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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

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are neither interchangeable nor bioequivalent.[6] One of the meta-analyses included trials performed with old, outdated preparations (e.g. 10% HES 200/0.5 or 6% HES 200/0.62).[5] The recommendations of the Surviving Sepsis Campaign (SSC)[7] propose that HES 130/04 should not be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