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What's new in the controversy on the renal/tissue toxicity of starch solutions?

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A systematic review in a recent issue of *Intensive Care Medicine* by Wiedermann and Joannidis [1] describes studies in which tissue accumulation of hydroxyethyl starch (HES) was documented by histological assessment. The review includes 635 patients from 37 mostly small observational studies or case reports, the majority of which used older HES preparations.

Focusing on the human studies it appears that after administration of HES solutions, tissue storage of HES is widespread, rapid, cumulative, frequently long lasting and potentially harmful. HES was localized in skin and several other organs, including the kidney, liver and bone marrow. The highest concentration of HES was found in the kidney. The most frequently encountered adverse clinical events associated with HES storage were pruritus, kidney and liver dysfunction, and bone marrow suppression. A clear-cut dose–response relation between dose of HES infused and tissue accumulation could not be demonstrated.

This review is relevant to the fiercely argued, sometimes emotional debate ongoing in the literature about the safety of HES solutions. The review found that the high incidence of pruritus could be associated with the accumulation of HES in the skin. However, the prospective follow-up study on 295 survivors of the 6S trial revealed that patients assigned to resuscitation with the modern HES 130/0.42 solution had worse self-perceived health-related quality of life than those assigned to Ringer's acetate but, remarkably enough, had a similar rate of pruritus [2]. The data on pruritus and its presumed relation with histological skin accumulation of starches as found in older studies should thus be viewed with caution. This new information illustrates that despite the more than 20 years of use of starch solutions, correct use is still hampered by a relative data poor environment with disparate and biased data.

The data assembled by Wiedermann and Joannidis fuels of course the arguments of the detractors of the use of HES solutions claiming that compared to alternative, mostly crystalloid solutions, they cause more harm than benefit and are associated with potentially serious nephrotoxicity and even mortality. This has resulted in a recommendation by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) that HES solutions must no longer be used in patients with sepsis, burn injuries or critically ill patients because of the risk of acute kidney injury (AKI) and mortality. They may continue to be used in patients with hypovolemic shock, where treatment by crystalloids only is not sufficient (decision on 25/10/2013, http://www.ema.europa.eu/ema/). The EMA review was triggered by three studies showing that patients with severe sepsis treated with HES were at a greater risk of AKI requiring dialysis than those treated with crystalloid fluids [3–6]. Two of the studies also

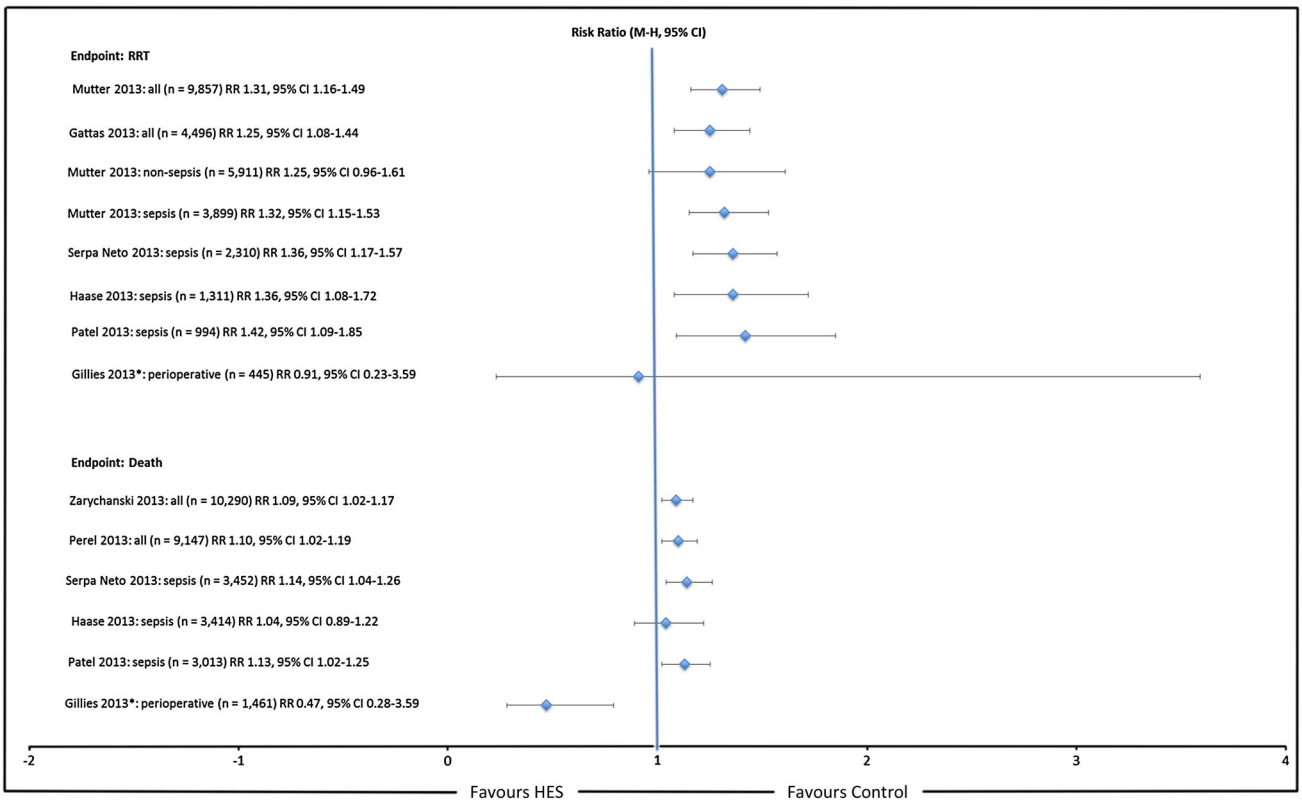

Fig. 1 Risk for renal replacement therapy and death as reported in recent meta-analyses. *M-H* Mantel Haenszel method, *RR* risk ratio, *CI* confidence interval. * RR and CI are calculated from the original data in the manuscript

showed a greater risk of mortality [3, 4, 6]. These results are corroborated by meta-analyses showing that HES solutions are associated with increased mortality and/or increased need for renal replacement therapy (RRT) [7–12] (Fig. 1). A recent Cochrane review analysed 42 randomised controlled trials (RCTs) and quasi-RCTs in which HES was compared to an alternate fluid therapy for the prevention or treatment of intravascular volume depletion [13]. Overall, there was a significant increase in the need for RRT and in the number of author-defined kidney failures in the HES-treated individuals compared to other fluid therapies. The volume of HES administered (more or less than 2 L) or molecular weight did not impact on these outcomes. In contrast, the risk of meeting RIFLE-R (risk) or greater criteria for AKI was in favour of HES therapies. However, when outcomes based on RIFLE-R urine output were excluded, the beneficial effect of HES administration disappeared. Two meta-analyses including only studies on HES administration in the perioperative period could not demonstrate an effect on mortality, development of AKI or need for RRT [14, 15]. Furthermore, HES-resuscitated patients with penetrating trauma had less AKI compared to saline-treated patients [16]. Also, the recently published multicentre CRISTAL trial comparing all types of colloids with a variety of crystalloids did not find a significant difference in 28-day mortality and even a lower mortality at 90 days in hypovolemic ICU patients [17].

The supporters of the HES solutions point out that in some of the clinical studies showing negative effects excessively high doses of HES were administered, and that not all HES solutions are equal and thus not equally toxic. In addition, the increase in serum creatinine with HES in the CHEST study was relatively minor and urine output was initially greater, leading to less AKI when assessed by the RIFLE-R and RIFLE-I stages [5]. In addition, although there was a greater use of RRT, the difference concerned only 39 out of a total of 7,000 patients.

Starch solutions are semi-synthetic colloid fluids and should, at least theoretically, enable faster and more effective intravascular expansion with less total volume than crystalloids, and with less risk of volume overload. HES solutions are produced by hydroxyethyl substitution of amylopectin obtained from maize or potatoes but whether these differences translate into clinically meaningful differences between HES solutions is not clear. Currently used HES solutions have reduced concentrations (6 %) with a molecular weight of 130 kDa and molar substitution ratios of 0.38–0.45 and are available in various types of crystalloid carrier solutions. A high degree of substitution on glucose molecules protects against hydrolysis by

nonspecific amylases in the blood, thereby prolonging intravascular expansion, but this action increases the potential for HES tissue accumulation. In contrast to the sustained plasma half-life of older starch solutions, HES 130/0.38–0.45 disappears from the circulation within hours and offers little advantage over crystalloids in terms of effective plasma volume expansion. In hypovolemic patients, intravascular volume expansion by crystalloids is much greater than that achieved in euvolemic volunteers and, if the endothelial glycocalyx is damaged (such as in septic shock), intravascular retention of colloids may not be substantially better than crystalloids.

However, the alternative crystalloid solutions used in fluid resuscitation are not so innocent as previously thought either e.g. their use is associated with risk of development of hyperchloremic metabolic acidosis.

In conclusion, the systematic review by Wiedermann and Joannidis has helped physicians to understand better the mechanisms whereby accumulation of starches in the interstitial tissue could induce organ toxicity. Unfortunately, the link between pruritus and HES storage in skin is not supported by a recent observation [2]. Whether the findings are scientifically convincing enough to accept the decision made by many experts, including the EMA, to ban starch solutions from clinical practice is not clear. We are afraid that this controversy remains at present a "believer versus non-believer" story. However, in light of the current evidence of their lack of clear clinical benefit, their potential nephrotoxicity, but above all their increased cost, the use of starch solutions for fluid resuscitation in critically ill patients is in these economically "depressing" times difficult to justify.

Conflicts of interest NL and EH declare no conflicts of interest.

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