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## REGULAR REVIEW

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### **'Physiological' 0.9% Saline In The Fluid Resuscitation Of Trauma**

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#### **Introduction**

The debate over which fluid is most suitable for resuscitation of hypovolaemia has been going on for more than five decades. The choice of colloid or crystalloid varies; largely depending on personal preference, clinical experience, availability, and cost (1). Although the evidence for, and understanding of, different fluids has increased, there is an urgent need for appropriately sized, prospective, randomised, controlled trials in fluid resuscitation (1,2). 'Physiological' 0.9% saline has been available for over one hundred years (3). Its use has been accepted by long practice and it is often used as a standard by which to compare other intravenous fluids. However, the scientific evidence base for the use of intravenous 0.9% saline is limited. This article will examine the actions and interactions of 0.9% saline in the context of trauma resuscitation and compare its advantages and disadvantages with other fluids which are commonly used.

#### **Physiology Of Fluid Loss In Trauma**

Major haemorrhage associated with trauma leads to tissue hypoxia, ischaemia and necrosis. The causes of cellular damage sustained during and after injury and during resuscitation are multifactorial. They include the severity and duration of hypovolaemia, associated injuries, co-morbidity, second hit injury and the management of resuscitation (4).

Under normal circumstances the body maintains a constant internal environment using various homeostatic mechanisms. When a physiological insult occurs, a number of mechanisms react to regain optimal cellular conditions. Haemorrhage causes hypovolaemia and leads to a decrease in cardiac output and reduced oxygen delivery to the tissues. In trauma this is often compounded by extensive tissue damage. The body's stress response aims to maintain oxygen delivery to the vital organs and to provide a proportional inflammatory response to injured tissues.

The stress response can be divided into the neuroendocrine response and the inflammatory response.

The neuroendocrine aspect of the stress response to hypovolaemia causes selective vasoconstriction and increases conservation

of sodium and water. A decrease in mean arterial pressure initiates cardiovascular baroreceptor responses leading to increased sympathetic tone and decreased parasympathetic tone. This results in enhanced cardiac chronotropy and inotropy. Increased sympathetic tone causes the release of catecholamines and steroids. This leads to selective vasoconstriction with increased blood supply to the brain, heart and lungs. The renin-angiotensin-aldosterone axis is stimulated, causing further arteriolar constriction as well as sodium retention. There is a decrease in the release of atrial natriuretic hormone. Sodium retention causes an increase in plasma osmolarity. The posterior pituitary reacts to the change in plasma osmolarity by releasing antidiuretic hormone. Antidiuretic hormone increases water retention by the kidneys and contributes to arteriolar vasoconstriction. The hypothalamus responds to increased plasma osmolarity by stimulating levels of thirst (5,6).

At the same time as the neuroendocrine response, there is a tissue inflammatory response at the site of injury. Tissue damage leads to release of inflammatory markers and acute phase proteins. In uncomplicated injury, local capillary leakage occurs within minutes of initial injury; it is proportional to the severity of the insult and will resolve within a few hours (5). The systemic inflammatory response syndrome occurs when local control of inflammation is lost. Widespread leaky capillaries cause movement of water and proteins from the intravascular space into the interstitium. This leads to tissue oedema. Intravascular hypovolaemia is compounded and organ function may be damaged by compromised capillary blood flow and oxygen delivery. Changes in haemostasis are inevitable in major trauma and haemorrhage. Extensive tissue damage, thrombus formation and massive blood loss leads to activation of the coagulation cascade and loss of inhibitors of coagulation and fibrinolysis. Inflammatory markers such as interleukin-1 and tumour necrosis factor also contribute to coagulopathy (7).

The body's initial response to injury will be followed by a recovery period which is affected not just by the initial injury but the time and extent of organ ischaemia and reperfusion injury. Recovery from trauma

may be complicated by a major catabolic response. The ability of the kidneys to excrete water and sodium becomes compromised by a large urea nitrogen load. The urea competes for excretion with sodium, leading to hypernatraemia and uraemia and resulting in a hyperosmolar state. The increase in osmolarity triggers an increase in antidiuretic hormone release, further fluid retention and an inability to offload sodium and urea (5).

### **Which Fluid Is Most Appropriate For Resuscitation In Trauma?**

The ideal fluid for resuscitation would combine the volume expansion and oxygen carrying capacity of blood (3). It would restore normal composition and distribution of the body fluids and would ameliorate the pathophysiological effects of the trauma insult and subsequent resuscitation on the body. In addition it would be safe, free from the risk of disease transmission, easy to administer and widely available.

Fluid resuscitation has been recognised as essential for the management of major trauma for a long time, but the use of fluids is not without debate. Points of controversy in this area appear to be when to give the fluid (8) and which type of solution is best suited to avoiding the sequelae of trauma (9). Some risks and side effects of fluid therapy are common to all fluids while others are more fluid specific.

The stress response to trauma described above leads to leaky capillaries and movement of fluid into the interstitium. This has a number of adverse effects. Interstitial oedema leads to poor pulmonary function with decreased gas exchange and the risk of acute respiratory distress syndrome. Myocardial oedema leads to decreased cardiac compliance. Cerebral oedema affects mentation and conscious level. Interstitial oedema impairs gastrointestinal function and increases the risk of bacterial translocation. Tissue swelling impairs healing (10). Fluids given to resuscitate intravascular volume and maintain cardiac output may worsen interstitial oedema by diluting the tonicity of the plasma and by increasing the water, sodium and chloride load at a time when the body is retaining fluid. Severe sodium and water retention are associated with interstitial oedema, poor lung function, acute respiratory distress syndrome and multiple organ failure (5).

### **Currently Available Fluids**

None of the fluids currently available meet all of the criteria for the ideal fluid as described above. Fluids are described by the extent of their distribution throughout the body's fluid compartments. They can be broadly grouped into isotonic crystalloids; hypertonic crystalloids with or without colloid; artificial colloids and blood products. Artificial haemoglobin solutions are not yet

available for clinical use, although one product is currently undergoing Phase III clinical trials in the USA with promising initial results (11).

The plasma, extracellular fluid and intracellular fluid compartments maintain similar osmolarity. Osmolarity is measured as the number of osmotically active particles per unit volume. The normal range is 285-295 mOsm/l. The principle particles exerting osmotic pressure in the plasma and interstitium are sodium and chloride ions; potassium and phosphate are the most predominant intracellular ions. The difference in ion concentration between compartments is maintained by active pumps in the cell membrane. If a difference in osmolarity occurs between compartments, water is drawn into the area of higher concentration by osmosis to equalise osmotic pressure (12).

Crystalloids are solutions containing ionic or non-ionic particles small enough to pass freely through a semi permeable membrane with pore size of 10 000 Daltons (12,13). The two most commonly available crystalloids are 'physiological' 'normal' 0.9% saline and Ringers solution. Traditionally Ringers solution has contained lactate as a buffer and source of bicarbonate, but in Scandinavia Ringers solution with acetate as the buffer is also used. Acetate causes vasodilatation and may cause redistribution of blood to the splanchnic bed (14). Acetate containing solutions can cause hypotension, cardiovascular instability and release of cytokines (15). Crystalloids distribute throughout the extravascular space. Measurement of the distribution of 0.9% saline in septic patients found that the increase in extracellular fluid volume was approximately the same as that of the 0.9% saline infused (16). An intravenous infusion of isotonic saline expands the intravascular space by one third maximum (13), but up to six times the intravascular volume required may need to be given to achieve the volume effect (17). The ratio of crystalloid volume required may be much higher in trauma resuscitation (up to 10:1) because of decreased serum protein concentration secondary to haemorrhage and haemodilution (1). In controlled hypovolaemia the volume effect of crystalloid may increase. In a study using human volunteers, 1500-2000ml of Ringers Lactate was needed to replace a blood loss of 450ml over one hour. Three to four times the volume lost was required for crystalloid resuscitation of hypovolaemia (18). In a volunteer study of volume kinetics, adult females were given Ringers Lactate. Measurement of haemodilution reflected an expandable volume of only five litres. This may be because crystalloid is sequestered throughout the entire extracellular fluid space whilst expanding only 40% of it, reflecting the heterogeneity of compliance

for volume expansion within the interstitium in different tissue regions (19). This may be different in health and during trauma resuscitation. In one study only 21% of the volume of 0.9% saline given was evident in the plasma volume at the end of intravenous infusion (16). In another study demonstrating that the intravascular effect of crystalloid is short lived; only 16% of the volume infused remained in the circulation at 30 minutes (20). Further crystalloid infusions may be cleared even more rapidly (17). The volume effect of crystalloids is inefficient, short lived and may be unpredictable in the trauma situation. Changes to the permeability of the capillaries and to the oncotic pressure of the interstitium will also contribute to sequestration of administered fluid, potentially worsening tissue oedema and impairing the microcirculation.

Hypertonic crystalloids create an osmotic gradient into the intravascular compartment. Their intravascular volume enhancing effect is greater than 100%. This effect may be prolonged by combining with a colloid.

Colloids contain molecules which are too large to pass through the capillary semi permeable membrane. In healthy tissue these larger molecules are confined to the vascular compartment. They create an osmotic pull that draws free water from the intracellular compartment and the interstitium into the vascular compartment. This pressure is called the colloid oncotic pressure. In theory, colloids will initially remain within the intravascular space, thus more efficiently expanding plasma volume than crystalloids. The degree to which this is achieved and the length of time for which it is effective varies between types of colloids. If intravascular pressure is low, or the integrity of the capillary walls is compromised, water will accumulate in other compartments causing tissue oedema (12). Colloid particles may cross through the leaky capillary wall and increase interstitial oedema.

### **0.9% Saline Compared With Ringers Lactate**

The crystalloids 0.9% saline and Ringers Lactate are presently the first line fluid of choice for resuscitation. They have proven effectiveness, high availability, low morbidity and low cost. They may be effective as sole fluid expanders for a blood loss of up to 30% (3).

Current ATLS guidelines recommend isotonic crystalloids for initial fluid resuscitation on the basis that crystalloids provide transient intravascular expansion and further stabilise the vascular volume by replacing losses from the interstitial and intracellular space (21). Iso-osmotic crystalloids are usually considered safe because of their low incidence of side effects (12). However they are not entirely without

side effects. Differences in action can be explained by the varying ionic compositions. The differing effects on fluid physiology of 0.9% saline and Ringers Lactate will now be considered.

### **Osmolarity**

Normal serum osmolality levels are 285-295mOsm/kg. 0.9% saline is slightly hyperosmolar with a measured osmolality of 308mOsm/kg, which is similar to its calculated osmolality. In contrast Ringers Lactate is hypo-osmolar with a measured osmolality of 254mOsm/Kg. The calculated osmolality of Ringers Lactate is 273mOsm/L; this discrepancy is due to incomplete ionization of the solutes in the Ringers Lactate solution.

In a study comparing 0.9% saline and Ringers Lactate, eighteen healthy human volunteers were given 50ml/kg of 0.9% saline and then Ringers Lactate over two occasions. Ringers lactate caused a decrease in serum osmolality of 4 +/-3 mOsmol/kg. There was no change in serum osmolality in those receiving 0.9% saline. Time to urination was longer with 0.9% saline than with Ringers Lactate. The authors postulated that the lowered osmolality seen with Ringers Lactate may inhibit secretion of antidiuretic hormone (22). Alternatively, because 0.9% saline is hyperosmolar, it may cause fluid retention by stimulating the production of antidiuretic hormone (5). Serum osmolality is a determinant of brain water content. Low serum osmolality contributes to cerebral oedema and so is undesirable in the serious trauma case where primary or secondary brain injury may be present. Large volumes of Ringers Lactate will reduce serum osmolality and contribute to cerebral oedema compared with 0.9% saline (22).

### **Hypernatraemia and Hyperchloraemia**

0.9% saline contains 150mmol/l sodium ions and 150mmol/l chloride ions. This is a relative excess compared to normal serum levels of sodium of 135-145 mmol/l and of chloride of 95-105 mmol/l. Intravenous infusion of large volumes of 0.9% saline causes hypernatraemia and hyperchloraemia compared with Ringers Lactate (23,24). Hyperchloraemia stimulates renal vasoconstriction which leads to a decrease in glomerular filtration rate and may contribute to fluid retention (5,22). Hyperchloraemia leads to a mild metabolic acidosis.

### **Metabolic Acidosis**

Excess chloride ions are excreted by the kidneys in place of hydrogen ions (12). The decreased excretion of hydrogen ions leads to a mild metabolic acidosis. In a study in patients undergoing major gynaecological surgery, infusion of approximately 70ml/kg (6000ml) of 0.9% saline during surgery led to a mild metabolic acidosis (pH 7.41 to 7.28).

This was not observed with similar volume infusions of Ringers Lactate (23).

In a study comparing normovolaemic volunteers who received 50ml/kg of either 0.9% saline or Ringer's lactate solution, the 0.9% saline group developed a mild hyperchloraemic metabolic acidosis. Blood pH decreased 0.04 $\pm$  0.04 with 0.9% saline and persisted for more than one hour. Blood pH transiently increased with Ringers Lactate by 0.04 $\pm$  0.04. (22).

In another perioperative study, patients received either 0.9% saline or Ringers Lactate to alleviate intravascular deficits. The patients received nearly 20 litres from induction of anaesthesia to the morning of the second post operative day. Hyperchloraemic acidosis occurred only in the 0.9% saline treated group (25).

It is evident that large volumes of 0.9% saline can cause hyperchloraemic acidosis. There is little basic scientific evidence available, but of itself, this acidosis seems to be of uncertain pathologic or physiological consequence (23,26). The danger lies in the fact that it may worsen, or confuse, the diagnosis of an underlying acidosis or that it is treated as an assumed lactic acidosis due to organ hypoperfusion. This may be of limited importance in initial fluid resuscitation of trauma where a limited amount of crystalloid is given before moving onto blood products.

#### ***Renal Function And Urine Output/Fluid Retention***

In a study with healthy human volunteers, Ringers solutions (both lactated and acetated) were approximately 10% less effective than 0.9% saline in diluting plasma over a 240 minute observation period. This may be accounted for by a slightly lower sodium concentration and higher urine output in the groups receiving the Ringers' solutions, there was considerable inter-subject variability (14). In another recent volunteer study, two litres of 0.9% saline was given over 60 minutes. By six hours only one quarter of the fluid had been excreted. 0.9% saline loading was accompanied by hypernatraemia, hyperchloraemia and a fall in serum albumin (24). Other studies have observed a smaller urine output after administration of saline compared with Ringers Lactate (23).

#### ***Immunomodulation***

Dilution with both isotonic crystalloids and artificial colloids causes activation of neutrophils and increased expression of neutrophil adhesion molecules in a dose responsive way. Large volumes of fluid given for resuscitation of haemorrhagic shock may contribute to the increased inflammatory cascade associated with reperfusion injury. In a laboratory study 0.9% saline caused a smaller increase in neutrophil CD18 expression than Ringers Lactate (27). The significance of increased leukocyte activation

and adhesiveness on actual clinical outcome in the context of vast clinical experience and scientific data demonstrating the efficacy and safety of crystalloid resuscitation is as yet unknown (28).

0.9% saline and Ringers Lactate have similar profiles in terms of volume of distribution. 0.9% saline causes hypernatraemia and hyperchloraemia when used in large volumes. It may increase fluid retention and impede urine output. Large volume infusions of 0.9% saline lead to a mild metabolic acidosis. 0.9% saline enhances neutrophil activation to a lesser extent than Ringers lactate.

#### **0.9% Saline Compared With Hypertonic Saline**

Hypertonic saline is discussed in another article in this series. Here its effects compared with 0.9% saline will be briefly reviewed.

Hypertonic (7.5%) saline is light, transportable, easy and quick to administer by intravenous or interosseous infusion. It has been shown to be safe in the volumes given for initial fluid resuscitation. Hypertonic saline may cause advantageous changes in the microcirculatory and immune responses to trauma and hypovolaemia (27,29). It increases intravascular volume by pulling intracellular water into the intravascular and interstitial spaces by osmosis (30,31) and improves haemodynamic parameters in hypovolaemia in volumes at which 0.9% saline is ineffective (32). Hypertonic saline solutions cause an increased arterial blood pressure in resuscitation at volumes as low as 4ml/kg. Trauma patients given 250ml 7.5% saline compared with 250ml 0.9% saline had significantly higher arterial blood pressures, but the complication and mortality rates were the same for both groups (12). There was no difference in mortality in a similar study in the pre hospital setting (33). A meta-analysis in 1997 found no difference in survival between patients treated with isotonic crystalloid or by hypertonic saline resuscitation (34). A Cochrane Review of the topic in 2002 was inconclusive (35).

Hypertonic saline may improve outcome for patients with shock and traumatic brain injury (34), but a significant advantage over 0.9% saline has not yet been demonstrated (3).

#### **0.9% Saline Compared With Colloids**

Colloids are more effective at restoring intravascular volume and achieve similar resuscitation end points with much smaller volumes than crystalloids (3). Colloid supporters argue that unlike colloids, hypotonic crystalloids leak out of the plasma, excessively expanding the interstitial fluid volume leading to all the risks of worsening organ compromise, in particular pulmonary oedema (16). However, severe trauma leads to the depletion of interstitial fluid as well as

intravascular fluid. By restoring volume to both, 0.9% saline may be working in a more physiological manner. There is some evidence that pulmonary function is not adversely affected by crystalloid resuscitation. Lymphatic flow can increase by up to 20 times. Colloids may increase extravascular water by passing through leaky capillaries into the interstitium and increasing the oncotic pressure outside the intravascular space (13).

Despite the theoretical advantages of colloids, to date no prospective randomised studies have clearly demonstrated the superiority of colloids over crystalloids for trauma resuscitation (10). A recent study using a porcine model of shock found no major differences in early systemic and pulmonary vascular changes between groups resuscitated with 0.9% saline and with 4% gelatine (36).

Colloids and crystalloids have a range of effects on different important physiological parameters. A meta-analysis of fluid resuscitation with colloid or crystalloid in critically ill patients with studies up to 1997 found that the use of colloids was associated with an increase in absolute risk of mortality of 4% (0-8%). There was no evidence of difference of effect amongst different types of injury requiring fluid resuscitation (37).

A meta-analysis of crystalloids versus colloids in fluid resuscitation by Choi *et al* in 1999 found no overall difference in pulmonary oedema, length of stay or mortality between crystalloid and colloid resuscitation. They demonstrated a statistically significant decrease in mortality associated with the use of crystalloids in patients in the trauma subgroup (2).

Rizoli's analysis of six meta-analyses of the use of crystalloids or colloids in trauma concludes that trauma patients should continue to be treated with crystalloids (1). A Cochrane review from 2000 concluded that there is no evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death compared to crystalloids in patients with trauma or burns. It recommended that because colloids are more expensive and not associated with an improvement in survival, their use over that of crystalloid in these situations is not justified outside the context of randomised controlled trials (38).

0.9% saline is cheaper and has less risk of transmission of infection than the animal or blood based colloid solutions (12). Colloids have a varying risk of anaphylaxis which does not occur with 0.9% saline. In the absence of evidence of additional benefit over crystalloids, the role of colloids in current management of trauma resuscitation must be limited (3). To date there is not enough evidence that one kind of colloid is more effective and safe than any other (39).

## Conclusion

Hypovolaemia leads to tissue necrosis and organ failure. The first priority in managing a trauma patient is surgical control of active bleeding. Whilst this is ongoing, controlled fluid resuscitation aims to maintain enough intravascular volume and oxygen delivery to vital organs to ensure viable survival. The fluid given must be able to achieve these goals and minimise any adverse sequelae of the therapy. In addition it should be widely accessible and safe. 0.9% saline has a long history of use in trauma resuscitation. This article has demonstrated that it is an appropriate fluid for use in these circumstances. It has an established safety record when given properly. The Consensus Working Group on Pre-Hospital Fluids (40) recommended isotonic 0.9% saline as the current first line fluid in resuscitation of the hypovolaemic trauma patient.

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