The role of hydroxyethyl starch in resuscitation in the ICU

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Synthetic colloid solutions have been used extensively for fluid resuscitation in critically ill patients for over 40 years. The imperative to develop these solutions has been driven by the need to produce an effective, alternative colloid to human albumin, which is widely regarded as the reference colloid solution. Outside Australia (where albumin is provided and distributed at no cost to public hospitals), provision of albumin is restricted by its availability, purity and cost. As a result, synthetic colloids, in particular hydroxyethyl starch (HES) solutions, are most commonly used, especially in Europe, although there is marked variation in the use of colloid solutions between and within countries.[1]

Protagonists of HES solutions have based their arguments on the benefits of colloids over crystalloids, specifically, better intravascular volume expansion and maintenance of colloid oncotic pressure. However, these physiologically based properties have increasingly been questioned following insights into the effects of acute inflammation on the regulatory role of the endothelial glycocalyx, and the role of the microcirculation, specifically autonomically mediated lymphatic clearance of interstitial fluid.[2] The improving knowledge of these effects has caused a re-evaluation of the effectiveness of colloids to remain within the intravascular space under pathological conditions such as sepsis, trauma and general anaesthesia, when resuscitation fluids are commonly administered. The potential for colloids to maintain intravenous volume and cause oedema is probably no different to that of crystalloids. The results of recent high-quality randomised controlled trials (RCTs) have added further to these observations. The ratio of albumin:saline observed in the Saline versus Albumin Fluid Evaluation (SAFE) study was 1:1.4, suggesting a relative equivalence in the volume expansion effect, and no difference in mortality or organ failure between albumin and saline.[3] However, there are differences in potential toxicity, as has been demonstrated with albumin and patients with traumatic brain injury.[4]

Concerns about tissue accumulation of HES are well recognised. Because these solutions undergo enzymatic metabolism and renal excretion, the concentration, molecular weight and degree of molar substitution of HES solutions have been implicated as factors responsible for nephrotoxicity due to tissue accumulation.[5,6] Currently used HES solutions are less concentrated, with lower molecular weights (130 kD) and molar substitution ratios (0.4). Until recently, the safety and efficacy of currently used HES solutions had not been evaluated in high-quality RCTs.[7]

HES was licensed for the first time in Australia in 2006, with substantial subsequent use (particularly in patients undergoing general anaesthesia for major surgery), and the need to conduct such trials, focused on patient-centred outcomes (mortality and acute kidney injury), was considered imperative.

The Crystalloid versus Hydroxyethyl Starch Trial, modelled on the SAFE study, was conducted in 7000 patients from 32 intensive care units in Australia and New Zealand. The trial reported no significant difference in 90-day mortality (relative risk [RR], 1.06; 95% CI, 0.96–1.18; $P = 0.26$), but reported a significant 21% relative increase in the use of renal replacement therapy (RRT) in the HES group in a heterogeneous population of adult ICU patients who received either a maize-based 6% (130/0.4) HES or saline for fluid resuscitation.[8]

The Scandinavian Starch for Severe Sepsis/Septic Shock trial reported a significant increase in 90-day mortality (RR, 1.17; 95% CI, 1.01–1.30; $P = 0.03$) and a significant 35% relative increase in the use of RRT in ICU patients with severe sepsis who received a potato-based 6% HES (130/0.42) compared with Ringer's acetate.[9] Both trials reported no differences in haemodynamic resuscitation end points, apart from transient increases in central venous pressure, similar HES:crystalloid ratios of 1:1.3, and significant increases in use of blood products and adverse events.

How should clinicians respond to these results? These investigator-initiated, high-quality, blinded trials were designed and conducted to determine the efficacy and safety of HES in high-risk patients, focusing on patient-centred outcomes. Neither trial demonstrated any substantial clinical benefit with HES, but showed potential harm, demonstrated by the increased requirement for RRT. While there are differences between the HES solutions, doses and patient populations between these two trials, the adverse effects of HES on mortality and the use of RRT are consistent, and the role of HES in critically ill patients needs to be carefully evaluated.

Whether these results can be generalised to other synthetic colloids is unknown. However, in the absence of high-quality RCTs, the use of solutions such as gelatins and polygeline cannot be assumed to be a "safe" alternative to HES, and requires caution. The role of colloid resuscitation as a whole requires re-evaluation in the absence of any high-quality trial reporting a clinical benefit.[10]

These observations do not, therefore, allow endorsement of the use of crystalloids, either saline or "balanced salt

solutions", none of which have been evaluated with high-quality scientific rigour.

A paradigm shift about fluid resuscitation is urgently required. Administration of any resuscitation fluid requires the same consideration as when using a drug with a narrow therapeutic index, taking account of the clinical indication for which the fluid is being administered, the type of fluid, cumulative dose, efficacy, toxicity and cost.

Primum non nocere.

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