HES and its clinical applications. As the data regarding HS-HES are sparse, hypertonic saline and hydroxyethyl starch are briefly reviewed individually before the clinical benefits of combining the solutions are considered. Hypertonic saline dextran will be considered in a later article in this series. Where data in a particular area relating specifically to HS-HES is not available, the evidence from studies on the component solutions is given, although extrapolation to the use of the combined solution merits caution.

The Rational For Hypertonic Resuscitation

Severe hypovolaemia leads to cardiovascular decompensation, reduced perfusion, oxygen delivery and lactic acidosis which may develop into irreversible cell damage and end organ failure, leading to death. Conventional fluid resuscitation aims to restore adequate tissue perfusion by replacing intravascular volume and in uncontrolled haemorrhage large volumes of crystalloid and colloid are likely to be required to maintain the circulation and peripheral perfusion. Over-vigorous fluid replacement results in loss of vasoconstriction, early thrombus disruption and dilutional coagulopathy and may lead to further bleeding. Acute anaemia decreases oxygen delivery and worsens metabolic acidosis (1). Excess fluid loading worsens cellular oedema.

Hypertonic saline (HS) solutions have been investigated for use in the management of hypovolaemic shock for more than twenty years (2). They rapidly expand intravascular volume by an osmotic effect (3-5) and improve haemodynamic parameters in hypovolaemia in volumes at which isotonic (0.9%) saline is ineffective (3). The term 'small volume resuscitation' has been defined as the primary resuscitation from hypovolaemia and shock by means of a rapid infusion of a small volume of hypertonic saline (4). This should not be confused with limited or hypovolaemic resuscitation where small volumes of "conventional" (ie isotonic) fluids are used, but a deliberately lower resuscitation endpoint is

chosen - typically the maintenance of a radial pulse. A 250ml infusion of HS has equivalent intravascular effects as to 2-3 litres of Hartmann's solution. Further investigation has shown that the effects of HS are far more wide ranging than its action as an osmotic agent alone (5). It has applications for the primary management of traumatic haemorrhagic shock both in hospital and in prehospital management of injury; in the management of critical illness and in major elective surgery.

Mechanism of Actions

Osmotic Effects

HS increases intravascular volume by drawing intracellular water into the intravascular and interstitial spaces (6-9). Under physiological conditions the balance of Starling's forces within the microcirculation causes a small net efflux of water from the intravascular space. Infusion of 4ml/kg 7.5% 2,400mOsm/l HS transiently increases serum osmolarity by 30-50mOsm. This leads to an osmotic shift into the interstitial and vascular spaces and the rapid movement of intracellular water into the interstitium both increases interstitial hydrostatic pressure and dilutes interstitial protein oncotic pressure. Transmicrovascular fluid shift into the intravascular space is further enhanced. These changes in intravascular volume occur almost immediately (10). Plasma volume increases by up to 3ml for each 1ml of HS infused (11). In a human volunteer study, 125-iodine-labelled albumin was used to measure plasma volume changes as hypertonic saline (7.5% HS 4ml/kg) was infused over 30 minutes. The mean volume infused was 260ml and the mean plasma volume increase one hour after infusion was 465ml (7).

This osmotic relocation is similar to the action of other hyperosmotic agents such as mannitol and hyperosmotic glucose (6) which although initially effective in mobilising intracellular water, lead to a significant diuresis and net fluid loss (10). Varying concentrations of HS (1.8 - 20%) have been investigated with 7.5%NaCl found to be the most suitable osmotic component, providing maximum efficiency with an absence of the side effects associated with higher concentrations (5,12).

Haemodynamic Effects

An increase in intravascular volume initiates a number of cardiovascular responses leading to an increase in cardiac output. HS causes peripheral vasodilatation and redistribution of

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regional blood flow. A prolonged increase in venous return increases cardiac preload (13). Cardiac inotropy and contractility are enhanced whilst afterload reduces (5, 11, 14).

Peripheral vascular changes augment blood flow and vasodilatation occurs by two mechanisms. During shock the vascular endothelial cells swell and obstruct the microvasculature, osmotic migration of water out of the cells increases capillary diameter and decreases resistance to flow. HS causes relaxation of vascular smooth muscle as a result of increased osmolarity. Decreased pulmonary vascular resistance results in reduced afterload (5, 10, 11, 14). In addition, there is a decrease in systemic vascular resistance as the increased intravascular water decreases plasma viscosity and improves flow (15). Studies with HS-HES in anaesthetised patients have also demonstrated increased left ventricular preload, increased left ventricular ejection fraction, decreased left ventricular afterload and increased cardiac output compared to isotonic controls (11, 16). Bolus or rapid infusion of HS has been reported to cause transient hypotension associated with vasodilatation (11).

Positive inotropic effects of HS solutions have been variously described (6, 14, 17) with a possibly greater effect in hypovolaemia (11). Enhanced chronotropy has been shown in animal models (18). Myocardial performance may be increased by reduction in myocardial cell oedema or by direct effect on contractility, possibly by increased intracellular uptake of calcium by the myocardium. Early reports suggested that part of the improvement in haemodynamics caused by an infusion of HS was a result of a possible cardiovascular baroreceptor reflex. These reflexes have not been definitively demonstrated and the primary mechanism of improvement appears to be due to volume expansion alone (10).

Microcirculatory Effects

The cellular ischaemia consequent upon the diminution of microvascular flow alluded to above is compounded by delayed reperfusion. Isotonic fluid resuscitation only partially restores blood flow whereas the osmotic reduction of endothelial swelling by hypertonic saline promotes blood flow by widening the capillary diameter (19). Animal models have demonstrated restoration of blood flow with HS after haemorrhagic shock and reduction of ischaemic lesions after regional ischaemia (20). Laser Doppler and intravital microscopy have directly demonstrated improved capillary patency and restoration of local blood flow after administration of HS (21). Improvements in blood flow after treatment with hypertonic saline have been in a variety of microcirculations above that seen in isotonic fluid resuscitation (22-24).

Immunomodulatory Effects

Tissue injury activates a defined immune response. Polymorphonuclear neutrophils (PMN) are chemotactically attracted to the site of injury and then marginate to the vessel walls where they 'roll' along the endothelium interacting with the surface selectins. There is adherence to specific endothelial molecules – a forerunner of intercellular diapedesis. Shock exaggerates the standard response with increased PMN/endothelial interactions, oxygen free radicals and protease release worsening tissue oedema. It is part of the pathophysiology of the systemic inflammatory response (25). Isotonic crystalloids and artificial colloids such as gelofusin, worsen this response by activation of neutrophils and increased expression of neutrophil adhesion molecules, in a dose responsive fashion. HS decreases neutrophil activation and expression (25, 26). Replacement of 10% blood loss in haemorrhagic shock with

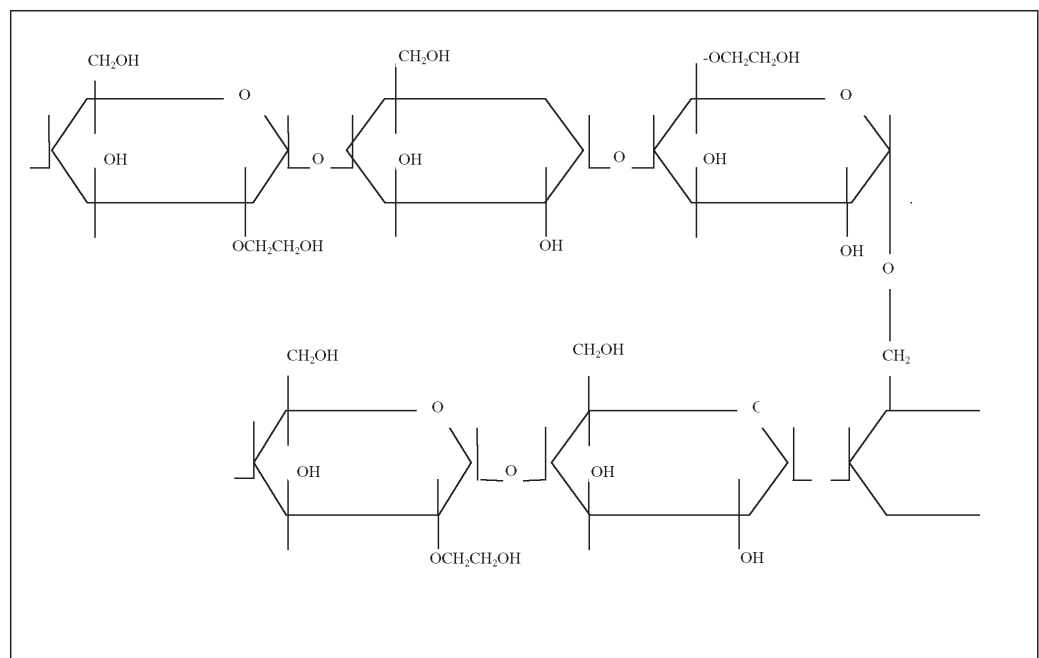


Fig. 1 Starch molecule with C2/C6 hydroxyethyl substitutions.

HS-HES can prevent reperfusion-induced leukocyte stasis/adherence (19). HS reverses Prostaglandin E2 (PGE2) suppression of T-cells – a mediator of immunodepression after trauma and haemorrhage – back to normal levels. (27)

Hydroxyethyl Starch

Hydroxyethyl starch (HES) is a well tolerated colloid associated with a low frequency of anaphylactic reactions. It is protective of the microvasculature in inflammatory states. Medium molecular weight hydroxyethyl starches have minimal effects on renal function and coagulation and are the most common artificial colloids in use in Europe. For historical and commercial reasons only high molecular weight HES is available in the USA (28).

Hydroxyethyl starches are modified natural polymers of amylopectin manufactured from waxy maize. Intravascular amylopectin is broken down by amylase at the 1-4 bonds within minutes of administration. Resistance to degradation by amylase can be increased by substitution of (-OH) groups by hydroxyethyl (-OCH²CH²OH) groups on the glucose rings (29) (Figure 1). Hydroxyethyl starches are classified by molecular weight, by the ratio of C2/C6 hydroxyethylation, by degree of substitution and by concentration (28). The intravascular molecular weight and speed of metabolic breakdown of the HES preparation is responsible for duration of effect with larger molecules persisting for longer. As they are hydrolysed by amylase into smaller molecules, the number of osmotically active molecules within the intravascular space is increased. The threshold for elimination by glomerular filtration is reached at a weight of about 50kDa. Hydroxylation can occur at position C2, 3, or 6 of the D-glucose rings. Hydroxylation at C2 confers greatest resistance to amylase action. Intravascular persistence is enhanced by a higher ratio of glucose molecules hydroxylated at the C2 compared to the C6 position. The degree of molecular substitution describes the number of glucose molecules substituted with hydroxyethyl groups as a proportion of the total number of glucose molecules in the starch molecule. The greater the degree of substitution, the more resistance there is to metabolism. The volume expanding effect is determined by the concentration of

the fluid. Most 6% solutions have a volume expansion of slightly over 100% and 10% solutions have an expansion of 130% (1, 29). Table 1 compares the classification of various types of HES.

Haematological Effects

High molecular weight HES is associated with haemorrhagic complications. Medium molecular weight HES with a low degree of substitution has a minimal effect on coagulation except at high doses (30). The data sheet advises 33ml/kg daily maximum of HES 200/0.5 although this is often exceeded in clinical practice without problems with bleeding (1). In common with all artificial colloids, high volume infusion may lead to decreased factor VIII, von willebrand factor and platelet dysfunction (28, 31). Medium molecular weight HES does not interfere with cross matching of blood (30).

Renal effects

One study has reported adverse effects of highly substituted HES 200/0.6 on transplanted kidney function. This was not replicated in similar studies. Other studies have shown lower molecular weight solutions are safe in kidney organ donors. Some extravasated HES is taken up by the reticuloendothelial system. Deposits have been found in skin, spleen, liver and intestine. In patients receiving more than three grams over a few days an enduring pruritis may occur (30).

Modulation of the inflammatory response

Medium molecular weight HES has been shown to be beneficial in reducing the inflammatory response associated with trauma by decreasing expression of leukocyte adhesion molecules and by physically plugging leaky capillaries. HES encourages the restoration of macrophage function after haemorrhagic shock (29, 32).

Addition of colloid to hypertonic saline

The osmotic effect of HS alone on haemodynamics is transient (33, 34). The duration of action of HS can be prolonged by combining it with a colloid (5, 6, 35, 36). Different colloids have been combined with HS in both laboratory and clinical investigations including a variety of hydroxyethyl starch (HES) and dextran solutions.

Prough *et al* demonstrated the additive effects of 20% HES to 7.2% saline in anaesthetised dogs. Infusion of HS alone caused transient resuscitation. HS-HES caused a prolonged improvement in haemostability (37). HS-HES has been shown to produce a greater improvement in haemodynamic and oxygen transport variables than 6% HES alone (16). Hyperosmotic saline and not the oncotic component of the infusion was found to cause rapid normalisation of the circulating blood volume, cardiac output

Table 1. Classification of hydroxyethyl starches by physical characteristics.

Initial molecular weight	High	450-480 kDa
	Medium	130-200 kDa
	Low	40-70kDa
C2 to C6 ratio	High	More than 8
	Low	Less than 8
Degree of substitution	High	0.6-0.7
	Low	0.4-0.5
Concentration	High	10%
	Low	6%

and systemic haemodynamics (34, 38). Christ *et al* (15) studied the effect of HS (7.5%)/HES (6%) in patients undergoing abdominal aortic aneurysm repair. Following HS-HES infusion there was a significant decrease in haemoglobin and haematocrit suggesting rapid expansion of intravascular volume.

Clinical applications for hypertonic saline-hydroxyethyl starch

Hypertonic saline – hydroxyethyl starch has the potential for use in a number of different clinical situations. The concept of small volume resuscitation was originally developed for the management of patients with traumatic hypovolaemia. This has been applied both at the scene of injury (39) and in the hospital emergency department (40). Hypertonic colloid solutions are being investigated in the ongoing development of resuscitation strategies for the battlefield (41). The microcirculatory and immunomodulatory effects of HS-HES described above mean that it is also useful in a variety of other non-trauma situations (20, 21, 42).

Fluid resuscitation in trauma and critical illness

In animal models of shock, HS-HES rapidly restores mean arterial blood pressure and cardiac output to near pre-shock levels (15, 33, 38). In contrast to isotonic solutions, HS-HES prevents intravascular leukocyte adherence (19) and attenuates the immunomodulatory response. Studies also show that both HS and HS-HES improve regional blood flow to vital organs. Microcirculatory failure and reperfusion injury are early contributors to hepatic failure after shock. HS-HES is effective in restoring perfusion to liver sinusoids after haemorrhagic shock by causing cell shrinkage, widening capillaries and increasing perfusion pressure. This is in contrast to crystalloid volume therapy in which sinusoids may remain non-perfused despite restoration of systemic haemodynamics (17, 19). Pancreatic ischaemia from shock can lead to active tissue damage and pancreatitis. In an animal model, HS-HES was as effective as a ten fold volume of isotonic HES and superior to a forty fold volume of Ringers Lactate in regard to restoration of the pancreatic microcirculation (24). In the same way isotonic fluid therapy after shock can cause a noticeable deterioration in intestinal perfusion as tissue oedema develops. A porcine model demonstrated hyperaemic reperfusion of the intestinal microcirculation with improvement in function (recovery of pH_i) after resuscitation with HS-HES (23).

Wade *et al* (43) performed a meta-analysis of prospective, randomised clinical trials of hypertonic hyperoncotic (hyperosmolar saline dextran) use in treatment of traumat-

ic injury. This included a total of 1170 patients. There was no significant difference in survival between patients treated with hypertonic saline and with ringers lactate. There was a 5.1% improved survival rate at thirty days for hypertonic dextran compared to ringers lactate alone. This demonstrates the importance of a colloid component on clinical impact (40, 43)). Hypotensive trauma patients with severe head injury are a subgroup that may benefit most from hypertonic saline resuscitation (44).

Concern has been expressed that fluid resuscitation before surgical control of haemorrhage may lead to dilution of clotting factors, dislodging of blood clots and worsening of clinical condition. Clinical observations of the use of hypertonic saline infusions for hypotensive trauma victims have not demonstrated any increase in rebleeding or need for blood products. An animal model of uncontrolled splenic bleeding demonstrated that controlled resuscitation with hyperoncotic hypertonic saline was superior to a no-fluid resuscitation approach (45).

Mols *et al* (39) compared 250ml HS-HES and 250ml HES given to trauma patients before transfer to hospital. These patients had mainly suffered blunt trauma. They found a higher initial blood pressure rise in the HS-HES group and decreased requirements for crystalloid (359ml vs 745ml) and colloid (84ml vs 268ml) compared with the HES group during transfer to the emergency department. No episodes of hypotension or thrombophlebitis associated with HS-HES were observed.

Sepsis

In septic shock the volumes of isotonic fluids required to restore adequate systemic perfusion pressure can be very large. This potentiates the development of tissue oedema through leaky capillaries, contributing to the reduction in organ oxygen extraction capabilities (46). Thus 'adequate' systemic arterial pressures are achieved at the expense of end organ perfusion. Animal studies show use of HS or HS-HES leads to more rapid restoration of arterial blood pressure and cardiac output, with a significant improvement in oxygen delivery and consumption compared with isotonic (0.9%) saline or hydroxyethyl starch alone (6, 14). Cardiac output is improved by changes in myocardial preload, and oxygenation, distribution of cardiac output to vital organs is altered and pathological oedema within the microcirculation is reversed. In a series of hyperdynamic septic patients infusion of HS-HES led to increased preload (PCWP), decreased afterload (SVR) and increased cardiac output. Oxygen delivery and oxygen consumption were improved. Haemodynamic parameters returned to baseline by 90 minutes (14).

Head injury

Hypertonic saline treatment causes osmotic dehydration and cell shrinkage. Dehydration of the brain reduces intracranial pressure and therefore improves cerebral perfusion pressure (20). HS and HS-HES improve cerebral blood flow in animal models of haemorrhagic shock (47). Strecker *et al* demonstrated return of somatosensory evoked potentials in rabbits treated after 15 minutes of global ischaemia with HS(7.5%) HES(10%) but failed to show improved functional recovery with HES 10% alone (48). Small volume resuscitation with hyperoncotic hypertonic saline may lead to improved survival in patients with haemorrhagic shock and head injury (44). HS-HES improves cerebral blood flow after cerebral ischaemia (48). HS-HES infusion also appears to protect brain function after recovery from cardiopulmonary arrest (20).

Adverse effects

“Hyperhaes[®]” (7.2%NaCl/6%hydroxyethyl starch) has been used in mainland Europe for more than a decade. An Austrian audit using pharmacovigilance data found a very low complication rate in the use of HS-HES of 6% from 1991 to 2000. They reported complication rates of 5 per 100 000 units given and 8-16 per 100 000 patients. There were three anaphylactic/anaphylactoid reactions to HES and one case of extreme overdose which resulted in hyperosmolar syndrome. No fatalities occurred (49).

Problems associated with administration

Sensations of heat and compression in the cannulated arm and the thorax have been reported by both normovolaemic and hypovolaemic subjects who received HS infusions while awake. Transient flushing, shivering and headache have also been described. Symptoms gradually resolved on completion of infusion (7). Similar symptoms occurred with the infusion of HS-dextran (50). Tissue damage caused by extravasation has been documented and intravenous line patency must be assured before infusion (51).

Cardiovascular complications

Transient self limiting hypotension and bradyarrhythmias may occur with rapid infusion of HS solutions, particularly in patients with limited cardiac reserve (15). Volume overload may occur with injudicious doses or repeated use (49). These effects were not seen in a study of hypovolaemic trauma patients. It may be that the vasodilating effect of HS-HES is less significant in patients with hypovolaemic vasoconstriction (39)

Biochemical complications

A 4ml/kg dose of HS-HES contains a considerable osmolar load. Repeated use causes hypernatraemia and raised osmolarity (36, 52). Hypernatraemia and hyperosmo-

larity can result in cerebral dysfunction manifesting as disorientation, confusion and seizures, by disruption of the blood brain barrier (33). The danger of pontine demyelination resulting from rapid transfusion of hypertonic saline is primarily relevant in hyponatraemic patients (14).

A number of studies using HS measured plasma sodium, chloride and osmolarity during and after infusion. In one study, when 8 healthy, normonatraemic volunteers received 4ml/kg 7.5% HS over 30 minutes, the highest sodium concentration was 158mmol/l at the end of infusion. The highest sodium at 90 minutes was 151mmol/l. Serum osmolarity was highest at the end of infusion at 326mosm/l and had decreased to 310mosm/l at 90 minutes (7). In other studies HS-HES caused transiently high plasma sodium and osmolarity which had returned to within normal limits by 12 to 24 hours. No neurological disturbances or other ill effects were reported (14, 15, 33). Transient hypokalaemia may occur at administration, presumably due to intracellular potassium shift (6). Repeated use may cause hyperchloraemic acidosis (36, 52).

Haematological complications

All intravenous fluids will cause a dose related dilutional coagulopathy. In an *in vitro* study of whole human blood, coagulation after addition of HS was measured with thromboelastography (TEG). Formation of clot was delayed when HS was added compared to the same volume of 0.9% saline, but the quality of the clot was not affected (53). In a study of 27 patients undergoing abdominal surgery, effects on coagulation of giving 4ml/kg of HS-HES or HES 6% were observed. The HS-HES group had more prolonged TEG, slowed platelet aggregation and increased ATP release compared to the HES 6% group. This was attributed to dilutional effects of HS increasing membrane osmotic stress (54). These studies did not look at clinically relevant coagulopathy. In the clinical situation larger volumes of iso-osmotic fluid would be given for volume resuscitation. Christ *et al* found that patients receiving HS-HES during abdominal aortic aneurysm repair surgery had significantly less blood loss than the controls. Prothrombin and partial thrombin times were not significantly different between the two groups (15). Effects on coagulation may be more pronounced in patients with haemorrhagic shock. Effective use of HS increases cardiac output and regional blood flow. This is postulated as a mechanism by which bleeding increases (53). Clinically relevant coagulation disorders may occur with repeated use or overdose (28).

Renal complications

In one study in burns patients HS was associated with worsened outcome (55). This

may be due to inadequately treated hypovolaemia. (30) HS has a diuretic effect in healthy volunteers. Renal function is improved by increasing MAP and reducing renal vascular resistance (7). In other clinical trials renal function was unaltered or better than the controls (15, 33).

Conclusion

The search for the ideal intravenous fluid continues unabated. Although there is a developing consensus regarding how much fluid to give albeit with a number of caveats, there is no generally accepted view about which fluid should be used or indeed whether different fluids may be of value in different circumstances or at different times in the same patient. This situation has been compounded by a lack of large scale comparative trials.

However, there is increasing evidence that both hypertonic saline and hydroxyethyl starch have a number of theoretical and practical advantages in terms of fluid haemodynamics and immuno-modulatory effects. The resuscitation of head injured patients, currently perhaps more controversial than any other aspect of fluid resuscitation appears to be a particular area where HS-HES solutions show promise.

Hypertonic saline-hydroxyethyl starch is administered via peripheral access and has a rapid onset of effect. It is inexpensive, is not derived from an animal source and has a low incidence of allergy. As well as osmotically mediated plasma expansion leading to rapid recovery of macrohaemodynamics, it has microcirculatory benefits. The manipulation of plasma tonicity has an immunomodulatory effect on the mechanisms of systemic inflammatory response syndrome associated with shock states. HS-HES provides protection to vital organs. HS-HES has a limited duration of action; effects are lost by 90-120 minutes post infusion. Initial resuscitation based on hypertonic saline must be followed by continuing conventional fluid resuscitation to avoid the risks of dehydration and significant hypernatraemia. HSHES is not without adverse effects and like all drugs injudicious use may lead to further injury. As with all fluids, overdose will cause volume overload.

Prediction of future trends in medicine is fraught with danger, but the currently available evidence suggests that HS-HES has properties that make it particularly suitable for the resuscitation of hypovolaemic shock, probably given as a single "dose" or in limited quantities during early resuscitation and followed by "conventional" (whatever that might be) fluid therapy. As a consequence, it may be more useful to think of HS-HES as a "drug" rather than a fluid. We are a very long way from a "magic bullet" for shock, but the careful use of HS-HES may be a step in the right direction.

References

- Nolan J. Fluid resuscitation for the trauma patient. *Resuscitation* 2001;48:57-69.
- Velasco IT, Pontieri V, Rocha-e-Silva M, Lopes OU. Hyperosmotic NaCl and severe hemorrhagic shock. *Am J Physiol* 1980;239:H664-73.
- Boldt J, Kling D, Weidler B *et al.* Acute preoperative hemodilution in cardiac surgery: Volume replacement with a hypertonic saline-hydroxyethyl starch solution. *Journal of Cardiothoracic and Vascular Anesthesia* 1991;5:23-8.
- Kreimeier U, Prueckner S, Peter K. Permissive hypotension *Schweiz Med Wochenschr.* 2000; 21;130(42):1516-24.
- Strecker U, Dick W, Madjidi A, Ant M. The effect of the type of colloid on the efficacy of hypertonic saline colloid mixtures in hemorrhagic shock: dextran versus hydroxyethyl starch. *Resuscitation* 1993;25:41-57.
- Armistead CW, Vincent J-L, Preiser J-C, De Backer D, Thuc Le Minh. Hypertonic Saline Solution-Hetastarch for fluid Resuscitation in Experimental Septic Shock. *Anesth Analg* 1989; 69:714-20.
- Jarvela K, Koskinen M, Koobi T. Effects of hypertonic saline (7.5%) on extracellular fluid volumes in healthy volunteers. *Anaesthesia* 2003,58:874-910.
- Mazzoni MC, Borgstrom P, Arfors KE, Intaglietta M. Dynamic fluid redistribution in hyperosmotic resuscitation of hypovolaemic haemorrhage. *Am J Physiol* 1988;255(3pt 2):H 629-37.
- Kreimeier U, Ruiz-Morales M, Messmer K. *Circ Shock.* 1993;39(2):89-99.
- Kramer GC. Hypertonic resuscitation: Physiologic mechanisms and recommendations for trauma care. *J Trauma* 2003;54:S89-S99.
- Goertz AW, Mehl T, Lindner KH *et al.* Effect of 7.2% hypertonic saline/6% hetastarch on left ventricular contractility in anaesthetised humans. *Anesthesiology* 1995;82:1389-95.
- Smith GJ, Kramer GC, Perron P, Nakayama S, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscitation of bled sheep. *J Surg Res* 1985;39:517-528.
- Kreimeier U, Frey L, Messmer K. Small-volume resuscitation. *Curr. Opinion Anaesth* 1993;6:400-408.
- Hannemann L, Reinhart K, Korell R, Spies C, Bredle D L. Hypertonic saline in stabilized hyperdynamic sepsis. *Shock* 1996;5(2):130-4.
- Christ F, Niklas M, Kreimeier U, Lauterjung L, Peter K and Messmer K. Hyperosmotic-hyperoncotic solutions during abdominal aortic aneurysm (AAA) resection. *Acta Anaesthesiol Scand* 1997; 41:62-70.
- Sirieux D, Hongnat J-M, Delayance S *et al.* Comparison of the acute hemodynamic effects of hypertonic or colloid infusions immediately after mitral valve repair. *Crit Care Med* 1999;27(10): 2159-2165.
- Bauer M, Marzi I, Ziegenfub T, Seeck G, Buhren V, Larsen R. Comparative effects of crystalloid and small volume hypertonic hyperoncotic fluid resuscitation on hepatic microcirculation after hemorrhagic shock. *Circulatory Shock* 1993;40:187-93.
- Mouren S, Delayance S, Mion G *et al.* Mechanisms of increased myocardial contractility with hypertonic saline solutions in isolated blood perfused heart. *Anaesth. Analg* 1995;81:177-182.
- Vollmar B, Lang G, Menger MD, Messmer C. Hypertonic hydroxyethyl starch restores hepatic microvascular perfusion in hemorrhagic shock. *Am J Physiol* 1994;266:H1927-34.
- Fischer M, Hossmann K-A. Volume expansion during cardiopulmonary resuscitation reduces cerebral no-reflow. *Resuscitation* 1996;32:227-40.
- Pascual JL, Khwaja KA, Chaudhury P, Christou NV. Hypertonic Saline and the Microcirculation. *J Trauma* 2003;54:S133-144.
- Boldt J, Zickmann B, Herold C, Ballesteros M, Dapper F, Hemplemann G. Influence of hypertonic volume replacement on the microcirculation in cardiac surgery. *BJA* 1991;67:595-602.

23. Jonas J, Heimann A, Strecker U, Kempshi O. Hypertonic/hyperoncotic resuscitation after intestinal superior mesenteric artery occlusion: Early effects on circulation and intestinal reperfusion. *Shock* 2000;14(1):24-9.
24. Vollmar B, Preissler G, Menger MD. Small-volume resuscitation restores hemorrhage-induced microcirculatory disorders in rat pancreas. *Crit Care Med* 1996;24(3):445-450.
25. Pascual JL, Khwaja KA, Ferri LE, Giannias B, Evans DC, Razek T, Michel RP, Christou NV. Hypertonic saline resuscitation attenuates neutrophil lung sequestration and transmigration by diminishing leukocyte-endothelial interactions in a two-hit model of hemorrhagic shock and infection. *J Trauma* 2003;54:121-132.
26. Rhee P, Wang D, Ruff P, Austin B, DeBraux S, Wolcott K, Burris D, Ling G, Leon S. Human neutrophil activation and increased adhesion by various resuscitation fluids. *Crit Care Med* 2000;28(1):74-78.
27. Coimbra R, Junger WG, Liu FC, Loomis WH, Hoyt DB. Hypertonic/hyperoncotic fluids reverse prostaglandin E2 (PGE2)-induced T-cell suppression. *Shock* 1995;4(1):45-9.
28. Treib J, Baron JF, Grauer MT, Strauss RG. An international view of hydroxyethyl starch. *Intensive Care Med* 1999;25(3):258-68.
29. Dieterich H-J. Recent developments in European colloid solutions. *J Trauma* 2003;54:S26-S30.
30. Sutcliffe AJ. Crystalloids and colloids for volume replacement. *Trauma* 1999;1:115-123.
31. Kapiotis S, Quehenberger P, Eichler H-G, Schwaringer I, Partan C, Schneider B, Lechner K, Speiser W. Effect of hydroxyethyl starch on the activity of blood coagulation and fibrinolysis in healthy volunteers: Comparison with albumin. *Crit Care Med* 1994;22(4):606-12.
32. Gosling P. Salt of the earth or a drop in the ocean? A pathophysiological approach to fluid resuscitation. *Emerg Med J* 2003;20:306-315.
33. Boldt J, Kling D, Herold C, Dapper F, Hemplemann G. Volume therapy with hypertonic saline hydroxyethyl starch solution in cardiac surgery. *Anaesthesia* 1990;45:928-934.
34. Maningas PA, DeGuzman LR, Tillman FJ, Hinson CS, Priegnitz KJ, Volk KA, Bellamy RF. Small volume infusion of 7.5% NaCl in 6% Dextran 70 for the treatment of severe haemorrhagic shock in swine. *Ann Emerg Med* 1986;15:1131-1137.
35. 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.
36. Schwarz S, Schwab S, Bertram M, Aschoff A, Hacke W. Effects of Hypertonic Saline Hydroxyethyl Starch Solution and Mannitol in Patients with increased intracranial pressure after stroke. *Stroke* 1998;29:1550-1555.
37. Prough DS, Whitley JM, Taylor CL, DD Deal, DeWitt DS. Small-volume resuscitation from hemorrhagic shock in dogs: Effects on systemic hemodynamics and systemic blood flow. *Crit Care Medicine* 1991;19(3):364-372.
38. Velasco IT, Rocha-e-Silva M, Oliveira MA, Olivera MA, Silva RI. Hypertonic and hyperoncotic resuscitation from severe haemorrhage in dogs: a comparative study. *Crit Care Med* 1989;17:261-264.
39. Mols P, Robert P, Henry B, Fox A, Gillet JB, Flamand JP, Bepperling F. Study on the feasibility and haemodynamic efficacy of intravenous administration of small volume 7.2% NaCl/6% hydroxyethyl starch 200/0.5 in trauma patients during the prehospital period - A pilot study. *JEUR* 1999;3: 99-104.
40. Kreimeier U. Blood volume--what brings us to the new millennium? *Anaesthesist*. 2001;50(6):429-31.
41. Dubick MA, Atkins JL. Small-volume fluid resuscitation for the far-forward combat environment: Current concepts. *J Trauma* 2003;54:S43-45.
42. Doyle JA, Davis DP, Hoyt DB. The use of hypertonic saline in the treatment of traumatic brain injury. *J Trauma* 2001;50:367-383.
43. Wade CE, Grady JJ, Kramer GC, Younes RN, Gehlsen K, Holcroft JW. Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma* 1994;42(5):S61.
44. Vassar MJ, Fischer RP, O'Brien PE, Bachulis BL, Chambers JA, Hoyt DB, Holcroft JW. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride: the added effect of dextran 70. *Arch Surg* 1993;128:1003-1013.
45. Varicoda EY, Poli de Figueiredo LF, Cruz RJ, Silva LE, Rocha e Silva M. Blood loss after fluid resuscitation with isotonic or hypertonic saline for the initial treatment of uncontrolled hemorrhage induced by spleen rupture. *J Trauma* 2003;55:112-117.
46. Marciel F, Mook M, Zhang H, Vincent J-L. Comparison of hypertonic with isotonic saline hydroxyethyl starch solution on oxygen extraction capabilities during endotoxic shock. *Shock* 1998;9(1):33-39.
47. Fischer M, Dahmen A, Standop J, Hagendorff A, Hoelt A, Krep H. Effects of hypertonic saline on myocardial blood flow in a porcine model of prolonged cardiac arrest. *Resuscitation* 2002;54:269-280.
48. Strecker U, Dick W, Heimann A, Kempshi O. Hypertonic-hyperoncotic HES improves outcome from global cerebral ischaemia. *Anaesthesiology* 1993;79:A577.
49. Schimetta W, Schohl H, Kroll W, Polz W, Polz G, Mauritz W. Safety of hypertonic hyperoncotic solutions- a survey from Austria. *Wein Klein Wochenschr* 200;114(3):89-90.
50. Tollosfrud S, Tonnessen T, Skraastad O, Noddeland H. Hypertonic saline and dextran in normovolaemic and hypovolaemic healthy volunteers increases interstitial and intravascular fluid volumes. *Acta Anaesthesiologica Scandinavica* 1998;42:145-53.
51. Perera AM, Porter KM. The role of hypertonic saline dextran in trauma resuscitation. *Trauma* 2002;4:189-201.
52. Moon PF, Kramer GC. Hypertonic saline-dextran resuscitation from haemorrhagic shock induces transient mixed acidosis. *Crit Care Med*. 1995;23:323-331.
53. Tan TS, Tan KHS, Ng HP and Loh MW. The effects of hypertonic saline solution (7.5%) on coagulation and fibrinolysis: an in vitro assessment using thromboelastography. *Anaesthesia* 2002;57:644-8.
54. Scherer R, Giebler R, Kampe S, Kox WJ. Effects of hypertonic saline hydroxyethyl starch on collagen-induced platelet aggregation and ATP secretion. *Infusionsther Transfusionsmed* 1994;21:310-4.
55. Huang PP, Stucky FS, Dimick AR et al. Hypertonic sodium resuscitation is associated with renal failure and death. *Ann Surg* 1995;221:543-57.