Hydroxyethyl starches in burns

To the Editor: Den Hollander[1] argues that 'the exclusion of severe burns from the indications for the use of colloids, as well as the exclusion of consultant surgeons and emergency specialists from those who will be allowed to prescribe HES-containing products, indicates little insight into the evidence and the clinical situation "at the coalface"'.

The author places considerable emphasis on the value of starch in light of its volume sparing effect,[1] and there is some support for this assertion,[2] but he also quotes a randomised controlled double blind trial which shows no such effect.[3] Of more concern, however, is the fact that although large randomised controlled trials are clearly lacking in the context of fluid resuscitation in major burns, evidence demonstrating actual harm with hydroxyethyl starches (HESs), albeit from the general critical care literature, should be acknowledged.[4,5] Haase and Perner[6] stated that there is 'no clear evidence for an overall beneficial effect of HES in any subgroup of critically-ill patients, but there are clear signs of harm'. These include adverse effects on renal and haemostatic function, with trends towards increased mortality. They recommended that its use be discontinued in these patients.

An international survey revealed that a considerable percentage of burn surgeons introduce albumin to their initially crystalloid-based resuscitation within the 1st 24 hours post burn.[7] Albumin facilitates adequate resuscitation with significantly less fluid in the initial 24 hours after burn injury. While unlikely to reduce the initial extravasation of fluid into the interstitium, as a result of the capillary permeability in the burn wound itself, albumin does appear to ameliorate the impact of the reduced colloid osmotic pressure in unburnt tissues and notably in the lung, manifesting as reduced 'fluid creep', ventilatory requirements, and ultimately, mortality.[8,9] In light of the best available evidence, I encourage the author to reconsider his staunch advocacy for synthetic colloids, and especially HESs, and instead make use of 5% albumin as a 'rescue' measure in the specific context of major burn resuscitation.

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Den Hollander responds: Many thanks for allowing me to respond to the above letter. The conclusion of my original letter was that although the scales are starting to tip in favor of hydroxyethyl starches (HESs), there is very little level 1 evidence for its effectiveness in burns, and until such evidence is available, decisions regarding its use should be left to the experts who regularly care for such complex cases.[1] Too often, decisions are forced onto them by those with little insight into the evidence and Roger's argument is no exception. The study by Béchir *et al.*[2] is, despite its title, not a randomised controlled trial (RCT) but – as I pointed out in my letter – a post-hoc analysis 10 years later of the 30 burn patients included in the Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study.[3] The latter was indeed an RCT, but a post-hoc analysis of an RCT is not itself an RCT. Although the Béchir study showed no effect of HESs over saline, there are major methodological problems with this study, not least of which the fact that the HES-treated group was more severely injured than the saline group. Rogers subsequently advised me to 'acknowledge evidence demonstrating actual harm with HES', quoting in support the crystalloid v. HES CHEST study and Vlachou's work, both of which were referenced in my letter. The CHEST study,[4] like the VISEP study,[3] has been severely criticised, recently again by Weisskopf and James,[5] who concluded that they both contain 'important methodological and interpretative flaws'. They also contained mainly patients in septic shock, and results could not be applied to other patient populations. In these studies, the HES was administered not as a resuscitation fluid but as a daily supplement for several weeks. There are now 59 RCTs in surgical patients, totaling nearly 5 000 patients, showing a benefit in blood loss and transfusion requirements without any reported increase in adverse effects.[6-8] A single RCT in trauma showed a more rapid lactate clearance and a lower incidence of renal injury in patients resuscitated by HESs.[9]

Rogers would do well to remember recent history. It was not so long ago that albumin was blamed for the same adverse events as HESs are now – renal failure and an increased mortality – until the Saline v. Albumin Fluid Evaluation (SAFE) study[10] demonstrated otherwise. It is also good to remember that the SAFE study reported no survival benefit of albumin over saline in their study population. A recent meta-analysis of albumin use in burns[11] concluded that albumin administration was associated with lower mortality and decreased risk of abdominal compartment syndrome than resuscitation with crystalloids only. However, this study cannot be used to justify a preference of albumin over HESs. Indeed, Vlachou[12] in a small RCT (26 patients) reached the same conclusions regarding HESs. These benefits seem to be rather effects of colloid over crystalloid resuscitation than evidence on which to base a choice between colloids. Other reviews of the use of albumin in burns and trauma resuscitation have confirmed the lack of untoward effects, but evidence of benefit has been harder to come by.[13-19]

In the basic science literature, our understanding of the microcirculation and the mechanisms responsible for oedema formation are radically changing, centreing on the role of the glycocalyx.[20] That colloid osmotic pressure does not play the role it was assigned by Ernest Starling is known to many burn surgeons, as burn oedema usually resolves in the face of dropping albumin levels. The mechanism responsible for 'leaky capillaries' seems to be not so much gaps that occur between endothelial cells, but rather a defective glycocalyx. One aim of resuscitation should be maintenance and restoration of the glycocalyx. The effects of various resuscitation fluids on the glycocalyx are still being worked out. Although albumin is an important constituent of the glycocalyx, experimental work has revealed that this structure is saturated with albumin at a plasma-albumin level of as little as a quarter of physiological levels.[21] It may turn out that that plasma would be the ideal resuscitation fluid, as it has been shown to restore damaged glycocalyx in rats,[22] probably as a result of its ability to replenish glycosaminoglycans, an essential component of the glycocalyx. These studies are, however, still very much in the preclinical stage. Furthermore, plasma is expensive and carries risks. Under these circumstances the choice of which colloid to use should be left to the clinician. If Rogers prefers albumin for

burns resuscitation, he may, as long as he realises that it is just that, a preference.

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