A critical appraisal of intravenous fluids: from the physiological basis to clinical evidence

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ABSTRACT

Fluid management has been a vital part of routine clinical care for more than 180 years. The increasing number of available fluids has generated controversy about the optimal choice of resuscitation fluid. In this review, we provide a critical overview of the different fluids available, their composition, the relevant physiology as well as the published evidence on clinical outcomes to guide their use. Commonly used infusion fluids include semisynthetic colloids and crystalloids; the latter comprises both normal saline (NaCl 0.9%) and the more chloride-restricted ‘balanced’ crystalloids. Despite their significantly greater intravascular persistence, semisynthetic colloids have an importantly adverse safety profile and are associated with greater incidence of renal failure and increased mortality; their use should be restricted. To date, evidence for clinical benefits associated with albumin solutions is generally lacking; its merits in specific clinical situations are the subject of further investigation. Infusion of normal saline, with its supraphysiological chloride content, is associated with higher serum chloride concentrations and metabolic acidosis, as well as renal vasoconstriction in animal and human models. Infusion of ‘balanced’ crystalloids is not linked to such changes. Although data on clinical outcomes associated with crystalloid infusion are homogeneous, advantages of balanced salt solutions might include a lower need of blood products, and lower incidence of renal replacement therapy, hyperkalaemia and postoperative infections. Taken together, a critical appraisal of the data suggests that balanced salt solutions deserve consideration as infusates of first choice.

Keywords: chloride, colloids, crystalloids, saline

INTRODUCTION

In 1832, Dr Thomas Latta first reported on an attempt to intravenously replace fluids and salts lost in cholera sufferers. He made up a solution containing ‘two to three drachms of muriate of soda and two scruples of the subcarbonate of soda in six pints of water’. Faced with failure of earlier attempts at oral rehydration, and with ‘no precedent to direct him’, he proceeded to ‘throw the fluid immediately into the circulation [1]’. This highly successful intervention led to a number of important experiments—in 1834, Dr John Mackintosh first used intravenous albumin [2], Ringer’s solution was introduced in 1876 by Dr Sydney Ringer and a modification was made by Dr Alexis Hartmann in 1932 to include lactate [3]. Given impetus by a better understanding of the principles of membrane permeability, fluid tonicity and osmosis at the time, it appears that the in vitro studies of the Dutch physiologist Hartog Jakob Hamburger in the 1890s led to the acceptance of NaCl 0.9% as isotonic to human blood. Noting that erythrocytes were least likely to lyse in this solution, he called it ‘indifferent’ saline [4, 5]. While the use of intravenous gelatin in animals was reported as early as 1894 [6], and a first study in humans was performed in 1915 [7], interest in gelatins as well as other larger molecules to expand the intravascular volume was renewed only in the Second World War [8]. Asanguineous infusion fluids are most commonly classified as crystalloids (small electrolytes in water) or colloids (larger molecules that are meant to remain in circulation for a longer time). Crystalloids include 0.9% NaCl (‘normal’ saline) as well as buffered and more ‘balanced’ solutions such as lactated Ringer’s solution.

Today, fluid management is a vital part of routine care for a wide range of settings. In volume replacement, the goal is to replete intravascular fluid volume in trauma or sepsis, while in ‘dehydration’ (contraction of the extracellular fluid volume), the total extracellular space is the target of fluid repletion. A third potential goal of infusion is to restore the composition of the extracellular fluid by altering its electrolyte contents or acidity, which will not be discussed in this review. Finally, another aim of fluid infusion may be the maintenance of flow in the distal renal tubules and urinary tract to prevent toxicity or precipitation of drugs or radiocontrast. Indeed, the question of the optimal choice of infusion fluid for this indication has led to a number of trials, mostly making a comparison
between colloid and crystalloid infusions or more specifically between infusion of normal saline and sodium bicarbonate solutions. A more in-depth discussion of this indication is beyond the scope of this article (for review, see [9–11]). Of note, infusion therapy often serves more than one purpose, e.g. fluid repletion and electrolyte correction.

The choice of a particular infusion fluid has generated considerable controversy. Arguments are predominantly based on theoretical and physiological considerations as well as preclinical studies (Table 1). The number of clinical studies is limited and restricted to the field of general surgery, kidney transplantation and intensive care medicine. The aim of this review is to provide a nephrological readership with an overview of the different fluids available for volume resuscitation and fluid repletion. This review will not consider blood products other than albumin. First, we give an introduction on infusion fluid characteristics and physiology. We then summarize the relevant chemical properties of commonly used infusates and discuss studies that evaluate their physiological effects and potential side effects. We proceed by highlighting the available evidence on outcomes in clinical studies in general surgery, kidney transplantation and intensive care units (ICUs). We conclude that the available evidence merits consideration as infusates of first choice for balanced salt solutions, although definitive large-scale studies are still needed.

REVIEW CRITERIA

We performed a search for original full-text English language papers in Medline, EMBASE and the Cochrane library, using the search terms ‘crystalloid’, ‘saline’, ‘Ringer’, ‘Hartmann’, ‘Plasma-Lyte’, ‘Sterofundin’, ‘colloid’ and their synonyms, alone and in combination (last accessed 21 November 2013). We also selected further relevant papers by following reference lists of identified articles.

INFUSION FLUID CHARACTERISTICS AND PHYSIOLOGY

The ionic composition of infusion fluids is important because it directly affects biological processes like signal transduction and coagulation. The choice of infusate can be guided by the intention to maintain or deliberately change the composition of body fluids. It is of note that clinical laboratories generally report the electrolyte concentrations in serum. Concentrations in the aqueous fraction of plasma are 7% higher due to the presence of proteins and lipids. It follows that if the electrolyte contents of an infused fluid are to be proportionate to the corresponding aqueous fraction of blood plasma and effects on acidity are to be minimal, it should contain 153 mmol/L Na⁺, 111 mmol/L Cl⁻, 4.8 mmol/L K⁺, 2.7 mmol/L Ca²⁺ and 1.35 mmol/L Mg²⁺, and be able to maintain a plasma pH of 7.35–7.45 [12]. Surprisingly, however, no such fluid is available (Table 2). A change in plasma Ca²⁺ concentration, for example, will change cellular (de)polarization, whereas changes in acidity directly influence processes like coagulation [13–17]. This is in line with the profound impairment in factor VIIa (FVIIa), FVIIa/tissue factor and FXa/FVa activity with decreases in pH [16]. In vitro and animal models also suggest increased extracellular acidity may alter the immune response in multiple ways, ranging from a change in production of proinflammatory mediators to impaired leucocyte chemotaxis and lymphocyte cytotoxicity [18, 19].

The distribution of infused fluids between the intracellular and extracellular compartments is dictated by the osmotic pressure in the different compartments. The osmotic pressure is determined by the amount of solutes and their osmotic coefficients, which describe the deviation of the osmotic behaviour of solutes from their theoretical osmotic behaviour. When considering the tonicity of an infused fluid, it is important to appreciate the differences between theoretical ‘osmolality’ (obtained by addition of all osmotically active molecules to 1 L of solution) and ‘actual’ ‘osmolality’ (mOsmol/kg solvent), especially in vivo. As sodium and chloride, when dissolved, only partially dissociate, and as such are only partially osmotically active (osmotic coefficient 0.926), the actual osmolality of a fluid in which they are dissolved is lower than their added moles. The osmolality of a fluid is derived from the ‘ideal’ osmolality, the osmotic coefficient and the solvent content (93% water for plasma) and may be directly measured via freezing point depression. Surprisingly, the measured osmolality of plasma (288 mOsmol/kg H2O) is practically identical to the calculated osmolality (291 mOsmol/L) [12, 20]. This is in stark contrast to the difference between the theoretical osmolality of NaCl 0.9% (308 mOsmol/L) and its actual osmolality of 286 mOsmol/kg H2O. It is of note that changes in the osmolality and volume of the blood plasma lead to more limited, yet potentially important changes in erythrocyte volume, and may have significant rheological effects [21].

In contrast to small solutes, plasma proteins move across the capillary wall only to a limited degree, subsequently acting as effective osmotes, impeding filtration of water into the interstitium. The osmotic pressure generated by plasma proteins is commonly referred to as the colloid osmotic or oncotic pressure [22]. The oncotic pressure depends on both the difference in plasma protein concentrations and the barrier between the intravascular compartment and the interstitium. This barrier is predominantly formed by the endothelial glyocalyx layer (EGL) but also by the endothelial basement membrane and extracellular matrix in the interstitial space [23, 24]. The EGL

<table>
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<th>Table 1. Summary of haemodynamic effects, advantages and disadvantages of commonly used infusion fluids</th>
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<tr>
<td><strong>Colloids</strong></td>
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<td><strong>Intravascular persistence</strong></td>
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<tr>
<td><strong>Advantages</strong></td>
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Various colloids are currently available. Human albumin is available in iso-oncotic 4–5% solutions and hyperoncotic 20–25% solutions. The high cost of human albumin has limited its use. Gelatins are proteins formed by hydrolysis of animal-derived connective tissue. Because high-MW gelatin solutions tend to gel, the average MW of present solutions is limited to 30–35 kDa, which reduces their oncotic pressure and intravascular persistence. Dextran ‘40’ (MW 40 kDa) and ‘70’ (MW 70 kDa) are the products of acid hydrolysis and ethanol fractionation of highly branched polysaccharide molecules synthesized by the B512 strain of Leuconostoc mesenteroides [37]. Finally, HESs are derivatives of maize or potato starch, amylopectin, in which intravascular amylase-driven degradation of the molecules is slowed by substitution of the hydroxyleyl radicals in positions C2, C3 and C6 with hydroxyethyl radicals [38]. This molecular modification renders HES more prone to accumulation in reticular connective tissues, such as the spleen, skin, liver and kidneys [39–42], and it may explain the finding of lesions with a histological appearance of osmotic nephrosis in animals subjected to HES infusion [43]. Semisynthetic colloids are considerably cheaper than human albumin, but still usually at least an order of magnitude more expensive than crystalloids.

The use of albumin solutions in volume replacement in resuscitation of critically ill patients has a number of theoretical advantages over crystalloids, but its actual clinical benefits and safety profile are uncertain. The addition of human albumin to normal saline, bringing the solution to iso-oncoticity, in theory expands this fluid’s capacity to provide intravascular volume expansion. Indeed, in one large randomized controlled trial comparing resuscitation with albumin or normal saline, 40% greater average volumes of saline were infused [44]. Similarly, greater increases in plasma volume and cardiac index were obtained with infusion of 5% albumin compared with normal saline in cardiac surgery and sepsis [45, 46]. Moreover, pre-clinical studies suggest albumin may reduce vascular endothelial leucocyte adhesion [47–49].

A first meta-analysis by the Cochrane collaboration was published in 1998, comparing the use of albumin or plasma protein fraction with crystalloids in patients with hypovolaemia,

**Table 2. Characteristics of commonly available infusion fluids**

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<tr>
<th>Plasma</th>
<th>Crystalloids</th>
<th>Colloids</th>
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<tr>
<td>0.9% NaCl</td>
<td>Lactated Ringer’s</td>
<td>Plasma-Lyte</td>
</tr>
<tr>
<td>Na&lt;sup&gt;+&lt;/sup&gt; (mmol/L)</td>
<td>142</td>
<td>154</td>
</tr>
<tr>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; (mmol/L)</td>
<td>103</td>
<td>154</td>
</tr>
<tr>
<td>K&lt;sup&gt;+&lt;/sup&gt; (mmol/L)</td>
<td>4.5</td>
<td>0</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt; (mmol/L)</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>Mg&lt;sup&gt;2+&lt;/sup&gt; (mmol/L)</td>
<td>1.25</td>
<td>0</td>
</tr>
<tr>
<td>Buffer&lt;sup&gt;b&lt;/sup&gt; (mmol/L)</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Colloid (g/L)</td>
<td>35–45</td>
<td>0</td>
</tr>
<tr>
<td>Osmotic pressure (mmHg)</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Osmolality (mOsmol/L)</td>
<td>291</td>
<td>308</td>
</tr>
<tr>
<td>Osmolality (mOsmol/kg)</td>
<td>288</td>
<td>286</td>
</tr>
</tbody>
</table>

<sup>a</sup>The buffer in plasma is bicarbonate, in lactated Ringer’s lactate, in Plasma-Lyte acetate (27 mmol/L) and gluconate (23 mmol/L), in Sterofundin acetate (24 mmol/L) and maleate (5 mmol/L).

<sup>b</sup>The buffer in plasma is bicarbonate, in lactated Ringer’s lactate, in Plasma-Lyte acetate (27 mmol/L) and gluconate (23 mmol/L), in Sterofundin acetate (24 mmol/L) and maleate (5 mmol/L).

**COLLOIDS**

Colloid is the collective noun for all infusion fluids that contain large molecules which are meant to keep the infusate in the intravascular space for a longer time by exerting an oncotic pressure [35]. Colloid infuscates comprise blood products such as human albumin solution and the more commonly used semisynthetic products: gelatins, dextrans and hydroxyethyl starch (HES) solutions. Their effect on plasma volume expansion depends on their oncotic pressure, influenced directly and indirectly by molecular weight (MW) and plasma half-life [36].

Consists of a dense network of proteoglycans associated with various glycosaminoglycans and coats the luminal side of healthy vascular endothelium [25]. The polyanionic nature of the glycosaminoglycans makes the EGL semipermeable to anionic macromolecules, such as albumin, depending on their size and structure [26]. Under physiological conditions, while continuously subject to degradation and reconstitution, its thickness is estimated to be as little as 0.2 μm in the microcirculation and up to 8 μm in the large vessels [27]. Several factors that contribute to EGL degradation, leading to shedding of its components and compromise of its function, have now been identified. Among them are inflammatory mediators [28–32], but also hypervolaemia, such as when induced by rapid crystalloid infusion in healthy volunteers [28, 33]. It is of note that the oncotic pressure gradient between the intravascular and interstitial spaces is insufficient to counter the hydraulic pressure found in the intravascular space [24, 34]. Since the subglycocalyx space is nearly protein free, it is likely the oncotic pressure gradient across the EGL, and not, as previously assumed, across the endothelium, which restricts water loss across the vascular wall [24]. Hence, in summary, the effect of a fluid infused in the intravascular compartment on its extravascular counterpart depends on hydrostatic and (colloid) osmotic pressure gradients as well as EGL function and factors in the endothelial basement membrane and the extracellular matrix.
burns or hypoalbuminaemia [50]. Its most important result, a pooled relative risk (RR) of death of 1.68 [95% confidence interval (CI), 1.26–2.23; P < 0.01] associated with albumin, caused a large uproar and a significant drop in the clinical use of albumin, but the investigators also attracted staunch criticism pertaining to limitations of included studies, review methodology and interpretation. The last decade saw publications of the Saline versus Albumin Fluid Evaluation (SAFE) study, in which 6997 critically ill, ICU-admitted adults were randomized to f

ly assigned to receive boluses of 5% albumin, normal saline or no bolus of resuscitation fluid [51]. While neither the FEAST nor the SAFE study detected differences in clinical outcomes between groups receiving normal saline or albumin, a post hoc subgroup analyses from the SAFE study showed higher mortality associated with albumin in 460 patients with traumatic brain injury (RR, 1.63; 95% CI, 1.17–2.26; P = 0.003) [52]. In contrast, another post hoc subgroup analysis of the SAFE study indicated a potential decrease in the adjusted risk of death with albumin in severely septic patients [odds ratio (OR), 0.71; 95% CI, 0.52–0.97; P = 0.03] [53]. A 2011 update of the above Cochrane review, which relied heavily on the SAFE study, no longer detected mortality differences between albumin and crystalloid solutions (RR, 1.02; 95% CI, 0.92–1.13, P = 0.35) [54]. Three trials addressing the use of albumin solutions specifically in early septic shock are under way (NCT00707122, NCT00327704 and NCT00819416).

Several clinical studies have confirmed that, in analogy to albumin solutions, semisynthetic colloids provide more intravascular fluid repletion than crystalloids. In a randomized clinical trial in 67 patients who had undergone cardiac or major vascular surgery, patients receiving colloid solutions (an average of 1600 mL of gelatin 4%, HES 6% or albumin 5%) had significantly greater increases, during the 90 min of infusion, in plasma volume (19 versus 3%) and cardiac index (22 versus 13%) compared with patients receiving normal saline [55]. Similarly, in a randomized trial with 25 septic patients and 24 non-septic hypovolaemic patients, fluid loading with semisynthetic colloids resulted in greater increases in cardiac filling, output and stroke work than loading with normal saline did [56]. The increased intravascular volume repletion was also demonstrated in a study with 10 healthy volunteers who received infusion with 1 L of gelatin (4% succinylated gelatin in 0.7% saline), HES (6% HES 130/0.4 in 0.9% saline) or 0.9% saline alone. HES and gelatin suppressed plasma renin activity (PRA) more than saline, but this difference did not reach statistical significance [57]. Finally, a study reported on a nurse-delivered algorithm, in which, after cardiac surgery, 237 patients were randomly allocated to receive 250-mL boluses of either normal saline or a HES solution based on haemodynamic parameters. Although the study did not report total volumes of infused fluids, significantly more catecholamines were used in the group assigned to receive normal saline [58].

However, serious concerns have risen over deleterious effects of semisynthetic colloids on specific systems, such as haemostasis [59] and renal function [60–62]. Significant reductions in FVIII and von Willebrand factor are observed after infusion of dextrans, gelatins and HES, with high-molecular HES and dextran having the greatest effect on haemostasis [59]. Moreover, concerns about nephrotoxicity have assumed prominence since the introduction of semisynthetic colloids, owing to a host of evidence published in the last few decades to suggest greater incidence of renal dysfunction and renal replacement therapy associated with semisynthetic colloid infusion. Importantly, evidence of a survival benefit of semisynthetic colloids over crystalloids has been lacking. Much of the attention has focused on HES. Four well-designed, large randomized controlled trials, published in 2008, 2012 and 2013, compared the use of HES with Ringer’s acetate or lactate [63, 64] with normal saline [65, 66], and demonstrated increased risk of death [63] and the use of renal replacement therapy [63–66] in the groups assigned to receive HES. A recent Cochrane review, which also included two of these studies, found no evidence from randomized controlled trials that colloids (dextran ‘70’, gelatins, HES, albumin and plasma protein fraction) are superior to isotonic or hypertonic crystalloids as a treatment for intravascular volume resuscitation in critically ill patients [67]. Notably, the pooled RR of mortality with HES versus crystalloids was 1.10 (95% CI, 1.02–1.19), implying a potential mortality hazard associated with HES [67]. A 2011 Cochrane review found no evidence of superiority of one particular colloid solution in critically ill and surgical patients requiring volume replacement, noting, however, a relative lack of direct comparisons and wide CIs [68]. Furthermore, two recent meta-analyses, including one Cochrane review, exclusively compared HES with other resuscitation fluids and found a significantly increased risk of mortality and acute kidney injury associated with the use of HES [69, 70]. Of particular interest is the finding that these detrimental effects only became visible after exclusion of seven pre-1999 trials initiated by Dr Joachim Boldt, whose subsequent publications have been retracted because of scientific misconduct [71, 72]. In addition, observational data suggest that gelatins may be nephrotoxic similarly to HES [73]. A very recently published, large, multi-centre, randomized controlled trial in patients admitted to the ICU and presenting specifically with hypovolaemic shock (CRISTAL) allocated 2857 patients to receive either exclusively colloids (various semisynthetic colloids and albumin solutions) or crystalloids in an unblinded fashion. Patients were randomized at the onset of resuscitation. Contrasting with previous studies, investigators found no difference in 28-day mortality (RR, 0.96, 95% CI, 0.88–1.04; P = 0.26), whereas the secondary outcome, 90-day mortality, was lower in the group receiving colloids (RR, 0.92, 95% CI, 0.86–0.99; P = 0.03) [74]. The latter finding should be interpreted with caution, since the CI approaches 1. No difference in the risk of receiving renal replacement therapy was found. Unfortunately, the pragmatic design of this study leaves questions on the contribution of individual fluid types to these outcomes, and especially the distinction between albumin and semisynthetic colloids.

Taken together, growing concerns about safety, especially concerning semisynthetic colloids, and the lack of consistent clinical superiority of colloids, suggest that their application
should be minimized and the less expensive crystalloids should be the infusates of choice, while we await clarification from ongoing trials on the potential benefit of albumin infusion specifically in septic shock.

**CRYSTALLOIDS**

The term crystalloid is typically used to refer to solutions in water of small inorganic ions and small organic molecules. Purely NaCl-based solutions are most commonly used. Alternatives include various concentrations of potassium, calcium, magnesium and organic anions such as lactate to more closely resemble the ionic pattern of blood plasma.

**Normal saline**

‘Normal saline’ (NS, 0.9% or 154 mM NaCl) is the most frequently prescribed crystalloid in clinical practice [75], yet remarkably few studies address the time scale and extent of its effects in normal subjects on haemodynamic parameters, blood dilution and excretion. After infusion, normal saline is rapidly distributed between the compartments of the extracellular space but remains in the body for a long time. In normovolaemic subjects, expansion of the intravascular volume persists for as long as 6 h after infusion of normal saline, even though most of the infused volume is found in the interstitial compartment. A study in 28 healthy volunteers found that 30 min after completion of a 20-min infusion of 10–30 mL/kg, 64% of the infused volume had diffused into the interstitial compartment [76]. Studies in pre-surgical patients and healthy volunteers receiving a 2-L normal saline infusion over the course of 1 or 2 h reported intravascular retention of the infused fluid of 18–24% (calculations based on haematocrit values) [77–79]. After 6 h, 60% of the fluid volume still remained in the body, an estimated 13% in the intravascular space [78, 79]. Finally, it is of note that during anaesthesia and surgery, distribution and elimination of infused crystalloids are delayed when compared with healthy volunteers [80].

Owing to the non-physiological ion content and the lack of buffering capacity, normal saline infusion can be complicated by metabolic acidosis. The determination of saline-induced acidosis is subject to vivid debate [81]. The most commonly used method for interpreting acid-base disturbances is the Henderson–Hasselbalch equation, in which the dependent variable pH is calculated from the variables PaCO₂ and plasma bicarbonate. The acidosis resulting from normal saline infusion is often interpreted as dilutional, i.e. the result of decreased bicarbonate concentrations relative to stable PaCO₂ [81]. The model assumes changes in the volume of distribution of bicarbonate with changes in pH [82, 83]. Advocates of the alternative Stewart approach, introduced in 1983 [84], argue that the essential change is not dilution of bicarbonate (HCO₃⁻) but infusion of the ‘strong ion’ Cl⁻. This explanation is based on the concept that independent variables—PaCO₂, the strong ion difference and the total concentration of non-volatile weak acids—influence the dependent variables pH and bicarbonate concentration [85]. Indirect effects of chloride loading might also be responsible for the acidosis. Intraluminal chloride is needed for pendrin-mediated bicarbonate excretion [86–88]. We therefore speculate that excessive chloride loading might be involved in disproportionate urinary bicarbonate loss. However, it should be noted that in animal models, pendrin protein expression is rapidly downregulated in response to induction of acidosis [89]. In addition, the presence of chloride ions in an infusion fluid is instrumental in this fluid’s capacity to suppress renin release, and subsequently its capacity to suppress aldosterone availability and bicarbonate retention [90]. The latter was demonstrated in experiments in healthy, sodium-restricted volunteers, in whom no suppression of PRA was found after infusion of 750 mL 1.4% NaHCO₃, whereas infusion of 500 mL 0.9% NaCl led to a 50% decrease in PRA [91]. Regardless of the explanatory model, reductions in blood pH on infusion of saline, not in the more balanced Ringer’s solution, were demonstrated in healthy human volunteers who received 50 mL/kg over 1 h (average pH reduction 0.04 ± 0.04) [92], and, as described later in this review, in patients undergoing gynaecological surgery (average pH reduction 0.13) [93] and pancreatostomato-hepatic surgery [94].

As normal saline contains a supraphysiological concentration of chloride [12], its infusion increases plasma chloride concentrations [93], which is associated with renal vasoconstriction and decreased glomerular filtration rate (GFR). In an animal model, intrarenal infusion of chloride-rich solutions to denervated kidneys resulted in decreases in renal blood flow (RBF) and GFR compared with low-chloride solutions of equal tonicity [95, 96]. Two studies with healthy human volunteers consistently showed a longer time to first micturition after infusion of normal saline compared with a low-chloride solution [79, 92]. Changes in plasma osmolality must be taken into account in these studies, where the low-chloride solution had a lower osmolality than normal saline, with a potential effect on the release of antidiuretic hormone. Strengthening the hypothesis of renal vasoconstriction by chloride infusion, however, a study in healthy volunteers showed significant reductions in renal artery flow velocity and renal cortical tissue perfusion during and after infusion of normal saline, but not with a low-chloride solution (Plasma-Lyte 148) [97]. Such increases in renal cortical tissue perfusion were also seen when healthy volunteers received 1-L infusions of 6% HES suspended in a low-chloride solution compared with 6% HES suspended in normal saline [98]. The effect may be due to luminal chloride concentrations in the cortical thick ascending limb of the loop of Henle being a rate-limiting step in tubuloglomerular feedback [95, 99–101], a mechanism that induces alterations in the GFR by influencing afferent arteriolar vasoconstriction. Finally, chloride has been shown to be actively involved in the suppression of renin release, as described above.

‘Balanced’ crystalloids

Some of the above effects can be prevented by using a solution that more closely mimics the ionic make-up of the aqueous fraction of plasma. Acidosis can be avoided by inclusion of bicarbonate or metabolizable anions, such as acetate, lactate, malate and citrate. Examples of more balanced crystalloid solutions are lactated Ringer’s solution, Hartmann’s
solution, featuring slightly different ionic concentrations, Plasma-Lyte and Sterofundin. Their characteristics are summarized in Table 2. As described above, the use of infusates with metabolizable anions instead of chloride has been shown not to increase plasma acidity [92, 93]. In addition, balanced salt solutions did not reduce renal artery flow and renal cortical perfusion seen after infusion of normal saline (see above) [97].

Unfortunately, some of the most commonly used ‘balanced’ solutions (like lactated Ringer’s solution) are neither isotonic nor precisely balanced. With an osmolarity of 273 mOsmol/L and a measured osmolality of 254 mOsmol/kg, infused lactated Ringer’s solution leads to a small decrease in plasma osmolality [79, 92]. Theoretical concerns with slightly hypertonic infusion fluids include a potential increase in brain water [102] and effects on diuresis. Interestingly, Hartmann’s solution (a slightly modified form of Ringer’s solution) when compared with normal saline, doubled urine output in the 6 h after infusion, and subsequently had a shorter persistence in the body [79]. Such effects may be relevant considering the goals of infusion therapy. Commercial initiatives, such as Plasma-Lyte 148 and Sterofundin, have attempted to address concerns over differences in tonicity and ionic composition between plasma and the infused fluid. Unfortunately, there are no published studies that address potential differences in kinetics and the effect on plasma osmolality between the more balanced solutions.

**CLINICAL STUDIES**

In light of concerns raised around colloids, their use should be restricted. For (intravascular) volume repletion, crystalloids deserve consideration as infusates of first choice. Below, we compare the use of normal saline with balanced salt solutions in clinical outcome studies.

**Surgery**

The risk of hyperchloraemic acidosis in patients receiving normal saline was demonstrated in surgical patients. Subjects undergoing intra-abdominal gynaecological surgery were randomly assigned to receive normal saline or lactated Ringer’s, with an average volume of 6 L over 2 h. Predictably, hyperchloraemia and metabolic acidosis were more prevalent in the normal saline group (average pH 7.28 versus 7.41, chloride 115 versus 107 mmol/L) [93]. Such metabolic derangements associated with the use of normal saline in comparison with Plasma-Lyte were also seen in a study including 30 patients undergoing major hepatobiliary or pancreatic surgery [94]. In a randomized controlled trial in 46 trauma patients, resuscitation with Plasma-Lyte resulted in a quicker resolution of acid-base disturbances compared with normal saline [103].

Although the data on clinical outcomes in patients undergoing surgery are heterogeneous, advantages of balanced salt solutions might include lower need of blood products, lower incidence of renal replacement therapy and postoperative infections. A 2012 Cochrane review, using pooled data, found no influence of the choice of buffered or non-buffered infusion fluids in the perioperative period on mortality, renal function and blood loss [104]. In the non-buffered group, however, the average volume of platelet concentrates transfused was 242% greater (95% CI, 24.61–848.77; P = 0.02) [104]. Unfortunately, the trials included in this review were highly heterogeneous with regard to study groups, outcomes reported and administered infusion fluids, which included hypertonic and colloid solutions. In a recent large observational study, outcomes of 30,994 adult patients undergoing major abdominal surgery who received normal saline were compared with 926 patients who received only a non-calcium-containing balanced crystalloid solution (Plasma-Lyte) [105]. Unadjusted in-hospital mortality was far greater in the saline group than in the balanced crystalloid group (5.6 versus 2.9%). After propensity matching, mortality in the saline group remained higher, but the difference lost its statistical significance. However, treatment with balanced crystalloids was associated with fewer complications (OR, 0.79, 95% CI, 0.66–0.97; P < 0.05). Recipients of normal saline infusions were 4.8 times more likely to require haemodialysis (P < 0.001), and had greater blood transfusion requirements and more frequent postoperative infections [105]. Another double-blind randomized trial in 66 patients undergoing abdominal aortic reconstructive surgery found no statistically significant difference in blood loss, but an increased need for fresh frozen plasma and platelet transfusions in the group that received normal saline compared with the lactated Ringer’s group [106].

**Kidney transplantation**

Balanced salt solutions appear to reduce the incidence of metabolic acidosis and hyperkalaemia after kidney transplantation, but no differences in transplant outcome have been reported. In one Turkish double-blind trial, 90 recipients of kidney transplants of living related donors were randomized to receive either normal saline, lactated Ringer’s or Plasma-Lyte. Patients receiving normal saline had a significant decrease in pH and increase in serum Cl\(^-\), which was not seen in patients receiving lactated Ringer’s or Plasma-Lyte. No significant differences in renal function were seen, although the 24-h urine output in the first three postoperative days was significantly larger in the group receiving normal saline, which is in contrast with the expected effect of the increased chloride load in the normal saline group [107]. In an Iranian double-blind randomized trial, 52 adults undergoing kidney transplantation were either prescribed normal saline or lactated Ringer’s. Mean serum potassium values were lower in the group receiving lactated Ringer’s, despite the presence of potassium in this infusion fluid. No statistically significant differences in urine output or renal function were seen [108]. In a Korean study in 60 kidney transplant recipients, the use of Plasma-Lyte was associated with lower plasma Cl\(^-\) concentrations and lower incidence of metabolic acidosis, and no differences in postoperative creatinine values or urine output [109]. Finally, another double-blind randomized trial in 51 renal transplant recipients was suspended prematurely after a planned interim analysis showed a greater incidence of hyperkalaemia and metabolic acidosis in patients administered normal saline compared with the group receiving lactated Ringer’s. No difference in the primary outcome, the serum creatinine
concentration on the third postoperative day, was seen [110]. Eight patients (31%) in the group receiving normal saline were prescribed NaHCO3 in an attempt to correct acidosis. Interestingly, those patients treated for acidosis had significantly higher 4- and 48-h postoperative urine output, and significantly lower 24-h and 1-week postoperative creatinine values compared with the patients who received normal saline but no correction for acidosis [110].

Published evidence on the optimal fluid choice in preconditioning kidney donors revolves around a very limited number of trials, in which comparisons usually involve a colloid. These studies have been reviewed elsewhere [111, 112]. There is no clinical evidence to guide the choice of a particular crystalloid in healthy donors in the preoperative and perioperative period.

**Critical care medicine**

Recently, a large prospective, non-randomized, before-and-after study in a tertiary ICU was published [113]. Investigators allowed intravenous fluid administration as usual in patients admitted to the ICU during a 6-month control period. During the 6-month intervention period, which was timed to start at the same season a year later, the use of chloride-rich fluids was restricted to specific conditions. Instead, patients received Hartmann’s, Plasma-Lyte or, less frequently, human albumin. Biochemical effects of the policy change included fewer episodes of severe acidosis, more episodes of metabolic alkalosis, slightly higher lactate levels and no differences in sodium or potassium concentrations [113]. Importantly, in a separate publication the investigators reported a significantly better kidney function during ICU stay in the chloride-restricted group as well as significantly less renal injury and failure according to the RIFLE criteria (OR, 0.52, 95% CI, 0.37–0.75; P < 0.001), and subsequently, fewer episodes of renal replacement therapy (OR, 0.52, 95% CI, 0.33–0.81; P = 0.004) [114]. Interestingly, no significant difference in mortality was seen between the chloride-liberal and chloride-restricted groups [114]. The latter finding is difficult to reconcile with the 50% reduction in renal replacement therapy in the chloride-restricted group.

**Miscellaneous**

A small number of studies compared the use of balanced crystalloids with saline in resuscitation in diabetic ketoacidosis and choleraiform diarrhoea, and found faster resolution of acidosis with the use of balanced crystalloids. One study in diabetics presenting with ketoacidosis randomly allocated 45 patients to groups resuscitated either with Plasma-Lyte or normal saline, and found that postresuscitation serum chloride was significantly higher (111 [110–112] versus 105 [103–108]) and bicarbonate significantly lower (17 [15–18] versus 20 [18–21]) in the normal saline group compared with the Plasma-Lyte group, respectively [115]. A retrospective analysis of 23 patients treated for diabetic ketoacidosis with either normal saline or Plasma-Lyte by another group yielded comparable results [116]. Finally, in a Peruvian study, 40 severely dehydrated patients presenting with choleraiform diarrhea received infusions of either lactated Ringer’s or normal saline, and faster resolution of acidosis was attained in the group receiving lactated Ringer’s [117].

**CONCLUSIONS**

We have reviewed the available experimental and clinical data on colloid and crystalloid infusates. In view of an overall lack of survival benefit with albumin, recent evidence on adverse safety outcomes associated with semisynthetic colloids, as well as the effects of the retraction of a large body of work by Dr Joachim Boldt due to integrity concerns, the use of colloid infusates is to be limited. Therefore, we have focused on balanced salt solutions and normal saline.

Infusion of normal saline is clearly associated with hyperchloraemia and metabolic acidosis [93, 94], and such derangements can be prevented by using balanced crystalloids [93, 94]. Studies in surgical and ICU patients reported a significantly lower incidence of renal replacement therapy in groups receiving balanced crystalloids compared with those receiving normal saline [105, 114]. Interestingly, one study involving kidney transplant recipients found that correction of acidosis was associated with significantly lower creatinine levels and increased diuresis [110]. One explanation for this phenomenon is that by inducing renal vasoconstriction, hyperchloraemia appears to reduce RBF and GFR [95–97]. Acidosis leads to a dysfunction of various cellular and extracellular mechanisms, most notably coagulation [13–17]. This may explain the increased need for blood products in surgical patients receiving normal saline [104, 105].

A shortcoming in the literature is the absence of a direct comparison between the various balanced crystalloids and the relatively small study participant numbers. Furthermore, in the largest meta-analysis on this subject to date, relatively heterogeneous data on various salt solutions were pooled to compare balanced with unbalanced crystalloids. Even though the documented negative safety outcomes pertaining to the use of normal saline seem relatively persistent across studies, the heterogeneity of studies leaves questions on the size of the mentioned effects in clinical scenarios, especially mortality, unanswered.

In conclusion, there is a growing body of evidence that balanced crystalloids are preferred over normal saline in clinical practice and that the positive effects of these solutions are not restricted to one specific application only. In our opinion, balanced crystalloids therefore deserve consideration as first choice infusates. Obviously, individual situations might require different infusion fluids. Knowledge of the physiologic characteristics of the different infusion fluids is important in guiding this choice. However, the quality of the evidence available leaves room for a large, well-designed randomized controlled trial.

**CONFLICT OF INTEREST STATEMENT**

All authors confirm they have no conflicts of interest with regard to this submission.
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FULL REVIEW


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Iron dosing in kidney disease: inconsistency of evidence and clinical practice

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ABSTRACT

The management of anemia in patients with chronic kidney disease (CKD) is difficult. The availability of erythropoiesis-stimulating agents (ESAs) has increased treatment options for previously transfusion-requiring patients, but the recent evidence of ESA side effects has prompted the search for complementary or alternative approaches. Next to ESA, parenteral iron supplementation is the second main form of anemia treatment. However, as of now, no systematic approach has been