Fluid therapy and acute kidney injury: a question of balance?

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ABSTRACT

Fluid therapy remains one of the fundamental treatment options available for patients with acute kidney injury. However, there remains debate over several aspects of this treatment with many questions unanswered. Firstly, how do we prescribe fluid in this group of patients? Secondly, what is the role of fluid therapy in patients with or at risk of developing acute kidney injury and thirdly, what role does fluid balance play, if any, in the development of acute kidney injury. The following narrative review will attempt to tie some of the aspects of the treatment of this devastating syndrome together and formulate an overall hypothesis for fluid management in acute kidney injury.

Key words: Acute kidney injury, glomerular filtration rate, fluid overload

INTRODUCTION

Since the introduction of the concept of acute kidney injury (AKI) over a decade ago much has been written about this syndrome that has numerous causes ranging from idiosyncratic drug reactions to the complications of septic shock. AKI is a common observation on the intensive care unit (ICU) with a recent international study reporting an incidence of 57.3% (95% confidence interval (CI) 55.0-59.6). (1) Despite the varied causes of AKI, both observed mortality and morbidity is high and with increasing AKI severity an increase in hospital mortality is observed even when adjusted for other variables. For example, the mortality from stage 1 AKI the odds ratio observed = 1.679 (95% CI 0.890-3.169), increasing to 2.945 (95% CI 1.382-6.276) for stage 2 and for stage 3 = 6.884 (95% CI 3.876-12.228) compared to case mix adjusted patients without AKI. Patients developing AKI also have worse kidney function at hospital discharge with an observed estimated glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m2 in 47.7% (95% CI 43.6-51.7) versus 14.8% (95% CI 11.9-18.2) in those without AKI ($p < 0.001$).

Few interventions have been shown to influence the outcomes from AKI. (2) However, fluid administration is often considered the mainstay of supportive therapy particularly in the face of oliguria and hypotension presumably in order to augment cardiac output. (3) However, there is now increasing evidence that volume overload is associated with impaired organ function particularly when associated with oedema (Table 1). (4) It is this balance that is fundamental to managing patients with AKI appropriately where, under certain circumstances no fluid prescription may be the correct approach!. This has been best demonstrated in mechanically ventilated patients with acute lung injury where restrictive fluid management strategies have been associated with reduced period of mechanical ventilation and improved oxygenation. (5, 6) Similarly, volume overload per se has been postulated as a potential cause of morbidity and mortality.

FLUID PRESCRIPTION IN AKI

Little evidence base exists for the prescribing of fluids in patients at risk of or with AKI although appropriate fluid management does play a vital role in the treatment of the critically ill. (7) This is particularly relevant in hypovolaemia and sepsis both conditions associated with AKI. (1) Although much has been published regarding the choice of intravenous fluid, little guidance is given as to the prescription. Indeed, a study from the UK suggested that as many as 1 in 5 patients may suffer harm through injudicious fluid use. (8) For this reason it has been recommended that the use of fluid therapy should be accorded similar status as drug prescribing with care taken as to the adverse effects of fluids, dependent not only on the type of fluid but also the dose administered as well as the clinical context. (9, 10) This has been addressed in part by the 12th Acute Dialysis Quality Initiative (ADQI) where a conceptual framework for fluid therapy was proposed rather than a "one size fits all" philosophy. (11) This includes individual assessment of the patient's fluid requirements, the timely administration of that fluid, and then the frequent re-assessment of response and ongoing needs and was conceptualized as having four distinct phases:

- Rescue: Period of immediate escalation of therapy normally through fluid bolus therapy
- Optimisation: More cautious titration of fluid therapy through fluid challenges
- Stabilisation: Ongoing low level maintenance fluids where needed
- De-Escalation: Fluids may well be removed to achieve a negative balance

This model could be applied to the patient at risk of or with AKI as is shown in Figure 1. The first phase (Rescue) focuses on the resuscitation of the patient particularly where shock is present. Under such conditions fluid bolus therapy may be used preferably with some form of haemodynamic monitoring. The Optimization

phase implies that life-threatening danger has passed and that fluid therapy is given to improve tissue perfusion and prevent further organ dysfunction. The Stabilisation phase implies that the patient is in a steady state and fluids are used primarily for on going maintenance whereas the De-Escalation or mobilization phase may well involve fluid removal aiming for a neutral or negative balance depending on the clinical scenario. The importance of the De-Escalation phase cannot be underestimated as there is now increasing evidence that overall volume balance may play a pivotal role in the development of, and outcome from, AKI. Clearly fluid prescription is a vital component of any patient's management and there may well be a classical dose response where prescribed volumes above a certain threshold may be associated with harm. Indeed, some recent evidence points to a 'therapeutic index' for fluids particularly in the critically ill which may determine outcome (Forni et al Unpublished Observations).

Whether protocol driven volume therapy will prove a 'magic bullet' for the management of those at risk or with AKI remains to be seen. Certainly the results of the pre-planned ancillary analysis of the ProCESS trial do not appear to support this where no difference was seen with regard to the primary endpoint of development of new AKI when protocolised care was used compared to usual care although this may reflect the patient selection. (12) Although protocolised care may not be the answer simple measures such as avoiding episodes of hypotension, restricting volume and avoiding nephrotoxins may improve outcomes which in this study demonstrate a mortality rate approaching 80% at 28 days for those not recovering from AKI. (13)

THE ROLE OF FLUID THERAPY IN PATIENTS AT RISK OF DEVELOPING ACUTE KIDNEY INJURY

With regard to the type of fluid to be used several options are available but evidence suggest that certain fluid regimes may have an impact on the development of AKI and should be avoided. The most commonly prescribed fluids are crystalloids with the choice being between saline or buffered (so-called balanced) solutions. Several studies have shown that infusions of large volumes of 0.9% saline can cause a hyperchloraemic or dilutional acidosis when compared to balanced crystalloids. (14) Numerous potential side effects of saline solutions with regard to renal function have been described including: (15-17)

- Renal Vasoconstriction
- Decreased Renal Artery Flow Velocity
- Reduced Renal Cortical perfusion
- Reduced Glomerular Filtration Rate
- Salt and Water Retention

Despite these perceived failings no large randomized study has yet demonstrated improved clinical outcomes for either balanced solutions or indeed saline. The most recent study (18) is the SPLIT trial which compared 0.9% saline to Plasma-Lyte® 148 for ICU fluid therapy in 2262 patients using a double-blind, cluster randomised, double-crossover design. The primary endpoint was development of AKI using the RIFLE criteria although only changes in creatinine were employed not urine output. Secondary outcomes included Δ creatinine (difference between pre-study enrolment and peak serum creatinine), AKI as defined by the KDIGO criteria, the use of renal replacement therapy, use and duration of mechanical ventilation, ICU readmission and length of stay as well as censored mortality. In terms of the primary endpoint there was no difference with 9.6% of patients receiving buffered solutions developing AKI compared to 9.2% with saline ($p = 0.77$). There was also no significant difference observed in any of the secondary outcomes between the groups. However, these results have not been met with universal acceptance. One could argue that these patients were not truly representative of many ICU patients given the relatively low APACHE II scores, low mortality and low RRT rates. Secondly, the volume administered was low averaging 1.5 litres on the day of inclusion and roughly 700 ml on the second day. Overall total fluid administration over 3 days was around 2500 ml and roughly 50% of the patients received their total amount of intravenous fluids on the first day. Consequently, the pro-balanced solution camp may argue this study adds little outside routine postoperative care and is not applicable to the septic patient in multi-organ failure: This, of course, remains to be seen. Importantly, it must not be forgotten that the so called 'balanced' solutions are neither balanced nor physiological in nature. For example, Plasma-Lyte® 148 contains 27 mmol/l of acetate and some 23 mmol/l of gluconate both of which are not benign. Indeed, acetate once used as the main buffering agent in intermittent haemodialysis has been implicated in direct myocardial toxicity and as such is rarely used and the metabolism of gluconate has been even less well studied although evidence suggest that its metabolism may feed through anapleurotic pathways into the hexose monophosphate shunt. (19, 20) The use of synthetic colloids, particularly the older higher molecular weight hyperoncotic hydroxyethyl starches (HES) are associated with an increased incidence of AKI and should not be used. This association has been observed in several multicenter randomized controlled trials with the effect of renal function being dose dependent and persistent. (21) Moreover, there is recent evidence that gelatins may also increase the risk of AKI. (22) As a consequence the clinical use of HES solutions has been subject to considerable regulatory restriction and this is reflected in the results of the FENICE trial which confirms that buffered crystalloid solutions have become the most commonly used fluids by intensivists worldwide. (23)

THE ROLE OF FLUID BALANCE IN THE DEVELOPMENT OF ACUTE KIDNEY INJURY

The association between fluid overload and mortality was first observed over 10 years ago in critically ill children with AKI requiring renal replacement therapy (RRT). (24, 25) Subsequently a secondary analysis of the SOAP study by Payen and colleagues suggested that fluid overload was an independent risk factor for death in critically ill patients with AKI and sepsis. (26) Similarly, examination of the Program to Improve Care in Acute Renal Disease (PICARD) cohort, demonstrated that fluid overload defined as an increase of >10% of hospital admission weight was associated with an increased mortality at 30 days, 60 days, and hospital discharge, as well as increased APACHE III score, number of failed organ systems, need for mechanical ventilation, and incidence of sepsis. Moreover, In patients requiring RRT, the OR for death was 2.07 at dialysis initiation whereas in non-dialyzed patients, the adjusted OR for death associated with fluid overload at AKI diagnosis was 3.14 after adjustment. (27) A recent systematic review and meat-

analysis has examined the association between fluid overload and renal recovery in patients with AKI with 12 cohort studies published from 2008 to 2014 were examined with a total of 5095 patients studied. (28) A significant positive association was found between fluid overload and mortality in patients with AKI (OR: 2.23; 95%CI 1.66- 3.01), with similar findings in sepsis (OR: 2.27; 95%CI 1.69-3.03) and non sepsis subgroups (OR,3.40;95%CI, 2.50-4.63). There was also a significant association between mean fluid balance and mortality (OR: 1.16; 95%CI 1.07-1.27). There was no significant association between fluid overload and kidney recovery (OR: 0.66; 95%CI 0.37-1.15) or dialysis dependence (OR: 0.72; 95%CI 0.38-1.35).

Clearly there is a consistent, reproducible association between volume overload and worse outcomes from AKI but it is difficult to disentangle the cause-effect relationship and translating the results into clinical practice is challenging given four major issues remain unresolved. (29) Firstly, defining fluid overload is not simple most studies defining fluid overload by a percentage increase in body weight from the day of admission to the ICU. This does, however, assume euvolaemia on admission and ignores insensible losses as well as fluid administration in the pre-ICU setting. Secondly, whether the consequences of fluid overload are fluid specific is unknown. Perhaps volume overload as a result of excessive crystalloid administration has a different impact compared with fluid accumulation following infusion of colloids or massive transfusion of blood products. Thridly, timing may also play a role for example a positive fluid balance of 5 litres over an initial 24-hour period followed by no further fluid gain may have a different outcome compared with the same net balance over a period of days. Finally, fluid overload may result from over zealous fluid administration or oliguria or a combination of the two. The differentiation is important since fluid overload caused by excessive fluid therapy is potentially avoidable whereas fluid overload as a result of oliguria may reflect AKI and may not be easily modifiable without RRT. Interestingly, a recent retrospective study demonstrated that fluid administration, rather than low urine output, was independently associated with AKI progression. (30)

CONCLUSION

The fact that fluid overload is associated with AKI does not prove causality given that the effects of volume overload and AKI are similar. Both lead to multi-organ dysfunction and they also are often associated with the same pathophysiological features including endothelial dysfunction due to inflammation or ischaemia/reperfusion injury with decay and shedding of the glycocalyx and subsequent capillary leakage. (29) Patients with more severe endothelial dysfunction tend to develop both fluid overload and AKI following fluid administration compounding the issue further.

However, the direct mechanism(s) by which fluid overload may cause AKI remains poorly characterised in human studies. A putative mechanism is outlined in Figure 2 where volume overload leads to intra-abdominal hypertension and the abdominal compartment syndrome leading compression of intra-abdominal vessels and compromised microvascular blood flow and raised renal venous pressure leading to renal oedema subsequently resulting in impaired renal plasma flow, decreased glomerular filtration rate and oliguria. The subsequent AKI with oliguria contributes further to volume overload leading to worsening of the condition.

Although the exact mechanisms of the pathophysiology remain to be fully elucidated there is now considerable data demonstrating that volume overload is associated with worse outcomes in AKI. Therefore treatment of patients at risk of, or with established, AKI must focus specifically on accurate volume assessment and fluid prescription in order to limit the potential catastrophic outcome from this devastating syndrome.

Table 1. Diverse Consequences Of Volume Overload:

ORGAN	CONSEQUENCES
Brain	Delirium Altered Mental State
Cardiac	Myocardial Oedema Impaired Contractility Conduction Abnormalities Diastolic Dysfunction
Lungs	Increased Work of Breathing Impaired Gas Exchange Reduced Compliance
GI Tract	Gut Oedema with Impaired Absorption Hepatic Oedema with Deranged Synthetic Function Ileus Intra-Abdominal Hypertension
Renal	Decreased Renal Blood Flow Reduced GFR Oliguria Salt & Water Retention

Metabolic	Electrolyte Abnormalities Hypoproteinaemia
Skin	Poor Healing Pressure Ulceration

GI – gastrointestinal
GFR – glomerular filtration rate

Figure 1. Conceptual framework for fluid therapy allowing individualised assessment

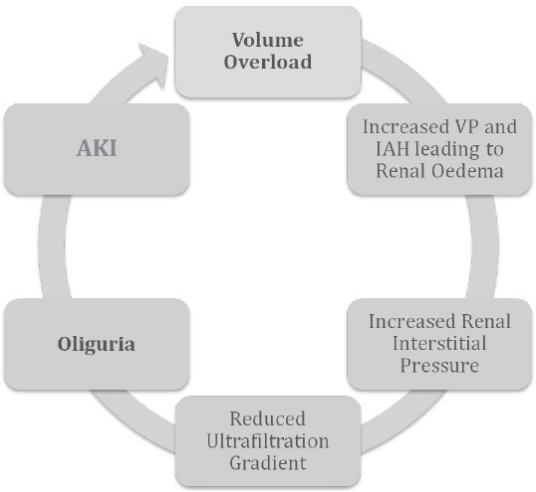

Figure 2.Potential mechanisms leading to acute kidney injury following volume overload demonstrating the relationship between oliguria and AKI

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