Colloids and crystalloids: does it matter to the kidney?

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Purpose of review

To highlight some of the recent key issues surrounding crystalloid and colloid fluid management of critically ill patients.

Recent findings

Significant developments have been made in the understanding of ionic balance of fluids and their effects on acid–base, the role of hydration and overhydration, alkalinization of fluids in patients at high risk for contrast induced nephropathy, and finally the role of colloids in acute kidney injury.

Summary

Despite hydration remaining a key principle in fluid management in many patients, volume overload is of considerable concern. Recent evidence also suggests that balanced electrolyte formulations are preferable to saline-based formulations in a variety of clinical settings. Furthermore, alkalinization of fluids is protective in the setting of contrast-induced nephropathy. Oncotic load appears to be the most important factor in acute kidney injury associated with colloid fluid therapy.

Keywords

acute kidney injury, colloid, crystalloid, fluids (intravenous)

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Introduction

Many truths and myths exist about the role of intravenous fluids in prevention and management of kidney injury. Although there is a substantial body of literature about the impact of various management strategies in the kidney at risk, there is also a lack of definitive evidence for many of the assumptions that we as clinicians take for granted. There are some excellent reviews on the subject, all essential reading [1•,2•,3]. This review aims to address a few of the more recent patterns of thought relating to intravenous fluid management, especially in the high-risk kidney. Key topics for this review are hydration, balanced electrolyte vs. saline-based fluids, alkalinization of intravenous fluids as prevention of contrast-induced nephropathy, and colloids and kidney injury.

Hydration

Dehydration or volume depletion is considered a high-risk factor for developing acute kidney injury (AKI), and much of our clinical practice in critical care and the perioperative setting is geared to reducing the risk of hypovolemia. During the acute, early stages of critical illness, adequate volume resuscitation remains a goal for optimizing tissue perfusion and oxygen delivery [4]. Interestingly, no randomized controlled trials (RCTs) have been reported investigating the impact of adequate hydration vs. placebo on AKI. There is also no evidence that fluid therapy can reverse established AKI. Small studies investigating types of fluids and kidney injury are reported, most of this in the setting of contrast-induced nephropathy. They will be discussed in greater detail in that section of the review.

In a large multicenter RCT investigating the role of conservative fluid management vs. traditional liberal fluid management on kidney injury in 1000 critically ill patients with acute lung injury, the investigators found that the fluid strategy did not affect the incidence of AKI [5]. An interesting result is reported, where dialysis requirement trended lower in the conservative fluid management group (10 vs. 14%; $P = 0.06$). This is compounded by the fact that despite receiving greater volumes of fluid, daily urine output was lower during the first seven days in the liberal fluid management group. Volume overload may well be implicated in the risk of abdominal compartment syndrome, and it may be this that caused the interesting result described.

Fluid overload in critical illness is an area of increasing attention, especially in the pathogenesis of abdominal compartment syndrome, with volume overload having an association with adverse clinical outcomes in critically ill

patients [6–8]. Moreover, it would be prudent to consider fluid management carefully in patients with oliguric AKI, where little evidence exists for repeated fluid challenges as a rescue measure. Indeed, the repeated fluid challenges may not only worsen abdominal compartment pressures, but also result in adverse outcomes of other organ systems.

Balanced electrolyte vs. saline-based fluids

It is well documented that large volume 0.9% saline administration causes a hyperchloremic metabolic acidosis (HCMA), a phenomenon well described by Stewart in the early 1980s [9–11]. Stewart explained the physicochemical approach to acid–base management as central to hydrogen ion regulation, where pH depends on, among others, plasma strong ion concentrations. A simplistic view implicates that should the plasma chloride concentration increase, more hydrogen ions need to be produced, leading to a metabolic acidosis.

Hyperchloremia causes afferent renal artery vasoconstriction in an animal model, suggesting a possible role in kidney function [12]. Saline-induced HCMA is associated with impaired organ function, for example, gut, central nervous system and coagulation, as well as delayed or slower urine production, but no differences in clinical outcomes have been reported [13–17]. It is important to note that these studies are underpowered to detect significant clinical outcomes.

A study of 51 patients undergoing mostly living-related kidney transplants (48 living-related, three cadaveric) randomized the recipients to receive either a 0.9% saline-based or a lactated Ringers-based fluid management algorithm [18]. Despite no difference in the primary outcome (creatinine concentration on day 3), there was a significantly higher rate of hyperkalemia and acidosis requiring treatment in the saline group, suggesting that (potassium-containing) lactated Ringers may be a well tolerated fluid choice in renal transplant recipients. These results have since been confirmed by another group using similar methodology [19].

Alkalinization of fluids in contrast-induced nephropathy

With ever increasing numbers of procedures being performed percutaneously, a greater number of patients are being exposed to radiocontrast agents. Besides the concern for contrast allergic reactions, contrast-induced nephropathy (CIN) is a significant risk factor for adverse outcomes. It has various definitions, most of which are diagnosed by absolute or relative increases in serum creatinine within 48 h of exposure to contrast agents. The currently understood pathogenesis of this phenomenon indicates that the contrast agents themselves cause both renal ischemia and renal tubular cell toxicity, where epithelial cell necrosis occurs primarily in the thin ascending limb of the renal medullary loop of Henle [20]. Worse clinical outcomes are associated with CIN, including increased morbidity, prolonged length of hospital stay, and mortality. Those particularly at risk are diabetic patients, patients with preexisting renal impairment, and those with congestive heart failure. Among other factors, the dose and type of contrast agent received is important [20], and the viscosity and osmolality of the contrast administered also affects the incidence of AKI, where the newer isotonic contrast agents appear to cause a lower incidence of CIN [21,22].

The role of intravascular volume is a significant factor, where simple intravenous hydration reduces the incidence of CIN. Recently, growing interest has also focused on the role of bicarbonate alkalinization of the intravenous fluid administered. The first single-center RCT to show a reduction in CIN, by Merten *et al.* [23], investigated fluid management using either 0.9% saline or sodium bicarbonate infusions. Their algorithm of 150 mEq $NaHCO_3$ per 850 ml 5% dextrose solution at 3 ml/kg per h for 1 h before the procedure, followed by 1 ml/kg per h for 6 h after the procedure produced a significantly lower incidence of CIN in the sodium bicarbonate-treated patients, although the mechanism remains unclear. More recently, studies have described varying results, from no difference to benefit with bicarbonate solutions, and two separate systematic reviews by Navaneethan *et al.* [24] and Meier *et al.* [25•] published this year described an overall perceived benefit of bicarbonate solutions over 0.9% saline in prevention of CIN. These systematic reviews reported similar odds ratios (ORs) (0.46 and 0.52) and confidence intervals (0.26–0.82 and 0.34–0.8). The overall message with CIN is that adequate hydration is essential, and it appears that bicarbonate solutions are better at reducing CIN. There remains some controversy over the role of *N*-acetylcysteine in the prevention of CIN, however, as these data are currently inconclusive.

Haase *et al.* [26] recently reported an interesting development using $NaHCO_3$ as a potential perioperative renoprotective strategy in cardiac bypass surgery patients. They reported a lower incidence of acute renal dysfunction in the bicarbonate-treated patients.

Colloids and renal function

The administration of fluid and the maintenance of plasma volume are most likely the only strategies that can reliably diminish the incidence of renal dysfunction

in surgical patients, victims of trauma, and the critically ill. As described earlier, growing interest in the problem of the abdominal compartment syndrome, particularly with its potential to impair renal function, has suggested that aggressive crystalloid resuscitation in a variety of clinical circumstances may increase the risk of abdominal compartment syndrome and may thus impair renal function. As colloids maintain the plasma volume efficiently, they ought to be associated with a reduction in the incidence of renal failure. However, there is no conclusive evidence that this is the case and, under certain circumstances, it appears that the colloids may have a detrimental effect on renal performance.

Acute renal failure following the infusion of colloids was first described with the dextrans, notably dextran 40. In early reports where dextrans were used in the treatment of acute stroke, the incidence of renal failure ranged from 0 to 4.3%, with the main difference relating to the degree of fluid supplementation with crystalloids in the studies, with generous crystalloid supplementation apparently preventing renal dysfunction associated with dextran 40 administration [27]. A number of risk factors were identified in a review including increasing age, latent renal disease, dehydration, and the administration of high doses of 10% (hyperoncotic) dextran 40 for several days [28]. A number of possibilities were considered to explain the renal injury including direct toxicity of the dextran molecule and the accumulation of hyperoncotic molecules within the plasma. The chemical toxicity of dextran is very low, but the occurrence of vacuoles in proximal tubular cells, referred to as osmotic nephrosis-like lesions, has been described [29]. Although these lesions were initially thought to be responsible for impaired renal function, they have subsequently been described in association with a wide variety of intravenously administered substances, including mannitol, gelatins, and hydroxyethyl starches, as well as agents not associated with renal failure; their appearance is not consistently associated with renal dysfunction. Mailloux *et al.* [30] showed that dextran could induce renal dysfunction rapidly in experimental animals with uncompensated hemorrhage and hypothesized that hyperviscous urine could be the cause. Subsequent reports, however, demonstrated that acute renal failure precipitated by dextrans could be reversed by the removal of dextran molecules from the plasma by plasmapheresis [31]. The renal dysfunction was shown to parallel an increase in plasma oncotic pressure sufficient to oppose hydraulic filtration pressure within Bowman's capsule. This led to the concept of hyperoncotic renal failure, and the syndrome has been reported not only with dextrans but also with hydroxyethyl starch (HES), gelatin, and hyperoncotic albumin.

Neither albumin nor gelatin is thought to have any direct toxic effect on the renal tubules, but a variety of reports have raised the possibility that HES may be associated with renal injury. The first of these described osmotic nephrosis-like lesions in transplanted kidneys where the donor had been resuscitated with HES 200/0.64, but these had no effect on renal function in up to 6 months following transplantation [32]. A randomized, but not blinded, comparison of HES 200/0.64 with gelatin in septic patients demonstrated a high creatinine in the HES group on days 6 and 7 compared with the gelatin group, but the baseline serum creatinine was nonsignificantly higher in the HES group ($P = 0.06$) and there was no outcome difference in either dialysis requirements or survival [33]. Finally, a study in septic patients compared 10% HES 200/0.5 with Ringer's lactate for fluid resuscitation and intensive care and showed a dose-related increase in renal failure and mortality in the patients receiving HES. However, many patients received very large quantities of HES, well in excess of the recommended doses. In a subgroup that received HES within the recommended specifications, renal function, and survival was at least as good as that in the Ringer's lactate group [34].

There is a large body of literature demonstrating an absence of adverse renal effects with a variety of HES products, but particularly related to the tetrastarches. An early review by Boldt and Priebe [35] described nine studies with a variety of HES products, none of which demonstrated adverse renal effects in perioperative patients. A study using high-dose HES for neurosurgical patients failed to demonstrate any deterioration in renal function despite doses of up to 70 ml/kg per day being administered in some patients [36]. Studies in high-risk surgical patients including those undergoing aortic aneurysm repair and cardiopulmonary bypass demonstrated that HES was at least as good at preserving renal function as albumin and possibly superior to gelatin [37,38]. In a multicenter observational study involving over 3000 patients, the use of HES was not shown to be associated with a decrease in renal function or an increase in the need for renal replacement therapy in intensive care patients [39].

A recent observational study by Schortgen *et al.* [40•] involving over 1000 patients examined the influence of different types of crystalloids and colloids solutions on the incidence of renal events. In this study, the use of artificial hyperoncotic colloids [OR 2.48 (1.24–4.97)] and hyperoncotic albumin [OR 5.99 (2.75–13.08)] was significantly associated with the occurrence of a renal event. Overall intensive care mortality was significantly increased with hyperoncotic albumin. This is a study of significant interest.

The conclusion from the currently available literature appears to be that no specific colloid solution is, of itself, directly nephrotoxic. Careful use of appropriate doses of all colloids solutions may offer some renal protection through optimal circulating volume expansion, and there is some evidence that HES solutions may protect renal endothelium to a greater extent than other colloids. There seems to be very little, if any, place for the use of hyperoncotic colloids for volume replacement. Wherever colloids are used for volume resuscitation, it is essential that adequate volumes of crystalloid are provided with a minimum of the daily water requirement being given as crystalloid solutions. Given the fact that all of the studies that have suggested possibility of an adverse renal effect of HES solutions have been in renal transplantation or in septic patients, there is some basis for suggesting that HES may be best avoided in these patient subgroups.

Conclusion

Many developments have occurred in fluid management in the last few years. Greater understanding of the harm of fluid overload is now appreciated, both in the surgical and critical care patient, and especially in those with oliguric AKI. It is now better understood that the risk of abdominal compartment syndrome and generalized edema are greater than was previously realized. Elevation of abdominal pressures clearly can lead to a reduction in perfusion gradients of the gut and the kidney, further compounding previous injury. Paradigm shifts in fluid management with regards to saline-based volume therapy and HCMA are now occurring, especially when considering the type of fluid in renal transplantation, for example. In this setting, centers are switching from saline-based volume therapy to balanced electrolyte formulations, even if they contain potassium. The risk of HCMA is no longer being considered innocuous; however, actual adverse patient outcome has not been proven as yet. Developments are being made in the prevention and management of contrast-induced nephropathy, from lower viscosity isotonic contrast preparations to the use of bicarbonate solutions as volume therapy. The role of oncotic load is once again being raised in patients at high risk for AKI, such as sepsis. The HES preparations were thought to have been implicated in AKI in these patients, but now it appears that the oncotic load of any colloid (including albumin) has a significant impact. Data are still lacking whether the newer generation HES products are any different in causing AKI in the high-risk patient with sepsis. Finally, it is most important to consider basic understanding of physiology, pathophysiology, and pharmacology when using fluids in the critically ill patient – where data are lacking, the clinician still should possess a healthy dose of common sense.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 600).

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