Starch safety in resuscitation

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The Western Cape Department of Health (WC DoH) has taken a decision to withdraw all intravenous fluids (IVFs) containing hydroxyethyl starch (HES) from hospitals in the Western Cape,[1] with similar action contemplated in the Free State and Gauteng. This was in response to recommendations from:

- The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA PRAC) that HES IVFs be withdrawn from clinical use.[2]
- The United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) which has issued a recall of all HES IVFs in the UK.[3]
- The United States Food and Drug Administration[4] which advises that HES IVFs be used with caution in ICU, cardiac surgery and patients with known kidney disease or coagulopathy. Further advice was that HES should be stopped if coagulopathy or renal dysfunction develops, as well as that renal function should be monitored for 90 days after HES administration.

The actions of the WC DoH could be justified if the recommendations from the regulators in Europe, the USA and UK were based on relevant scientific evidence. Unfortunately, the evidence provided is not only flawed, but also has been applied to clinical scenarios not included in the studies used in evidence. Regarding these studies, HES IVFs were administered to critically ill patients with sepsis. The oldest study,[5] from 2008, used a hyperoncotic (10%) solution of HES 200/0.5 that is no longer used in South Africa and differs significantly from the HES IVFs currently in use. This caveat applies equally to the recent meta-analysis of starches in *JAMA* where the majority of starches used were outdated or hyperoncotic or used in unnecessary volumes over prolonged periods of time.[6] Subsequent studies include 6S[7] from Scandinavia and CHEST[8] from Australasia, which were published in 2012.

The 6S[7] trial used a potato-derived 6% (iso-oncotic) HES 130/0.4 (Venofundin, B Braun) IVF and compared this with Ringer's acetate solution. The study involved 798 patients with an average age of 65. Renal replacement therapy (RRT) was used more frequently in the HES group (22% v. 16%; p=0.04). However, there was no significant difference in the number of patients with a doubling of creatinine levels, and only one patient in each group was dialysis-dependent at

day 90. This finding could be explained by the lack of a protocol for RRT. There **was** a significant difference in 90-day mortality (51% v. 43%; p=0.03). This study may therefore be summarised as a trial of a potato-derived HES IVF v. Ringer's acetate in an elderly population of critically ill septic patients that, although showing a significant increase in use of RRT and 90-day mortality, might have been influenced by lack of RRT protocols.

The CHEST[8] trial used a waxy maize-derived 6% (iso-oncotic) HES 130/0.4 (Voluven, Fresenius-Kabi) IVF compared with 0.9% saline. The study involved 6 651 patients with an average age of 63. Patients who were included had been admitted to the ICU for more than 10 hours and received an average of 3.5 l of other fluids before first receiving study fluid. Lactate and base deficit data suggest that these patients were already fluid resuscitated on entry to the study. The administration of any further volume expander would not seem to have been appropriate in these cases. RRT was used more frequently in the HES group (7.0% v. 5.8%; p=0.04) but renal injury occurred more commonly in the saline group (38.0% v. 34.6%; p=0.005). The incidence of renal failure was similar in the two groups, at 10.4% and 9.2% respectively (p=0.12), which did not correlate with the increased use of RRT in the HES group. An additional problem was that, prior to randomisation, HES IVF was given to 509 patients in the HES group and 508 patients in the saline group.

Importantly, there was a significant increase in new cardiovascular failure in patients receiving saline (39.9% v. 36.5%; p=0.03) but more blood products were used in the HES group.

The CHEST trial may be summarised as a trial of HES IVF compared with 0.9% saline in an elderly population of critically ill, septic patients that showed a significant increase in use of renal replacement therapy (but with no difference in mortality at 28 or 90 days), less renal injury and similar rates of renal failure.

Taken together, the two most recent studies[7,8] indicate, at most, that HES is associated with an increased risk of renal replacement therapy in elderly, critically ill septic patients. The risk of mortality is less clear, with only the 6S study showing an increase in 90- but not 28-day mortality, and the substantially larger CHEST study showing no difference.

None of the studies used by the regulatory agencies addressed the use of HES IVF in patients with trauma or those undergoing major elective or emergency surgery for non-septic disease. One of the few randomised control trials of HES IVF compared with 0.9% saline was undertaken in Cape Town.[9] A total of 109 patients was studied, with the 67 patients who suffered penetrating trauma requiring more saline (7.4 l v. 5.1 l; p<0.001). Renal injury occurred more frequently in the saline group than the HES group (16% v. 0%; p=0.018).

Major trauma or surgery where transfusion is likely is most appropriately managed by early administration of blood and blood products to maintain oxygen delivery and limit coagulopathy. The role of clear fluids, either crystalloid or colloid, is limited where transfusion is required.[10] However, a substantial number of patients suffering trauma or undergoing elective or emergency surgery require intravascular volume replacement but not transfusion.

Caesarean section is an example of a procedure requiring volume loading owing to spinal anaesthesia and blood loss, where transfusion is seldom necessary. A recent meta-analysis has demonstrated the efficacy of colloid solutions, including HES IVF for this indication.[11]

Enhanced recovery programmes for major elective surgery, such as colectomy, also advocate the use of colloids such as HES IVF for replacement of intraoperative blood loss in preference to crystalloids, which have a greater potential to cause bowel oedema, leading to ileus and anastomotic dehiscence.[12]

Alternatives in such situations (including crystalloids, gelatin solutions, blood products such as albumin or plasma) are limited. Crystalloids are associated with development of peripheral and organ oedema increasing the incidence of abdominal compartment syndrome, cardiac and renal failure and exacerbating the acute respiratory distress syndrome.[13]

Gelatin solutions are associated with a risk of anaphylaxis and have minimal advantages over crystalloids in terms of intravascular persistence.[14] Blood products are expensive, are not available in large volumes and should only be administered for specific indications.[15]

The authors appeal for a more rational thought process about the use of HES IVFs. Owing to possible renal harm in elderly, critically ill patients with sepsis, HES IVFs should be withheld from them. There is, however, no evidence that HES IVFs should be withheld from non-septic patients without critical illness who require intravascular volume replacement, but not transfusion. HES IVFs for this indication should be retained for use by anaesthesiologists, emergency physicians and intensivists.

Conflict of interest. Drs Hodgson, Spruyt and Gopalan and Proff. Richards and Dickerson received speaker honoraria from Fresenius Kabi.

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