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Julian Bion
Rinaldo Bellomo
John Myburgh
Anders Perner
Konrad Reinhart
Simon Finfer

Hydroxyethyl starch: putting patient safety first

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J. Bion (✉)
University of Birmingham, Birmingham, UK
e-mail: j.f.bion@bham.ac.uk

R. Bellomo
University of Melbourne, Melbourne, Australia

J. Myburgh
The George Institute for Global Health and the University of New South Wales, Sydney, Australia

A. Perner
Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

K. Reinhart
Friedrich Schiller University, Jena, Germany

S. Finfer
Royal North Shore Hospital and The George Institute for Global Health, University of Sydney, Sydney, Australia

Background

In November 2012 the European Medicines Agency (EMA) received a request to examine the risks and benefits of intravenous fluids containing hydroxyethyl starch (HES). The main concerns were that the administration of HES was associated with a number of harmful effects, most notably an increased risk of kidney injury [1–5] and an increased risk of death [6, 7], particularly in critically ill patients and patients with sepsis.

The first EMA Pharmacovigilance Risk Assessment Committee (PRAC) expert meeting in April 2013 unanimously recommended suspension of licensing of HES for all indications [8]. This position was subsequently supported by the UK's Medicines Healthcare Regulatory Agency.

Second EMA–PRAC review position

Following an appeal by companies that manufacture HES, the EMA–PRAC convened a second meeting using different advisors. The recommendations from this are that (1) HES may continue to be used in severe haemorrhage at the discretion of the treating physician and (2) its continued use in the perioperative environment must be subject to further research including monitoring of renal function for 90 days [9]. These recommendations received majority approval by the EMA's Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh) [10] and will be sent to the European Commission for ratification.

Is there new evidence that proves that HES is safe?

The statement from the EMA's CMDh explains that their recommendations 'are based on a review of all available safety and efficacy data, including recent data from clinical studies, meta-analyses and post-marketing experience'. The only new peer-reviewed information referenced by the EMA is the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial [11]. CRISTAL was an open-label, randomised trial that compared outcomes of patients resuscitated with crystalloids or colloids. The trial data available to date suggest that randomisation failed to match the colloid and crystalloid groups at baseline and that the proportions of patients randomised to the two groups to receive either

crystalloid or colloid fluids prior to randomisation were very different ($P < 0.0001$ and $P = 0.0001$, respectively, chi-squared analysis). How this difference occurred is currently unexplained.

The EMA–PRAC also relied on two other non-peer-reviewed sources of information. The first is Rational Fluid Therapy in Germany (RaFTinG), an industry-sponsored clinical registry of fluid use in intensive care [12]. The second source is the Basel Starch Evaluation in Sepsis (BaSES) study, which was a single-centre, randomised, double-blind comparison of either HES or saline treatment alternating with Ringer's lactate in 241 patients with sepsis [13]. Data from this trial are still unpublished, but data on the 1-year mortality and use of renal replacement therapy (RRT) in BaSES were made available for a recent meta-analysis [5], demonstrating overall an increased risk of RRT in patients receiving HES.

Is the second EMA–PRAC decision in the best interest of patients?

The issue of HES is not a trivial matter given that it is likely that around six million patients receive HES-based fluids every year worldwide. If the estimates from meta-analyses are correct (risk ratio [RR] for death 1.09, RR for renal failure 1.27 [7]), the potential for harm is considerable, especially in the context of severe haemorrhage given the evidence for HES coagulopathy [14, 15] and the increased risk of bleeding or transfusion in patients undergoing major surgery [16–19], blunt trauma [20] and critical illness [2, 6, 21]. Concerns that banning HES will result in increased use of other potentially harmful fluids, such as gelatins, may be allayed by the evidence in vulnerable populations that HES is inferior to both 0.9 % saline and Ringer's acetate [4, 6]; these crystalloid fluids may therefore be used with confidence. We and many colleagues in Europe and worldwide have serious concerns that the continued use of HES, even if severely restricted, will harm patients. We have expressed these concerns in an Open Letter to the EMA [22, 23].

Could there be a place for HES in the future?

The EMA–PRAC has recommended that continued perioperative use of HES should be accompanied by further research and 90-day evaluation of renal outcomes. A proper assessment of HES could only occur within a robust and unbiased clinical trial framework, and the research would have to be carried out by respected independent researchers who have neither links to HES manufacturers nor academic conflicts of interest. Previous industry-sponsored trials conducted at the behest of regulators have failed to address the important clinical questions and have been too small, focused on inappropriate surrogate endpoints and subject to bias, including outcome reporting bias [24, 25]. Conducting trials of HES may prove difficult as patients or their surrogate decision-makers must give fully informed consent, which includes knowledge of the concerns surrounding the safety of HES and that the primary purpose of further study is to rule out harm, rather than to demonstrate benefit. We believe that many human research ethics committees will see such trials as unethical and that few informed patients would wish to participate.

Conclusions

With hindsight it is easy to note that much of the current controversy and past harm to patients could have been avoided if proper outcome trials had been conducted before HES was licenced and before it was made widely available. Information in the public domain suggests that the data on which the second EMA–PRAC determination is based appear to carry a high risk of bias and do not justify continuing to expose patients to the risk of receiving HES. Our personal opinion is that patient safety considerations require that the marketing authorisation for HES be withdrawn.

Conflicts of interest J Bion: Chair of Data Safety Monitoring Board for International Study of Dexmedetomidine for Orion 2008–2009; honoraria paid to hospital charity. Member of scientific advisory board for Nestle; honoraria (if any) to be paid to hospital charity. Research grants from Health Foundation; NIHR Health Services Research & Delivery Programme; NIHR Research for patient Benefit Programme; EU Leonardo Programme.

R Bellomo: Consultancy fees from Gambro, Baxter and Philips Medical.

John Myburgh: Travel support vian The George Institute for Global Health, Sydney, Australia, this author's institution, from Fresenius Kabi in relation to the development and conduct of an investigator-initiated randomised-controlled trial (the Crystalloid vs. Hydroxyethyl Starch Trial) and travel expenses and honoraria from Baxter in relation to participation on advisory boards.

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