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Hyperosmotic–hyperoncotic solutions

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Since the first descriptions of the use of 7.5% hypertonic saline for resuscitation of haemorrhage in 1980, there has been substantial animal research and clinical evaluation of small volume resuscitation. Most interest has focused on combined hyperosmotic and hyperoncotic colloid formulations. Infused hyperosmotic NaCl rapidly expands plasma volume, while the hyperoncotic colloid sustains the volume expansion. Other contributing factors to the efficacy of these solutions are increased cardiac effectiveness and peripheral vasodilation. The most often studied solution, 7.5% NaCl/6% dextran 70, offers promise to reduce the mortality of traumatic hypotension and head injury when used as an initial treatment. Future hyperosmotic–hyperoncotic formulations with different solutes may provide specific beneficial pharmacological properties in addition to the established cardiovascular effects of hyperosmolarity. A particularly promising formulation might be a combination solution of an oxygen carrier colloid, for example, haemoglobin, and a hyperosmotic crystalloid.

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The ideal fluid for intraoperative volume support and for resuscitation of trauma, haemorrhage and burn injuries remains to be developed. Substantial interest and extensive pre-clinical and clinical experience has been

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accumulated with the use of hypertonic saline solutions for these purposes (Baue et al, 1967; Messmer et al, 1967; Monafo, 1984; Shimazaki et al, 1977; Shackford et al, 1983; Cross et al, 1989). Mildly hyperosmotic saline solutions (1.5–2.0%) have been used in studies of intraoperative volume replacement (Shackford et al, 1983; Cross et al, 1989) and for the resuscitation of major burns (Monafo, 1970; Shimazaki et al, 1977). In general, these mildly hypertonic solutions are reported to reduce fluid volume requirements, but to date such formulations have not received widespread usage. More recently, there has been a focused research effort on the use of hyperosmotic 2400 mOsm saline mixed with a hyperoncotic colloid for small-volume resuscitation.

In this chapter, we review the discovery, physiology and clinical testing of 2400 mOsm hyperosmotic–hyperoncotic solutions for the treatment of trauma. We conclude with a short discussion of possible future formulations. In this review, more emphasis will be placed on the hyperoncotic colloid component as Chapter 6 in this volume focuses on the hyperosmotic crystalloid component. Other recent reviews consider the use of hypertonic saline dextran for the military (Dubick and Bruttig, 1996), pre-hospital trauma (Moore, 1991; Vassar and Holcroft, 1992; Dubick and Wade, 1994), and the overall clinical record of 7.5% NaCl (Kramer and Poli de Figueiredo, 1995).

7.5% HYPERTONIC SALINE

The first studies

Velasco et al studied dogs subjected to haemorrhagic shock and reported that 7.5% NaCl infused in a volume equal to only 10% of shed blood volume rapidly restored arterial pressure and cardiac output to base-line values and led to 100% long-term survival (Velasco et al, 1980). A control group had 0% survival when resuscitated with normal saline in a volume equal to that of the hypertonic saline. The first study of 7.5% NaCl by our group showed that a 2 minute bolus infusion of 7.5% NaCl equal to 10% shed blood volume rapidly normalized blood pressure and cardiac output in haemorrhaged conscious sheep, but the improvements were transient (Nakayama et al, 1984). Despite the transient nature of the response, we were impressed by the rapid onset of the effects; nearly all the haemorrhaged sheep treated with hypertonic saline stood up before the infusion was finished and exhibited normal blood pressures.

Different hyperosmotic solutes

Rapid but transient improvements were found to occur with most hyperosmotic solutes. Smith et al compared resuscitation in haemorrhaged sheep using small-volume infusions of different 2400 mOsm solutions, including: sodium chloride; sodium acetate–sodium chloride in a molar ratio of 1:1;

glucose; mannitol–sodium chloride in a molar ratio of 3:2; and sodium bicarbonate (Smith et al, 1985). The rapid improvement in blood pressure and cardiac output was produced by the increased osmolality *per se* and did not require either sodium or chloride. Figure 1 shows data comparing the effectiveness of a 4 ml/kg bolus infused over 2 minutes for these five hyperosmotic solutions for the treatment of haemorrhaged sheep (Smith et al, 1985). Mean arterial pressure and cardiac output are plotted at the end of a

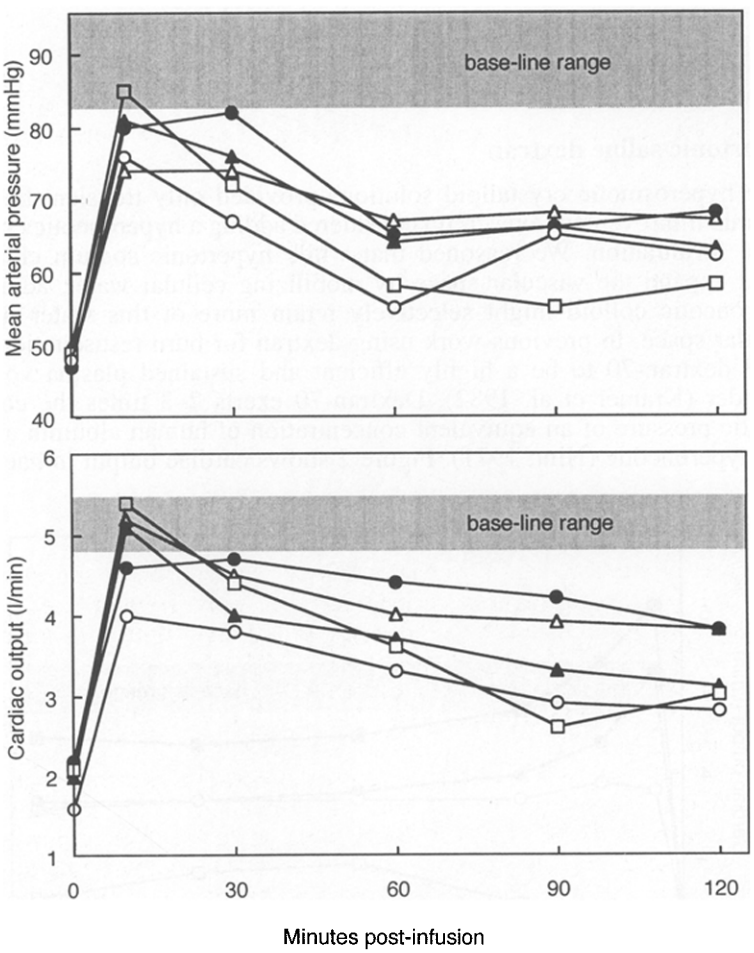

Figure 1. The effectiveness of five different 2400 mOsm solutions—sodium chloride (●——●); sodium acetate–sodium chloride in a molar ratio of 1:1 (△——△); glucose (□——□); mannitol–sodium chloride in a molar ratio of 3:2 (▲——▲); and sodium bicarbonate (○——○) all infused as a 4 ml/kg 2 minutes bolus over 2 minutes to treat haemorrhaged sheep (Smith et al, 1985). During the induced haemorrhage, mean arterial pressure was maintained at 50 mmHg for 2 hours. The graph shows mean arterial pressure and cardiac output at the end of haemorrhage and for 120 minutes post treatment.

2 hour haemorrhage (blood loss = 40–45 ml/kg) and thereafter, for 120 minutes after the bolus infusion of each solution. Blood pressure and cardiac output were rapidly restored to near-normal levels after infusion. Subsequently, arterial pressure and cardiac output slowly declined. However, the decline was slowest with the hypertonic NaCl and the hypertonic NaCl–Na acetate. Hypertonic bicarbonate caused marked alkalosis and was the least effective solution. Hypertonic glucose and mannitol were initially effective but were associated with a large diuresis and fluid losses substantially greater than the infused dose.

HYPERONCOTIC COLLOID

Hypertonic saline dextran

Since hyperosmotic crystalloid solutions provided only transient haemodynamic improvement, our group considered adding a hyperoncotic colloid to the formulation. We reasoned that while hypertonic sodium chloride would expand the vascular space by mobilizing cellular water, adding a hyperoncotic colloid might selectively retain more of this water in the vascular space. In previous work using dextran for burn resuscitation, we found dextran-70 to be a highly efficient and sustained plasma volume expander (Kramer et al, 1982). Dextran-70 exerts 2–3 times the colloid osmotic pressure of an equivalent concentration of human albumin and is thus hyperoncotic (Hint, 1971). Figure 2 shows cardiac output in haemor-

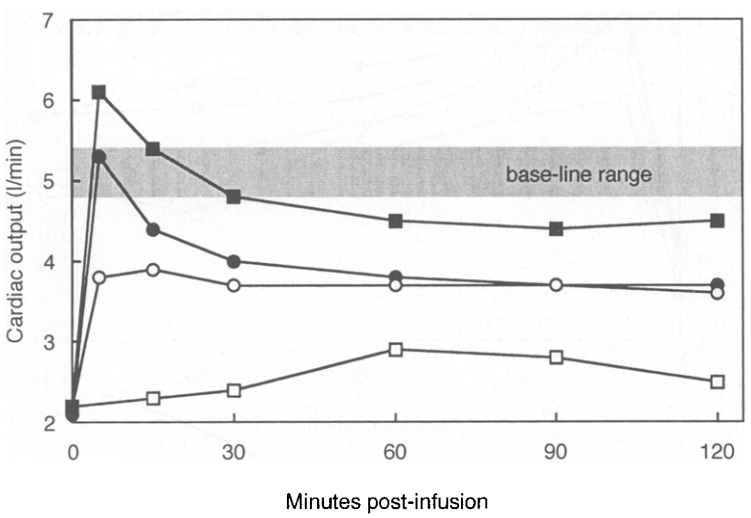

Figure 2. Comparison of cardiac output in haemorrhaged sheep resuscitated with HS alone (●——●), HSD (■——■), isotonic dextran (○——○) and no resuscitation (□- - - -□) (Smith et al, 1985). All solutions were 4 ml/kg; hypertonic saline alone = 7.5% NaCl; HSD = 7.5% NaCl–6% dextran-70; and isotonic dextran = 6% dextran-70 in 0.9% NaCl.

rhaged sheep after resuscitation with: (a) a mixture of hypertonic 7.5% NaCl mixed with 6% dextran-70 (HSD); (b) hypertonic 7.5% NaCl alone (hypertonic saline); (c) 6% dextran-70 in isotonic saline; and (d) no resuscitation (Smith et al, 1985). HSD resulted in a significantly higher and more sustained cardiac output, mean arterial pressure and plasma volume, while the total peripheral resistance was lower when compared with hypertonic saline alone or dextran alone.

Several groups subsequently evaluated the resuscitation effects of HSD compared with hypertonic saline alone in haemorrhaged pigs, dogs and sheep (Maningas et al, 1986; Kreimeier et al, 1987; Velasco et al, 1989; Wade et al, 1989, 1990). Together, these studies confirmed that the addition of dextran to hypertonic saline initially caused slightly greater plasma volume expansion and higher cardiac output. More importantly, a better sustainment of the haemodynamic variables, as well as increased survival compared with hypertonic saline alone, were reported (Maningas et al, 1986; Velasco et al, 1989). Similar results were achieved with hypertonic saline mixed with hetastarch (Kramer et al, 1989a).

PHYSIOLOGICAL MECHANISMS

Small-volume intravenous infusions of hyperosmotic–hyperoncotic solutions into haemorrhaged animals cause profound and multifactorial physiological effects, including increases in arterial pressure, cardiac output, plasma volume, mean circulatory systemic pressure, cardiac contractility and oxygen delivery and consumption (Kramer et al, 1986; Lopes et al, 1986; Kien and Kramer, 1989; Velasco et al, 1989). Associated physiological responses include peripheral arteriolar dilatation, diuresis/natriuresis, restoration of membrane potentials, attenuation of cellular oedema, and lower subsequent volume requirements (Nakayama et al, 1985; Kramer et al, 1986; Rocha e Silva et al, 1987; Hannon et al, 1989; Mazzoni et al, 1990). One of the most striking features of hypertonic resuscitation is the rapid onset of the cardiovascular effects. Figure 3 shows the systolic and diastolic pressures of a haemorrhaged sheep during a 2 minute infusion of 200 ml HSD (Kramer et al, 1986). Mean arterial pressure began to increase after only half the dose had been administered and was normalized by the end of the infusion. Cardiac output starting at about half of base-line values before the infusion had increased to 30% above base-line by the time the infusion ended. It was initially believed that volume expansion could not occur rapidly enough to account for the fast onset of improvements in blood pressure and cardiac output. Studies showing better resuscitation with venous compared with arterial infusion of hypertonic saline initially suggested that a neurogenic cardiovascular reflex might be involved (Lopes et al, 1980, 1981; Rocha e Silva and Velasco, 1989). These early reports of the importance of a possible pulmonary osmoreceptor which, when stimulated, causes reduced venous capacitance or a release of catecholamines were challenged by subsequent studies (Kramer et al, 1986; Hands et al, 1988; Schertel et al, 1990).

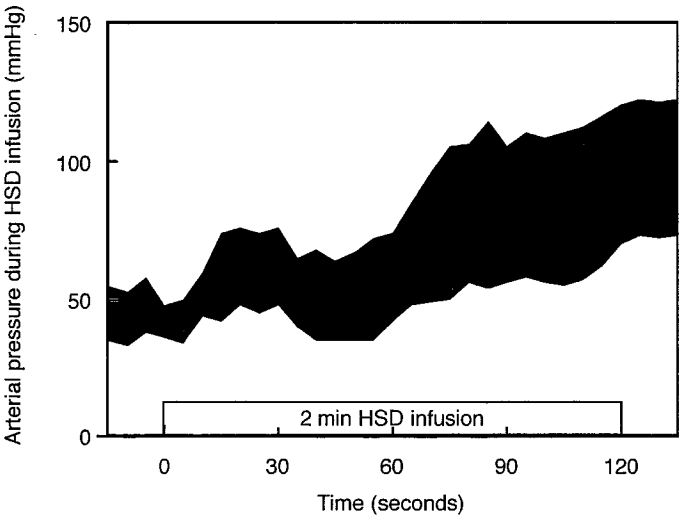

Figure 3. Rapid improvements in systolic and diastolic pressures are shown for a sheep haemorrhaged for 3 hours (bled volume = 42 ml/kg) and then resuscitated with a 2 minute intravenous 4 ml/kg infusion of HSD. Data are from previously described experiments (Kramer et al, 1986).

PLASMA VOLUME EXPANSION

Osmotic forces and capillary absorption

Extensive studies on volume expansion in normovolaemic animals after infusion of hypertonic saline were conducted by Wolf (1971) who made serial measurements of plasma volume using multiple isotope dilution techniques. His data clearly showed that maximum volume expansion occurred immediately at the end of infusion and then returned toward base-line. An analysis of transcapillary driving forces supports a nearly immediate vascular expansion after hypertonic saline infusions. Each mOsm generates an osmotic pressure of 19.3 mmHg at 37°C across an ideal semi-permeable membrane. The capillary wall, however, is not an ideal membrane and has an osmotic reflection coefficient of 0.1–0.3, which results in 10–30% of the total osmotic pressure being exerted across endothelial cells (Wolf and Watson, 1989). Infusion of 4 ml/kg 2400 mOsm hypertonic saline transiently increases serum osmolality by 30–50 mOsm, depending on the rate of infusion. Such osmolalities generate large transcapillary absorptive forces of at least 50–100 mmHg after correcting for the capillary wall reflection coefficient. Under most physiological conditions, there is steady outwardly directed capillary filtration due to a high hydraulic conductivity of the capillary wall and a normal net imbalance of microvascular Starling forces of only a few mmHg. Infusion of hypertonic saline rapidly reverses the transendothelial pressure gradient from a small filtration force to a large absorptive force.

Rate of plasma volume expansion

The volume expansion and the improvement in haemodynamics occur concurrently, as can be seen by comparing Figures 3 and 4. Rapid changes in plasma volume can be calculated from the dilution of the haemoglobin or plasma protein concentration in the blood. Figure 4 shows the concentration of plasma protein and haemoglobin of the arterial blood of sheep sampled every 15 seconds during a 235 second infusion of HSD. These data

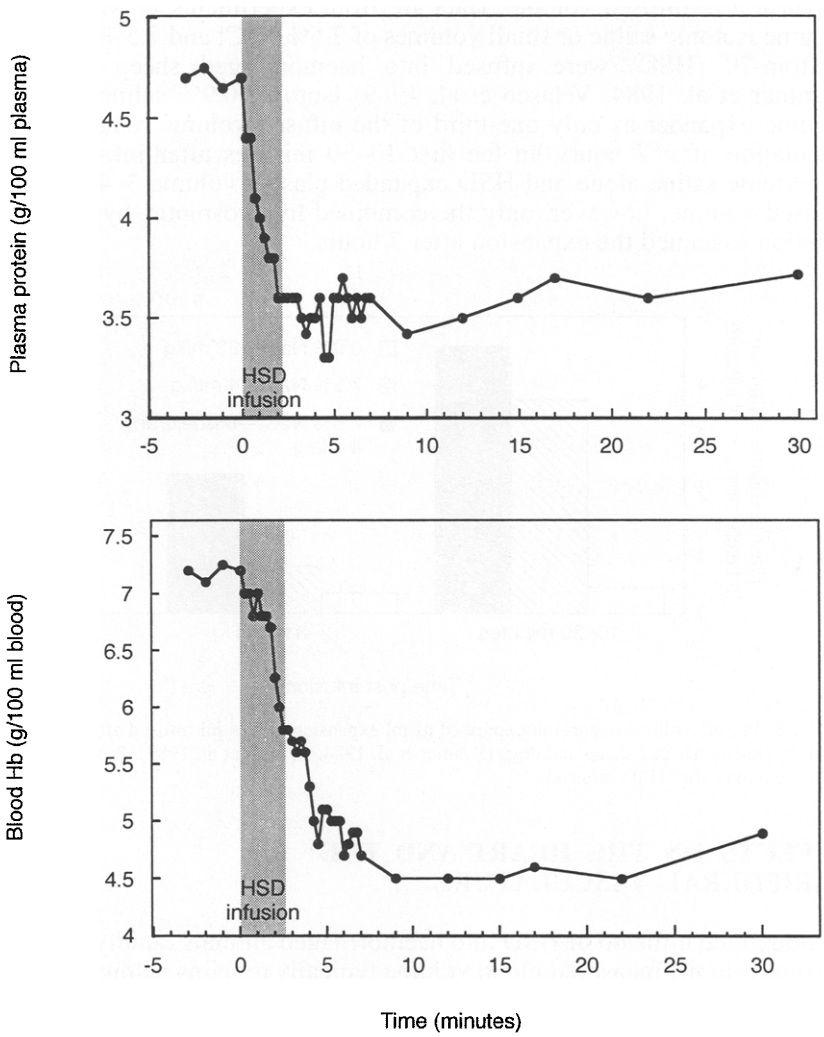

Figure 4. Measurement of blood haemoglobin concentration (Hb) and plasma protein sampled from the aorta every 15 seconds during a 2 minute 15 second intravenous infusion of 4 ml/kg HSD. Rapid dilution of blood solutes illustrates the rapid rate of volume expansion.

show, as in Wolf's experiments, that most of the volume expansion occurs as the solution is being infused.

Effects of the dextran component on volume expansion

The addition of dextran to the hypertonic saline sustains the plasma volume expansion. Plasma volumes can be measured by multiple injections of Evans Blue dye. Figure 5 shows Evans Blue measurements of vascular expansion after resuscitation, expressed as the ratio of plasma volume expansion to infused volume. Data are from experiments in which large-volume isotonic saline or small volumes of 7.5% NaCl and 7.5% NaCl–6% dextran-70 (HSD) were infused into haemorrhaged sheep and dogs (Kramer et al, 1984; Velasco et al, 1989) Isotonic 0.9% saline is a poor volume expander as only one-third of the infused volume remains in the circulation after 2 hours. In the first 10–30 minutes after infusion, both hypertonic saline alone and HSD expanded plasma volume 3–4 times the infused volume; however, only the combined hyperosmotic–hyperoncotic solution sustained the expansion after 3 hours.

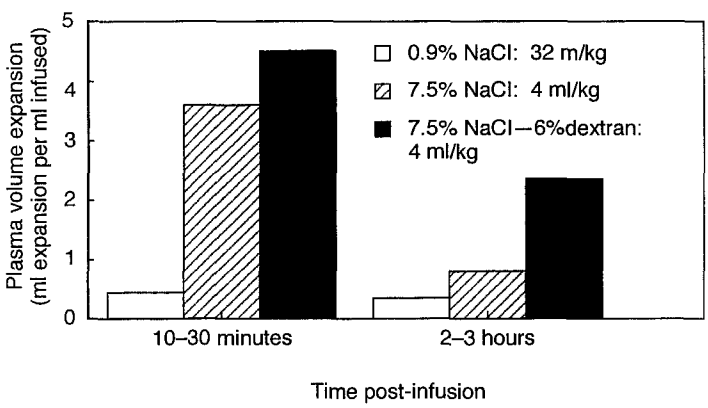

Figure 5. Plasma volume expansion expressed as ml expansion versus ml infused after infusion of HSD into haemorrhaged sheep and dogs (Kramer et al, 1984; Velasco et al, 1989). Results shown at two time points after HSD infusion.

EFFECTS ON THE HEART AND THE PERIPHERAL VASCULATURE

Although the infusion of HSD into haemorrhaged animals rapidly increases plasma volume, measured blood volume typically remains below base-line, while cardiac output is often above. (Smith et al, 1985; Velasco et al, 1989). Walsh and Kramer (1991) plotted the increased plasma volume against the increased cardiac output after infusion of 2400 mOsm NaCl mixed with different doses of dextran. Their extrapolation to zero volume expansion showed that 20–30% of the increased cardiac output occurs without

relation to volume. These data suggest that mechanisms in addition to volume expansion contribute to the haemodynamic responses of hypertonic resuscitation.

Cardiac effects

Infusions of hypertonic saline increase both heart rate and contractility (Wildenthal et al, 1969; Kien and Kramer, 1989). Additionally, increased plasma osmolality has a direct vasodilatory effect (Gazitua et al, 1971). Increases in vascular volume (pre-load) and contractility associated with reductions in peripheral vascular resistance (afterload) contribute together to the increased cardiac output. The chronotropic response can be completely blocked by propanolol or nerve resection, while the inotropic effects are only partially blocked (Wildenthal et al, 1969; Kien and Kramer, 1989). The best evidence for the nature of the inotropic effect is increased calcium influx across the sarcolemma from the extracellular fluid into the cytosol; cell shrinkage may further increase intracellular calcium concentration (Mouren et al, 1995).

Most recently, there have been studies providing conflicting results on the effects of hypertonic saline and HSD infusion on cardiac function. Recent reports show that the infusion of hypertonic saline solution into veins or coronary vessels increases contractility (Kien et al, 1995; Mouren et al, 1995), has little effect on contractility (Hellyer and Meyerr, 1994; Goertz et al, 1995; Suzuki et al, 1995; Welte et al, 1995), or decreases contractility (Brown et al, 1990; Waagstein et al, 1995). At least some of the negative reports may be a result of studying very high doses or very fast infusion rates of hyperosmotic saline. Such doses or infusion rates can transiently cause very high concentrations of extracellular sodium or osmotic pressures that are above the range known to occur with clinical use. Such experimental conditions apparently produce negative effects on cardiac function. There is also evidence that hypernatraemia can be a negative inotrope opposing hyperosmolality, which is a positive inotrope (Newell et al, 1980; Brown et al, 1990). Non-ionic hypertonic solutions, for example glucose or sucrose, have been shown to exert more positive inotropic effects than ionic NaCl solutions (Newell et al, 1980; Amirfarzam et al, 1992). Additionally, hypertonic saline treatment has been reported to prevent a cardiac contractility deficit induced by burn and septic shock (Horton et al, 1990. Ing et al, 1994). Despite conflicting views of the mechanisms for the direct cardiac effects of hypertonic saline, small-volume infusions of hyperosmotic–hyperoncotic solutions in intact mammals consistently increase cardiac effectiveness, in association with increased pre-load and reduced afterload.

Peripheral circulatory effects

The effects of hyperosmotic–hyperoncotic solution infusions on the peripheral vasculature and the microcirculation are generally to induce changes that augment flow. These are observed as a reduction in peripheral

vascular resistance, which is primarily due to arteriolar vasodilatation. A direct effect of increased osmolarity is relaxation of vascular smooth muscle (Gazitua et al, 1971). Reductions in blood viscosity associated with haemodilution also contribute to the fall in calculated peripheral vascular resistance. Capillary perfusion may be further augmented by HSD's ability to reverse some specific cellular effects of ischaemia and ischaemia–reperfusion. HSD infusion shrinks endothelial cells that are swollen by haemorrhagic shock (Mazzoni et al, 1990) and reduces leukocyte rolling and sticking in the microcirculation (Nolte et al, 1992a). The cell shrinkage is probably due to the hyperosmotic crystalloid, while the attenuation of leukocyte sequestration in the microcirculation is exclusively due to a pharmacological effect of dextran (Steinbauer et al, 1997).

EFFECTS OF THE DOSE AND TYPE OF COLLOID

Concentration and dose

There have been well over 300 reported studies in which a small-volume solution of 7.2–7.5% NaCl combined with 6–10% dextran or hetastarch has been studied. Interestingly, the original choice of 7.5% NaCl by Velasco et al (1980) and of 6% dextran by Smith et al (1985) was arbitrary. Only a few subsequent studies have evaluated variations in concentration or total dose (Halvorsen et al, 1991; Walsh and Kramer, 1991; Dubick et al, 1995). These studies show that it is not a specific concentration of the crystalloid or the colloid component that contributes to a particular efficacy; rather, it is the total dose of each solute delivered to the circulation and the timing of the infusion that determines the physiological effectiveness. Higher solute loads of salt and dextran produce greater mobilization of cellular water and greater vascular retention of fluid respectively (Dubick et al, 1995).

In retrospect, the currently most used solution, 7.5% NaCl/6% dextran-70, does appear to be an excellent choice as clinical studies support efficacy, and there has not been a single adverse event reported with HSD out of 923 patients treated to date in published clinical trials (Kramer and Poli de Figueiredo, 1995). The safety of a 250 ml dose of 7.5% concentration of NaCl would appear to be established for adults, based on the clinical experience. Higher doses or concentrations of hypertonic saline may also be safe, but at some level hypertonic saline is expected to have deleterious side-effects. The US Army's extensive toxicology studies suggest that this level might be by at least 2–3 times greater than the prescribed dose (Zaucha et al, 1988, 1989).

Clinical trauma trials on 7.5% NaCl without dextran

A meta-analysis of all known clinical trials of 7.5% NaCl alone, without dextran, for the early treatment of hypotensive trauma suggests little long-term benefit of such treatment (Wade et al, 1997). In prospective controlled trials, a 250 ml infusion of hypertonic 7.5% saline without dextran was administered pre-hospital or in the emergency room as first infusion and

was compared with a concurrent control group treated with 250 ml of isotonic fluid (Vassar et al, 1990, 1993a,b; Younes et al, 1992; Fabian et al, 1994). Thereafter, both groups were administered subsequent infusions of isotonic fluid as deemed necessary in accordance with the Advanced Trauma Life Support guidelines used in the USA (American College of Surgeons Committee on Trauma, 1993).

In essence, these trials compared the effects of an initial 250 ml infusion of hypertonic saline without dextran versus the current standard of care of isotonic crystalloid treatment. The summary data of all clinical experiences on hypertonic saline without dextran for the treatment of traumatic hypotension compared with concurrent control groups treated with standard of care fluid therapy are shown in Table 1 (Wade et al, 1997). Overall, the survival rate of patients treated with HS without dextran were no different than for treatment with the isotonic standard of care patients.

Table 1 Summary data of all known hypotensive trauma patients treated with 250 ml of hypertonic saline without dextran compared with isotonic control groups

Groups	Hypertonic saline without dextran	Isotonic fluid standard of care
N	340	379
Discharge survival	69.1%	69.7%

Data from Wade et al (in press).

Clinical trauma trials on hypertonic saline dextran

The advantage of adding 6% dextran-70 to hypertonic saline is supported by clinical studies and has been demonstrated in several animal studies (Maningas et al, 1986; Velasco et al, 1989). There have been eight controlled double blind trials comparing 250 ml of HSD with 250 ml of isotonic fluid as the initial fluid infusion (Maningas et al, 1989; Vassar et al, 1990, 1991, 1993a,b; Mattox et al, 1991; Younes et al, 1992, 1997). HSD treatment resulted in a higher mean survival in seven out of the eight trials. In only one individual trial was this overall survival difference statistically significant (Younes et al, 1997). However, significant improvement in survival was reported in important sub-groups: trauma patients with head injury and trauma patients requiring surgery (Mattox et al, 1991; Vassar et al, 1991). In the one trial in which the HSD group had a lower mean survival rate, the injury scores were not well matched as the more severely injured patients were found in the HSD group (Vassar et al, 1993b). Overall, combining all trials, the mean discharge survival across trials was 3.6% higher with HSD treatment (Table 2); however, this difference did not reach statistical significance using a patient-weighted meta-analysis ($P = 0.071$) two-tailed t-test (Wade et al, 1997).

A detailed *a priori* designed analysis using all available individual patient data from the HSD trauma trials has been undertaken for further evaluation of efficacy and safety. The definitive role of HSD's usefulness in trauma resuscitation awaits such further analysis and perhaps new clinical trials.

Table 2 Summary data of all known hypotensive trauma patients treated with 250 ml of 7.5% NaCl–6% dextran 70 compared with isotonic control groups

Groups	Hypertonic saline without dextran	Isotonic fluid standard of care
N	615	618
Discharge survival	74.6%	71.0%

Data from Maningas et al (1989); Mattox et al (1991); Vassar et al (1990, 1991, 1993a,b); Younes et al (1992, 1997).

DIFFERENT SOLUTES

Resuscitation using hyperosmotic solutes other than NaCl or hyperoncotic colloids other than dextran may be useful to meet specific clinical needs.

Novel hyperosmotic crystalloids

A 2400 mOsm mixture of NaCl, glucose and amino acids (IsoSal) has been shown to resuscitate haemorrhagic shock while reducing or eliminating hypernatraemia (Sheikh et al, 1996a,b). This solution may offer increased safety in certain clinical scenarios, such as when large or multiple doses of resuscitation fluid are needed, in the presence of pre-existing hypernatraemia, or when nutritive support and volume resuscitation are both concurrently indicated. Another new formulation—hypertonic 2400 mOsm NaCl–Na acetate/6% dextran-70 (HAD) mixture—has been shown to offer potential benefits compared with HSD (Rocha e Silva et al, 1993; Nguyen et al, 1995). These benefits include higher cardiac contractility, elimination of hyperchloraemia and a more rapid correction of acidosis compared with treatment using either HSD or large-volume lactated Ringer's solution (Rocha e Silva et al, 1992, 1993; Frey et al, 1994; Nguyen et al, 1995). HAD also produces increased cardiac output with only a modestly increased arterial pressure. This 'high flow–low pressure' form of resuscitation could be more effective for the treatment of penetrating trauma and uncontrolled haemorrhage in which increased blood pressure could increase internal bleeding (Rocha e Silva et al, 1992; Nguyen et al, 1995). However, some experimental studies using IsoSal and HAD for the treatment of haemorrhage have suggested that these formulations offer only slight benefits when compared with formulations made with a 2400 mOsm NaCl component (Frey et al, 1994; Krausz and Amstislavsky, 1995; Matsuoka et al, 1995). Further experimental studies are necessary to determine whether the above solutions have better efficacy and safety for specific clinical indications. Additionally, hyperosmotic multi-ingredient 'cocktail' solutions containing solutes with both volume expansion properties and beneficial pharmacological effects should be studied.

Hyperoncotic colloids

While most animal experiments and clinical trials on hyperosmotic–hyperoncotic solutions have used HSD, there has also been a considerable effort directed toward the study of hypertonic saline hetastarch formulations. In particular, several European trials of 7.2–7.5% NaCl combined with 6–10% hetastarch have been reported (Kroll et al, 1991, 1993; Albrecht et al, 1995; Ellinger et al, 1995). In the USA and some parts of Europe, hetastarch is more widely used compared with dextran. There are few direct comparisons of HSD (7.5% NaCl–6% dextran) with 7.5% NaCl–6% hetastarch. The few comparisons that have been performed to date suggest slightly better volume expansion with 7.5% NaCl–6% dextran-70 versus 7.5% NaCl 6%–hetastarch in the treatment of controlled haemorrhagic shock (Kramer et al, 1989b). Treatment of combined haemorrhage and traumatic crush injury with 7.2% NaCl–10% dextran-60 or 7.2% NaCl–10% hetastarch suggests that the dextran component contributes to a reduction in secondary pulmonary oedema (Frey et al, 1990). This may be due to the ability of dextran to attenuate trauma and ischaemia-induced white blood cell accumulation in the microcirculation (Steinbauer et al, 1996, 1997). However, in general, nearly all the early cardiovascular effectiveness of HSD appears to be similarly achieved with HS hetastarch (Kramer et al, 1989b; Frey et al, 1990).

The selection of the most efficacious colloid component of a future hyperosmotic–hyperoncotic formulation may not be only a function of the colloid's ability to generate oncotic pressure, but rather due to the colloid's beneficial pharmacological actions. All synthetic colloids have non-oncotic pharmacological properties that are not fully understood. Dextran has been repeatedly shown to enhance microcirculatory rheological flow (Hint, 1971; Litwin, 1976; Lalla et al, 1980). More recent studies have shown a marked ability of dextran to inhibit leukocyte sticking and rolling even with doses of dextran too small to be effective as a volume expander. (Huneidi et al, 1990; Nolte et al, 1992b; Steinbauer et al, 1996, 1997).

Pentafraction is a specific fraction of hetastarch composed of a narrowed molecular weight range that has been shown to be superior to regular hetastarch or albumin due to an anti-inflammatory effect that reduces microvascular permeability (Zikria et al, 1989; Webb et al, 1991; Traber et al, 1992). Pentafraction has been used only in animal experiments and is not commercially available at the present time. A full understanding of the cellular and physiological anti-inflammatory and microcirculatory effects of dextran and hetastarches will probably lead to the hyperoncotic colloid component of choice for future small-volume formulations.

HYPERTONIC OXYGEN CARRIERS

Substantial clinical interest has been generated by efforts towards the development of blood substitutes (Dietz et al, 1996). Synthetic oxygen

carrier solutions composed of free haemoglobins or perfluorocarbons may well provide a significant clinical benefit compared with most currently used fluid therapies. Acellular haemoglobin solutions manufactured to have the same oxygen-carrying capacity as blood (15 g/100 ml) are hyperoncotic. The first suggestion that haemoglobin could be used as the colloid component of a hyperosmotic–hyperoncotic solution for small-volume resuscitation was published in 1990 (Kramer and Holcroft, 1990). Subsequently, haemoglobin was suggested as a component of a hypertonic solution for pump prime in cardiovascular bypass (Runge, 1992). A hyperosmotic perfluorcarbon oxygen carrier (Oxyreplete) was tested and was shown to improve brain oxygenation and reduce oedema during long bypass procedures (Runge, 1992; Runge et al, 1994). Oxyreplete does not have a colloid component. Initial proposals for hypertonic haemoglobin solutions did not rapidly lead to experimental testing because of the general unavailability of purified haemoglobin solutions. The first report on the actual use of a hypertonic haemoglobin formulation was by Rabinovici et al (1993) who studied the US Navy's liposome-encapsulated haemoglobin combined with 7.5% NaCl and found it to be an effective small-volume formulation (Rabinovici et al, 1993). Interestingly, when haemoglobin is encapsulated in liposomes or in erythrocytes, as is the normal state, the oncotic pressure of haemoglobin can not affect transcapillary fluid exchange.

Computer model analysis was used to compare small-volume infusion of hypertonic 7.5% NaCl–6% dextran-70, 15% haemoglobin, and hypertonic 7.5% NaCl–15% haemoglobin (Kramer et al, 1994). The model was based on published data on the haemodynamic effects of HSD and hyperoncotic dextran (Smith et al, 1985; Kramer et al, 1986) and on the assumption that the hyperoncotic colloid 15% haemoglobin had the same plasma volume expansion and haemodynamic effects as 6% dextran-70. Figure 6 shows oxygen delivery predicted by model analysis during a 30 minute simulated pre-hospital phase after a 4 ml/kg bolus infusion of the test fluid in a haemorrhaged patient and during a 2 hour hospital resuscitation phase, where lactated Ringer's is infused as needed to maintain cardiac output at base-line. The analysis showed that HSD, which greatly increases cardiac output, is significantly better at improving oxygen delivery than a 15% haemoglobin solution, which increases the oxygen content of blood but produces only small increases in cardiac output. However, the most effective formulation predicted by the model was a combination of 7.5% NaCl and 15% haemoglobin.

Future pre-hospital and emergency room resuscitation may be optimized by the use of a single, small-volume formulation constituting a mixture of hyperosmotic crystalloids, hyperoncotic colloids and oxygen carriers. Conversely, operating room needs might be better met by administering the individual components separately. Future anaesthesiologists may have access to an assortment of new solutions, including hyperosmotic crystalloids, hyperoncotic colloids and oxygen-carrier solutions. Each patient may be treated with an individualized mix of the components needed to address specific clinical and physiological need. Clearly, we need

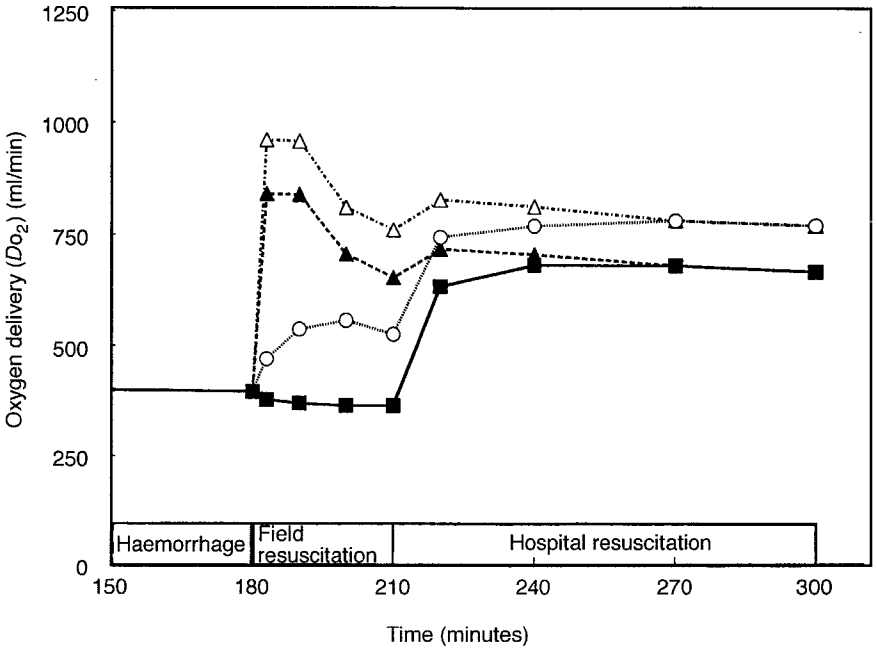

Figure 6. Computer model analysis of oxygen delivery in haemorrhaged sheep after a 4 ml/kg infusion of 7.5% NaCl–6% dextran (HSD; ▲——▲), 15% haemoglobin (○——○) and hypertonic saline–15% haemoglobin (△——△) (Kramer et al, 1994). The model is based on assumptions stated in text and the published results of sheep resuscitated for 30 minutes of simulated pre-hospital resuscitation in which only 4 ml/kg of test fluid was infused, followed by a 2 hour period of simulated hospital resuscitation where lactated Ringer's solution (■——■) was infused as needed to maintain cardiac output at base-line levels (Smith et al, 1985; Kramer et al, 1986).

a better understanding of how each component works separately as well as how they interact. This knowledge will be a primary goal for resuscitation research in the next 10 years.

SUMMARY

Infusion of hyperosmotic 2400 mOsm NaCl into haemorrhaged mammals causes a large and immediate plasma volume expansion and improvements in cardiovascular function. The addition of a hyperoncotic colloid to the solution increases the initial haemodynamic effects and greatly sustains them. Clinical trials suggest that 250 ml 7.5% NaCl–6% dextran-70 (HSD) is an effective early treatment for trauma and haemorrhage. Other hyperosmotic–hyperoncotic formulations may find specific clinical uses. Future research is needed to define the specific physiological and pharmacological properties of such new formulations.

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