Hydroxyethyl Starch

Here Today, Gone Tomorrow

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After a review of the available evidence, on June 14, 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded that the benefits of hydroxyethyl starch (HES) solutions no longer outweighed their risks and recommended that the marketing authorizations for these medicines be withdrawn.\(^1\) The United Kingdom (UK) Commission on Human Medicines (CHM) concurred and on June 27, 2013, the Medicines and Healthcare Products Regulatory Agency (MHRA) announced the withdrawal of HES products from the UK, giving just 48 h to return all unexpired stock.\(^2\) In contrast, on June 24, 2013, the United States (US) Food and Drug Administration (FDA) recommended that HES products not be used in critically ill patients or in those with pre-existing renal dysfunction but did not withdraw them completely.\(^3\)

HES solutions were first used in humans in the 1960s,\(^4\) and have evolved to become globally the most commonly used colloid in intensive care units (ICUs).\(^5\) In recent years, there has been increasing use of HES perioperatively as part of a goal-directed (GD) strategy.\(^6\) The HES solutions have been popular because in hypovolaemic humans, they are more efficient volume expanders than crystalloids.\(^7,8\) There is also some evidence in humans that HES solutions achieve better resuscitation of the microcirculation than normal saline.\(^9\)

So what has precipitated the 'hero to zero' downfall of HES solutions? Ultimately, the EMA's recommendation was based mainly on three randomized trials in critically ill patients comparing HES with crystalloids, which showed greater risk of kidney injury requiring renal replacement therapy in the HES group.\(^10-12\) One of these studies, which compared HES 130/0.42 with Ringer's acetate in patients with severe sepsis, also showed a higher 90 day mortality rate in those treated with HES [relative risk (RR) 1.17; 95% confidence interval (CI) 1.01–1.36; \(P=0.03\)].\(^11\) Recent meta-analyses have also concluded that the use of HES solutions is associated with increased mortality, increased use of renal replacement therapy in critically ill patients, or both.\(^13-17\) In this journal, Gillies and colleagues\(^18\) report the results of a systematic review and meta-analysis of trials of 6% HES vs alternative i.v. fluids in patients undergoing surgery. Nineteen studies comprising fewer than 1600 participants were included and there was no difference in hospital mortality, the requirement for renal replacement therapy, or acute kidney injury. The lack of evidence of harm in surgical patients presumably accounts for the FDA's decision not to withdraw HES solutions completely in the USA; however, many would argue that the absence of demonstrable benefit combined with increased cost is a strong reason not to use them.\(^13\)

What is the mechanism for the renal failure caused by HES solutions? Concerns were first raised 20 yr ago when an association between the use of HES in brainstem-dead patients and the occurrence of 'osmotic-nephrosis-like lesions' in renal transplant recipients was reported in an observational study from France.\(^19\) Although this initial report did not document a significant effect on renal function, a later prospective randomized trial of gelatin vs HES 200/0.62 in 121 brain-dead patients documented an increased requirement for renal replacement therapy among transplant recipients receiving kidneys from donors given HES.\(^20\) In vitro studies have shown that both gelatin and HES solutions reduce human proximal tubular cell viability, but the precise mechanism for this toxicity remains unknown.\(^21\)

In 2001, a prospective randomized trial documented an increase in the incidence of acute renal failure among patients with severe sepsis receiving HES 200/0.62 compared with those receiving gelatin solution.\(^22\) In the correspondence that followed this study, HES protagonists proposed several 'flaws' to account for the findings: inadequate free water was given to patients in the HES group, the baseline creatinine values were higher in the HES group, and the use of a two-fold increase in creatinine values to define acute renal failure was inappropriate.\(^23\) Many clinicians were probably
persuaded by these arguments and were also likely to have been reassured by the introduction of HES solutions of lower molecular weight and substitution ratio, which were considered to be even less likely to cause renal injury. Clinicians’ practice is also likely to have been influenced by numerous positive HES reviews[24] even though high-quality analyses, such as systematic reviews, were more likely to recommend against the use of HES.[25] The three trials[10–12] that precipitated the recent EMA recommendation were high-quality studies and the more recent two involved modern tetra starches (HES 130/0.42 and 130/0.4).[11,12] A limitation of all three trials is that the patients were not recruited into the study until after admission to an ICU, which in most cases will be after the initial, and arguably the most important, period of fluid resuscitation. In this sense, these studies were not optimally designed to assess fluid resuscitation; recruiting patients in the emergency department, for example, would be more challenging but would provide a better indication of the impact on outcome of colloid vs crystalloid in the resuscitation phase.

What are the options for fluid resuscitation in the UK now that HES solutions are no longer available? Those clinicians who have been using HES solutions may still have a strong preference for colloids and may choose to use a gelatin solution instead. Although gelatin is a better volume expander than crystalloid,[26] if the endothelial glycocalyx is damaged (such as in septic shock), intravascular retention of gelatin (or any other colloid) may not be substantially better than crystalloids.[27,28] Importantly, the in vitro data showing that gelatin may cause renal injury[21] are supported by a recent observational study showing that fluid therapy that includes gelatin in patients with severe sepsis was associated with a higher incidence of acute kidney injury compared with the exclusive use of crystalloids.[29] I.V. colloids cause ~4% of all perioperative anaphylactic reactions and the vast majority of these are caused by gelatin.[30] A recent systematic review and meta-analysis of gelatin for volume resuscitation concluded that there were insufficient data to assess reliably the safety of gelatin.[31] These considerations, combined with the fact that in hypovolaemic patients, intravascular volume expansion by crystalloids is much greater than that achieved in euvo laemic healthy volunteers,[32] make the value of gelatin solutions highly questionable. An unblinded randomized trial comparing any crystalloid with any colloid for fluid resuscitation in critically ill patients in France (CRISTAL: Colloids Compared to Crystalloids in Fluid Resuscitation of Critically Ill Patients: A Multinational Randomised Controlled Trial; ClinicalTrials.gov NCT00318942) has been completed and will provide more data to inform the debate.

What about human albumin solution (HAS)? A pre-defined subgroup analysis of a randomized controlled trial showed that the use of albumin compared with saline in sepsis does not impair renal function.[33] A meta-analysis of clinical trials of fluid resuscitation with albumin-containing fluids compared with other fluid resuscitation strategies in patients with sepsis documented a lower mortality among those receiving albumin.[34] Although the international Surviving Sepsis Campaign recommends crystalloids as the initial fluid of choice for the resuscitation of patients with severe sepsis, 4.5% HAS is also recommended in such patients requiring ‘substantial amounts’ (undefined) of crystalloid.[35] Albumin is expensive and although one study from France has shown that it is cost-effective for fluid resuscitation among patients with severe sepsis,[36] this has yet to be demonstrated elsewhere. A randomized trial of volume replacement with albumin vs crystalloid in severe sepsis has been completed and the findings will add to the debate [Volume Replacement with Albumin in Severe Sepsis (ALBIOS); ClinicalTrials.gov NCT000707122]. Albumin is not recommended for fluid resuscitation in patients with traumatic brain injury because, in comparison with saline in a post hoc study, its use in such patients was associated with a higher mortality rate.[37]

Perioperative GD therapy reduces complications such as renal impairment, respiratory failure, and postoperative wound infection, and reduces hospital length of stay.[6,38] Further data on this topic will be provided when the results of the OPTIMISE (Optimisation of Peri-operative cardiovascular Management to Improve Surgical outcome) —http://www.icnarc.org) study are available later this year. Most studies of perioperative GD therapy have used colloids but adequately powered studies comparing crystalloid with colloid as part of a GD strategy have not been undertaken. A blinded randomized trial comparing HES 130/0.4 with Hartmann’s solution for GD therapy during colorectal surgery has been completed and will provide further data on this topic. Some will consider as controversial the MHRA’s decision to withdraw HES products completely rather than just from the critical care setting (as the FDA has done). In the operating theatre, relatively small volumes of colloid are used, generally to treat haemorrhage (i.e. true acute volume deficit), and it may not be valid to generalize to the perioperative setting the results of studies
undertaken in critically ill patients on the ICU.

A draft Clinical Guideline on Intravenous Fluid Therapy commissioned by the National Institute for Health and Care Excellence (NICE) recommends that fluid resuscitation should be undertaken with crystalloids that contain sodium in the range 130–154 mmol litre⁻¹.[39] The question that remains is should we be using physiologically 'balanced' solutions (e.g. Hartmann's solution, Ringer's lactate, or PlasmaLyte 148) instead of 0.9% sodium chloride? There is evidence that the hyperchloremia caused by fluid resuscitation with 0.9% sodium chloride reduces renal blood flow in humans[40] and, in an observational study, the introduction of a chloride-restrictive fluid strategy reduced the incidence of acute kidney injury in critically ill patients.[41] In a propensity-matched cohort study, hyperchloremia (plasma chloride >110 mmol litre⁻¹) after non-cardiac surgery was associated with increased risk of mortality at 30 days (3.0% vs 1.9%; odds ratio 1.58; 95% CI 1.25–1.98).[42] Prospective, controlled, and blinded clinical studies are required to determine whether the use of physiologically 'balanced' solutions offers significant clinical benefits over 0.9% sodium chloride.

Fluids should be considered as drugs and, as is the case with any drug, timing and dose is important. Correct and careful use of fluids is essential regardless of the type of fluid. As recommended by NICE in its draft Clinical Guideline on Intravenous Fluid Therapy,[39] patients receiving i.v. fluids should be monitored and assessed regularly, complications should be documented and audited, and all healthcare professionals involved in prescribing and delivering i.v. fluid must receive appropriate training that includes the use of local practice guidelines.

Studies comparing gelatin with crystalloid, and 0.9% sodium chloride with a balanced crystalloid, are essential to enable us to provide high-quality clinical care that is evidence-based. The perioperative setting may enable us to make a more reliable assessment of the impact of these fluids when given for true acute volume deficit compared with fluid therapy that is given later on ICU. As Gillies and colleagues[18] have indicated, the relatively low event rates associated with the perioperative setting will mean that these studies will have to enroll many patients if they are to have the statistical power to detect small, but clinically significant differences in outcomes. We encourage healthcare professionals to face the challenge and contribute to these large and very important trials.

References


3. Food and Drug Administration. FDA safety communication: boxed warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. 2013.

