

## Review Article

# Could Molecular Studies Save Hydroxyethyl Starch from Total Disappearance

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## Abstract

Hydroxyethyl starch (HES) solutions have mainly been indicated as "volume expanders". Recent unfavorable reports of these solutions such as probability of kidney injury or inducing coagulopathy have relatively ejected these solutions in many centers, particularly in European countries. Despite several confirming studies, multiple anecdotal letters or reviews has challenged total disappearance of these colloids from medicine practice. In addition, some novel observations emphasized to distinguished ability of HES to preserve the microvascular integrity even at the presence of an inflammatory process. Despite extreme statements has been published demanding immediate suspension of these fluids from the market, it seems logical to revise the most recent studies which may declare new pathways to approach HES family of solutions.

**Keywords:** Colloid; Hydroxyethyl starch; fluid resuscitation; HES; Glycocalyx

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## Introduction

Hydroxyethyl starch (HES) solutions were introduced 8 decades ago, rapidly gained popularity in critical situations such as intensive care units or veterinary hospitals. They have become one of the pillars of fluid resuscitation, primarily in emergency hypovolemic situations. Since 2013 different communities have been exclaiming recommendations to suspend marketing of HES solutions (1-3). In less than ten years, HES usage has dropped crucially and this modification tends to be center-located which can be indicative of localized decision-making. Whether this downfall is logical or not, an overview of ideas around the subject is valuable to know where we are standing today.

### Renal Effects

During the last decade, an escalating obsession

on HES-induced renal injury has arisen, especially within critical conventions (4-7). In the largest meta-analysis by Cochrane Database including 142 studies and 11,399 patients of different populations, all HES products were blamed to increase the risk of acute kidney injury and renal replacement therapy (RRT). In addition it was concluded that no safe volume of any HES solution has been approved till the publication time in 2013 (8). This was the beginning for many other clinical trials searching for declaration of the truth. Five years later, in another reported by Cochrane (9), starches were compared to other fluids in resuscitation of critically ill patients. This time, slight increase in RRT rate was described, while, no difference to mortality was observed.

Even so, anecdotal advices do not endorse such intense disapproval of HES. The most significant protest to withdrawal of all colloids from medicine

practice are published in the Lancet (10) and Anesthesia-Analgesia (11) journals just recently. In addition, recent studies on animal or non-septic human observed no kidney injury following HES administration (12, 13). Related to the present data, it seems practical to choose these types of fluids cautiously in critically ill patients or the ones at higher risk for kidney injury (11). However, it would be unwise to retire them entirely while present evidences are controversial.

### Coagulopathy

*Li et al.* reported decrease in platelet count in pediatric intensive care unit (ICU) patients. Although, in this meta-analysis, activated partial thromboplastin time or blood loss showed no significant difference within the given setting (14). Same results were reported by others as changes in clot structure (15), increased thrombin-antithrombin complex levels (16), or facilitation of clot initiation (17). Despite all, in a human randomized clinical trial (RCT) study on patients undergoing craniotomy for tumor resection, 20 cc.kg<sup>-1</sup> of HES 130/0.4 did not change thromboelstographic findings compared to 5% human albumin (18). Other study described the same results (19). Controversial observation on coagulation effects of HES solutions indicates the urge for further specified studies.

### Extracellular leakage

Different organs profit from perioperative HES administration. Ghodratty and colleagues reported improvement of intestinal motility and shortened duration of ileus after gastrointestinal operations in patients who received 6% hydroxyethyl starch to replace intraoperative fluid losses (20). Significant decrease in anastomotic leakage was observed following abdominal major surgery when colloids were given intraoperatively (21, 22), confirming previous beneficial findings.

One of the most interesting studies on HES mechanism of action has manifested protective effects on vascular glycocalyx integrity (23). In this 2018 interventional trial on animal model of inflammation, vascular permeability of the lungs, liver, kidney, and brain was measured by Evans blue extravasation. Both types of systemic and inhalational inflammation were induced which resulted in increased vascular

permeability in mentioned organs. 6% HES 130/0.4 infusion led to significantly preserved glycocalyx thickness in lung capillaries. This is the most precisely-explained subcellular mechanism for HES intravascular end results.

Through the last two decades, the role of glycocalyx in vascular functioning has been determined. The endothelial glycocalyx is a carbohydrate-rich layer connected to the endothelium of vessels via several types of proteoglycans. On its luminal site, it is consisted of plasma elements bonded via soluble glycosaminoglycans. This living layer interacts with the blood actively. The blood flow itself, constantly alters the composition and the thickness of the glycocalyx layer (24, 25).

This bidirectional process is a dynamic equilibrium dictating the ability of endothelium as a "gatekeeper" (26). The permeability of glycocalyx is directly affected by the changes in the flow, turbulence or the composition of the blood. In hemorrhagic animal models, increased permeability of the endothelium due to glycocalyx shedding is reported. Resuscitation with different fluids has shown to have variable impacts. While normal saline resuscitation has the worst results (reduced glycocalyx thickness and increase in microvascular permeability), HES and albumin somehow preserved the endothelial stabilization (27). Although, HES and albumin control the extravasation of fluids via distinct mechanisms.(28) Further subcellular studies are in immediate need to answer our many substantial questions.

## Discussion

Our knowledge about HES utilization in perioperative medicine is not complete yet. One of the main considered fields in fluid management inside and or outside the operating theater is to keep the infused fluid "inside" the circulatory system. Colloids, and in particular HES solutions, appear to be superior in some conditions. As scientists and academicians, we are obliged to ask questions about specific situations that each drug behave in our favor. Early, aggressive decisions may deprive us from beneficial products for years until resurrection of them by an unbiased physician, as happened before for many other medications. Reporting bias is described in the form of retraction of studies could be considered as one of

many reasons to question the available results (29).

In some perioperative fields the principal focus has been on the probable side effects rather than advantages. For instance, in neurosurgical patients several studies assessed the plausible coagulopathy or renal dysfunction (13, 18), while scarcely any has reviewed their impacts on permeability of blood brain barrier despite reported benefits as osmotic agents in treatment of increased intracranial pressure (30). In summation HES might be beneficial in situations where increased vascular permeability and the increased transcapillary leakage of plasma fluid accompanies hypovolemia, and interstitial edema formation as observed in the mentioned 2018 study (23). This field is also quite appealing for researchers in the perioperative field.

In addition, several studies detected different profile based on starches' molecular weights (31, 32), which can be defined in the importance emphasis of selection of patient or fluid. For instance, during acute normovolemic hemodilution, high-molecular-weight HES (650/0.42) disturbed hemostasis more than low-molecular-weight HES (130/0.42). Besides, HES 650/0.42 was reported to restore plasma volume less efficiently (33). Differentiation between the types of HES solutions may be the key to overcome the unwanted presentations and generating a smarter remedy.

## Conclusion

We should justify the hazards of HES in septic patients or others in the risk of nephrotoxicity. Nevertheless, examining these fluids in situations which they are put in application anecdotally is yet incomplete. It is rational to be open to further molecular studies to find the relevant mechanisms for these solutions to make them profitable while subtracting unwanted adverse effects.

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## Conflicts of Interest

The authors declare that there are no conflicts of interest.

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