LETTER TO THE EDITOR

ACUTE KIDNEY INJURY IN CRITICALLY BURNED PATIENTS TREATED WITH HYDROXYETHYL STARCH: A RESPONSE TO SÁNCHEZ-SÁNCHEZ ET AL.

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A recent publication by Sánchez-Sánchez and colleagues investigated the incidence of acute kidney injury (AKI) in critically burned patients resuscitated with Ringer's solution supplemented with hydroxyethyl starch (HES).[1] The authors report no differences in the incidence of AKI between patients resuscitated with or without HES. Based on these results, the authors conclude that the use of low doses of HES in burn injury may be safe and that further investigation is warranted. However, these results contradict a number of earlier studies and are also not in line with current guidance on the use of HES products. Furthermore the study has several limitations that raise questions regarding the validity of these findings.

Firstly, the study by Sánchez-Sánchez et al. was not adequately designed to directly investigate the incidence of AKI in burn patients treated with HES. Most notably, the lack of a control group makes it difficult to assess the efficacy and safety of HES. Furthermore, the patient follow-up time of 3 days is insufficient to fully assess the incidence of AKI. Following a review in 2013 of the accumulated evidence concerning the risks associated with HES, monitoring of renal function in hospitalized patients for at least 90 days was suggested, as use of renal replacement therapy has been reported up to 90 days after administration of HES products.[2] The shorter follow-up time utilised in this study means that incidence of HES-induced AKI may have been missed. Secondly, the original aim of the study by Sánchez-Sánchez et al. was to report the incidence of AKI in burn patients, and not to evaluate the efficacy and safety of HES. Whilst this may provide a reason for the lack of a control group, the authors' conclusions on the safety of HES are based on comparisons to other studies, which are not statistically supported nor valid due to differences in study methodology. For example, the authors report that incidence of AKI was not increased in patients treated with HES compared to those not treated with HES. However, in the absence of a control group, this finding is based upon comparisons to other studies, e.g. Bèchir et al.[3] Since careful control of fluids is critical for the evaluation of HES efficacy,[4,5] comparisons between studies may not be valid due to differences in study methodology or patient groups. Finally, the authors report no differences in AKI incidence between patients that received HES in the first 12 hours and patients that did not; however, these data and analyses are not provided in the manuscript.

In addition to the methodological limitations outlined above, the use of HES to treat patients with burn injury is not supported by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). The FDA and EMA have both established recommendations for the use and marketing of HES products.[6,7] In 2013, the FDA and EMA advised against the use of HES products in critically ill patients. This recommendation was based on the outcome of several randomized controlled trials, which found no clinical benefits of HES and reported increased mortality and renal failure in critically ill patients treated with HES solutions.[8-10] As a result of these and subsequent findings the use of HES solutions in burn injury is contraindicated.[11] Although the patients in Sánchez-Sánchez et al. were treated prior to this guidance, greater awareness of the indication, use and risks associated with HES products should have been made by the authors. More recently, further high-quality systematic reviews outlining the risks associated with HES have been published.[12-16] As a result of the growing evidence for the negative side effects associated with HES a petition was submitted on February 2017 to urge the EMA and FDA to completely ban the use of HES.[17,18]

In light of this evidence it is difficult to support the authors' suggestions that the harms of HES for fluid resuscitation are inconclusive and questionable. Various well-designed randomised clinical trials and rigorous systematic reviews have demonstrated consistent evidence for the adverse effects of HES products.[8-10,12-16] It is well-established that patients treated with HES are at increased risk of mortality, AKI and renal replacement therapy (RRT).[8-10,12-16,19] Consequently, the use of HES is contraindicated in patients with renal impairment or at

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risk of AKI.[20] Considering AKI is one of the most important complications in burn injury, why would a physician risk increasing the chances of AKI in these patients by suggesting treatment with HES? Furthermore, Sánchez-Sánchez et al. argue in favour of the safety of newer and lower doses of HES; however, there is no evidence to support either claim. It has not been proven that newer HES preparations are safer than older HES solutions,[9,10,12,16,21-23] and no safe dose for HES has been identified.[22] The authors also claim that there is a lack of evidence of the harms of HES in burn injury. However, increased mortality has been demonstrated independent of infused volume, molecular weight or patient group.[12] Finally, many of the supporting studies identified by Sánchez-Sánchez et al. (e.g.[24-27]) have demonstrated reporting bias, incomplete data reporting and lack of statistical power. Recently, it has been asserted that to evaluate HES, studies necessitate adequate sample size (>500 patients), control of fluids and length of follow-up (90-day).[4,5] There is a need for greater awareness amongst physicians of these biases to prevent the unwarranted and unnecessary use of HES products.[28]

In conclusion, the evidence presented by Sánchez-Sánchez and colleagues is insufficient to support the use of HES in burn injury. Given the current safety concerns associated with HES, the lack of data suggesting that HES may be beneficial for burn injury and limitations of the present study design, it is difficult to support the authors' findings that HES may be beneficial for fluid replacement in burn injury. In line with this, HES is not indicated for use in burn patients and guidance from the EMA suggests that HES products should no longer be used in patients with sepsis, burn injuries or in critically ill patients.

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