EDITORIAL

Where Has All the "HES" Gone: A Case in Point vs "Crusade" to Obscurity

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Volume resuscitation is one of the most common therapeutic interventions undertaken in intensive care units (ICUs).

Although crystalloids are being proposed as the go-to fluids for almost all conditions including sepsis, their use is not safe across all geographic areas and patient populations.[1] More so when higher doses of crystalloids are needed to be transfused we intensivists have no options but to choose between the devil (i.e., colloids) or the deep sea (i.e., risk of higher positive fluid balance). Colloid solutions, when compared with crystalloids, are associated with faster hemodynamic stability with less total volume, and thus a less-positive fluid balance, the latter has consistently been associated with improved clinical outcomes including the chimera of mortality benefit.[2] Synthetic colloids like hydroxyethyl starch (HES) when used are both cheaper than albumin and as well have longer shelf lives.

Regulatory agencies advice around the world have made it almost impossible to use HES solutions in critically ill patients.[3,4] Most of these recommendations are based on 6S and CHEST trials which have long been criticized for their faulty design (using starches late and in patients who were already volume resuscitated) and CHEST being a peculiar case, where many have asked for open access of data, unfortunately without success. The 6S trial had 800 patients with severe sepsis and high illness severity (control group mortality 43%) demonstrated increased 90-day mortality along with an increased need for renal replacement therapy, and increased requirement for blood products in the HES group.[5] The CHEST trial had 7,000 less sick (control group mortality 17%) ICU patients, did not show a difference in 90-day mortality but reported an increased need for renal replacement therapy, somewhat higher creatinine levels, and an increased need for blood products in the HES group.[6] The key question is whether these findings are sacrosanct enough to preclude short-term use of starch solutions, e.g., in the initial hemodynamic stabilization of acutely hypovolemic patients.

In this issue of IJCCM, the authors of the article, "Effect of fluid resuscitation with colloids on patient outcomes in Asian intensive care units", have taken a bold step by testing a dogma that has led to severe limitations concerning the option of fluids available to carry on volume resuscitation. In the case of colloids, the only choice left on ICU shelves now is albumin, which has a rather narrow usage spectrum and is economically damaging to patients if compared with HES, except may be in the USA.[7] This has far-reaching consequences in countries where health care is not state subject and at times choice of therapy gets guided by the cost of treatment. Authors have very eloquently tried to address the contentious issue of timing of colloid therapy, as an attempt to decipher inconsistencies in the outcome of previous studies about 90-day mortality and acute kidney injury (AKI). Their idea was to gather safety signals related to colloid and crystalloid treatment when used as a targeted volume therapy for initial hemodynamic instability, which is mostly performed on day 1 or day 2 in the ICU.

The authors have done exploratory analysis on retrospective registry data and hence the risk of clinician bias on the choice of therapy is taken out of the picture. While some of us will find it inconvenient to extrapolate finding based on a data set from a registry that dates back almost a decade (2011–2012), this can also be seen as a strength of the study, since it reflects fluid practices carried out in the era of 6S and CHEST trial, so are more likely to replicate the findings if they were universal as per these studies.

In contrast to popular belief, authors publish a subgroup analysis in patients receiving colloids early (day 1 or 2) or late during their ICU stay (day 3 or later), which concludes that timing of the first colloid is clearly associated with outcome and might affect possible benefit or harm of the specific drug. These results might be interpreted as support of the CRISTAL protocol and suggests, colloids might be beneficial for early resuscitation in individual patients.[8] CRISTAL was a large (2,857 patients with acute hypovolemia in intensive care) international, industry-independent trial found significantly lower 90-day mortality in the colloids group with more vasopressor-free and ventilator-free days by day 28. The study found no evidence that colloids increased the risk of AKI or any other serious adverse event.

In summary, harm from correcting acute hypovolemia with colloids including HES has not been clearly demonstrated. The evidence of benefit does exist for short-term effects on hemodynamics and fluid balance. Large-blinded randomized trials evaluating long-term outcomes concerning survival and morbidity, including kidney function are impossible to be carried out on HES given the adverse advisory from most regulators. The worst part is to trudge through the quagmire of less than unbiased scientific literature in search of a biblical answer regarding the choice of fluid for large volume resuscitations. Recent findings of the FLASH trial[9] again endorse far efficacious hemodynamic effects of HES

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in comparison with crystalloids just like previous CRISTAL and CRYSTMAS trials.[10] For now, we clinicians should consider fluids as IV drugs that are to be dosed with careful consideration of the possibility of toxicity in certain at-risk populations. While trying not to be the devil's advocate, it is prudent to look at scientific literature with a prism that is unbiased, so to have shelves donned with options that are safe and beneficial, beyond crystalloids and albumin.

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