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Perspective

Clinical use of hydroxyethyl starch and serious adverse effects: Need for awareness amongst the medical fraternity

Hydroxyethyl starch (HES) was developed between 1944 and 1962. Since then, HES has been used to treat or even prevent hypovolemia in thousands of patients. Contrary to the existing scenario, drugs or fluids developed before the eighties were simply registered without mandatory clinical trials. The legislation was changed only in the wake of the thalidomide tragedy, leading to the regulatory requirement of phase 1–3 clinical trials to demonstrate efficacy and safety prior to the approval of new drugs. HES, however, was never properly evaluated for the long term mortality and morbidity before it became available in the market.

HES is a non-ionic starch derivative used most frequently as a volume expander under various trade names. HES is a broad category and can be sub-classified according to average molecular weight (i.e. 130–200 kDa), molar substitution (i.e. proportion of glucose units replaced by HES units), concentration (grams/dl), and maximum daily dosage.¹ Elimination of HES from the body depends essentially on the degree of molar substitution. Molecules smaller than the renal threshold (60–70 kDa) are excreted in urine. Larger molecules are metabolized by α -amylase before degradation products are excreted by the kidneys. However, it is important to note that HES is only partially degraded and excreted from the body. The precise mechanism of HES metabolism is still unclear. Approximately one-third to two-thirds of HES administered cannot be accounted for in the 24-h urinary excretion. Only 50% of the administered dose was found to be excreted over 72 h by one study. Studies have reported HES accumulation in plasma and several other tissues with worrisome persistence for prolonged periods running into several years.²

HES has evolved to become the most commonly used colloid in intensive care unit (ICU) patients. In recent years, there has been a constant increase in the use of HES perioperatively. HES solutions have gained popularity because of its efficacy as volume expanders in treating hypovolemic patients when compared with crystalloids.³

This view point aims to emphasize some of the safety issues and concerns regarding routine usage of HES products. The unfavorable interaction of HES molecule with the coagulation pathways with resultant impaired blood clotting has

always been a matter of concern. In addition, recent studies have revealed possibility of high risk of acute kidney injury and increasing mortality when HES was used in certain groups of patients. The etiopathogenesis of such adverse effects is probably due to deposition of HES products in various tissues instead of remaining in the circulation.⁴

Worldwide evidence in support of the serious adverse effects of HES is elaborated by the extensive research carried out in this field. The existence of adverse effects of HES products was partly neutralized by relatively favorable reports in studies done by Dr Joachim Boldt and colleagues. However, many such studies were allegedly involved in scientific misconduct and this has complicated the issue further in the assessment of clinical outcomes worldwide. Appropriately, taking cognizance of such issues, a recent (2013) meta-analysis published in JAMA, seven such tainted studies were excluded. The results of this meta-analysis confirmed association of HES products with an increased risk of mortality and AKI.⁵

Several other important studies have also established the association of HES with serious adverse effects. In 2012, United States Food and Drug Administration (US FDA) collaborated with various organizations to elaborate on the risks and benefits of HES products. Research data from several studies was analyzed which showed increased mortality and severe renal injury, when HES was used in critically ill patients, including patients with septicemia. In a study on patients undergoing cardiopulmonary bypass, use of HES products was associated with increased bleeding.⁶

A large study (6 S study) was conducted comparing 6% HES with Ringer's acetate for management of hypovolemia in patients with septicemia. The study confirmed the toxicity of HES, manifesting as mortality and severe renal injury.⁷ Another similar study, (Crystalloid versus Hydroxyethyl Starch Trial (CHEST)) compared 6% HES with 0.9% saline in adult ICU patients including patients with septicemia. Patients receiving HES showed signs of severe renal injury.⁸ A meta-analysis of 34 Randomized Controlled Trials using various HES products for the therapy of hypovolemia found a significant increase in severe renal injury in HES-treated septicemic patients.⁵

After a review of the available evidences, on June 14, 2013, the Pharmaco-vigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded that the benefits of HES solutions no longer outweighed their risks and recommended that these fluids be withdrawn. On June 24, 2013, the US FDA recommended that HES products should not be used in critically ill patients or in those with pre-existing renal dysfunction.⁶

The possible mechanisms for acute renal injury and deranged coagulation (both of which can cause mortality) can be explained as follows: several in vitro studies have shown that HES solutions reduce human proximal tubular cell viability which may precipitate renal injury. But the precise mechanism for this toxicity remains unknown. It is established that HES products can alter coagulation by adversely affecting von Willebrand factor and platelet aggregation. Clot formation is also adversely affected.⁹

The glycocalyx covering normal vascular endothelium plays an important role in maintaining endothelial barrier properties. An endothelial surface layer is formed by the glycocalyx along with plasma proteins and bound fluids. The glycocalyx contains various anticoagulant proteins like anti-thrombin, protein C components, and tissue factor pathway inhibitors. Glycocalyx is important for nitric oxide release in endothelial cells. It also modulates immune response by preventing adhesion of leucocytes and platelets to the endothelial cells. Glycocalyx damage results in extravasation of proteins and tissue edema and alters all the physiological mechanisms described earlier. HES molecules have surface negative charges which repel them from the glycocalyx, which also is negatively charged. The end result is that they cannot contribute to endothelial integrity by a mechanism by which albumin maintains endothelial integrity by a relatively favorable distribution of positive and negative surface charges. It has also been postulated that, there is a reduction in factor VIII levels and prolonged aPTT after HES product administration, all of which contribute collectively in causing deranged coagulation parameters in the patients.¹⁰

Over the years, HES products have appeared in several resuscitation guidelines and have often been advocated as the cornerstone of resuscitation therapy. However, these recommendations are being now reconsidered by regulatory authorities in the light of recent trials, meta-analysis and systematic reviews, which have strongly associated HES in causing mortality due to AKI and/or deranged coagulation. In view of the above, clinical use of HES products for acute volume resuscitation is not warranted anymore due to serious safety concerns.

The issue of HES is loaded with fraudulent studies conducted by German anesthesiologist Dr. Joachim Boldt and colleagues. These studies may have encouraged the use of HES for hypovolemic patients that now appear to do more harm than good. Most of the articles published from 2012 till date highlight the harmful effects of HES and recommend a ban on its use. It's impossible to gauge how many patients suffered adverse effects of HES by Boldt's fabricated research.

My personal experience along with experience of some of my fellow clinicians indicates that several of our patients exhibited signs of unexpected DIC and renal failure when administered with HES. Some of the adverse effects were fatal too. However when discussed in clinical forums or otherwise,

most of our colleagues from various disciplines did not believe that HES could be harmful, quoting their personal experiences limited to probably a hundred cases at the best. Their perception about use of HES prompted me to write this perspective to create awareness amongst the medical fraternity about serious complications attributed to HES.

At this juncture, I would like to bring to the attention of present day clinicians the results of several high powered randomized control trials involving thousands of cases, highlighting unacceptable toxicity of HES. All these studies are available on the internet; just type HES and Google it or go through PubMed and you will find enough articles from reputed journals to change the view point. To keep it simple, we need not wait for someone to die to change our view point.

REFERENCES

1. Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H. Hydroxyethyl starches: different products-different effects. *Anesthesiology*. 2009;111:187–202.
2. Jungheinrich C, Neff TA. Pharmacokinetics of hydroxyethyl starch. *Clin Pharm*. 2005;44:681–699.
3. Feldheiser A, Pavlova V, Bonomo T, et al. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. *Br J Anaesth*. 2013;110:231–240.
4. Sirtl C, Laubenthal H, Zumtobel V, Kraft D, Jurecka W. Tissue deposits of hydroxyethyl starch (HES): dose dependent and time-related. *Br J Anaesth*. 1999;82:510–515.
5. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. *JAMA*. 2013;309:678–688.
6. Food and Drug Administration. FDA Safety Communication: Boxed Warning on Increased Mortality and Severe Renal Injury, and Additional Warning on Risk of Bleeding, for Use of Hydroxyethyl Starch Solutions in Some Settings. 2013.
7. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.4 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367:124–134.
8. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–1911.
9. Neuhaus W, Schick MA, Bruno RR, et al. The effects of colloid solutions on renal proximal tubular cells in vitro. *Anesth Analg*. 2012;114:371–374.
10. Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, oude Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. *Pflugers Arch*. 2007;454:345–359.

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