Original Research Article

A Questionnaire based study on practice and safety concerns of hydroxyethyl starch as fluid management among Critical Care Physicians, Gynecologists and Surgeons in India

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Received: 12-01-2021 / Revised: 20-02-2021 / Accepted: 10-03-2021

Abstract

Introduction: Use of natural and synthetic colloid solutions to replenish intravascular volume depletion is common in diverse clinical settings. Hydroxyethyl starches (HES) are a common choice for fluid resuscitation and are preferred over albumin because of their relatively lower price However its association with increased risk of bleeding, renal dysfunction and mortality in patients who had sepsis or were critically ill compared with crystalloids usage posed concern. In 2013, the FDA issued a "black box" warning about increased mortality and severe renal injury in critically ill patients, advising that it should not be used in this population. The present study highlights the issue and probes on its current usage in India. **Objective:** To assess the usage pattern and adverse events of synthetic colloids such as hydroxyethyl starch in fluid management through a questionnaire survey among critical care physicians, gynecologists and surgeons. **Methodology:** A questionnaire based study was conducted among 156 critical care physicians, gynecologists and surgeonspan-India, where physicians were approached through emails and a pre-designed, pre-tested questionnaire presented in Google form was sent to potential respondents. Data was checked for completeness and then analyzed by appropriate statistical methods as applicable. **Results:** Majority of the respondents were noted usingHES despite its adverse potential, due to its availability at government hospitals. Surprisingly a few of the interviewed surgeons use HES as a volume expander. Similar results were obtained from the interviewed gynecologists and obstetricians. Among 52 interviewed gynecologists, only 2% use HES as volume expander. **Conclusion:** Considering the adverse potential of this synthetic colloid and justifying the risk and benefit analysis one has to be very wise in selecting the right synthetic colloid for the right patient. However with current concerns about safety of hydroxyethyl starch products, almost all interviewed physicians recommended regulatory restriction over their use in India.

Keywords: Hetastarch, Synthetic Colloids, regulatory restriction.

Introduction

Use of natural and synthetic colloid solutions to replenish intravascular volume depletion is common in diverse clinical settings. Fluid resuscitation is indicated for the management of hypovolemia (decreased blood plasma volume) and hypovolemia shock [1], and its ultimate objective is to restore organ perfusion and tissue oxygenation [2]. Hypovolemia can be induced by a wide range of clinical conditions such as dehydration, burns, sepsis, malignancies, trauma, hemorrhage, and surgical anesthesia.There are two main types of fluids used for fluid resuscitation, colloids and crystalloids. Crystalloid solutions include normal saline and balanced fluids such as Ringer's lactate [3].Human albumin; a natural colloid is generally considered safe but is expensive. Synthetic colloids like dextran, gelatin and hydroxyethyl starches (HES) are cheaper but have safety concerns. The inherent risks of synthetic colloids are well known – namely, renal failure, coagulopathy, anaphylactoid reactions, reticuloendothelial dysfunction, hepatic dysfunction, severe pruritus, etc. However, different synthetic colloids vary greatly in their physicochemical properties, and therefore in the benefit-risk ratio. Gelatin, derived from bovine collagen, is small molecules (approximately 35 kDa) and are more rapidly broken down and eliminated. Dextran, a polysaccharide mixture derived from bacterial source, used in solutions of either 40- or 70-kDa molecules, have a high water-binding capacity and are effective for reducing blood viscosity. Hydroxyethyl starches are a common choice for fluid resuscitation [4]. They are preferred over albumin

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because of their relatively lower price [5]. These starches are supplied with different molecular weights ranging from 120 kDa to >450kDa. Based on MW there are three categories of HESs:

- high MW (450 kDa) (for example, Hespan®)
- medium MW (200 to 260 kDa) (for example, HemoHES® and Pentaspan®)
- low MW (70 to 130 kDa) (for example, Voluven®)

The low MW HES solutions have a shorter half-life in vivo because they are more quickly broken down by serum amylase to 50-kDa molecules that can be excreted in the urine. To slow metabolism by amylase, HES molecules have hydroxyethyl radical groups substituted onto individual glucose units. The degree of hydroxyethyl substitution is expressed by the molar substitution ratio (ratio of the number of substituted glucose molecules to the total number of glucose molecules.). Highly substituted HES solutions have a ratio of 0.6 to 0.7 and are metabolized slowly. Less substituted HES solutions have a ratio of 0.4 to 0.5 and are metabolized quickly. Finally, the point of attachment of the hydroxyethyl group is also important. Hydroxyethyl groups attached at the C2 position on the glucose ring slow metabolism more than those attached at the C6 or C3 position. Thus, a high C2/C6 ratio (>8) slows metabolism more than a low C2/C6 ratio (<8). It is believed that the molecular weight and degree of substitution can affect patient outcomes [6].The present status of synthetic colloids in fluid management appears to have been vulnerable following a plethora of safety concerns. In view of this it was thought worthwhile to take stock of the current scenario of usage of such products in India through a questionnaire study where in expert doctors in relevant medical superspeciality were be approached for their opinions. The present study aimed to assess the usage pattern and adverse events of synthetic colloids such as hydroxyethyl starch in fluid management through a questionnaire survey among critical care physicians, gynecologists and surgeons.

Methodology

A questionnaire based study was conducted among physicians pan-India, where physicians were approached through emails and a pre-designed, pre-tested questionnaire presented in Google form was sent to potential respondents. A convenient sample size of 150 comprising of critical care physicians, gynecologists and surgeons in West Bengal and other states in India (at least 50 in each category) was estimated.The study was conducted over a period of 6 months, commencing from 01.10.2019 to 01.04.2020 after obtaining the approval from the Institutional Ethics Committee. The questionnaire was circulated to over 230 physicians of various domains like critical care, surgery, gynecology and obstetrics, of which 156 physicians responded back. Confidentiality of the respondents was ensured. The questionnaire assessed the usage pattern and adverse events of synthetic colloids such as hydroxyethyl starch in fluid management. Data was checked for completeness and then analyzed by appropriate statistical methods as applicable.

Results

The questionnaire was responded by 156 physicians of various fields like critical care, surgery and gynecology. The order of preference with regard to colloid usage was observed to be dextran (42%), HES (28%), albumin (22%) and Haemacel (8%) respectively as depicted in fig.1. The various common conditions which necessitate the use of volume expanders include hypovolemic shock, burn patients, septic shock, and road traffic accidents, while other causes like dengue shock syndrome, hypovolemic shock prompted the use of volume expanders among various intervened physicians (Table 1). Among the interviewed critical care physicians it was noted that about 80% of them have been using HES despite its adverse potential, due to its availability at government hospitals. Surprisingly a few (2%) of the interviewed surgeons use HES as a volume expander. Similar results were obtained from the interviewed Gynecologists. Among 52interviewed gynecologists, only 2% use Hetastarch as volume expander.

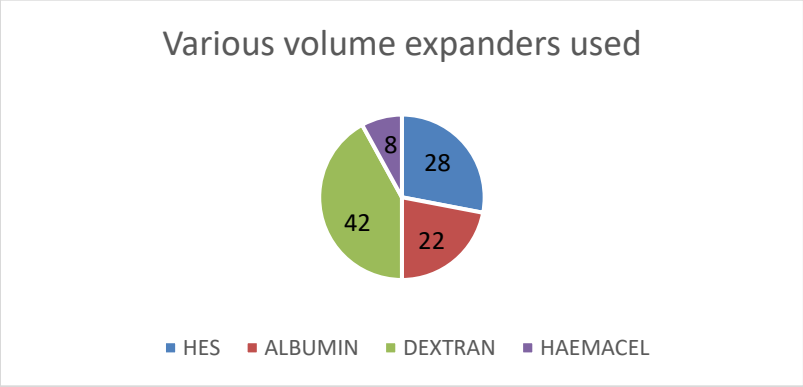

Fig 1: Percentage usage pattern of various volume expanders

Table 1: Distribution pattern of different indication for volume expanders

Indications	No. of Patients (%)
Hypovolemic shock	67(43)
Burn	34(22)
RTA	31(20)
Septic shock	11(7)
Dengue hemorrhagic shock	8(5)
Hypovolemic shock post spinal anesthesia	5(3)

According to this questionnaire based survey the use of hydroxyethyl starch was associated with increased risk of mortality (30%) and renal dysfunction (25%) when used for fluid resuscitation in critically ill patients and patients with severe sepsis. It was also noted that the use of hydroxyethyl starch in patients undergoing surgery may be associated with increased risk of bleeding (18%) and reoperation due to bleeding.

Table 2: Outcome with HES according to the questionnaire based survey

Outcome parameter	Percentage (%)
Renal dysfunction	25%
Bleeding disorder	18%
Anaphylactoid reaction	14%
Pruritus	13%
Mortality	30%

Discussion

Concerns regarding serious side effects of HES began to emerge in the 1970s, soon after its first licensing. [6] Data submitted to the US Food and Drug Authority for licensing purpose in 1972 was majorly based on inadequate data from pivotal clinical trials which were uncontrolled, short term studies with inadequate observation periods. However the concerns grew exponentially after results surfacing from recent randomized controlled trials conducted between 2008 and 2012, suggesting its association with increased risk of bleeding, renal dysfunction and mortality in patients who had sepsis or were critically ill compared with crystalloids usage. The first trial showed significantly increased rates of acute renal failure and need for renal replacement therapy, increased use of blood products, and a higher 90 day mortality in patients with sepsis resuscitated with HES compared with other fluids like crystalloids, albumin, and gelatin. The other two found that modern tetrastarch, which was thought less toxic than earlier HES formulations, was nephrotoxic and increased the need for blood transfusion. Not restricted to a single manufacturer, molecular weight, or molar substitution of HES, it seemed a class effect of starches [7]. A subsequent meta-analysis published in JAMA reinforced these findings and increased their generalisability. In 2013, after these three large trials showed harms, the FDA issued a "black box" warning about increased mortality and severe renal injury in critically ill patients, advising that it should not be used in this population. At about the same time, an EMA Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the evidence and recommended suspension of all marketing authorisations for HES. However, after requests from manufacturers the decision was reviewed which permitted ongoing HES use under limited circumstances [7].Nevertheless, HES usage has been associated with significant concerns. Though the mechanisms of HES toxicity are not clear, the rapid accumulation of HES in tissues and macrophages can play a role. HES administration is associated with reduction in circulating factor VIII and von Willebrand factor levels, impairment of platelet function, prolongation of partial thromboplastin time and activated partial thromboplastin time and thus increases bleeding complications.High molecular weight (HMW) HES are associated with greater degree of accumulation in interstitial spaces and reticulo-endothelial system [8]. It gets deposited in various tissues including skin, liver, muscle, spleen, intestine, trophoblast and placental stroma. Such depositions have been associated with pruritus. The pruritus arises from long-term cutaneous storage of HES molecules, and it may last for months after exposure. The incidence appears to be resistant to treatment with glucocorticoids, antihistamines, acetaminophen, and neuroleptic drugs. Though rare, HES is associated with higher incidence of anaphylactoid reactions as compared to other synthetic colloids as well as albumin.HMW HES has been also found to be associated with increased creatinine levels, oliguria, acute renal failure in patients who were critically ill with existing renal impairment. HES induces tubular swelling and osmotic necrosis due to cytoplasmic vacuole formation which is believed to cause renal toxicity. HES infusion is an occasional elevation of the serum amylase levels, though no clinical implications ensues [9, 10]. Recent studies however postulates that third-generation products due to their lower tendency of tissue accumulation, may have better renal profile as compared to other congeners. Extra caution should be exercised while treating high-risk groups like children, elderly, pregnant mothers and those with renal impairment. Due to a higher incidence of comorbidities and changes in lung, kidney and cardiovascular function, the elderly are at increased risk for impairment of renal function. The waxy maize-derived tetrastarch HES has shown a safer profile in this regard [11]. Fluid therapy may have beneficial effects on microcirculation and tissue oxygenation, as hypovolaemia initiates a cascade of pathophysiological processes, such as stimulation of the sympatho-adrenergic and renin angiotensin systems that may result in inadequate tissue perfusion and decreased oxygen supply to the tissues. Tetrastarch has been found to produce a greater and earlier increase of tissue oxygen tension as compared to its pentastarch alternatives. Hypotheses suggest that HES with lower MS may decrease erythrocyte aggregation, thereby reducing low-shear viscosity of the blood. However, more studies are needed to infer upon the same [12].In this present questionnaire based study, which analyzed responses from potential respondents comprising of all critical care physicians, gynecologists and surgeons in West Bengal and other states of India, it was found that majority of the physicians ill-favored HES owing to absence of robust evidence of superiority over other colloids coupled with its increased cost and enhanced risk of side effects. In a resource constraint setting and considering the economic background of the majority healthcare seekers many a time the treating physician has to carry out his treatment based on the drugs available in the hospital inventory. The use of hydroxyethyl starches was shown to be associated with increased risk of mortality and need for renal replacement therapy when used for fluid resuscitation of patients with severe sepsis and critically ill patients. The use of hydroxyethyl starch in patients undergoing surgery was associated with increased risk of bleeding and reoperation due to bleeding.However with current concerns about safety of hydroxyethyl starch products, almost all interviewed physicians recommended regulatory restriction over their use in India.

Limitations: Data from this questionnaire based study in a convenience sample of specific physician was not generalizable thus prospective multicentric studies involving larger sample size is required to establish the study finding. Secondly, possibility of participant's subjective bias would affect the outcome parameters.

Conclusion

Considering the adverse potential of this synthetic colloid and justifying the risk and benefit analysis one has to be very wise in selecting the right synthetic colloid for the right patient. Therefore, conclusions should be made on the safety of starches rather than effectiveness.

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Conflict of Interest: Nil
Source of support:Nil