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EDITORIAL I

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solutions no longer outweighed their risks and recommended that the marketing authorizations for these medicines be withdrawn.[1] The United Kingdom (UK) Commission on Human Medicines (CHM) concurred and on June 27, 2013, the Medicines and Healthcare Products Regulatory Agency (MHRA)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 hospitality 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 higher-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 tetrastarches (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 euvolaemic 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—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 hyperchloraemia 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, hyperchloraemia (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.

Declaration of interest

J.P.N. is a member of the NICE Intravenous Fluid Therapy Guidelines Development Group. M.G.M. is the expert advisor to the NICE Intravenous Fluid Therapy Guidelines Development Group. He has received honoraria, grant funding, and has consulted for a number of fluid manufacturing companies (for further details, see *BJA* website).

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EDITORIAL II

Tetrastarch solutions: are they definitely dead?

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During the last decade, colloids have frequently been infused in patients with shock to increase the volume effect of fluid resuscitation and, thus, reduce the total amount of fluids and subsequently oedema formation. However, in patients with severe sepsis, inflammation, and capillary leakage, the volume expansion effect of colloids appears to be much lower than expected.[1]

Recently, the European Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that the benefits of infusion solutions containing hydroxyethyl starch (HES) no longer outweigh their risks, and recommended that the marketing authorizations for these drugs be suspended.[2] Recently, three meta-analyses on the use of HES for fluid resuscitation in critically ill patients have been published.[3–5] They all

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suggest an increased use of renal replacement therapy, and one of them reports a significant increase in mortality, associated with the use of HES solutions. It is important to note that HES solutions studied are derived from different raw materials which have been mixed up, and that it has been shown that the two starch preparations are neither interchangeable nor bioequivalent.[6] One of the meta-analyses included trials performed with old, outdated preparations (e.g. 10% HES 200/0.5 or 6% HES 200/0.62).[5] The recommendations of the Surviving Sepsis Campaign (SSC)[7] propose that HES 130/04 should not be used to resuscitate patients with sepsis due to their potential harm on kidney function. The recommendations regarding the use of HES solutions are based on previously published trials (VISEP, 6S, CHEST, CRYSTMAS). We aim to examine their design and the results.

The inclusion of the VISEP[8] study to support the recommendation is surprising. The starch used in this study has a different molecular weight than the one used nowadays, the solution is hyperoncotic, and the daily and accumulated doses used are higher than the ones advised by the manufacturer.

The study 6S[9] involved 798 patients with severe sepsis, and compared the incidence of kidney dysfunction associated with HES 130/0.42 or Ringer's acetate. It concluded that HES 130/0.42 led to an increased use of kidney replacement techniques [relative risk (RR) 1.35; 95% confidence interval (CI) 1.01–1.80; $P=0.08$] and had a higher 90 days mortality rate (RR 1.17; 95% CI 1.01–1.36; $P=0.03$). However, the resuscitation therapy in this study was not directed by haemodynamic aims. In fact, many of the patients lacked static parameters such as central venous pressure or venous oxygen saturation. Therefore, it is probable that the absence of haemodynamic monitoring may have led to excessive fluid therapy. The fluid resuscitation phase was already completed at the time of enrolment as suggested by a median central venous pressure of 10 mm Hg, a relatively low plasma lactate concentration, and pre-randomization infusion volumes >3000 ml. It is known that the strategies which aim at maximizing stroke volume are only evidence-based for a duration of 6 h[10] and may even be harmful if extended for more than 24 h or even up to 3 days as in the 6S trial. It is also known that liberal fluid therapy and fluid accumulation are associated with worse organ function and increased mortality.[11] These facts could have influenced the complications seen in the study population.

The CHEST study[12] was performed on a heterogeneous population of 7000 patients. An objective-based resuscitation was used comparing HES 130/0.4 with saline. The study concluded that a quicker and permanent haemodynamic stability was attained in the group that received HES, and no differences exist in the mortality at 90 days. However, kidney replacement therapy was more often used for HES patients (7% *vs* 5.8%, RR 1.21, 95% CI 1.00–1.45, $P=0.04$). When the data were adjusted for co-variables, the statistical significance disappeared ($P=0.05$). The indications of kidney replacement therapy in both the groups were not defined. Also, the patients did not comply with the severity criteria when they entered the study (normal heart rate, mean arterial pressure >65 mm Hg, central venous pressure >5 cm H_2O, and lactate <2 mmol litre^{-1}). Perhaps, we may conclude that stable critical patients do not need aggressive resuscitation with starches.

In this context, it is understandable that the recent meta-analyses,[2–4] where 6S and CHEST studies are very prominent, led the PRAC to recommend that the use of tetrastarch in hypovolaemic critically ill patients be avoided. However, any pooled analysis of different studies is unlikely to offset the inconsistencies of the data within those studies.

On the other hand, there are other studies which show different results. The aim of the CRYSTMAS study[13] was to assess the effectiveness and safety of HES 130/0.4 in resuscitation therapy of patients suffering from severe sepsis according to the SSC criteria.[14] It concluded that patients of the HES group attained earlier haemodynamic stability and required a smaller volume of fluids than the patients of the group treated with 0.9% saline. The requirements for vasoactive drugs, rate of kidney impairment during the critical period, length of the hospital stay, and mortality at 28 and 90 days were similar in both groups.

In the study by Muller and colleagues,[15] the authors analysed the impact of a series of clinical measures, including fluid resuscitation with crystalloids and colloids, to optimize the management of patients with severe sepsis, septic shock, or both. They showed that these clinical measures led to a 13% reduction in mortality among patients with severe sepsis, septic shock, or both. Neither an univariant nor a multivariant analysis of the data could demonstrate that the use of HES 130/0.4 was a risk factor for kidney dysfunction or for the need of kidney replacement therapy.

Similarly, Boussekey and colleagues[16] reported a retrospective study on 363 patients who were treated in an intensive care unit (ICU) for more than 72 h. They observed that resuscitation with low volumes of HES during the first 48 h was not associated with an increased rate of acute kidney injury (AKI) or mortality in the ICU. They did not find any between-group differences in urinary output, or in the scores related to AKI indicators, although the HES group showed higher indices for the severity of illness. It is important to emphasize that fluid resuscitation was done with HES volumes <15 ml kg^{-1}, because the HES-kidney injury can be associated not only with their molecular weight and molar substitution but also with the volume administered.

The CRYSTAL trial randomly assigned patients admitted very early to an ICU to treatment with any available crystalloid compared with any available colloid. Most of the patients randomized to the crystalloid group were treated with isotonic saline, whereas 6% HES 130/0.4 was the most commonly used fluid in the colloid group. In the preliminary analysis, colloid resuscitation tended to reduce 28 day mortality and significantly reduced 90 day mortality even in septic patients.[17]

In the BaSES trial, about 240 patients with severe sepsis or septic shock were randomly assigned to volume replacement with isotonic saline or saline-based 6% HES 130/0.4. Also on the initial analysis of data, the study confirmed the safety of 6% HES 130/0.4 compared with sole crystalloids and suggested benefits of HES infusion on patient survival.[17] Nevertheless, thorough interpretation of the CRYSTAL and BaSES data will only be possible once the full-text publications are available.

Notably, the controversy regarding the use of modern starch solutions in septic patients does not exist for other clinical situations, such as controlled haemorrhagic shock. The 'Fluids in Resuscitation of Severe Trauma' (FIRST) trial confirmed the safety and efficacy of waxy maize-derived 6% HES 130/0.4 in patients with severe trauma.[18] In this study, 6% HES 130/0.4 was associated with less kidney injury and organ dysfunction compared with isotonic saline in penetrating trauma. It is also remarkable that a strong evidence exists in the surgical patients that fluid therapy guided by haemodynamic aims significantly reduces the incidence of postoperative complications.[19–21] A higher volume of colloids is used in such fluid therapy; nevertheless, neither complications in blood coagulation nor in kidney function nor increased rates of mortality could be demonstrated in surgical patients treated with third-generation starches.[21]

One might argue that studies in surgical patients were underpowered to show the adverse effects observed in the critically patients. But in a recent systematic review, Van der Linden and colleagues[22] showed that the intraoperative use of colloids was not associated with adverse clinical events, including blood losses, increased requirements of blood transfusions, impaired kidney function, or kidney failure, even in patients with higher risks of kidney injury. It is worth emphasizing that creatinine clearances and levels, among heterogeneous surgical populations, were similar in the group that received starch than in any other group even until 14 days after surgery.

Likewise, Martin and colleagues[23] found that there is currently no verifiable association between the administration of waxy maize-derived HES 130/0.40 and changes of serum creatinine and calculated creatinine clearance or the incidence of AKI in patients undergoing surgical procedures.

It is likely that the safety differences found in the use of colloids in surgical and critically ill patients could be due to the differences in vascular integrity. Sepsis and hypoxia impair the vascular integrity and its ultrafiltration function. In such circumstances, leakage of large molecules and fluid to the extravascular space can lead to microcirculation and organ failure.[24] It has been demonstrated in animal experiments that 6% HES 130/0.4 has a non-inflammatory effect[25], and a protective action on microcirculation.[26]

In view of the range of evidence related to the use of HES, the important considerations are:

(i) It is important to consider that fluids for resuscitation are drugs that have indications, doses, and contraindications in a given clinical situation. An ideal resuscitation fluid would accomplish long-lasting volume expansion, while improving microcirculation in the absence of immunosuppression and toxic effects. Not all tetrastarches are the same, differences in the percentage of amylopectine and C2/C6 substitution can impact on time of persistence in intravascular space, fluid viscosity, and HES-endogenous lipophilic molecules complexes with clinical impact yet unknown.

(ii) Fluid selection must always be adapted to clinical conditions of each moment, considering factors such as fluid losses, oedema level, potential side-effects, and costs.[27] Currently, protocols exist for resuscitating the patients with crystalloid and colloid solutions, vasoactive drugs, and blood transfusion. The main consideration has to be the best risk/benefit relationship for an individual patient.

(iii) Resuscitation involves much more than volume expansion. Fundamentally, resuscitation is the restoration of cellular perfusion and oxygenation. Treatment of hypovolaemia must always be guided by haemodynamic monitoring in order to avoid hypervolaemia states with clinical consequences which can be as disastrous as hypovolaemia.[28] In this context, the concept of early haemodynamic optimization during the initial 6 h of disease presentation (so-called 'golden hours') has been shown to markedly improve patient outcomes.[10 29]

To conclude, the definitive results of the studies which are currently in progress—CRYSTAL, FENICE, BaSES, and RaFTinG—will shed more light on the HES controversy; nevertheless, a very large randomized trial of 6% HES solutions would be required to demonstrate either significant benefit or harm associated with the use of these solutions in surgical patients.

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Declaration of interest

None declared.

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EDITORIAL III

Neuraxial block, death and serious cardiovascular morbidity in patients in the POISE trial: propensities, probabilities, and possibilities

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This month in the *BJA* is published an important, and perhaps controversial, study by Professor Leslie and colleagues.[1] The authors have used data from the POISE study (which randomized patients with increased risk of cardiovascular events to