Grand Rounds

Perioperative Intravenous Fluid Therapy for Adults

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ABSTRACT

Fluid and electrolyte homeostasis is a highly evolved mechanism, designed to conserve sodium and water in periods of illness. The advent of intravenous fluid therapy has challenged this system to operate in an opposite manner and excrete perioperatively administered sodium and water. Excessive fluid generates oedema and is associated with organ dysfunction and even death. Numerous fluid types have been developed, with recent large scale randomized controlled trials identifying clear signals of harm with hydroxyethyl starches, culminating in their withdrawal from clinical practice. Prescribing intravenous fluids requires a clear understanding of the requirement for fluid, the formulation of the various solutions available, the scientific evidence for and against these solutions, and the ability to identify a patient's pathology, volaemic status and response to the fluid administered.

INTRODUCTION

The prescribing of intravenous (IV) fluids for patients recovering from surgery is often delegated to the most junior member of the surgical staff, as if this were a task of little consequence. Nothing could be further from the truth. Just as oxygen administration is increasingly being recognised as being potentially harmful, so too is the infusion of IV fluids. Each bag of fluid charted can have as much significance as a drug on the medicines administration chart, an effect supported by their requirement for a prescription. Getting the fluid prescription right requires an understanding of the patient, their physiology, the composition and effect of the fluid prescribed, the pathophysiological processes ongoing or developing, and the body's response to the administered fluid. Getting the fluid prescription wrong will, at best, lead to a delayed recovery; at worst, organ dysfunction[1,2] and death[3]. Maintaining *the milieu intérieur* of a sick patient requires an assessment of the patient's volaemic state, done using simple, basic tools – history taking, examination and interpretation of charts of vital signs, fluid balance and body weight. These should be augmented by the interpretation of laboratory investigations (electrolytes and urea) and where necessary, the chest radiograph.

The aim of this Grand Rounds article is not to provide a comprehensive review, but to provide the junior doctor caring for postoperative patients with some pointers to safer care.

FLUID AND ELECTROLYTE HOMEOSTASIS: WATER AND ELECTROLYTE VALUES

An average 75 kg adult male contains approximately 45 L of water, functionally held in two compartments - the intracellular space (~ 30 L) and the extracellular space (~ 15 L). Extracellular fluid (ECF) can be further subdivided into interstitial (~ 12 L) and plasma (~ 3 L) volumes. To maintain these fluid compartments, average water intake is about 25-35ml/kg/day (2 to 3 litres per day for an adult), which permits the obligatory outputs of evaporation from the lungs and skin (500mls), stool loss (200ml), and urine production (500 -2000ml) to be matched. Electrolyte balance is similarly tightly regulated, with strict control of intracellular and extracellular anion and cation concentrations (Table 1). In tandem with the obligatory, insensible fluid loses, the body also loses approximately 1 mmol/kg/day of both sodium and potassium, a value which is matched by daily electrolyte intake. Fluid balance homeostatic mechanisms are so highly developed a healthy individual's daily water flux is approximately 0.2% (~ 165 ml).[4]

RESPONSE TO HYPOVOLAEMIA/DEHYDRATION

The physiological response to water deficit is complex, involving water consumption and conservation, preferential organ perfusion, and metabolic compensatory responses to dehydration. Water consumption is driven by the sensation of thirst, produced by hyper-osmolarity and hypovolaemia. Both mechanisms also promote water conservation. Hyper-osmolarity induced osmoreceptor activation causes anti-diuretic hormone secretion from the posterior pituitary, enhancing renal water conservation via upregulated aquaporin insertion into collecting duct and distal convoluted tubule cell membranes. Hypovolaemia activates baroreceptors and the renin-angiotension-aldosterone system, promoting renal sodium and water retention, in parallel with potassium loss, and inactivating atrial natriuretic peptide, lessening renal water loss, manifesting as oliguria. Both mechanisms are intrinsically linked to the sensation of thirst,[5] a symptom lost in the unconscious or neurologically impaired patient. A low extracellular fluid volume induces circulatory changes, including tachycardia, postural initially, and preferential vital

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Normal plasma biochemistry ranges in mmol/L (except creatinine in µmol/L.).

Na^{+}	K^{+}	Urea	Creatinine	Cl^{-}	Mg^{2+}	iCa[2+]	HPO$_4$[2-]
135-145	3.5-5	3.5-10	70 -110	95-105	0.7 – 1.0	1.03-1.23	0.8 – 1.5

organ perfusion, manifesting as increased capillary refill time and cool peripheries. Hypotension and tachypnoea develop as the spectrum of water deficit progresses, eventually resulting in shock and organ dysfunction, evident as confusion, acute kidney injury, hypernatraemia, and metabolic acidosis.

RESPONSE TO HYPERVOLAEMIA

Human physiology has evolved to cope with states of illness by developing regulatory mechanisms aimed at conserving sodium and water. It is unprepared to excrete sodium and water during injury states, a current requirement resulting from the recent development of artificial IV fluid administration, which interferes with homeostatic mechanisms. Excessive volumes of infused saline may take days to be excreted, even in healthy volunteers.[6] Fluid overload is implicated in numerous organ dysfunctions, including brain, lung, heart, liver, kidney, gut, and microcirculation.[6,7]

DURING ILLNESS

The administration of IV fluids bypasses the normal protective mechanism of thirst. By prescribing an IV fluid regimen the clinician undertakes responsibility for this intricate, protective function. IV fluids should be restricted to those patients whose fluid and electrolyte needs cannot be met by the oral or enteral route.

Each type of surgery has both general effects on the patient (stress response), and effects specific to the organ system operated on. For example, gastrointestinal surgery can be accompanied by huge losses of water and electrolytes, especially into the ileum. The exact electrolyte losses vary according to the source of loss. A biliary drain could contain about 145 mmol/L of sodium, whereas the losses from a low ileal fistula might contain half this. Broadly speaking, gastrointestinal losses are similar to the extracellular fluid, except for vomiting, which typically results in less sodium loss per litre (20-60 mmol/L), more potassium loss (15 mmol/L) and higher chloride (140 mmol/L) and hydrogen ion (60-80 mmol/L) losses. Liver surgery can result in complex physiological changes including hyperaldosteronism and the retention of sodium and water. Patients undergoing lung surgery are particularly vulnerable to pulmonary oedema (either due to an acute lung injury, or less usually, cardiac insufficiency). Neurosurgery can result in damage to the hypothalamus and pituitary systems giving rise to diabetes insipidus, cerebral salt wasting, or conversely the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). Burns, and the ensuing excision of burned skin, are always accompanied by large losses, primarily of the extracellular space. An adult with a large (50%) total body surface area burn may require in excess of 14 litres of fluid in the first 24 hours to prevent life-threatening hypotension. It is easy to see that for major surgery there is no single postoperative fluid regimen. Each patient should receive intravenous fluids to firstly resuscitate them, then replace their fluid losses to provide maintenance fluids (as in a healthy patient) and to account for redistribution of both administered fluids and their own body fluids. Clinical examination is essential and attention must be paid to the intake and output charts, with at least daily blood tests for all patients receiving IV fluids.

INTRAVENOUS FLUIDS

The Basics

Intravenous fluids can be categorized as either crystalloid or colloid solutions, with colloid solutions further classified as natural or artificial. Crystalloid solutions contain low molecular weight electrolytes or sugars in water and pass freely across a semipermeable membrane (i.e. between the intravascular and interstitial compartments)(Table 2). Colloid solutions contain high molecular weight molecules which fail to cross a semi-permeable membrane, and exert a high oncotic pressure. Natural colloid solutions are human albumin solutions. Artificial colloid solutions are starches, gelatins and dextrans. Many colloid solutions simply contain the colloid molecule in 0.9% saline. Fluids can also be described as being balanced (more physiological, with an electrolyte composition less likely to induce a metabolic acidaemia) or not. Solutions may be described in terms of concentration, such as 20% albumin. This refers to 20g of albumin per 100 ml of carrier solution, which, for albumin, is usually 0.9% saline.

Composition of IV solutions Values in mmols/L, with osmolality in mOsmol/kg

	Na^{+}	Cl^{-}	K^{+}	Ca^{2+}	Glucose	Lactate	Osmolarity
Plasma (approximate)	140	100	5	2	5	0.5	290
Hartmann's solution	131	111	5	2	-	29	278
0.9% saline	154	154	-	-	-	-	308
5% dextrose	-	-	-	-	278	-	278

Two further important related concepts are that of osmolarity and tonicity. The osmolarity of a solution is the number of osmoles of solute per litre of solution, and determines its osmotic pressure. Tonicity refers to the effective osmolarity. For example, dextrose molecules may be taken up by cells and metabolised, leaving free water. Thus, although 5% dextrose is relatively iso-osmolar (the fluid, whilst still in the bag, contains a similar number of osmoles per litre as plasma) but once infused, is grossly hypotonic (dextrose is metabolised, provided insulin metabolism is normal).

The volume expanding effect of colloids, in comparison with that of crystalloids, has been explained on the basis of the Starling equation, whereby elevating the vascular oncotic pressure results in retention of the volume infused. Accumulating evidence suggests this effect is less marked, and only temporary (see below). The vascular glycocalyx, an extra-endothelial layer of membrane-bound glycoproteins, proteoglycans and glycosamionoglycans, provides a major barrier against extravasation of large molecular weight molecules out of plasma.[8] In illness, and hypervolaemia, this layer becomes injured allowing leak of colloid molecules into the interstitium, lessening volume expansion. Furthermore, any intended effect of a hyperoncotic plasma resorbing interstitial fluid is also unlikely, with the majority of interstitial fluid being returned to the circulation via the lymphatic system, not local microcirculatory absorption. Based on large multi-centre studies, the true superior volume expanding effect of colloid solutions is only approximately 30% greater than crystalloid solutions,[9,10] rather than a presumed 200 % (so-called 3:1 rule), and is short-lived, lasting several hours only.

Crystalloids

Hartmann's solution is a balanced crystalloid solution, which, of all the available IV solutions in the UK, most closely resembles plasma. Dextrose solutions are a means of administering free water, as dextrose is rapidly metabolised. Dextrose is included as the IV administration of even moderate volumes of water causes intravascular hypotonicity resulting in haemolysis of red blood cells due to the influx of water into the cell. Concentrated dextrose solutions retain a place in the management of hypoglycaemia and 5% dextrose may be used in the treatment of hypovolaemic hypernatraemia. Dextrose solutions have little indication outside these areas and should not be used as maintanence solutions and certainly not as resuscitation fluids. Normal saline (0.9% saline) is anything but normal in physiological terms. It is grossly hyperchloraemic, containing approximately 50% more chloride than plasma, and as such, is not a balanced solution. Hyperchloraemia induces intra-renal vasoconstriction[11] and is associated with the development of acute kidney injury.[1] The high-normal sodium load can also be problematic. A daily infusion of 3 litres 0.9% saline constitutes a high sodium load (462 mmols or 27 grams; more than four times the guideline daily amount[12]). The normal stress response to surgery or illness involves the retention of sodium, impairing the ability to excrete both this excessive sodium load and free water. This concentration of saline is also slightly hyperosmolar (308 mOsmol/L).

Colloids

Human albumin is a protein consisting of a single polypeptide chain of 585 amino acids and has a molecular weight of 66 500 Da. Human albumin solution is produced from pooled albumin, a by-product of whole blood fractionation. It is formulated as 4.5% or 20% preparations in 0.9% saline. Hydroxyethyl starches are derivatives of amylopectin and produced from maize or potato. They are characterized by their concentration, average molecular weight, molar substitution (a reflection of the magnitude of addition of hydroxyethyl groups, conferring resistance to degradation) and C2:C6 ratio (referring to the site of substitution and a measure of half-life). Gelatins are derived from hydrolysed animal collagen, and are succinylated, urea-crosslinked or oxypolygelatins. Dextrans are highly branched polysaccharide molecules, coming in 6 % and 10 % formulations, but are rarely used to due multiple complications including anaphylaxis, coagulopathy, interference in blood cross-matching and renal failure.

EVIDENCE

The choice of fluid administered should be based on the scientific evidence available, not a feeling, based on intrinsic biases of uncertain origins, that a certain theoretical pharmacological profile would be favourable. Critical care has recently seen many high quality trials investigating the comparative efficacy of different IV solutions for fluid resuscitation. This has been mirrored by a number of new, or updated, meta analyses on this topic. In addition, the provisional results of several newly completed studies have been presented orally at major conferences, with publication due imminently.

The first major study of the past decade, performed by the Australian and New Zealand critical care trials group, was the SAFE (Saline versus Albumin Fluid Evaluation) study.[9] This was a landmark multi-centre, randomized, double-blind trial published in 2004, comparing fluid resuscitation with 4% albumin or 0.9% saline on 28 day mortality in 6997 critically ill patients. Fluid administration was based on the judgement of the treating clinician for the need for the maintenance or expansion of intravascular volume in the presence of at least one prespecified criterion. There was no difference in mortality at 28 days (albumin group 726 deaths versus saline group 729 deaths; relative risk of death 0.99; 95% CI 0.91 to 1.09; P=0.87). Similarly, there were no differences in secondary outcomes, including the proportion of patients with new single-organ or multiple-organ failure, or durations of mechanical ventilation, renal replacement therapy, ICU stay, or hospital stay. In two pre-specified subgroup analyses, there were trends for improvement with albumin in sepsis and saline in traumatic brain injury.

The VISEP (Efficacy of Volume Substitution and Insulin

Therapy in Severe Sepsis) study was published in 2008.[10] This was a multi-centre, randomized study comparing intensive insulin therapy with conventional insulin therapy and 10% pentastarch (a low-molecular-weight hydroxyethyl starch; HES 200/0.5) with Ringer's lactate, using a two-by-two factorial, open-label design. Although the insulin arm of the study was stopped for safety concerns after the recruitment of 448 patients, the fluid arm continued until a planned interim analysis after 600 patients had been investigated showed a greater incidence of renal failure (34.9% vs. 22.8%, P=0.002) and a trend toward higher 90-day mortality among patients who received HES than those who received Ringer's lactate (41.0% vs. 33.9%, P=0.09). HES was associated with increased complications, including more days of renal-replacement therapy, lower platelet count and transfusion of more units of packed red cells.

There were several major randomized controlled trials of note published in 2012, including CRYSTMAS, FIRST, 6S and landmark CHEST study.

The Crystmas study was a multi-centre, active-controlled, double-blind, randomized study in 196 critically ill patients comparing the efficacy and safety of 6% HES 130/0.4 with 0.9% saline for haemodynamic stability in patients with severe sepsis.[13] There was no difference in the number of patients achieving haemodynamic stability between the two therapies. Although less fluid was required to achieve this endpoint using HES (1,379 ±886 ml versus 1,709 ±1,164 ml; mean difference -331± 1,033, 95% CI -640 to -21; P = 0.0185), there was no difference in total quantity of study fluid administered over four days, or either duration of ICU or hospital stay. Acute renal failure rates were similar between groups (HES group 24.5% versus saline group 20%, P=0.454), as were pruritus, coagulation and 90-day mortality.

The single-centre, randomized, double-blind FIRST study investigated 109 severely injured patients requiring >2 litres of crystalloid resuscitation to receive further fluid resuscitation with either 0.9% saline or HES 130/0.4.[14] Penetrating (n=67) and blunt (n=42) trauma patients were randomized and analysed separately, leading to small sample sizes and less robust conclusions. Total fluid volume administered was similar between the two therapies in blunt trauma, but was significantly lower with HES than saline in penetrating trauma (5.1 versus 7.4 litres; P<0.001). Blunt trauma patient receiving HES received significantly greater volume of red cell transfusion than those receiving saline (2943 versus 1473 ml, P=0.005). In penetrating trauma, HES was associated with reduced renal injury (0% versus 16%; P=0.018), and lower plasma lactate concentrations. There was no mortality difference.

The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial randomized 800 critically ill patients with severe sepsis or septic shock to 6% HES 130/0.42 (Tetraspan) or Ringer's acetate.[2] Ninety day mortality was increased in those receiving HES (51% versus 43%; relative risk 1.17; 95% CI 1.01 to 1.36; P=0.03), as was the requirement for renal replacement therapy (22% versus 16%, relative risk 1.35; 95% CI 1.01 to 1.80; P=0.04).

Almost a decade after the publication of the SAFE study, the same trials group repeated the basic methodology of their original study, but this time compared 0.9% saline with 0.9% saline containing hydroxyethyl starch (6% HES 130/0.4, Voluven) in 7000 critically ill patients (Crystalloid versus Hydroxyethyl Starch Trial, CHEST).[3] There was no difference in the primary endpoint of 90 day mortality (HES group 18% versus saline group 17%; relative risk in the HES group, 1.06; 95% CI 0.96 to 1.18; P=0.26). However, patients receiving HES were 21% more likely to require renal replacement therapy (HES group 7.0% versus saline group 5.8%, relative risk 1.21; 95% CI 1.00 to 1.45; P=0.04). Consistent with this, HES was associated with significantly more complications (5.3% vs. 2.8%, P<0.001).

In a prospective, open-label, sequential period pilot study in 1533 critically ill patients, the administration of chloride rich solutions (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution), in comparison with chloride restricted solutions (Hartmann's solution, Plasma-Lyte 148 or chloride-poor 20% albumin) was associated with increased renal injury and failure (14% vs 8.4%, P< 0.001, adjusted odds ratio 0.52, 95% CI 0.37-0.75; P 0<.001), and need for renal replacement therapy (odds ratio 0.52, 95% CI 0.33-0.81; P = 0.004).[1] This harmful effect has been ascribed to hyperchloraemia induced intra-renal vasoconstriction. There were no differences in hospital mortality, hospital or ICU length of stay, or need for RRT after hospital discharge. This comparison of buffered versus unbuffered crystalloid solutions was also examined by Burdett and colleagues in a Cochrane Review of 13 studies and 706 patients.[15] Their analysis, excluding dextrose solutions, showed reduced metabolic complications, such as hyperchloraemic metabolic acidosis, although patient-centred outcomes, such as the need for renal replacement therapy were not different.

In parallel with the reporting of ongoing randomized controlled trials, several new or updated systematic reviews and meta analyses have also been performed. The Cochrane Collaboration have summarised the data for colloid use in fluid resuscitation, and, in three separate systematic reviews and meta analyses, found both a general lack of superiority of one colloid over another, and a lack of superiority of colloid over crystalloid. Bunn et al compared different colloid formulations in 86 studies investigating a total of 5,484 patients.[16] Comparing albumin or plasma protein fraction (PPF) with hydroxyethyl starch (HES) in 31 trials (n=1,719) the pooled relative risk for mortality was 1.06 (95% CI 0.86 to 1.31). After excluding data by the fraudulent German researcher Joachim Boldt, the lack of difference between these two therapies remained (pooled relative risk 0.90; 95% CI 0.68 to 1.20). Nine trials (n=824) reporting mortality compared albumin or PPF with gelatin. Again, there was no difference between these solutions (relative risk 0.89; 95% CI 0.65 to 1.21). The exclusion of data by Boldt did not

change the analysis results. In four studies (n=360) comparing albumin or PPF with dextran, there was again no difference in pooled relative risk for mortality (3.75; 95% CI 0.42 to 33.09). Gelatins were compared with HES in 22 trials (n = 1,612) with no difference in mortality (relative risk 1;02, 95% CI 0.84 to 1.26). Removing trials by Boldt had no effect on this analysis. The mortality relative risk was not estimable in either the gelatin versus dextran analyses or the HES versus dextran groups.

Roberts examined 38 trials (n=10,842) investigating human albumin solution for resuscitation and volume expansion in critically ill patients.[17] The relative risk for death using albumin was not significant when used either for hypovolaemia (1.02; 95% CI 0.92 to 1.13) or hypoalbuminaemia (1.26; 95% CI 0.84 to 1.88). Albumin was associated with an increased risk of death in the setting of burns (relative risk 2.93; 95% CI 1.28 to 6.72). Overall, the pooled relative risk of death with albumin administration was 1.05 (95% CI 0.95 to 1.16), indicating no benefit from this therapy based on the available evidence.

In 2013, Perel et al updated their previous systematic review and meta analysis comparing crystalloids with colloids for fluid resuscitation in critically ill patients.[18] Twenty four studies (n=9,920) assessing the comparative effect of human albumin or plasma protein fraction versus crystalloid on mortality demonstrated no difference in mortality risk between these fluids; pooled risk ratio 1.01; 95% CI 0.93 to 1.10. Hydroxyethyl starches failed to demonstrate a mortality benefit over rystalloids in 25 studies (n=9,147) with a pooled RR of 1.10 (95% CI 1.02 to 1.19). Data from 11 trials (n=506) also failed to show any superiority of modified gelatins over crystalloid therapy, with a pooled RR of 0.91 (95% CI 0.49 to 1.72). Similarly, analysis of nine trials (n=834) evaluating dextrans failed to establish a mortality advantage over crystalloid therapy (pooled RR 1.24; 95% CI 0.94 to 1.65). Based on the available evidence, the authors concluded by questioning the continued use of colloids in clinical practice.

In 2013 Leitch and colleagues performed a systematic review and meta analysis, including nine trials and 1,435 patients, evaluating human albumin solution for the resuscitation of critically ill patients.[19] Albumin resuscitation was associated with a trend to lower mortality (relative risk 0.90; 95% CI 0.79 to 1.02), but the methodological quality of studies was variable. The authors concluded "routine administration of human albumin solution to patients with severe sepsis and septic shock is difficult to justify on the basis of current knowledge". Interestingly, this contrasts with a slightly older 2011 meta analysis in 17 studies and 1,977 patients, suggesting the use of albumin for fluid resuscitation in sepsis was associated with a mortality reduction (pooled estimate of the odds ratio 0.82; 95% CI 0.67 to 1.0; p = 0.047).[20]

Some very recently completed studies have been presented at conference level with early results reported in discussion articles. Following the SAFE subgroup analysis suggesting benefit with albumin in sepsis, the randomized controlled

ALBIOS (Albumin Italian Outcome Sepsis) study has also examined the role of albumin in sepsis, comparing albumin with crystalloid. Doses of 200 or 300 ml 20% albumin were administered targeting a serum albumin level >30g/L in patients with severe sepsis or septic shock. Currently it has been presented at two international meetings, with full publication imminent. There were 903 patients in the albumin group, and 907 in the crystalloid-only group. There was no overall 90-day mortality benefit (41.1% versus 43.6%). In pre-specified subgroup analysis 90-day mortality was reduced in patients with septic shock (42.6% vs 48.4%; P=0.03). There was also benefit with albumin administration in patients with a higher number of organ failures.

The multi-centre EARSS (Early Albumin Resuscitation in Septic Shock) study compared human albumin solution with 0.9% saline, in early septic shock. There was no difference in the primary outcome of 28-day mortality.[19]

The BaSES (Basel Starch Evaluation Study) trial randomized 240 patients with severe sepsis or septic shock to volume replacement with 0.9% saline or 6% HES 130/0.4. In an unusual design, both groups received a litre of Ringer's lactate after each litre of study fluid to prevent elevation of urinary oncotic pressure. The primary endpoint was the length of intensive care unit stay. Other endpoints included 1-year mortality and acute kidney injury. Full results are awaited, though it is reported that 6% HES 130/0.4/Ringers lactate combination was safe compared to saline/Ringer's lacate combination and may improve patient survival.[21]

The CRISTAL trial randomly assigned patients admitted to an ICU to treatment with any available crystalloid (n=1,443) compared to any available colloid (n=1,414). Study drugs consisted of isotonic and hypertonic saline or balanced solutions as crystalloids, as well as gelatins, dextrans, HES or albumin as colloidal solutions. The primary endpoint was 28-day mortality, with 90-day mortality and organ dysfunction being among the secondary endpoints. Patients were included early in the course of their disease and were hypotensive at the time of enrollment. Most of the patients randomized to the crystalloid group were treated with 0.9% saline, whereas 6% HES 130/0.4 was the most commonly used fluid in the colloid group. Notably, colloid resuscitation tended to reduce 28-day mortality and significantly reduced 90-day mortality. In a priori defined subgroup analyses, 90-day mortality was reduced in patients suffering from sepsis or nonseptic shock, but not in trauma patients.[21]

CURRENT STATUS

Fluid therapy is a dynamic area of research, with many recent high quality studies being published and more imminently awaiting publication. What has become apparent is a clear safety issue with starches, at least in the critically ill. At best, they are non-superior to crystalloids for fluid resuscitation, with a small, short-lived larger volume expanding effect. At worst, they vastly more costly (by a factor of 30 for starches in comparison with crystalloids) and are directly

harmful, requiring increased rates of blood transfusion, renal replacement therapy, and in sepsis, being associated with a higher mortality. This lack of clinical efficacy is unsurprising, as the underlying vascular physiology upon which they are based has been seriously questioned. A profile of no theoretical advantage, increased cost, real world evidence of lack of benefit combined with increased organ failure and death, has belatedly (May/June 2013) lead to regulators from Europe, the UK and America all effectively rescinding the marketing licence for hydroxyethyl starches. Over 12 months earlier, the European Society of Intensive Care Medicine issued guidance advising against the administration of starches and gelatins in the critically ill.[22] The apparent move of some clinicians from starches to gelatins is difficult to reconcile, given an absence of safety data for these formulations,[23] and a lack of superiority over crystalloids. In contrast, there appears to be momentum for the therapeutic use of albumin in sepsis. Whether this is due to an anti-oxidant, or other metabolic effect, rather than a volume replacement effect, remains to be seen. Full publication of ALBIOS and the other recently completed trials, and the subsequent discussion surrounding them, is eagerly awaited.

In the meantime, what fluid should be prescribed for the post-operative patient? There are two competing interests in the setting of maintenance fluid therapy - the avoidance of hyponatraemia with hypotonic solutions, and the avoidance of an excessive sodium load, with iso-tonic solutions. Based on a healthy adult's daily requirement of 25-35 ml/kg/day of water, plus approximately 1 mmol/kg/day of potassium, sodium and chloride and approximately 50–100 g/day of glucose to limit starvation ketosis, draft NICE guidance on Intravenous Fluid therapy in Adults in Hospital,[24] released for consultation May 20th 2013, suggests the use of 0.18 % saline with 5 % dextrose for maintenance fluid therapy. This solution has largely been removed from Northern Ireland due to multiple episodes of fluid and electrolyte complications. Similarly, the GIFTSUP British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients[25] suggest the use of sodium poor maintenance fluids. Both guidelines highlight the potential for hyponatraemia and stress specific indications for the use of other fluids, such as 0.9 % saline for chloride depletion from vomiting or gastric drainage. In the absence of clear data from randomised controlled trials in this area, many clinicians continue to use Hartmann's solution in an effort to avoid either excessive sodium loading and oedema, or hyponatraemia. For resuscitation, the use of Hartmann's solution, or possibly 0.9 % saline, would appear best. Albumin may be considered for resuscitation in sepsis, although it currently does not appear to be superior to 0.9% saline. There is no convincing evidence for the use of gelatins in any circumstance, while dextrans are no longer in contemporary practice and starches have effectively joined them in antiquity. For haemorrhagic shock, blood product therapy is indicated if bleeding is severe.

COMMON SCENARIOS

Case 1: Postoperative Oliguria

A 72 year old gentleman develops oliguria 36 hours post umbilical hernia repair, with a urinary output decreasing to an average of 12 ml/hr for the past 8 hours. Intra-operatively, the small bowel was ischaemic and it was decided to keep the patient fasting for a period. His decreased urinary output has been treated with an increase in his rate of maintenance fluids and successive fluid boluses. His fluid balance is now 8L positive since his operation.

Learning Points:

The scenario of postoperative oliguria remains a common postoperative problem delegated to junior members of the surgical team; however, oliguria is merely a number and a temporary decrease of urine output does not necessarily imply a decrease of glomerular filtration rate.[26] Instead, it may reflect an appropriate physiological response to conserve fluid and electrolytes ("acute renal success"). Oliguria of 6 hours duration or less has poor ability to discriminate between patients who will and will not progress to meet creatinine criteria for acute kidney injury.[27] The current KDIGO definition of acute kidney injury[28] based on a urinary output of 0.5 ml/kg/hr for 6 hours has not been validated, and in a recent single-centre study was not associated with in-hospital or 1-year mortality.[29] However, a 6 hour value of 0.3 ml/kg/hr provided best association with mortality and need for dialysis.

The simplest approach to identify the likely abnormality is to use the time honoured pre-renal, renal, post-renal structure, with the latter two categories being beyond the scope of this article. Pre-renal failure implies a state impaired renal perfusion. This can be rectified by ensuring the patient is normoxic, euvolaemic, not grossly anaemic (Hb > 70 g/L), has reasonable cardiac function and systemic arterial pressure, and there is no reason to suspect aortic or renal arterial disease. Markers of hypovolaemia include thirst, dry mucous membranes, decreased skin turgor, collapsed veins, tachycardia, tachypnoea, elevated urea and sodium, metabolic acidosis and hypotension. The urine is often sent for osmolarity and urinary sodium levels, with a presumption that a low urinary sodium represents sufficient renal tubular function to conserve this electrolyte. Unfortunately, little evidence supports the utility of such biomarkers in differentiating pre-renal from renal injury.[30]

If the problem is a simple state of intravascular depletion, repletion with Hartmann's fluid is the preferred choice, due to the nephrotoxicity of some colloids and the association of 0.9% saline with acute kidney injury. Once the volaemic state has been satisfactorily addressed, the temptation to give further fluid should be resisted, as a vasopressor or inotrope may be required instead. Alternatively, there may be intrinsic renal pathology. Excessive fluid administration merely delays focusing on the true problem and worsens fluid balance, with a positive fluid balance in the setting of severe acute kidney injury (plasma creatinine > 310 µmol/L) associated

with worse outcomes.[31] Diuretics are not recommended to convert an oliguric state to an non-oliguric state, and may be harmful in the setting of acute kidney injury,[32] with a possible exception being a state of fluid overload, although this decision is recommended to be made by a senior clinician. If, despite these measures, renal function deteriorates (deteriorating biochemistry, fluid overload, acidosis) expert opinion should be sought and renal replacement therapy may be required.

Case Study 2: Hyponatraemia

A 67 year old gentleman with a history of alcohol abuse is admitted to the surgical ward following banding of a bleeding oesophageal varix. He is complaining of thirst, and although nil by mouth, wants to drink. His routine observations are: oxygen saturations 92% breathing 50% oxygen via Hudson facemask, heart rate 120 bpm, blood pressure 98/50 mmHg. Following investigation his haemoglobin is 75 g/l, platelet count 60x10 9/L, white cell count 15x10 9/L and creatinine 50μmol/L. The surgical foundation doctor is asked by the nursing staff to prescribe some intravenous fluids and prescribes 2 litres of 5% dextrose and 1 litre of 0.9% saline each to be given over 8 hours. The following day Mr Smith's biochemistry is: Na 120 mmol/L, K 3.9 mmol/L, urea 20 mmol/L and creatinine 100 μmol/L. He is confused and nauseous, he remains clinically dehydrated and his urine output is low.

Learning Points:

The fluids prescribed are not appropriate for this patient. Mr Smith has pre-existing liver disease and probably a long-standing hyponatraemia secondary to hyperaldosteronism, with a possible contribution from its treatment with spironolactone (a potassium sparing diuretic). He has acute blood loss and clinically is intravascularly depleted. Although his calculated plasma osmolarity is low, he feels thirsty due to hypovolaemia (which activates the renin-angiotensin system and also mediates thirst via arterial baroreceptors). Cases with large fluid losses such as this require careful fluid resuscitation and further management involving senior doctors. Dextrose 5% is not a resuscitation fluid, and may induce hyponatraemia in the sick patient, a complication associated with increased morbidity and mortality. Post-operative patients are at high risk of hyponatraemia due both to fluid losses (loss of sodium due to extracellular fluid losses the stress response to surgery) and iatrogenic use of hyponatraemic fluids. Isotonic salt solutions, such as Hartmann's or 0.9% saline, should be the standard IV fluid for the correction of hypovolaemia. Until consistent evidence for the superiority of colloids over crystalloids is available, it is difficult to justify their use in this setting.

Case Study 3: Hypernatraemia

Mr Black is a 27 year old man who is 24 hours post-operative removal of a pituitary adenoma, and is recovering on a neurosurgical ward. The ward nurse bleeps the foundation doctor to inform him that Mr Black has passed large volumes of urine for the past 3 hours of 400, 550 and 800ml respectively. He is receiving 80 ml / hr 0.9% saline and is taking sips of water. On examination he is slightly tachycardic with a heart rate of 112 beats per minute, but observations are otherwise normal. His catheter bag contains a large amount of dilute urine and he is complaining of lethargy and thirst. Blood samples are sent for biochemistry and his sodium level (normal pre-operatively) is 151 mmol/L. Serum osmolality and urine osmolality is 325 mOsm/kg and 290 mOsm/kg respectively. (Normal values serum osmolality: 285-295 mOsm/kg; urinary osmolality 500-800 mOsmol/kg).

Learning Points:

Post-operative neurosurgical patients and patients with head injuries can develop neurogenic diabetes insipidus (DI), a state of reduced ADH secretion, diagnosed by a raised serum osmolality, an inappropriately dilute urine and a rising serum sodium level. The resulting hypernatraemia may cause vague symptomatology of lethargy, weakness and decreased consciousness.

Therapy is aimed at restoring both the ADH deficiency and water deficit. Desmopressin (DDAVP), the long acting analog of ADH, may be required, although this should be discussed with an endocrinologist. Usual dosing is 1-2 mcg IV/SC BD. It can also be administered orally and intra-nasally. Its effect after IV administration is immediate. As DI is associated with aquaresis, it is appropriate this free water should be replaced with free water. A ward-based patient with intact cerebral function may be allowed to drink to replace this loss. IV fluids may be required for patients unable to drink adequately, with 5% dextrose or Hartmann's the fluids of choice, supplemented with potassium chloride as needed. Plasma electrolyte levels should be monitored every 6 hours and there should be diligent recording of urinary output and neurological state.

CONCLUSION

Intravenous fluid therapy has the potential to induce serious harm, including death. For colloids, hydroxyethyl starches have lost regulatory approval due clear signals of harm from large multi-centre studies; this has led many to change to gelatins, despite a lack of superiority over crystalloids and an undetermined safety profile. Albumin is safe, but, pending publication of new trial data, presently appears to lack clear evidence of superiority over other solutions. For crystalloids, dextrose 5% is a means of administering free water; saline 0.18% with dextrose 5 % has largely been withdrawn from Northern Ireland due to repeated complications, but is now being recommended in national guidelines for maintenance fluid therapy, and 0.9% saline causes hyperchloraemic metabolic acidosis and is associated with the development of acute kidney injury. Arguably, this leaves the default IV fluid to be Hartmann's solution, although it too is far from perfect and exchanges a risk of hyponatraemia for that of oedema.

In summary, prescribe IV fluids only where necessary, for as short a period as possible, and monitor the patient clinically and biochemically. Use Hartmann's solution, unless there

is a specific reason to use saline or dextrose, and seriously consider what advantage the prescription of a colloid will actually provide.

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