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EDITORIAL

Hydroxyethyl starch for perioperative fluid management: a critical appraisal

Fluid therapy is an essential component of perioperative care, and fluids are powerful tools to maintain or restore the effective circulating blood volume of patients undergoing major surgery. In fact, perioperative fluid management affects clinical outcomes, and appropriate fluid balance may reduce postoperative morbidity.[1] However, the type, dose, and timing of fluid administration have been debated for many years, and evidence in the field is constantly emerging. Perhaps the foremost dispute on this topic is related to the type of fluid, with the choice between colloids versus crystalloids remaining the most controversial.

Hydroxyethyl starch (HES) solutions are artificial colloids used for volume replacement and are currently indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone are deemed insufficient.[2] HES solutions are classified by three numbers corresponding to concentration, molecular weight, and molar substitution.[2] These products have undergone numerous studies on their benefit-risk balance over many years. The first revision of the labeling was solicited by the Blood Products Advisory Committee, recommended by the Food and Drug Administration (FDA), and introduced in 2003 — as a warning statement — to underline how the use of 6% HES in patients with impaired coagulation and scheduled to undergo cardiopulmonary bypass could induce an increased risk of bleeding.[3]

Following a safety review in 2013, restrictions on the use of HES were introduced in the European Union (EU) due to an increased risk of kidney injury and death in certain populations. The product information was updated to include new contraindications and warnings. In 2017, a second safety review triggered by the European pharmacovigilance authorities was performed. These studies raised concerns regarding non-adherence to key restrictions in clinical practice, with significant use of HES in contraindicated populations. After several meetings and repeated evaluations, there was a vote for more rigorous monitoring of policy adherence. This included restricting the supply of HES solutions for infusion only to hospitals where healthcare professionals expected to prescribe or administer them have undergone mandatory training on the appropriate conditions of use and with the addition of more prominent warnings on the packaging of these solutions.

In February 2022, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that non-adherence to the product information persists despite the extensive additional risk minimization measures implemented in 2018. PRAC determined that HES solutions for infusion are still being used in contraindicated populations where there is an increased risk of serious harm, including mortality. They concluded that the risks outweigh the benefits of HES-containing products. As a result, the marketing of these products should be suspended, and therapeutic alternatives should be selected according to relevant clinical guidelines. On May 24, 2022, the European Commission ultimately issued a legal decision confirming the suspension of the marketing authorizations of HES solutions for infusion.[4] It is worth noting that in 2021, the FDA also imposed further restrictions on HES-containing solutions, requiring additional warnings about the risk of death, bleeding, and acute kidney injury (AKI).[5] The Brazilian Health Regulatory Agency (Anvisa) issued a warning in 2018 as well, urging health professionals to be aware of the risks associated with the use of HES infusion solutions, particularly in patients with sepsis, renal failure, or critically ill patients.[6]

Since HES products impair platelet reactivity and decrease circulating plasma concentrations of coagulation factor VIII and von Willebrand factor, HES administration results in the weakening of clot formation and may lead to increased transfusions of blood products.[7] Although HES products with low molar substitution may have a lesser effect on hemostasis, a somewhat recent systematic review in critically ill patients demonstrated a higher incidence of transfusion in those receiving starch solutions compared to those receiving crystalloids.[8]

Three major intensive care unit (ICU) clinical trials have suggested that using HES negatively impacts mortality and kidney function in critically ill patients, particularly those with severe sepsis or septic shock.[9-11] A 2018 systematic

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review observed a higher incidence of renal replacement therapy in those receiving HES solutions compared to those receiving crystalloids.[12] Furthermore, a 2010 systematic review in mixed surgical and nonsurgical patient populations found an overall increased risk of kidney failure in patients receiving HES solutions compared to those receiving various other types of fluid therapy.[13] In cardiac surgery patients, a meta-analysis of randomized trials has shown that the administration of HES solutions increases the risk of postoperative bleeding, reoperation for bleeding, and blood product transfusion after cardiopulmonary bypass compared to albumin. Notably, the authors did not observe any evidence that these risks could be mitigated by lower molecular weight and substitution.[14]

Although there is a physiologic rationale for using colloids for volume therapy (as they remain longer in the intravascular compartment), and plenty of experimental studies have shown that resuscitation with colloid solutions is faster compared to crystalloid solutions,[1] most clinical trials and systematic reviews have not demonstrated any benefit in relevant outcomes.[15,16] It is a fact that the debate on the better fluid type continues, and there are still unresolved questions regarding colloids in perioperative management. However, the lack of significant and consistent benefits in clinical outcomes and the potential for harm make it difficult to justify the use of HES in clinical practice. In this context, the findings of two ongoing surgical trials on 6% HES 130/0.4 (PHOENICS and TETHYS studies)[17,18] are urgently needed to add evidence to this controversial discussion.

In light of the available evidence, it is our responsibility as physicians to treat patients with interventions that provide more benefits than risks. Although there is still room for more scientific evidence, it seems clear that additional restrictions on the use of HES-containing solutions are needed. Considering that many professionals are not fully aware of the risks associated with HES and continue to use those solutions despite international health agencies' warnings, it is time for a worldwide suspension of the marketing authorizations of HES-containing solutions until further evidence of their safety and efficacy emerges from new clinical studies.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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