

Evidence-based approach to the use of starch-containing intravenous fluids: an official response by two Western Cape University Hospitals

To the Editor: Circular 114/2013 issued by the Western Cape Pharmacy Services entitled, *Suspension of use of infusion solutions containing hydroxyethyl starch at Western Cape Government Health Facilities until further notice*, resulted in the non-availability of starch-containing solutions for clinical use. The reasoning behind the circular was based on the Medicines and Healthcare Products Regulatory Agency (MHRA) class 2 recall of starch solutions and the European Medicines Agency's Pharmacovigilance Risk Assessment Committee, who stated that: "The benefits of infusion solutions containing hydroxyethyl starch no longer outweigh the risks, and (we) therefore recommend that the marketing authorisations for these medicines are suspended". The two Western Cape University Hospitals have responded with a joint statement which is presented to SAJAA readers. The statement suggests withdrawals of corn-based starch solutions are based on flawed interpretation of the available data, particularly the suggestion that they cause renal dysfunction. The statement then interrogates why the use of corn-based starch solutions benefits patient care and improves outcome. Lastly, the problems of the alternative therapeutic options are examined. The conclusion reached is that the use of corn-based starch solutions should be reinstated. We believe this well-researched, evidence-based approach is worth publishing to a wider audience.

1. The evidence supporting the withdrawal of hydroxyethyl starch is critically flawed and does not stand up to analysis, particularly with reference to perioperative use and acute resuscitation

1.1 We refer to the letter stating that the evidence presented by the European Medicines Agency's Pharmacovigilance Risk Assessment committee: "That the benefits of infusion solutions containing hydroxyethyl starch no longer outweigh the risks, and therefore (we) recommended that the marketing authorisations for these medicines are suspended". The letter continues: "The review of infusion solutions containing hydroxyethyl starch was triggered by the German Medicines Agency... following three recent studies (that) have compared hydroxyethyl starch with other products, called crystalloids, used for volume replacement in critically ill patients. The studies showed that patients with severe sepsis

Summary of the main points

1. The three recent studies used as a basis for condemning the use of colloids are seriously flawed and do not apply to the perioperative and acute resuscitation period.
2. The context of fluid administration appears to be increasingly important. There is no real conflict. The liberal use of colloids in the intensive care unit (ICU) after the initial resuscitation appears to be problematic.
3. However, there is significant evidence that perioperative and post-trauma outcomes, e.g. the incidence of multiple organ dysfunction and ICU stay, and better acute resuscitation is accomplished early and follows established, well-recognised haemodynamic goals. A balanced approach (the combined use of crystalloids and colloids) is important, and the inclusion of modern hydroxyethyl starch products derived from maize is associated with improved outcomes.
4. The current maize-based hydroxyethyl starches must be viewed as drugs with their own indications, contraindication and complications. As such, they do not have significant organ toxicity and the associated renal dysfunction is not attributable to the fluid alone, but rather to the context in which they are used. Alternative strategies, such as the use of albumin, gelatins, hypertonic saline, crystalloids alone, and blood and blood products, all have serious potential complications.

who were treated with hydroxyethyl starch were at greater risk of kidney injury, requiring dialysis. Two of the studies also showed that patients treated with hydroxyethyl starch were at greater risk of mortality".

- 1.2 In points 2 to 5, we comment on these opinions since the restriction placed on the use of starch solutions for volume resuscitation requires a carefully considered, logical, unbiased and scientific response, as the evidence presented is not nearly

as strong as the proponents of the moratorium would have us believe.^{1,2} With this in mind, we will initially present a critical review of the three studies mentioned by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee.

1.3 In points 6 and 7, we present arguments as to why the use of these solutions are beneficial to patient care and have been shown to improve outcome. We also examine alternative therapeutic options and suggest they may be worse than the proposed "disease" or complications suggested above.

1.4 Lastly, in points 8 and 9, we will draw conclusions from the current debate.

2. The "VISEP" study: The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study is conceptually and ethically flawed and should never be quoted as evidence of direct nephrotoxicity, since hyperoncotic colloids will impair renal function and damage the kidney, irrespective of colloid type³

2.1 *Flawed methodology:* This study employed prolonged infusions of hyperoncotic starch with inadequate crystalloid support.¹ It has been known for over 20 years,⁴ and was confirmed recently,⁵⁻⁷ that hyperoncotic colloids impair renal function, irrespective of colloid type. Therefore, the VISEP study was conceptually and ethically flawed, and should never be quoted as evidence of direct nephrotoxicity.

2.2 A recent meta-analysis using the VISEP study also came to the conclusion that colloids are nephrotoxic.⁸ As the VISEP study contained strong renal damage and mortality signals, all meta-analyses that included these data would be biased and must be set aside.¹

3. The CHEST study: The conclusion of The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) study, that "more patients who received resuscitation with hydroxyethyl starches were given renal replacement therapy" reflects a secondary end-point, which for numerous reasons, does not withstand statistical or methodological interrogation⁹

3.1 The CHEST study⁹ was powered for a single primary end-point, namely mortality. The result of CHEST is as definitive as the *Saline* versus Albumin Fluid Evaluation (SAFE) study, and indicates clearly that the starch solution employed in this study does not increase mortality, compared to normal saline.¹⁰

3.2 The reasons that the secondary end-points do not withstand interrogation include the fact that there

was no significant difference between groups with respect to renal failure. Although the p-value for this secondary end-point was 0.04, the 95% confidence interval (CI) for the unadjusted and adjusted relative risks for the two fluids [1.21 (1-1.45) and 1.20 (1-1.44) respectively] both included one. The span of CIs is much more valuable than a p-value in determining whether differences actually exist between groups. This was confirmed as once the data were adjusted for known covariates, the p-value of this observation also ceased to be significant. Furthermore, the incidence of renal failure, and the number of dialysis days, the latter a robust indicator of renal injury, were not different between the groups.

4. The 6S study: The methodology of the study to detect renal injury was flawed

4.1 The study was not designed to investigate this secondary end-point, as no criteria were specified for the initiation of renal replacement therapy. The criteria for implementing renal replacement therapy were entirely at the discretion of staff in the 32 intensive units involved. Indeed, criteria that were specified in the study, including RIFLE criteria (risk, injury, failure, loss of kidney function and end-stage kidney disease), contradict the "finding" suggesting that starch induced renal failure, and in fact, favour the starch. In this respect, another important indicator of renal injury, the number of days on dialysis, was identical between the two groups. Therefore, it is difficult to understand how, in this large study, a supposedly nephrotoxic substance failed to increase the rate and severity of renal failure or the duration of renal replacement therapy. Indeed, much larger doses of hydroxyethyl starch than those used in the CHEST study have not caused renal injury.¹¹ Graft survival after renal transplantation is not deleteriously, but beneficially, affected, after hydroxyethyl starch 130/0.4 administration,¹²⁻¹⁵ belying the association of hydroxyethyl starch and nephrotoxicity. The use of the maize-derived hydroxyethyl starch 130/0.4 was associated with better renal function after aortic surgery when compared with gelatins, the latter reputedly having "no" deleterious effects on the kidney.¹⁶ This suggests that renal injury is more complex than the hypothesised direct nephrotoxic effect of starch solutions and is probably not the effect of the colloid itself. The conclusion in the CHEST study abstract: "However, despite a lower overall rate of acute kidney injury, more patients who received resuscitation with hydroxyethyl starch were given renal replacement therapy", is therefore

incorrect. The only valid conclusion from CHEST is that the hydroxyethyl starch product that was used is not associated with increased mortality. Therefore, the 6S study was methodologically flawed, owing to enrolment following effective resuscitation, and subsequent excessive ICU fluid administration.¹⁷

4.2 Study enrolment followed effective resuscitation: Interrogation of the markers of tissue perfusion (lactate, central venous oxygen saturation and central venous pressure) used in the 6S study¹⁷ indicated normal values at study entry. This indicated resuscitation had been completed before enrolment. A recent publication demonstrated that fluid boluses given more than six hours after initial resuscitation (mainly with albumin) were of no value and potentially harmful. This questions the entire paradigm that underlies the studies on which the withdrawal of hydroxyethyl starch is based.¹⁸

4.3 Fluid excess in the ICU: Despite the adequacy of initial resuscitation, in excess of 4.5 litres of study fluid was administered on day one, a trend sustained for the next three days. The consequence was that “more patients in the starch group than in the Ringer’s acetate group received ... packed red cells” (relative risk, 1.28, 95% CI: 1.12-1.47, p-value < 0.001). Excessive transfusion was likely because fluid overload and haemodilution is substantially easier to achieve with colloid than with crystalloid. Comparable fluid excess has been associated with intensive care mortality^{19, 20} and may account for the high overall renal injury and mortality reported in the study.^{8, 21-25} The reasons for administration of these large fluid volumes were not specified. This may have been because early goal-directed resuscitation end-points were neither clarified nor targeted, or attempts at goal-directed haemodynamic resuscitation continued beyond the period shown to be of benefit (12-24 hours).^{1, 26, 27}

5. All three studies that were quoted by the European Medicines Agency’s Pharmacovigilance Risk Assessment committee as evidence of renal damage by starches suffer from the so-called “pragmatic” design. Common flaws are exclusion of the initial resuscitation phase and failure to apply early goal-directed resuscitation

5.1 Exclusion of the initial resuscitation phase: All three of these studies commenced after the initial resuscitation phase. For example, CHEST enrolled patients on average, 11 hours after ICU admission (10.9 ± 156.5 and 11.4 ± 165.4, for the starch and saline groups, respectively).

5.2 Absence of hypovolaemia: No evidence is advanced in any of these studies that the patients enrolled were, in fact, hypovolaemic. Indeed, 411 of the 798 patients included in the study (52%) had already received colloids before randomisation.²⁵

5.3 Failure to apply goal-directed resuscitation: The time of entry into the studies also raises questions about whether or not any of the above studies utilised the well-recognised principles of “early” goal-directed therapy in critically ill patients with sepsis, trauma and pancreatitis.^{26, 28-33} Four meta-analyses on the use of cardiac output monitoring to guide fluid administration in high-risk surgical patients clearly showed benefit in terms of reduction in postoperative complications and hospital stay, particularly in the most sick individuals.³⁴⁻³⁸ Two of these studies used colloids exclusively for volume support. That hydroxyethyl starch is superior to crystalloid for this use has been confirmed recently.³⁹ Inspection of the article protocols indicates no evidence that these basic principles were applied in any of the three studies in question.

6. Safety of modern starch solutions for perioperative use and in trauma

6.1 Perioperative colloid (modern maize-based hydroxyethyl starch) administration and crystalloid restriction is associated with improved outcome. The most significant recent advances in perioperative fluid therapy have included crystalloid restriction,⁴⁰⁻⁴² with reliance on colloid administration using robust markers of volume deficiency. The perioperative use of colloid solutions for resuscitation is associated with improved outcome.⁴³ Some of the cornerstones of Enhanced Recovery After Surgery programmes are based on the above principles.⁴⁴

6.2 The largest volume of colloid (over 80%) administration occurs in trauma and in the perioperative setting. Yet all but one publication in this area has been excluded from the meta-analyses, suggesting poorer renal outcome with the hydroxyethyl starches. In studies enrolling in excess of 4 000 trauma and perioperative patients, there was no evidence of renal injury associated with the use of colloids, and modern hydroxyethyl starches, in particular.^{11, 45} Recent trauma studies have suggested that the use of colloids is beneficial in acute resuscitation.^{43, 46, 47} This is supported by provisional data from the CRYSTAL study that suggested that the combination of early use of crystalloids and colloids is advantageous in acute resuscitation.

6.3 *The use of starches to prevent hypotension in Caesarean section:* Current evidence suggests that combining a prophylactic vasopressor regimen with hydroxyethyl starches preloading or co-loading is the most effective method of preventing maternal hypotension after initiation of spinal anaesthesia. Crystalloid preloading is clinically ineffective and thus should no longer be used.⁴⁸⁻⁵² Based on first principles, hydroxyethyl starches are preferable to crystalloid in patients at high risk of pulmonary oedema, such as those with severe pre-eclampsia.

6.4 *Not all starch solutions are the same.*⁵³⁻⁵⁶ It is also important to note that the potato-based starch product used in the 6S study is a very different chemical entity from the corn starch-based versions that are commonly available in South Africa. Wise et al state the following: "Given that most published safety data for low-molecular-weight starch are from maize-derived products, including the recent, positive results of the Effects of Voluven on Hemodynamics and Tolerability of Enteral Nutrition in Patients with Severe Sepsis (CRYSTMAS) trial, the Fluids in Resuscitation of Severe Trauma (FIRST) trial, and the unpublished results of the Basel Starch Evaluation in Sepsis (BaSES) (ClinicalTrials.gov number, NCT00273728) trial, perhaps 6S is an indictment of potato-based starches, rather than starches as a whole".⁵⁷

7. Is the alternative clinical option a return to using crystalloid solutions alone for resuscitation, and blood and blood products for resuscitation?

7.1 Greater volumes of crystalloid for resuscitation have consistently been shown to be harmful⁵⁸ with far stronger signals indicative of harm than those indicated by the Medicines and Healthcare Products Regulatory Agency, US Food and Drug Administration and European Medicine's Agency.

7.1.1 The basic reason for the difference is that because crystalloids are not constrained to the intravascular space, a greater volume (two to eight times the shed blood volume) is needed to restore intravascular volume. This is unlike effective colloid-containing solutions, in which case the ideal ratio of replacing it is unity. In other words, volume resuscitation is faster and more effective.⁵⁹ The larger volume of crystalloids that are needed aggravate the problems discussed below. These previous statements can only hold true provided the endothelial glycocalyx is largely intact.^{56,60,61}

7.1.2 Rapid crystalloid infusion, in opposition to the

use of modern balanced starches,⁶² results in unphysiological reductions of colloid osmotic pressure. This deleteriously affects fluid pharmacokinetics, with greater transudation of crystalloid into the interstitium.⁶³⁻⁶⁵

7.1.3 The resultant tissue oedema has multiple, predictable, deleterious consequences for the critically ill patient. Because of increased diffusion distance, tissue partial pressure of oxygen decreases while increasing the volume of "Krogh's deadly corner".^{66,67} The latter consequence is likely to be a driver of multiple organ dysfunction. The mechanical consequences include decreases in splanchnic oxygenation,^{68,69} abdominal compartment syndrome^{58,70} and accompanying renal failure, oedematous pulmonary tissue with poorer arterial oxygenation⁷¹ and a restrictive pulmonary defect,⁷¹ greater neutrophil activation with acute lung injury,^{71,72} and greater ICU mortality.⁷³ Some of these complications also occur with the colloids that have inherently shorter intravascular dwell time, such as the gelatins.^{67,74-76} However, these considerations only apply when the tissue entry of macromolecules and colloids is limited by an intact endothelium and glycocalyx. Once the endothelial glycocalyx layer is damaged by longstanding ischaemia or sepsis, all compounds leak into the interstitium to a lesser or greater degree.^{77,78} This is frequently seen in the ICU a day or so after the initial resuscitation, and the solution is to give as little extra fluid as possible.

7.2 Recent research indicates that the administration of colloids in the presence of normal or increased plasma volume damages the endothelial glycocalyx, resulting in increased transudation into the interstitium, and contributes to coagulopathy.⁷⁹⁻⁸¹

7.3 *Is albumin the answer?* Possible alternative strategies to the use of synthetic colloids are all problematic. Albumin is simply too expensive to be used for this purpose.

7.4 Another alternative, the increased use of blood and blood products, is equally unsound.

8. What are the take-home messages? What can we learn from the recent data?

8.1 Extrapolation from one to another context is inappropriate and dangerous. In particular, the use of intensive care fluid data to guide fluid management

in perioperative and acute trauma care is flawed.

- 8.2 The studies on which decisions were made are flawed. Magder stated: "The designs of these studies ignore basic physiological principles... Before potentially useful products are discarded, one must thus ask whether the problem is the colloids or the protocols".²³
- 8.3 In acute resuscitation, indication, timing and definitive end-points are paramount. The calls for universal bans on life-saving drugs have not considered the data that uniformly favour modern hydroxyethyl starches as part of goal-directed haemodynamic optimisation. In this respect, colloids must be considered as drugs⁸² with specific indications, contraindications and complications. They require precise indications for administration (inadequate intravascular volume in high-risk surgery and trauma), and need to be dosed against end-points known to improve outcome (cardiac output), and administered for the correct duration (12-24 hours).⁸³
- 8.4 Our current static and dynamic fluid administration triggers do not withstand scrutiny after the acute resuscitation phase. The unrestricted use of colloids to treat non-volumetric markers, such as hypotension, central venous pressure and inadequate urine output, particularly in the later stages of critical illness, is inappropriate and harmful. Similar to any drug used in acutely ill patients, clinicians ordering a volume prescription must recognise that context is crucial.⁸²
- 8.5 One common aspect that has been highlighted by this current debate is that excessive fluid administration is harmful. Fluid overload is undeniably easier to achieve with inappropriately administered colloid, than it is with similar crystalloid volumes. Fluid, and particularly colloid overload in the patient with renal dysfunction, is hazardous.
- 8.6 There is no evidence of harm from any of the modern colloids, including hydroxyethyl starches, apart from anaphylaxis, particularly with the gelatins, when these solutions are used for the appropriate indications.^{11,43,54} Where clear markers of hypovolaemia are present, colloids appear to be superior to crystalloids for initial resuscitation.
- 8.7 The alternatives, particularly the excessive use of crystalloid, are associated with significant harm.
9. In conclusion, the decision of the European Medicines Agency's Pharmacovigilance Risk Assessment committee that "benefits of infusion solutions containing hydroxyethyl starch no longer outweigh the risks" is not valid in the perioperative and acute resuscitation periods.

We are of the opinion that the opposite is in fact the case, and that we would be doing our patients a significant disservice to withhold the reliable, tested modern corn-derived hydroxyethyl starches. Indeed, we welcome this opportunity to clarify the issues involved.

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