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REVIEW

Intravenous fluid therapy

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SUMMARY

Topical studies have reinforced the view that there is little evidence in choosing starches as the fluid of choice in resuscitation, especially in critical care. They may increase mortality when used in the resuscitation of patients with severe sepsis. This has led to the partial withdrawal of starch-based colloids in the U.K. What is more unclear is whether colloids as a whole are beneficial compared to crystalloids with conflicting evidence in the literature.

Administration of large amounts of physiologically 'un-balanced' fluids can result in the development of hyperchloraemic acidosis but the question remains as to whether there is a resultant effect on morbidity or mortality. Goal-directed therapy has been demonstrated as being beneficial although the best method of assessing the response to fluid remains to be elucidated.

With the publication of recent trials, the basis for deciding which intravenous fluids to give, when to give it and how much to give, more than ever before, can be based on sound scientific evidence.

1. Introduction

Historically, fluid management strategies involved trying to predict the amount of fluid deficit based on the degree of dehydration, the patients' illness or the duration and severity of an operation. This estimate was then used to empirically replace any shortfall. The risks of this arbitrary 'blind' approach have recently been highlighted by the FEAST trial which showed a decreased mortality in African children who did not receive a fluid bolus after presenting to hospital with fever and impaired perfusion compared to those who received a 20–40 ml/kg bolus of either albumin or 0.9% sodium chloride.[1] This goes against 'classic' thinking and highlights a need for a modern approach to fluid therapy, including an understanding of the type of fluid to use, the amount to give, and which end-points to measure when giving it.

Many of these issues have been addressed in a number of randomised trials as reviewed here.

2. Review

2.1. Starches

Analogous trials have, of late, been undertaken evaluating the effectiveness and safety of starches. A large, multi-centre, randomized controlled trial, the **S**candinavian **S**tarch for **S**evere **S**epsis/**S**eptic **S**hock (6S) trial evaluated the effects of hydroxyethyl starch (HES) 130/0.4* in Ringer's acetate compared with Ringer's acetate alone (both made by B. Braun Medical) on the composite outcome of death or end-stage kidney failure in patients with severe sepsis.[2] They found that the use of HES as the medium for fluid resuscitation significantly increased 90 day mortality (by 8%). Furthermore, there was an increased likelihood of these patients receiving renal replacement therapy (RRT) although this had no effect on the incidence of end-stage renal failure. These results proved similar to the earlier VISEP study (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) which showed that use of HES was associated with higher rates of acute renal failure and RRT, compared with Ringer's lactate.[3]

Possible criticisms of the 6S trial include the omission of haemodynamic monitoring and goal-directed therapy from the protocol design. Many of the patients lacked static parameters such as central venous pressure or venous oxygen saturation leading to potential over-transfusion and volume overload, or haemodilution and the associated need for blood transfusion of patients thus affecting outcomes.

The results of the largest randomized control trial of its type, CHEST (**C**rystalloid versus **H**ydroxy-**E**thyl **S**tarch **T**rial) included over 6500 patients and reported no difference in 90 day mortality between patients in intensive care given 6% HES 130/0.4 (Voluven, Fresenius Kabi) in 0.9% sodium chloride and those given 0.9% NaCl.[4] The results did show a trend towards increased mortality in the group receiving HES (relative risk 1.06, $p = 0.26$) but this was not

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significant. The investigators did however find a significant increase in the need for RRT in those who had been given HES (RR, 1.21; $P = 0.04$) despite there being no difference in the incidence of being 'at risk' for the development of renal failure (using the RIFLE criteria) between the two groups.

Constraints of the CHEST trial included the exclusion of patients whom clinicians considered unlikely to survive (i.e. those who may require the most fluid resuscitation) as well as the inclusion of patients who had undergone elective surgery (i.e. those who may require the least). In both the 6S and CHEST trials patients were recruited after admission to the ICU, when the requirements for fluid resuscitation are often less than those for patients in the emergency department or the operating room and is arguably the most important period of fluid resuscitation. It could therefore be argued these studies were not optimally designed to assess fluid resuscitation.

Another recent trial involving tetrastarches, the CRYSTMAS (Crystalloids Morbidity Associated with Severe Sepsis) study enrolled 196 patients with severe sepsis to compare the haemodynamic efficacy and safety of 6% HES 130/0.4 with 0.9% NaCl.[5] They found that significantly less HES was needed to achieve haemodynamic stability in these patients, with an average difference of 331 mls ($p = 0.0185$) administered between the fluids. However, although statistically significant, it can be argued that this is not a clinically significant volume, especially given the large volumes of fluid some patients received. There was no difference in ICU or hospital stay and no effect on mortality. Unlike the 6S and CHEST trials, the CRYSTMAS study showed that HES had no effect on renal function with no difference between the treatment groups in the incidence of ARF (defined as the doubling of the baseline creatinine or the need for RRT). Urinary biomarkers suggested that 6% HES did not induce acute kidney injury (AKI) with tubular and glomerular function and the median change in serum creatinine unaffected. These findings are in agreement with another recent observational study which showed no association between HES 130/0.4 with RRT or renal dysfunction in patients with septic shock.[6]

Criticism surrounding the CRYSTMAS trial includes the use haemodynamic stability instead of mortality as a primary outcome and that data was not analysed on an intention to treat basis meaning that patients who did not reach haemodynamic stability were excluded.

Based on the strength of these trials and associated data many consider it difficult to defend the use of colloids, especially HES in critically ill patients. In March 2012 the European Society of Intensive Care Medicine (ESICM) Task Force advised that HES preparations with molecular weights greater than 200 kDa and/or a degree of substitution > 0.4 in addition to 6% HES 130/0.4 and gelatins should not be used in those with severe sepsis or risk of AKI.[7]

Recent meta-analyses have concluded that the use of HES solutions is associated with increased mortality and/or an increased use of renal replacement therapy in critically ill patients.[8–13] After reviewing all this evidence the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded that the benefits of HES solutions no longer outweighed their risks and recommended that the marketing authorization for these medicines be withdrawn.[14,15] This was supported by the U.K. Commission on Human Medicines (CHM) with the Medicines and Healthcare Products Regulatory Authority (MHRA) who quickly followed with an announcement withdrawing the use of HES products from the U.K.[16] In October 2013 the European Medicines Agency revised its statement and said that HES should no longer be used in critically ill or septic patients.[17] However the PRAC agreed that HES could continue to be used in patients with hypovolaemia caused by acute blood loss where treatment with crystalloids alone is not considered to be sufficient. However, the PRAC acknowledged the need for measures to minimise potential risks in these patients and recommended that HES solutions should not be used for more than 24 h and that patients' kidney function should be monitored for at least 90 days.

The United States Food and Drug Administration (FDA) and Health Canada did not withdraw HES solutions completely but recommended they should not be used in critically ill patients or those with pre-existing renal failure.[18,19] This decision was influenced by several studies such as those highlighted in the meta-analysis which reported on trials of 6% HES versus alternative intravenous fluids in patients undergoing surgery.[20] It showed no difference in hospital mortality, the requirement for renal replacement therapy or acute kidney injury. Another systematic review showed no association between tetrastarch use and blood loss, increased use of allogeneic red cells, increased incidence of renal impairment or failure, or mortality if administered during and/or immediately before surgery.[21] Similarly, another study found no association between the administration of HES and the incidence of acute kidney injury (measured by change in creatinine clearance) in patients undergoing surgical procedures.[22]

*Hydroxyethyl starches are identified by three numbers e.g. 6% HES 130/0.4. The first number represents the solution concentration (e.g. 6%), the second represents the molecular weight (e.g. 130 kilodaltans) and the third represents the molar substitution (e.g. 0.4.).

2.2. 'Crystalloids versus colloids'

Although the starch debate is ongoing, confidence as to when they should be used is increasing with the recent studies published as mentioned above. What is more unclear is the debate surrounding whether colloids as a whole have any benefit over crystalloids in fluid resuscitation.

The use of colloids in place of crystalloids is disputed given the uncertainty regarding their safety. A recent meta-analysis by the Cochrane group has further reinforced this view by stating there is little good evidence that choosing colloids over crystalloids for fluid resuscitation reduces the risk of death in patients with trauma, burns or following surgery. In view of the fact that colloids are more expensive and do not improve survival the authors concluded that their ongoing therapy for resuscitation cannot be justified.[23]

Published in October 2013, the CRISTAL Trial sheds further light on whether the use of colloids compared with crystalloids for fluid resuscitation alters mortality in patients admitted to the intensive care unit (ICU) with hypovolaemic shock.[24] Patients in this multicentre trial were randomised to receive colloids or crystalloids for all fluid interventions other than fluid maintenance. The type of colloid (gelatins, dextrans or starches) or crystalloids were not dictated thus trying to reflect normal clinical practice. Among ICU patients with hypovolaemia, the use of colloids instead of crystalloids did not result in a significant difference in 28-day mortality. 90-day mortality was lower amongst patients receiving colloids but the investigators suggested this finding should be considered exploratory and requires further study before reaching conclusions about efficacy.

Looking at specific colloids, experimental research has shown gelatins to be a better volume expander than crystalloids, but if the endothelial glycocalyx is damaged (as in septic shock) intravascular retention of colloid is not substantially better than crystalloids.[25–27] This suggests that in critically ill patients such as those studied in the trials mentioned above, gelatins have no benefit over crystalloids in fluid resuscitation.

In addition to the effect of crystalloids and colloids on the sick patient, the amount of each fluid administered is also under debate.

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