Review Article

Hydroxyeyhyl starch: Controversies revisited

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Abstract

Hydroxyethyl starch (HES) family has been one of the cornerstones in fluid management for over four decades. Recent evidence from clinical studies and meta-analyses has raised few concerns about the safety of these fluids, especially in certain subpopulations of patients. High-quality clinical trials and meta-analyses have emphasized nephrotoxic effects, increased risk of bleeding, and a trend toward higher mortality in these patients after the use of HES solutions. Scientific evidence was derived from international guidelines, aggregated research literature, and opinion-based evidence was obtained from surveys and other activities (e.g., internet postings). On critical analysis of the current data available, it can be summarized that further large scale trials are still indicated before HES can be discarded.

Key words: Controversies, hydroxyethyl starch, colloids

Introduction

Hydroxyethyl starch (HES) comprises of a family of semi-synthetic, polydisperse colloid solutions made up of large ethylated, polymerized amylopectin molecules [Figure 1]. The HES-family differ widely in their physicochemical and pharmacokinetic properties, composition, and adverse effect profiles [Table 1, Figure 2].[1-3] HES solutions with average molecular weight (MW) of 70-130 kDa are classified as low MW (LMW HES), those with 200 kDa as medium MW (MMW HES) and those with a molecular weight >450 kDa as high MW (HMW HES) [Table 2].

The first-generation HES was introduced in the early 1970s as a replacement for human albumin [Figure 3]. The prolonged intravascular persistence along with restoration of cell-mediated and macrophage functions theorized that the solutions would have efficient hemodynamic stabilization in shock.[4,5]

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Subsequent studies reported mixed evidence of benefits and significant adverse effects. Introduction of rapidly degradable HES solutions added new controversies. Fuelling the controversies was the retraction (due to grounds of ethical and scientific misconduct) of studies reporting benefits of HES.[6] Recently, the European Medicines Agency (EMA) has recommended that HES be suspended in the European Union (EU).[7] The United States Food and Drug Administration (US FDA) also issued a warning on increased mortality, severe renal injury, and risk of bleeding, for use of HES solutions in some settings.[8]

Scientific evidence was derived from international guidelines, aggregated research literature, and opinion-based evidence was obtained from surveys and other activities (e.g., internet postings). In view of these controversies there is a need to revisit the use of HES.

Controversies

HES was introduced in the market without large phase III trials to evaluate the efficacy and safety. Reports of deterioration in renal functions in patients who had undergone renal transplantation as well as in critically ill patients soon started emerging.[9-13]

Some studies did not detect adverse effects even with large doses of starch solutions except for impaired coagulation; however, these were limited by their design, small size, and short observation periods.[14-16] The ability of HES to interfere with coagulation had already prompted warning labels and

dose limitations.[17,18] Further, long-term tissue storage of the colloid was labeled potentially toxic, considered responsible for the observed increase in mortality at 90 days, particularly with higher and cumulative doses.[19-21]

A multicentric study, the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) compared Ringer's lactate with 10% HES 200/0.5 for volume replacement therapy in 537 patients with severe sepsis. The authors concluded that colloids, led to an increased incidence of renal failure with a non-significant but definite, trend toward higher 90-day mortality.[22]

The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial compared Ringer's acetate to 6% HES 130/0.42 for fluid resuscitation in 800 septic patients. The authors also reported an increased incidence of renal replacement therapy (RRT) after HES and a significantly higher 90-day-mortality.[23]

The HES or Saline for Fluid Resuscitation in Intensive Care (CHEST) trial randomized 7000 patients, at mean 11 h after intensive care unit (ICU) admission, to receive saline or 6% HES 130/0.4 for fluid resuscitation. The authors found no differences in mortality or renal function according to the RIFLE criteria, but an increased incidence of RRT after HES infusion in the non-adjusted analyses.[24]

The Surviving Sepsis Campaign, 2012 Guidelines, which is a collaboration between the US Society of Critical Care

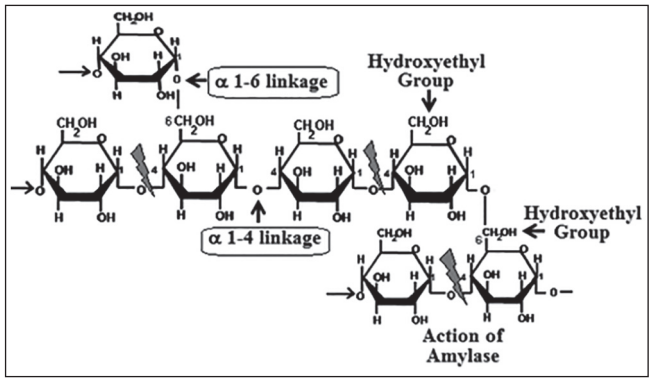

Figure 1: Hydroxyethyl starch molecule

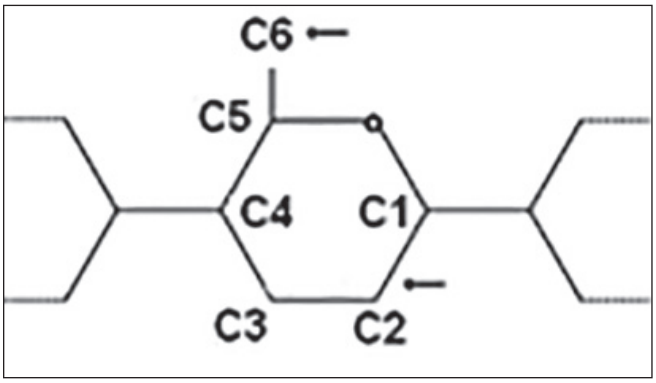

Figure 2: Carbon positions in hydroxyethyl starch molecule

Table 1: Physiochemical properties of the HES family

Property	Available Choices	Clinical Effects
Concentration	6% or 10%	Determines the initial volume effect 6% is iso-oncotic with a volume effect of 100% 10% is hyper-oncotic with a volume effect 145%
Average molecular weight	Low (~70 kDa), medium (200 kDa) or high (~450 kDa)	Determines the intravascular persistence, the duration and extent of tissue storage, side effects such as itching, anaphylaxis, effect on blood coagulation, especially on factor VIII and von Willebrand factor and renal functions
Molar substitution	Low (0.45-0.58) or high (0.62-0.70)	Determines the water solubility and molecular weight
C2/C6 ratio		Determines the rates of HES degradation by serum α-amylase High C2/C6 ratios of >8 are more slowly degraded
Solvents used	Normal saline and ringer solution	Balanced HES preparation has overall less negative effects on hemostasis and platelet aggregation than the saline preparation
Source of starch	Potato-derived and waxy maize-derived	Potato-derived HES exhibits a faster clearance from the circulation as it has a lower average degree of branching and a higher degree of esterification with phosphoric acid

HES = Hydroxyethyl starch

Table 2: Classification of HES by molar substitution

Molar substitution	Classification	Description	Trade names
0.7	Hetastarch	High molecular weight HES	Hespan, Plasmasteril, Hexend (Balanced)
0.6	Hexastarch	High-medium molecular weight HES	Elohes
0.5	Pentasrarch	Medium molecular weight HES	HAES-Steril, Pentaspan, Hemohes
0.4	Tetrastarch	Low molecular weight HES	Voluven, Venofundin, Tetraspan (Balanced), Volulyte (Balanced), Plasma Volume Readybag (Balanced)

HES = Hydroxyethyl starch

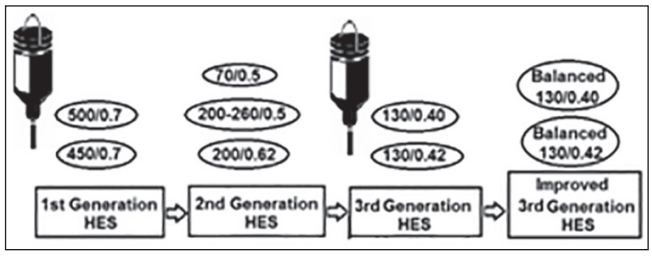

Figure 3: Generations of hydroxyethyl starch

Medicine, the European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum recommended not using HES >200 kDa MW as resuscitative agents (Grade 1B). They did not comment on the use of lower MW HES or gelatins as these were yet to be evaluated.[25]

The consensus statement of the ESICM Task Force on Colloid Volume Therapy in critically ill patients (2012) recommended not to use HES with ≥200 kDa MW and/or degree of substitution >0.4 in patients with severe sepsis or risk of acute kidney injury (AKI) and suggested not to use 6% HES 130/0.4 or gelatin in these populations. They recommended not using colloids in patients with head injury and in organ donors. They also suggested not to use hyperoncotic solutions for fluid resuscitation and recommended that any new colloid should be introduced into clinical practice only after its patient-important safety parameters are established.[26]

Following these publications which concluded that their benefits do not outweigh the risks of kidney injury and mortality, the US FDA, convened a Public Workshop in collaboration with the National Heart, Lung, and Blood Institute at the National Institutes of Health, the U.S. Army Material Command, Department of Defense, and the Office of the Assistant Secretary of Health, Health and Human Services on September 6-7, 2012 to discuss the risks and benefits of HES solutions. Subsequently, the FDA issued a warning on increased mortality and severe renal injury, and risk of bleeding, for use of HES solutions in some settings.[8] Canada also followed.[27] Across the Atlantic, HES-containing solutions were suspended in the EU on June 14, 2013[7] and the UK on June 27, 2013. However, at the time of writing, process to implement the EMA Pharmacovigilance Risk Assessment Committee's recommendation across the EU has not yet begun since a number of marketing-authorization holders have exercised their legal right to request a re-examination of the recommendations.

Critical Analysis of Three Large Trials

The three trials, VISEP, 6S and the CHEST trail evaluated HES along with Ringer's lactate, Ringer's acetate and saline respectively.[22-24] On analysis, the initial 6-h phase was not evaluated in any of the trials. In all three, colloids were given initially and patients subsequently randomized to two groups. Hemodynamic stabilization was defined by the usual recommended "goals" (Goal Directed Fluid Therapy and Surviving Sepsis Guidelines). Majority of patients in the VISEP trial had median values of mean arterial pressure (MAP), central venous pressure (CVP), central-venous oxygen saturation ($ScvO_2$) and lactate at the time of randomization as 75 mmHg, 12 mmHg, 74% and 2.2 mmol/l, respectively. In the 6S trail, the baseline median values of CVP, $ScvO_2$ and lactate were 10 mmHg, 75% and 2.0 mmol/l, respectively. Baseline values in the HES group in the CHEST trial were MAP 74 mmHg, CVP 9.5 mmHg and lactate 2.1 mmol/l. As per general recommendations, colloids are not indicated once these goals have been achieved.[28-31]

In the VISEP trial, 58% of the "crystalloid" group had already received 1 L of HES for initial resuscitation and a further 33% in this group received colloids during the trial. In the "colloid" group, a hyperoncotic solution was given to patients in daily and cumulative dosages beyond any manufacturer's recommendation. In the 6S trial, 60% of the "crystalloid" group had already received up to 1 L of colloid for initial resuscitation and a further 32% received colloids during the trial. A total of 216 (27%) patients in both groups were included in the 90-day follow-up under the intension-to-treat principle but had discontinued the trial fluid. 508 patients in the saline group in the CHEST trial had received HES prior to randomization. Use of other colloids was not reported. Moreover, the protocol was violated 953-times in 634 (9.5%) patients by infusing the wrong study fluid. All these patients remained in the trial.[28-30]

In the 6S trial, in the 90-day period, 87 patients (22%) assigned to HES 130/0.42 were treated with RRT versus 65 patients (16%) assigned to Ringer's acetate (relative risk, 1.35; 95% confidence interval [CI], 1.01-1.80; $P = 0.04$), similar to a previously published report.[32] In both, the mortality started to increase around 20 days with HES, which might be due to the late adverse effects of HES. A high fraction of HES is taken up and deposited in the tissues, where it cannot be metabolized and acts as a foreign body.[1,2,33,34]

In the CHEST trial, no differences in mortality or renal function, but an increased incidence of RRT after HES infusion in the non-adjusted analyses were found. The authors tried to explain this by *post-hoc* tests, showing higher relative risks for the HES receivers to develop renal insufficiency states i.e., "RIFLE-R" (risk of renal failure) or "RIFLE-I" (kidney injury). In the adjusted analysis (a standard procedure

to eliminate age, gender or severity of illness difference), no difference in the incidence of RRT was detected. Furthermore, 54.0% (1788/3309) of the HES group were at risk as per the RIFLE-R criteria as compared to 57.3% (1912/3335) in the saline group and as per the "RIFLE-I" criteria, 34.6% (1130/3265) of the HES group were at risk as compared to 38% (1253/3300) in the saline group [Table 1]. Fewer patients in the HES group as compared to the saline group had urine output <0.5 ml/kg/h for 6 h (52.7% vs. 56.5%) and <0.5 ml/kg/h for 12 h (36.2% vs. 39.7). Moreover, 36% of the patients had acute renal failure (ARF) at the time of randomization and should not have been included in the study.[24,30,31]

HMW, a poorly biodegradable HES preparation, presents an independent risk-factor for AKI in patients with sepsis or septic shock.[13] This was ignored in the VISEP trial. Furthermore, the exclusion criterion of a serum-creatinine value of >320 micromol/l (>3.6 mg/dl) was double that of the manufacturer's specification.

In addition, in the 6S trial, hemodynamic parameters have been reported only for the first 24 h. The data on mechanical ventilation, length of hospital and ICU stay and the individual cause of death has not been reported. In the CHEST trial, 30% of the patients were septic and in this subgroup no differences in mortality, renal failure or RRT were observed.[29,30]

The VISEP, 6S and CHEST study are limited to the management of the critically ill patient and as mentioned are silent on the management strategies prior to ICU admission or have violated prescribed daily limits for the administration of HES and or received other forms of fluid/colloid therapy. In addition, extrapolation of these findings to patients receiving or requiring HES for resuscitation, with various causes for hypovolemia including those with trauma and in the peri-operative period, would be an extreme response to studies specifically designed to look at a subset of the patient population.

Controversies Revisited

Tissue storage of HES molecules is the proposed mechanism underlying complications such as anaphylaxis, pruritus, increased rates of ARF and need for RRT. Direct coating by the HES molecules is implicated in coagulopathy and bleeding. An increase in amylase levels is the result of induced metabolism.[1,2,34]

HES can persist indefinitely intracellular as there are no known intracellular catabolic enzymes. At the present time, the precise mechanism of complete elimination of HES is still the subject of discussion.[2,5,34,35] Cumulative doses cause HES to accumulate in the body. Two studies[36,37] used ^{14}C radioactive-labeled 130/0.4, 200/0.5 and 450/0.7 HES in a multi-dosing regimen of 0.7 g/kg body weight/day for 18 days in rats. The authors concluded that even at day 52, the remaining activity in the kidneys was low, but indicated that continued excretion of residual HES was still occurring even in the case of lower whole-body storage for HES 130/0.4.

HES molecules with a high degree of substitution (with a molar substitution >0.4) and a high C2/C6 ratio[1,2,5,34,35,38] are taken up by the monocyte-macrophage system of various tissues through pinocytosis. Accumulation is dose and time-dependent. Tissues include blood, liver, striated muscle, spleen, intestine and skin. In the kidneys, the lesion is described as "osmotic nephrosis" of the proximal tubular epithelial cells.[1,38-42]

Clinical Implications of Tissue Accumulation

Pruritus

The incidence of HES-induced pruritus has been variously reported as none to 55% of patients.[2,5,34,35,43,44] Ellger *et al.* in their study found no incidence of pruritis in any of the 40 patients undergoing elective urologic surgery; although relatively high doses derived HES 130/0.4 (6%) were given.[44] Long-term follow-up of 295 patients of the 6S trial resuscitated with HES was done to assess the health-related quality of life (HRQoL) and the occurrence of pruritus. The patients assigned to resuscitation with HES 130/0.42 had worse self-perceived HRQoL than those assigned to Ringer's acetate, whereas there were no statistically significant differences in the occurrence of pruritus (49% vs. 43%). The group differences were mainly in the scales of vitality and mental health. There was no difference in the physical component summary scores between groups.[45]

Non-immunologic anaphylaxis

This has been well documented, and may include angioedema, hypotension, and urticaria. True anaphylaxis, due to specific antibody production (IgE), is believed to be extremely rare.[1,34,35,46,47]

No data on the incidence of anaphylactic reactions after intravenous administration of the HES 130/0.4 are available. The 1-year post-approval Adverse Event Review of US FDA in 2009 reported only one case with a past medical history of spina bifida and multiple orthopedic surgeries who received HES 130/0.4 during orthopedic surgery in 2007. 2 h after induction

of anesthesia, the patient suffered an anaphylactic reaction and severe hypotension. The patient had also received treatment with antibiotics (ceftriaxone, Claforan, and Cefuroxime) which were suspected as a possible cause of the allergic reaction. The patient was later re-exposed to three different cephalosporins but did not experience any allergic symptoms. The patient was then re-challenged with increasing doses of HES 130/0.4 (3 mL, 10 mL and 30 mL); after the 30 mL dose, the patient developed urticaria, redness, pruritus and bronchial symptoms. These symptoms were treated with steroids and anti-histamines and resolved after an hour. The patient had a history of concomitant allergies to pollen and latex.[48]

It is unlikely that the modifications of the MW, molecular substitution and the C2/C6 ratio could have resulted in increased anaphylactic potency, because histamine liberation appears to be induced by the substance itself (starch) and not by the modifications of the substrate.[1,2,4,5,34]

Acute renal injury

Legendre *et al.* have reported 80% rate of "osmotic nephrosis lesions" in transplanted kidneys after administration of MMW HES (200/0.62) to brain-dead donors. These, however, had no adverse effects on graft function or serum creatinine after transplantation.[42] Two studies with 65 and 62 patients each concluded that choice of colloid had no impact on renal parameters and outcome in patients with pre-existing renal dysfunction undergoing elective abdominal aortic surgery.[49,50] Neff, *et al.* demonstrated that use of high doses of 6% HES 130/0.4 in neurosurgical patients (up to 66 L over 21 days) was not associated with deteriorating kidney function after 7 days.[51] Martin *et al.* found no evidence for renal dysfunction caused by modern waxy maize-derived HES 130/0.40 in surgical patients.[52]

Wiedermann concluded that HES possesses a significant negative impact on renal function. They, however, did not elaborate the types of HES preparations used, patients type or disease condition, pre-existing kidney dysfunction or fluid regimen used.[53] A recent Cochrane meta-analysis opined that all HES products increase the risk in AKI and RRT in all patient populations and a safe volume of any HES solution has yet to be determined.[54]

In severe sepsis, there are concerns of increased mortality though significantly less volume was required to achieve the hemodynamic goals in the initial phase of fluid resuscitation.[54-56] Zhong *et al.* concluded that the severity score is improved in HES, but the CI are wide.[57]

Newer formulations of HES and more focused indications for use show benefit on surrogate endpoints, but these trials are currently underpowered to ensure safety. Hence HES is currently not recommended for sepsis, those with previous mild to severe renal dysfunction, the elderly and those receiving high-dose therapy.[54-58]

Coagulation disturbances

HMW and MMW-HES preparations (200-450/0.5-0.7) had shown to induce a decrease in factor VIII activity, von Willebrand factor (vWF) antigen and factor VIII-related ristocetin cofactor due to dilution as well as coating of the platelets. As a result, there is reduced binding to platelet membrane receptor proteins GPIb and GPIIb/IIIa and decreased platelet adhesion. The effect of both MMW and LMW HES is less.[2,58-61]

Felfernig M showed that LMW HES with MS <0.5 effects the clot maturation process significantly less than other HES preparations.[62] I Gallandat Huet *et al.* compared HES 130/0.4 with HES 200/0.5 in coronary artery bypass grafting patients. In this study, vWF increased significantly more in the HES 130/0.4 treated patients. Blood loss and transfusion requirements were lower in patients receiving HES 130/0.4, indicating considerable benefits with HES 130/0.4.[63]

Mittermayr *et al.* have reported the effects of 20 mL/kg of lactated Ringer (LR), HES 200/0.5, and HES 130/0.4 on expression of platelet membrane glycoprotein cluster differentiation (CD) CD42b, CD41/61, and CD62p *in vivo* on non-stimulated platelets and adenosine diphosphate-activated platelets. Platelet dysfunction was observed in both HES groups, with faster recovery of platelets function after HES 130/0.4 than HES 200/0.5.[64]

However, when blood samples from healthy donors were diluted (30 and −60%) using crystalloids (saline, Ringer's lactate, Plasmalyte [TM]) or colloids (6% HES130/0.4], 5% human albumin, and gelatin), HES 130/0.4 had the most deleterious effect on hemostasis parameters.[65] HES 130/0.4 has similar adverse effects as HES 200/0.5. Both types of HES impair coagulation capacity and stimulate pro-inflammatory platelet function.[66]

Peri-operative period

LMW HES has been shown to be safe in cardiovascular surgery[67-70] and liver transplant.[71] In major abdominal surgeries Staikou *et al.* demonstrated that HES 130/04-0.42 have a tendency toward reduced coagulability on the thrombelastography. HES 130/0.4 and HES 130/0.42 were equally safe when administered in doses up to 30 ml/kg.[72] In 100 patients undergoing elective surgery post trauma 100% patients in the gelatin group, 84.2% patients in the NS group, 94.4% patients in the RL group, and 66.7% patients in the

HES group were hypocoagulable (R time >14 min) in the post-operative period.[73] Hamaji *et al.* demonstrated that during hip arthroplasty, patients treated with hypervolemic hemodilution with HES 130/0.4 required less transfusion and lower infection rate compared to LR solution.[74]

Monitoring and minimizing pulse pressure variation by 6% HES 130/0.4 loading during gastrointestinal surgery has been shown to improve post-operative outcomes and decreases the discharge time of patients.[75]

Regarding prevention of maternal hypotension for cesarean sections, three strategies of colloid preload, colloid coload and crystalloid coload are equivalent for the prevention and a reduced need for vasopressors. Crystalloid preload is not as effective as any of those three strategies.[76] No difference was reported in the cardiac output, vasopressor requirements or hemodynamic stability on colloid or crystalloid coload.[77]

More studies are required utilizing the entire range of tests on platelet functions and coagulation profiles.[78-80]

HES in traumatic and non-traumatic brain injury

Serious complications of HES administration have been repeatedly demonstrated in clinical trials of acute ischemic stroke and other brain injuries, prompting premature termination of several randomized trials.[2,5,26,34]

Safety of HES solutions have been typically assessed in highly selected low-risk patient populations receiving relatively small HES doses, hence the results cannot be generalized to routine clinical practice.[51,81] In the present scenario, considering the cerebral and other systemic adverse effects coupled with existing higher mortality data, colloids does not seem to be fluid of choice for resuscitation in patients with TBI.[82]

HES in burns resuscitation

During Operation Iraqi Freedom, a protocol for the difficult fluid resuscitation was developed using albumin if projected 24-h resuscitation requirements exceed 6 ml/kg/% burn. The Israeli Haifa formula combines plasma and crystalloid and recommends substitution of colloids in part of the Fresh Frozen Plasma dosage.[26,83]

HES facilitated improved hemodynamics, oxygen delivery and prolonged plasma expansion yet concerns regarding the adverse effects of starches, particularly on coagulation, limited their use. However, LMW HES may exert beneficial effects on endothelial function by stabilization of fragile cell membranes or by avoiding endothelial swelling. Moreover, HES 130/0.4, because of the heavy hydroxyethylation at the C-2 position, may promote specific interactions with the endothelial glycocalyx and thereby inhibit leakiness.[26,34,35,61]

Organ donors

Blasco *et al.* used HES 130/0.4 or HES 200/0.62 for resuscitation of brain-dead donors. HES 130/0.4 was associated with a better effect on renal function 1 month and 1 year after transplantation, S. Creatinine was significantly lower in the HES 130/0.4 treated donors.[84]

Although, there are no studies comparing HES 130/0.4 and crystalloids in organ donors, it is recommended that any new colloid should be introduced into clinical practice only after its safety parameters are established.[85]

Trauma and hemorrhagic shock

There is still no consensus regarding the optimal treatment of hypovolemia in trauma patients. ATLS recommends the use of Ringer's lactate solution in trauma whereas the USA Institute of Medicine recommends a Ringer's lactate-based volume-replacement strategy.[26,86]

Crystalloids are often recommended as the first choice to treat hemorrhage due to low cost and easy availability. A randomized, controlled, double-blind study of 115 severely injured patients requiring >3 L of fluid resuscitation showed that the biochemical markers of resuscitation and renal function were better in those who received HES 130/0.4 as compared to saline after penetrating trauma. Outcomes were similar after blunt trauma, although numbers in these subgroups were modest.[87]

LMW HES is used and advocated by various militaries for pre-hospital, low-volume boluses hemorrhagic shock. HES 130/0.4-0.42 are associated with beneficial effects beyond their volume-replacement properties (e.g., improving micro-perfusion, capillary integrity, inflammatory response, and endothelial integrity).[88] Several near-fatal hemorrhage models have demonstrated that LMW HES is associated with significantly lower mortality compared with Ringer's lactate.[89] In case both HES and a crystalloid is used, peripheral accumulation of the latter is promoted by HES[90] A multicenter, randomized clinical trial stratified by case mix (sepsis, trauma, or hypovolemic shock without sepsis or trauma), the Therapy in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial among ICU patients with hypovolemia opined that the use of colloids versus crystalloids did not result in a significant difference in 28-day mortality. Although 90-day mortality was lower among patients receiving colloids, this finding should be considered exploratory and requires further study before reaching conclusions about the efficacy.[91]

Conclusions

The HES family has evolved since its introduction almost four decades ago. Lower MW and MS have improved its safety profile. Newer formulations of HES and more focused indications for use show benefit on surrogate endpoints, but these trials are currently underpowered to ensure safety. Most studies about adverse effects have either been meta-analysis of small trials or have compared HES with another colloid. The effects of HES on coagulation parameters are well-documented and hence are a cause for concern.

The increased need for RRT in patients receiving HES was not a cause for concern when adjusted for confounding variables in some trials.

The use of HES cannot be condemned yet and though large RCT s are needed, given the current importance given to the European pharmacovigilance ban and US FDA warning, it will take some time for such trials to happen. In addition, in the absence of HES for resuscitation, the role for Ringers acetate/lactate will be under the spotlight and given the large volumes needed, probably the acetated solutions will find favor.

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