

REGULAR REVIEW

Sugar Solutions Used In Resuscitation

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Introduction

The maintenance of proper intravascular volume (IVV) and ventricular preload is the foundation for cardiovascular resuscitation in the trauma patient. The principles set out by Starling in the early part of the 20th century form the basis of our understanding of the haemodynamic physiology, the sequelae of pathophysiologic derangements and the aims of treatment (1,2). Maintenance of adequate renal function, avoidance of lung water accumulation, reducing splanchnic and hepatic circulatory failure and ensuring gastrointestinal integrity are principle goals of cardiovascular resuscitation after major trauma (3). Proper fluid management is the most important aspect governing haemodynamic stability in the early stages of treating the trauma patient. Although it is important to maintain electrolyte and acid base balance, to provide sufficient oxygen-carrying capacity and coagulation factors during the early resuscitation of the trauma victim, haemodynamic stability by the maintenance of sufficient IVV is paramount (4).

Fluid resuscitation in the trauma patient is an often controversial issue reflecting the complex interaction of several factors. It is affected by the presence of pre-injury cardiovascular and renal insufficiency, the degree of haemorrhage and the presence of head injury all combine to affect decision making in fluid resuscitation. The need for urgent surgery adds the pharmacology of anaesthesia and positive pressure ventilation to the equation (5,6). Unsurprisingly the type of resuscitation fluid used will also influence outcome depending on both its pharmacokinetics and dynamics.

This article reviews the use of sugar (dextrose and dextrans) and sugar derived (mannitol) fluids in resuscitation for trauma. It summarises the distribution of fluids across body compartments and the principles that govern fluid shifts across membranes into these compartments as well as reviewing the pharmacology of sugar fluids in trauma and their applicability to current practice in resuscitation.

Fluids and their compartments

Body fluids are described as intracellular or extracellular, depending on their relationship to the cell membrane (Figure 1). Approximately 25 litres of the 40 litres of total body

fluid (in the average 70 Kg adult) are intracellular; the remainder is extra cellular. The extracellular fluid (ECF) can be further sub divided into interstitial and plasma fluid, with the former present in a gel like form between the cells and plasma, or intravascular, fluid (approximately 3.5L) being the non-protein portion of blood within the capillary membrane.

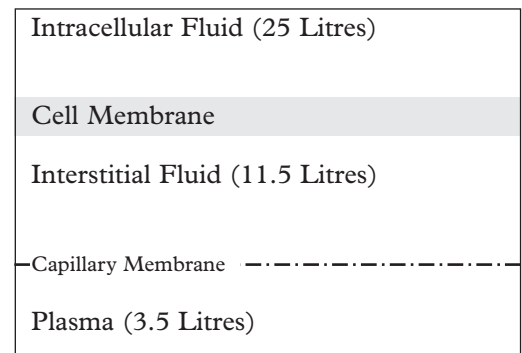


Fig 1. Total Body fluids can be divided into intracellular and extra cellular fluids depending on their relationship to the cell membrane. Extra cellular fluid is divided into plasma and interstitial fluid by the capillary membrane. Approximate volumes for a 70Kg adult are given.

It is important to understand the relationship of these fluid compartments and how intercompartmental fluid shifts occur in both health and disease states such as trauma. Plasma communicates continuously with the interstitial fluid through pores in the capillaries, as a result the interstitial fluid is in a dynamic equilibrium with the plasma and acts as a reservoir of water and electrolytes for the plasma explaining the similarity of composition of the two fluids (Table 1). Both plasma and interstitial fluid contain high levels of sodium and chloride ions but small amounts of potassium, calcium and magnesium ions and the levels of all are closely regulated by the kidneys to ensure that the cells are bathed in fluid containing the concentrations of electrolytes and nutrients for optimal cell function. Any resuscitation fluid should, therefore, be of a similar constituency so that normal cell function is not compromised.

In contrast intracellular fluid contains only small quantities of ionised sodium and chloride and almost no calcium. Potassium, and to a lesser extent magnesium, ions are present in high concentrations creating an electrical potential difference across the cell membrane. In addition intracellular fluid has a four times greater protein concentration

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	Plasma (mmol/l)	Interstitial Fluid (mmol/l)	Intracellular Fluid (mmol/l)
Sodium ions	140	140	10
Potassium ions	5	5	150
Chloride ions	110	110	3
Calcium ions	5	5	3
Magnesium ions	3	3	30
Bicarbonate ions	28	30	10
Phosphate ions	2	2	100

Table 1. Composition of fluid compartments highlighting the similarities between plasma and interstitial fluid and the differences with intracellular fluid. There is four times as much protein in plasma as in the interstitial space and four times as much protein in the intracellular space as in the plasma.

and more acidic pH (6.8-7.2) than extra cellular fluid.

There are two barriers to intercompartmental fluid shifts. The porous capillary membrane allows fluid movement from plasma to the interstitial space, restricted only by the oncotic pressure produced by the plasma proteins in the blood as Ernest Starling described (7, 8), and the cell membrane which regulates fluid movements between the cell itself and the interstitial space. A reminder of the concepts of diffusion, osmosis and osmolarity is presented in Box 1.

About 90% of the osmolarity of plasma and interstitial fluid is due to sodium and chloride ions, whilst half of the intracellular

in the intravascular space such as 5% dextrose. The dextrose is rapidly metabolised leaving the water to dilute the extra cellular compartment with respect to the intracellular one. Osmosis begins instantly at the cell membrane transferring large amounts of water into the cells and within a few minutes the infusion has been distributed evenly throughout all the body compartments.

The pathological effect of injury on the fluid compartments

The extra cellular environment is maintained within very tight limits by a series of homeostatic mechanisms including the rennin-angiotensin-aldosterone system, brain and atrial natriuretic hormones and the posterior pituitary-vasopressin-renal axis, which allow the kidneys to regulate the tonicity and sodium concentration of extra cellular fluid and contribute to the maintenance of blood pressure. After insults such as haemorrhage, blunt trauma, burns and infection these same processes lead to a response that is directed towards maintenance of the extra cellular environment. As a result, in the injured patient fluid therapy aimed at preserving IVV and thus oxygen delivery to the tissues is superimposed upon a powerful homeostatic response. There is still no consensus on which fluid regime is best for acute volume resuscitation after trauma and attempts at mortality based meta-analysis have been unsuccessful. (9,10). As well as the normal homeostatic mechanisms complicating the physiological picture of fluid movement between compartments, pathological processes also have an effect. There is evidence from clinical and animal studies that acute injury and inflammation leads to intracellular sequestration of sodium, chloride and water producing cellular oedema and damage (11). Cellular hypoxia leads to a decrease in intracellular energy (ATP) reducing the activity of the cellular Na⁺/K⁺ pump allowing an influx of sodium, an effect confirmed in animal studies (12). Prolonged release of nitric oxide in severe inflammation irreversibly inhibits mitochondrial function (13).

It is not just the cell membrane that is altered due to the insult of trauma. The capillary barrier between plasma and the interstitium is also affected. Systemic capillary leak is a key feature of the inflammatory response to localised injury, infection, hypoxia and reperfusion injury. It occurs within minutes of the injury, is proportional to the injury and may resolve itself within hours (14). The leak from the capillaries allows plasma proteins (predominantly albumin) to migrate into the interstitial space and for each gram of albumin leaking into the interstitium, 18 grams of isotonic fluid follows producing

- Osmosis is the net movement of water across a cell membrane because of a concentration difference between components.
- A semi-permeable membrane allows free diffusion of water but limits egress of certain molecules and ions such as sodium and chloride.
- Water crosses semi-permeable membranes towards the highest concentration of non-diffusible ions and this diffusion can be stopped by the application of an opposing pressure (the osmotic pressure).
- The osmotic pressure exerted by non-diffusible particles in a solution (molecules or ions) is determined by the number of molecules rather than their mass and the number of particles capable of exerting osmotic pressure in a solution is expressed in Osmoles - or more commonly milliOsmoles (mOsm).
- Normal plasma osmolarity is 280 mOsm /l, which is about 1.3 mOsm greater than that of the interstitial and intracellular fluids because of the osmotic effect of the plasma proteins acting to maintain a higher pressure in the capillaries.

Box 1. Diffusion, osmosis and osmolarity.

osmolarity is due to potassium ions. Any change in the osmotic equilibrium, by either increasing the osmotic pressure within a compartment by adding a solute that cannot move from that compartment or decreasing the osmotic pressure by adding water to a compartment, will lead to a flux of water from one compartment to another. The transfer of water through cell membranes by osmosis occurs rapidly so that any difference in osmotic equilibrium is corrected within seconds. A practical example of this is administration of a fluid that does not remain

hypoalbuminaemia, increased packed cell volume, hypovolaemia and further accumulation of interstitial oedema fluid (15).

Any resuscitation fluid used must take these pathophysiological consequences into consideration so that the IVV may be maintained while at the same time reducing the complications of sodium and water retention in the wrong fluid compartments.

Dextrose

Dextrose is D-glucopyranose D-glucose monohydrate, a mono-saccharide obtained by the hydrolysis of corn starch. It is presented as a clear, colourless solution containing 5, 10, 20, or 50% dextrose in water; the preparations are sterile, contain no buffers or bacteriostatic agents and the pH varies between 3.5 - 6.5 depending on the concentrations. The 5% solution contains 170Kcal/l and has an osmolarity of 250 mOsmol/l. The 5% solutions can be used to provide water, whereas the more concentrated solutions can be used to provide calories in the treatment of hypoglycaemia. The main actions of dextrose solutions are to increase the blood sugar concentration and glycogen deposition; ketosis and nitrogen loss are decreased. The cardiovascular effects of a dextrose infusion depend on the overall cardiovascular status of the patient. In hypovolaemia there will be an initial, temporary, restoration of the circulating volume, however dextrose rapidly equilibrates between the intra- and extravascular spaces following the metabolism of glucose by the cells and tissues to carbon dioxide and water that are excreted by the lungs and kidneys. Over-hydration with dextrose solutions leads to water intoxication, hyponatraemia, mental confusion; fits may occur. Hyperglycaemia and venous thrombosis may occur with the higher concentrations of dextrose solutions.

The role of dextrose fluids in resuscitation is limited. They essentially provide free water because of the rapid glucose metabolism. As the total body water is approximately 60% of the body weight and plasma volume about 5%, less than 10% of an administered solution of dextrose remains in the intravascular space. Dextrose solutions are ineffective plasma expanders (16).

Dextrans

Dextrans are polysaccharides containing chains of glucose units up to 200,000 units long. They are produced by the fermentation of a sucrose medium with the bacterium *Leuconostoc mesenteroides* and the preparation is further processed by hydrolysis and fractionation. Partial hydrolysis produces molecules of average molecular weight 40,000, 70,000 and 110,000 Daltons giving rise to Dextrans 40, 70 and 110 respectively.

Dextran 40 is prepared as a 10% solution

in either 5% glucose or 0.9% saline and the resulting compound contains glucans with an average molecular weight of 40 KDa (90% of molecules have a molecular weight within 10,000 to 75,000) and an osmotic pressure slightly higher than that of plasma proteins. Predictably, Dextran 70 contains glucans with an average molecular weight of 70 KDa (90% range: 20,000 to 115,000 Daltons) and is produced as a 6% solution in either isotonic saline or dextrose. Dextran 70 has an osmotic pressure similar to plasma. Dextran 110 is now rarely used.

Dextran 70, and previously 110, have been used for plasma volume expansion in haemorrhage, burns and excessive fluid and electrolyte disturbances, whereas Dextran 40 is mainly used to promote peripheral blood flow i.e. in arterial insufficiency and in the prophylaxis of post operative thromboembolism.

Dextran 70's role as a plasma expander in resuscitation is due to the size of its constituent molecules, as molecular size determines the degree of both plasma expansion and intravascular longevity. Half-life's range from 15 minutes for small molecules up to several days for larger ones. Molecules greater than 55KDa are generally retained in the vascular space and for each gram of dextran added to the circulation approximately 20ml of water is retained by its osmotic effect - an infusion of 500ml of Dextran 70 will increase the plasma volume by approximately 750ml.

When added to blood *in vitro*, dextrans exert no effect on platelet function, however *in vivo*, bleeding time may be prolonged, polymerisation of fibrin impaired and platelet function reduced. Thus, in addition to their use as plasma expanders they are also used to improve peripheral blood flow and prevent thromboembolic disease. Dextran 40, but not 70, is absorbed on to erythrocytes and interferes with fibrinogen binding.

When used as a plasma expander Dextran 70 infusions should be titrated to effect which, in the face of hypovolaemia, aims to restore cardiovascular parameters towards normal. Dextrans reduce serum lipid and albumin levels to a greater than expected level than by plasma dilution and in victims of multiple trauma Dextran 70 appears to protect against the development of ARDS (17,18).

Dextran Metabolism

Dextrans exhibit no significant protein binding and have a volume of distribution of less than 8 litres, i.e. they are retained mainly in the intravascular space. Molecules below the renal threshold of 50,000 Daltons are excreted unchanged in the urine whereas larger dextrans are metabolised to water and carbon dioxide by dextranases in the lung, liver, kidney and spleen. Seventy percent of Dextran 40 is excreted unchanged by the kidney resulting in a plasma half-life of 4-9

hours. Dextran 70 has an elimination half-life of 23-25 hours reflecting its higher molecular weight and only about half a 500ml infusion will have been excreted in 48 hrs (19).

Side Effects of Dextrans

Anaphylactic reactions. These are thought to result from previous cross-immunization against bacterial antigens and have an incidence of 1: 45,000. This can be halved by pre-treatment with dextran 1 (molecular weight 1000) to block the antigen binding sites of circulating dextran antibodies. The histamine release during dextran anaphylaxis manifests itself as urticaria, angioedema, hypotension and bronchospasm, but discontinuation of the dextran infusion is usually sufficient treatment - however fatal allergic reactions have occurred with as little as 10 mls of Dextran 70 (19).

Renal failure. Dextran 40 infusions in hypovolaemia may cause tubular obstruction from dextran casts as a reflection of the high level of renal excretion of Dextran 40. Concurrent crystalloid infusion tends to overcome this problem.

Haematological problems. Dextran solutions, regardless of their molecular weight, can induce rouleaux formation and interfere with cross matching of blood. For this reason blood for cross matching should be obtained prior to administration of dextrans. They may also interfere with some blood tests of renal and hepatic function. Dextrans may induce a bleeding tendency in patients and initial administration should be limited to 500-1000 ml and the total amount restricted to 10 ml/Kg/day for dextran 40 and 20 ml/Kg/day for dextran 70. Fluid overload has also been reported following the excessive use of dextran 70 during resuscitation (20).

The ideal plasma expander - which probably does not yet exist - should remain within the vascular space, not affect haemostasis and be both inert and completely excreted. Dextrans do not fulfil these criteria. Dextran 70's molecules are of the correct size to exert some plasma expansion through increasing the osmotic pressure in the vascular space. However its side effect profile (coagulopathy, hypersensitivity and abnormalities with blood analysis) prevent its widespread use in this role. In one study, changes in the coagulation time with Dextran 40 and 70 were compared to gelatine and hydroxyethyl starch. Coagulation time was most markedly effected when the dilution ratio of blood volume to dextran was greater than 10:4, i.e. after a 2 litre infusion in the normal 70 Kg adult - gelatin solutions had much less intrinsic effect on coagulation (21). Dextrans are, however, unique amongst colloids because of their ability to modulate the immune response associated with inflammation. Leukocyte rolling, an endothelial event intrinsic to inflammation

and capillary leak, is reduced by all types of dextrans and leukocyte adhesion is attenuated by dextrans above 40,000 Da (22). However dextrans do not suppress T cell activation and cause immunosuppression (23) unlike blood transfusions.

One area of resuscitation in which dextrans may have a role is in burns. Animal models suggest that resuscitation using fluids containing dextran may reduce the overall volume of fluid resuscitation required and subsequent wound oedema by reducing the protein leak from the plasma to the lymph secondary to reducing the capillary filtration coefficient (24).

Mannitol

Mannitol is a six carbon sugar derived from plants. Reduction of the monosaccharide mannose produces a polyhydric alcohol with a molecular weight of approximately 200 Da. It is commercially available in a variety of concentrations (10, 15, 20 and 25% solutions in water) and crystallisation may occur at low temperatures.

Mannitol's clinical application is as an osmotic diuretic to prevent acute renal failure, treat raised intracranial pressure, reduce intraocular hypertension and as a bowel preparation before colorectal procedures. Its actions are all related to its physical structure. Mannitol has a low molecular weight of approximately 200 Da - below the renal threshold for filtration. The drug shows a biphasic distribution to plasma and extracellular fluid with a volume of distribution of 0.47 l/Kg. Mannitol undergoes no metabolism in man and is excreted unchanged in the urine; it has a renal clearance of 7 ml/min/Kg and an elimination half life of 72 minutes. It is freely filtered at the glomerulus raising the osmolarity of the renal tubular fluid and preventing the resorption of water. Sodium ion concentration is diluted in the retained tubular water leading to less resorption of sodium. This produces a diuresis of water, sodium, chloride and bicarbonate ions, but the urinary PH is not affected.

The concentration of any nephrotoxin present in the renal tubule is also diluted and potentially prevented from reaching toxic levels. Mannitol is, therefore, used to prevent acute renal failure after severe trauma, cardiovascular surgery, surgery in the presence of jaundice and severe haemolytic reactions. It does not cross the intact blood brain barrier. Circulatory overload and rebound increases in intra cranial pressure may occur following the use of mannitol. A total dose of more than 3g/kg/day may produce a serum osmolarity of greater than 320 mOsm/l.

Mannitol in Intracranial Hypertension

Many of the effects of mannitol can be described by examining how it behaves in its

commonest clinical application - the treatment of raised intracranial pressure, particularly that following trauma, to reduce the incidence of secondary brain injury.

Primary brain injury is the direct mechanical damage that occurs at the time of trauma (25), whereas secondary brain injury occurs later and is defined as neuronal damage due to the systemic physiologic responses to injury (26). The release of a variety of biochemical substances including the excitatory amino acids glutamate and aspartate, cytokines and free radicals (27,28), are thought to propagate neural injury by initiating a deleterious cascade of continued cell membrane breakdown and ionic shifts that further harms the injured brain.

The importance of hypotension and hypoxia as contributors to secondary brain injury is well known (29,30). During the first 14 hours after head injury, cerebral blood flow is less than half that of normal individuals and may approach the ischemic threshold (31-33); volume resuscitation with the restoration of a normal IVV is, therefore, essential in patients with acute cerebral insults; mannitol is not suited for this purpose because of its volume depleting diuretic effect (34). In a pre-hospital trial, administration of mannitol did not significantly change systolic blood pressure (35). The effective use of mannitol in the prevention of secondary brain injury lies in its osmotic diuretic effect. (36-39). It is thought to decrease intracranial pressure by reducing overall brain water content - by increasing plasma osmolarity it draws fluid from the intra- to the extra-cellular space, expanding the circulating volume. The intracranial pressure decreases as this fluid leaves the fixed volume of the cranium. The acute increase in cardiac output and blood pressure from augmentation of the intravascular volume also serves to increase the global cerebral blood flow in patients with intact cerebral autoregulation. In patients where the blood brain barrier is disrupted or cerebral autoregulation is impaired after trauma then mannitol may be counterproductive as the mannitol lies in the extra vascular space maintaining an elevated intracranial pressure. Similarly, in common with other osmotically active agents, mannitol may 'open up' the blood brain barrier allowing mannitol itself to leak into the brain (40,41). Intracerebral accumulation of mannitol after repeated dosing then causes a reverse osmotic shift, raises brain osmolarity and exacerbates the intra cranial hypertension. It also serves to decrease cerebrospinal fluid production (42) and blood volume by vasoconstriction (42-44). Further improvements in cerebral perfusion because of mannitol are due to decreased blood viscosity (45, 46), altered erythrocyte rheology (43) and protection

against biochemical injury by acting as a free radical scavenger (47). Mannitol should initially only be used in patients demonstrating signs of transtentorial herniation (48) in a dose of up to 1g/Kg iv over 15 minutes with repeated doses of 0.25 - 0.5g/Kg every 2-6 hours as required to increase the serum osmolarity to 310-320 mOsm/Kg H₂O. If required over a protracted period, mannitol should be administered as separate boluses rather than an infusion to reduce the risk of accumulation in the brain and reversed fluids shifts (49). Sudden cessation of mannitol may also cause rebound increases in intra cranial pressure. The osmotic movement of fluid out of the cellular compartment is followed by a diuresis 15 - 30 minutes later, after the establishment of ionic gradients between plasma and cells (50). This diuresis lasts between 90 minutes and 6 hours (51,52) and the prolonged use of mannitol may lead to intravascular dehydration and hypotension (53).

It is unclear as to whether mannitol contributes to acute renal failure - cases of ARF in association with mannitol infusions (54) are reported but large animal models have shown a protective effect by maintaining renal blood supply in the ischaemic kidney (55). It is prudent to monitor the renal function of these patients closely.

Summary

Although recent studies have shown that the timing of volume replacement deserves careful consideration (56), which fluid to use is less clear, with the perennial debate of crystalloid v colloid and now colloid v colloid still unresolved. This review has examined three sugar solutions, two colloids and one crystalloid. In general, all three agents are unhelpful in the immediate resuscitation of hypovolaemic trauma by virtue of a combination of pathophysiology and side effects. Dextran solutions and mannitol are useful in specific situations.

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