CME Modern Rapidly Degradable Hydroxyethyl Starches: Current Concepts

Joachim Boldt, MD

Hydroxyethyl starch (HES) is a widely used plasma substitute for correcting perioperative hypovolemia. HES preparations are defined by concentration, molar substitution (MS), mean molecular weight (M_w), the C_2/C_6 ratio of substitution, the solvent, and the origin. The possible unwanted side effects of HES are anaphylactic reactions, alterations of hemostasis resulting in increased bleeding, kidney dysfunction, accumulation, and pruritus. In view of the potential side effects, it is crucial to distinguish among the different HES preparations; all HES preparations are not the same. The first generation of HES preparation showing a high M_w (>450 kD) and a high MS (>0.7) was associated with negative effects with regard to coagulation, organ function, and accumulation. This review is focused on whether modern (third generation), more rapidly degradable HES preparations with a lower M_w (130 kD) and a lower MS (<0.5) are safer and have fewer side effects. Several studies demonstrated that such modern HES preparations appear to be safe with regard to hemostasis, kidney function, itching, and accumulation. Modern HES preparations are dissolved in balanced, plasma-adapted solutions that no longer contain unphysiological amounts of sodium and chloride and are thus suitable for correcting hypovolemia.

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Fluid deficits are common among surgical, trauma, and intensive care unit (ICU) patients. Hypovolemia can occur in the absence of obvious fluid loss secondary to vasodilation or generalized alterations of the endothelial barrier resulting in diffuse capillary leak. Thus, especially in the inflammatory setting, large fluid deficits may occur. This situation is characterized by a panendothelial injury with subsequent development of increased endothelial permeability, leading to a loss of proteins and a fluid shift from the intravascular to the interstitial compartment resulting in hypovolemia and interstitial edema. Although there is consensus regarding avoidance of blood transfusion, the optimal nonblood plasma substitute is still a matter of debate. This debate includes a crystalloid/colloid controversy but must be broadened to include a colloid/colloid debate. When discussing different intravascular volume replacement strategies, both benefits and potential side effects must be considered.

From the Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Ludwigshafen, Germany.

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Address correspondence and reprint requests to Prof. Dr. Joachim Boldt, Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Bremserstr. 79, D-67063 Ludwigshafen, Germany. Address e-mail to BoldtJ@gmx.net.

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Characterization of Hydroxyethyl Starch

Hydroxyethyl starch (HES) refers to a class of synthetic colloid solutions that are modified natural polysaccharides and are similar to glycogen.[1] HES is derived from amylopectin, a highly branched starch that is obtained from waxy maize or potatoes. Polymerized D-glucose units are joined primarily by 1-4 linkages with occasional 1-6 branching linkages. The degree of branching is approximately 1:20, which means that there is one 1-6 branch for every 20 glucose monomer units. Natural starches cannot be used as plasma substitutes because they are unstable and are rapidly hydrolyzed by circulating amylase. Substituting hydroxyethyl for hydroxyl groups results in increased solubility and retards hydrolysis of the compound by amylase, thereby delaying its breakdown and elimination from the blood (Fig. 1). The hydroxyethyl groups are introduced mainly at carbon position C2, C3, and C6 of the anhydroglucose residues. After infusion of HES, there is initially a rapid amylase-dependent breakdown and renal excretion of up to 50% of the administered dose within 24 h. The hydroxyethyl residues, especially when bound to the C2 position of glucose, inhibit plasma amylase, hence increasing the intravascular half-life of the HES solution.

A higher molecular weight (M_w) range and a more extensive molar substitution (MS) also result in slower elimination. Smaller HES molecules (<50–60 kD) are eliminated rapidly by glomerular filtration. Renal elimination by filtration continues as larger HES molecules are hydrolyzed to smaller molecules. A small amount of the administered dose is forced into the

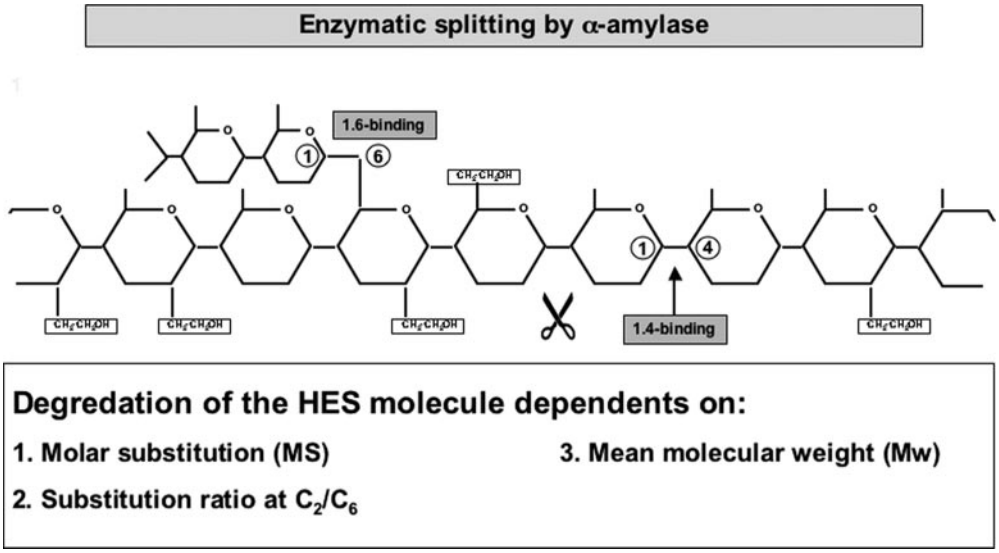

Figure 1. Structure of hydroxyethyl starch and its degradation by α-amylase.

Product	Concentration and solvent	Mean molecular weight (kDa)	Molar substitution	C_2/C_6 ratio	Max. daily Dose (ml/kg)	
HES 670/0.75	6% - balanced	670	0.75	4.5 : 1	20	
HES 600/0.7	6% - saline	600	0.7	5 : 1	20	Hetastarch
HES 480/0.7	6% - saline	480	0.7	5 : 1	20	
HES 200/0.62	6% - saline	200	0.62	9 : 1	20	Hexastarch
HES 200/0.5	6% - saline 10% - saline	200	0.5	5 : 1	33 20	Pentastarch
HES 70/0.5	6% - balanced	70	0.5	3 : 1	20	
HES 130/0.42	6% - saline and balanced 10% - saline and balanced	130	0.42	6 : 1	50 33	Tetrastarch
HES 130/0.42	6% - saline and balanced 10% - saline and balanced	130	0.42	6 : 1	50 33	

Figure 2. The different characteristics of hydroxyethyl starch (HES) preparations. bal: solved in balanced, plasma-adapted solution instead of saline solution.

interstitial space for later redistribution and elimination. Another fraction is taken up by the reticuloendothelial system, where the starch is slowly broken down. HES solutions can be classified by their M_w or their MS (Figs. 2 and 3).

HES is the most often used colloid in the Europe[2] and the last ("third") generation of HES has also been approved by the Food and Drug Administration (FDA) early in 2008 (Fig. 4). It is important to distinguish among the different HES preparations, as their physicochemical characteristics are widely different (Fig. 5) and they differ with respect to the extent and duration of plasma volume expansion, the effects on blood rheology and coagulation system.[1,3] Being equivalent in terms of colloid oncotic pressure and hemodilution effect, potato HES exhibits a faster clearance from the circulation.[4] HES preparations based on maize have a higher mean degree of branching and a much lower degree of esterification with phosphoric acid compared with potato-derived HES preparation.[4] Moreover, potato-derived HES contains less amylopectin (about 80%) than maize-derived HES preparations (about 99%).[4] Potato-based HES contains about 20% amylase compared with about 1% in maize-based HES.[4] There is, however, no clear evidence that there is a clinical difference between potato- and waxy maize-derived HES products.

Side Effects of HES

Coagulation

Studies showing severely compromised blood coagulation and increased bleeding tendency included mostly a HMW-HES preparation (M_w >450 kD) and a high MS (>0.7) (Hetastarch). This preparation has

Classification of HES by molar substitution (MS) patterns

MS	Classification	Trade Names
0.7	Hetastarch	Hespan®, Plasmasteril®, Hextend® (balanced)
0.6	Hexastarch	Elohes®
0.5	Pentastarch	HAES-Steril®, Pentaspan®, Hemohes®
0.4	Tetrastarch	Voluven® , Venofundin® , Tetraspan® (balanced), Volulyte® (balanced), Plasma Volume Readybag® (balanced),

Figure 3. Classification of hydroxyethyl starch according to the degree of hydroxyethylation (molar substitution [MS]).

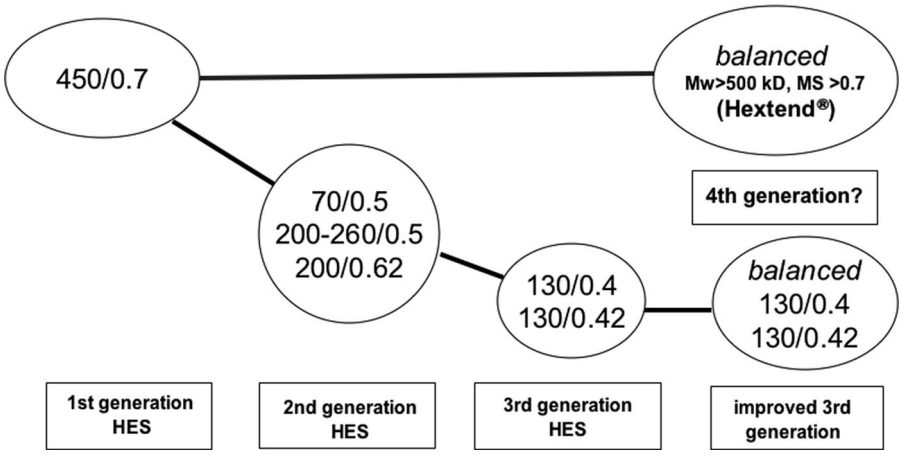

Figure 4. Development of hydroxyethyl starch (HES).

Concentration	Mean molecular (Mw)	Molar substitution (MS)	C_2/C_6-ratio	Solvent	Origin
3% (hypo-oncotic)	low-molecular weight [LMW]: 70 kD	low MS: <0.5	9:1	Unbalanced (dissolved in saline solution)	potato-derived HES
6% (norm-oncotic)	medium-molecular weight [MMW]: ranging from 130 to 270 kD	medium MS: 0.5	6:1	Balanced (dissolved in plasma-adapted solution)	waxy maize-derived HES
10% (hyper-oncotic)	high-molecular weight [HMW]: >450 kD	high MS: >0.5	4:1		

Figure 5. Modifications of the different hydroxyethyl starch preparations.

been demonstrated to induce a von Willebrand-like syndrome with decreased factor VIII coagulant activity and von Willebrand factor (vWF) antigen and factor VIII-related ristocetin cofactor.[5–7] In animal experiments, it has been shown that in low-substituted HES (MS 0.42), the M_w is not a key factor in deteriorating coagulation.[8] Impaired platelet function has also been reported after administration of HES.[6–11] With reduced factor VIII-related ristocetin cofactor, there is reduced binding to platelet membrane receptor proteins GPIb and GPIIb/IIIa, resulting in decreased platelet adhesion.[9] HES with a high M_w, high MS, and a high C_2/C_6 hydroxyethylation ratio (e.g., HES 450/0.7 or HES 200/0.62) reduced concentrations of vWF and factor VIII:c more than HES with lower M_w and a lower MS. As the result of all reports on HES

with a high M_w and a high MS, the FDA approved a major change in the labeling of 6% Hetastarch in saline (M_w >450 kD, MS >0.7) which applied specifically to cardiopulmonary bypass surgeries and did not recommend Hetastarch in this situation.[10] Because of this inhibition of hemostasis, there appear to be few reasons to use such HES preparations in other clinical settings as well. Subsequently, more rapidly degradable HES preparations with lower M_w (200 kD) and MS (0.5) were shown to improve safety with regard to coagulation ("second generation" HES).[11–13] The last, "third-generation" HES has a M_w of 130 kD and a MS of <0.5 and appears to be associated with negligible negative effects on coagulation. No platelet function abnormalities have been observed in *in vitro* studies using HES 130/0.4.[14] Using SONOCLOT-analysis and *in vitro* hemodilution, HES 130/0.4 affected the maturation process significantly less than other HES preparations.[15] In another *in vitro* study, infusion of HES 450/0.7/4.6 had the greatest effect on thrombelastography parameters, whereas HES 130/0.4/9 has the smallest effect.[16] In a double-blind multicenter study in patients scheduled for coronary artery bypass grafting (CABG), Gallandat Huet et al.[17] compared HES 130/0.4 with HES 200/0.5. In this study, vWF increased significantly more in the HES 130/0.4- than in HES 200/0.5-treated patients. Blood loss and transfusion requirements were lower in patients receiving HES 130/0.4, indicating considerable benefits with HES 130/0.4.

Haisch et al.[18] compared intravascular volume replacement with HES 130/0.4 with gelatins in cardiac surgery patients. There were no significant differences between the two groups with regard to thrombelastography data and bleeding. In another study of CABG patients, the effects of either 6% HES 200/0.5 (in doses up to 33 mL/kg) or 6% HES 130/0.4 (up to 50 mL/kg) on coagulation were measured.[19] Coagulation, bleeding, and transfusion requirements did not differ when using high dose of HES 130/0.4. In a double-blind study in 52 patients undergoing major orthopedic surgery, factor VIII and vWF returned more rapidly to normal in HES 130/0.4- than in HES 200/0.5- treated patients.[20] Kozek-Langenecker et al.[21] analyzed pooled data from all available studies in major surgery comparing HES 130/0.4 and HES 200/0.5 with regard to estimated blood loss, drainage loss, calculated blood loss, transfused blood product volumes, and coagulation variables. The authors concluded that blood loss and transfusion requirements could be reduced significantly when using HES 130/0.4 compared with HES 200/0.5 (Fig. 6).

However, negative effects of modern HES preparations on coagulation have also been reported. In a prospective, double-blind, placebo-controlled, crossover study, the influence of HES 130/0.4, HES 200/0.62, and lactated Ringer's solution (LR) on platelet function were studied in chronic back pain patients scheduled for peridural anesthesia.[22] The platelet-

HES 130/0.4 reduces blood loss in major surgery: Pooled analysis (n=449 in 7 studies)

	6% HES 130/0.4 versus 6% HES 200/0.5	p value
Estimated blood loss (mL)	-404 [-689; -119]	0.006
Drainage loss (mL)	-271 [-474; -70]	0.009
Calculated RBC loss (mL)	-149 [-247; -50]	0.003
RBC transfusion volume (mL)	-137 [-231; -43]	0.004

Figure 6. Blood loss by 6% hydroxyethyl starch (HES) 130/0.4 in comparison with 6% HES 200/0.5 (modified from Ref. 19).

inhibiting effect of HES 200 was more than that of HES 130. Adenosine diphosphate- (ADP) and epinephrine-induced platelet function was also significantly reduced by HES 130; the changes, however, were within normal range, indicating that these were statistically, but not clinically, significant changes. In 60 patients undergoing minor elective surgery, the effects of 20 mL/kg of 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 nonstimulated platelets and ADP-activated platelets were assessed.[23] Platelet dysfunction was observed in both HES groups, but recovery of platelets to normal function was faster after HES 130/0.4 than after HES 200/0.5. In a study in orthopedic surgery patients, HES 130/0.4 showed more pronounced disturbances of fibrinogen/fibrin polymerization than gelatins or LR.[24]

Changing the Solvent: Balanced HES Preparations

Dissolving modern HES preparations in a plasma-adapted, balanced solution rather than in saline solution further improved safety with regard to coagulation. In an *in vitro* study, the effects of HES 130/0.42 prepared in a balanced solution on hemostasis were compared with a conventional HES preparation in saline.[25] The balanced HES preparation overall showed less negative effects on thrombelastographic data and platelet aggregation than the saline HES preparation, especially when using a higher dilution. In another *in vitro* study, it was shown that in contrast to a nonbalanced HES 130/0.4, a HES 130/0.42 preparation dissolved in a physiologically balanced electrolyte solution did not affect activated partial thromboplastin time, FVIII:C and vWF.[26] The balanced, but not the nonbalanced, HES preparation increased the expression of activated platelet GP IIb/IIIa induced by ADP, indicating improved hemostasis with this balanced HES preparation.

Kidney Function

Older patients with significant comorbidities are at greater risk of developing kidney failure. As hypovolemia is an important etiology of kidney dysfunction,

especially in the critically ill patient, correcting hypovolemia is fundamental to maintaining kidney integrity. There is increasing interest concerning the effects of HES on renal function. Several hypotheses and risk factors have been proposed to explain the mechanism of renal dysfunction with HES. Some histological studies have shown reversible swelling of renal tubular cells after the administration of certain HES preparations ("osmotic nephrosis like lesions") probably secondary to reabsorption of macromolecules.[27] Similar tubular lesions have been described with other substances as well (e.g., mannitol).

The most likely mechanism of renal dysfunction is the induction of hyperviscosity of the urine by infusion of hyperoncotic colloids in dehydrated patients. Glomerular filtration of hyperoncotic molecules from colloids may cause a hyperviscous urine and stasis of tubular flow, resulting in obstruction of the tubular lumen.[28] The effective glomerular filtration pressure (P_{eff}) is $P_{eff} = (P_{cap} - P_{bow}) - P_{pla}$ (where P_{cap} is hydrostatic capillary pressure, P_{bow} is hydrostatic pressure in Bowman space, and P_{pla} is plasma colloid oncotic pressure). An increase in plasma oncotic pressure by hyperoncotic colloids may be one reason for subsequent renal dysfunction.[29] Considering this pathogenesis, it can be hypothesized that all hyperoncotic colloids can induce renal impairment ("hyperoncotic acute renal failure"). Adequate hydration using crystalloids may prevent this injury.

Information on the effects of HES in the clinical setting is not uniform. In a retrospective study, Legendre et al.[30] reported 80% rate of "osmotic nephrosis-like lesions" (vacuolization of the proximal tubular cells) in transplanted kidneys after administration of HES with a medium M_w (200 kD) and a high MS (0.62) to brain-dead donors. These changes, however, had no adverse effects on graft function or serum creatinine after transplantation. Cittanova et al.[31] also demonstrated that the use of 6% HES 200/0.62 in brain-dead donors resulted in impaired renal function in kidney transplant recipients. In a multicenter, prospective study, 129 patients with sepsis or septic shock received either gelatin or HES 200/0.62 for intravascular volume replacement.[32] Acute renal failure (defined as a twofold increase in serum creatinine concentration [sCr] or need for renal replacement therapy [RRT]) developed in 42% of the HES- and in 23% of the gelatin-treated patients ($P < 0.028$). Unfortunately, the two groups of patients are difficult to compare, because they had different baseline creatinine levels before the start of volume therapy. The need for RRT and mortality were not significantly different between the two groups. In another multicenter study of patients with septic shock, use of a hypertonic (10%), second generation HES preparation with a medium MS and a medium M_w (10% HES 200/0.5), without regard to exclusion criteria (creatinine levels >3.6 mg/dL) and dose limitations (20 $mL \cdot kg^{-1} \cdot d^{-1}$) resulted in a significantly higher incidence of late acute renal failure (>28 days after infusion) than in LR-treated patients (34.9% vs 22.8%).[33] Interestingly, other colloids (including dextrans) had been used in almost 30% of the HES-treated patients. Two meta-analyses not distinguishing the different HES preparations, including different kinds of patients (general/cardiac/trauma surgery, septic/severe septic/septic shock patients) and patients with and without preexisting kidney dysfunction, using fixed volumes or goal guided-directed therapy and using varying definitions of "renal dysfunction" concluded that HES possesses a significant negative effect on renal function.[34,35] In contrast, a large observational study in 3147 critically ill patients in ICU, 1075 of whom received HES (not separated concerning the type of HES given), did not show a significantly higher incidence of acute renal failure requiring RRT.[36] No significant differences in renal failure scores were documented in patients treated with other plasma substitutes (including albumin).

The development of the last generation of HES (M_w 130; MS <0.5) may represent a significant advance. In a prospective, randomized study of 40 cardiac surgery patients aged >70 yr either 6% HES 130/0.4 or gelatin was administered.[37] Concentrations of kidney-specific proteins increased in cardiac surgery patients but returned to normal at 2 days after surgery, indicating no relevant alterations in renal integrity with HES 130/0.4.

The last generation of HES also appears to be safe with regard to long-term renal function effects. In a retrospective, matched-paired study, HES 130/0.4 or HES 200/0.62 was used for resuscitation of brain-dead donors.[38] Use of HES 130/0.4 was associated with a better effect on renal function than HES 200/0.62; 1 mo and 1 yr after transplantation, sCr was significantly lower in the HES 130/0.4- than in the HES 200/0.62-treated donors.

Use of extremely 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.[39] In a study in cardiac surgery patients >80 yr, volume therapy with HES 130/0.4 was associated with fewer changes in kidney function than gelatin.[40] Creatinine clearance did not change in the HES-treated patients and concentration of kidney-specific proteins recovered to normal 2 days after surgery. Kidney function was without significant differences from baseline even 60 days after discharge from the hospital, and no patient developed acute renal failure requiring RRT after hospital discharge. In another prospective, randomized study, cardiac surgery patients aged >80 yr with preoperative hypoalbuminemia received either 5% human albumin (HA) or 6% HES 130/0.4.[41] sCr increased slightly and glomerular filtration rate decreased after bypass and in the ICU in both groups. Approximately 3 mo after hospital discharge both sCr and glomerular filtration rate had returned close to baseline.

Even in patients with altered kidney function, use of the last generation of HES appears to be safe. In volunteers showing mild-to-severe renal dysfunction (mean creatinine clearance <50 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}), kidney function was not affected by the administration of 500 mL of HES 130/0.4.[42] Use of 6% HES 130/0.4 compared with gelatin in 65 patients with compromised renal function (creatinine clearance <80 mL/min) undergoing abdominal aortic surgery was not associated with changes in serum creatinine up to day 6 after surgery, and the need for RRT also did not differ between the two groups.[43] In a study of cardiac surgery patients with preoperative compromised kidney function (serum creatinine >1.5 mmol/L) use of 6% HES 130/0.4 did not negatively influence kidney integrity compared with a HA-based volume replacement strategy up to 2 mo after hospital discharge.[44]

Anaphylactic/Anaphylactoid Reactions

All colloids used for intravascular volume replacement, including the natural colloid albumin, have the potential to induce anaphylactic/anaphylactoid reactions.[45] Most common in frequency and of most intense severity are dextran-induced anaphylactic reactions, and even prophylaxis with monovalent hapten dextran cannot completely eliminate their occurrence.[46] In a large clinical trial that included approximately 20,000 patients, it was demonstrated that use of HES was associated with a low incidence of anaphylactic/anaphylactoid reactions similar to that of albumin, and significantly less than that of other colloids.[47] No data on the incidence of anaphylactic reactions after IV administration of the last generation of HES are available. However, it is unlikely that the modifications of the M_w, the MS, and the C_2/C_6 ratio 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.

Accumulation and Storage

Depending on the characteristics of the HES preparation, a varying amount of the infused HES leaves the vascular space and is taken up by the reticuloendothelial system or mononuclear phagocytic system. The sequelae of storage of HES preparations are not well delineated, but it does not appear that storage will negatively influence the function of the mononuclear phagocytic system.[48]

The last generation of HES (M_w 130 kD; MS <0.5) showed favorable physicochemical properties that are associated with significantly less storage in animal experiments than other HES preparations, especially after repetitive administration.[1,3] Although large clinical studies focused on tissue storage of the latest HES generation are missing, there are some convincing data that accumulation is reduced. In humans, the percentage of administered HES 130/0.4 remaining in the plasma 24 h after infusion is approximately 2%. This is in contrast to the 8% that is retained after administration of HES 200/0.5.[20] In a prospective crossover study in nine healthy volunteers, 500 mL/d of 10% HES 130/0.42 or 10% HES 200/0.5 was infused for 4 days.[49] Repeated administration of HES 130/0.42 showed no accumulation, whereas the remaining amount of HES 200/0.5 increased continuously from one infusion to the other.

Pruritus

Special features of HES-induced pruritus include long latency of onset and persistence. A dose-dependent uptake of HES was first detected in macrophages and, thereafter, in endothelial and epithelial cells. Patients suffering from pruritus consistently showed additional deposition of HES in small peripheral nerves.[50] Pruritus has been reported after use of large doses of HES over a long period, mostly using HES with a high M_w or a high MS. Single reports on pruritus have been published, even after a single use of approximately 2000 mL of HES.[51] In a prospective multicenter study, more than 500 patients were observed over 3–9 wk postoperatively.[52] No significant differences with regard to pruritus were reported between HES-treated and control patients. In a study that included more than 700 patients undergoing minor elective surgery, the incidence of pruritus after infusion of HES 200/0.5 from two different manufacturers was compared with LR.[53] There were no differences in the three patient groups: 9.1% and 12.0% in the two HES groups and 11.5% in the LR group. Using the last generation of HES, only rare reports on the incidence of pruritus are available, mostly after high or repetitive doses of HES 130/0.4 in the nonsurgical, non-ICU setting.[3,54–57]

Intravascular Volume Replacement with HES and Outcome

Whether the choice of plasma substitute can be lifesaving is still a matter of debate. Even the SAFE study[58] that included approximately 7000 ICU patients did not show differences between saline- and HA-treated patients. This study, however, was not focused on HES efficacy or influence on outcome but on unwanted side effects of new HES preparations. Two large studies showed increased mortality when using older HES preparations. In a retrospective chart analysis of 19,578 patients undergoing CABG surgery, patients receiving HA or nonprotein colloids (dextrans or HES with a high MS [HES 450/0.7; Hetastarch in saline]) were studied.[59] Mortality was lower in the HA group (2.47% vs 3.03%, $P = 0.02$). Both dextrans and Hetastarch have detrimental effects on coagulation and kidney function. Thus, the FDA has already recommended avoiding the use of Hetastarch in saline in cardiac surgery patients. In a multicenter study of 537 patients with septic shock, the use of large doses (>22 mL $\cdot$ kg^{-1} $\cdot$ d^{-1}) of a hypertonic (10%) HES 200/0.5

solution was associated with a higher mortality than use of LR.[30] The recommended maximum dose of this HES preparation is reported to be $<20\ mL \cdot kg^{-1} \cdot d^{-1}$. In a subgroup analysis, the group in whom $<22\ mL \cdot kg^{-1} \cdot d^{-1}$ of HES had been administered showed the lowest mortality rate, even lower than the group in whom LR has been given for volume therapy.

Although millions of units of the new generation of HES preparations have been used for almost 10 yr in several countries, there is no large study showing increased mortality with the new HES preparations.

CONCLUSIONS

A well-balanced intravascular volume therapy is essential in the surgical, the burn, and in the patient in ICU. The ideal plasma substitute for volume replacement remains a matter of debate. HES is the most widely used plasma substitute in the Europe and is widely used in the rest of the world. The efficacy of HES in restoring hypovolemia and thus improving systemic hemodynamics as well as microcirculation appears to be without doubt.

What did we learn with regard to safety of HES over the years? All volume replacement strategies have their risks and benefits. Because of the important physicochemical differences between the varying HES preparations, it would be inappropriate to categorize them all as a "HES group." The majority of studies indicate that unwanted alterations in coagulation and increased bleeding (aside from that induced by extensive hemodilution) appear to no longer be a clinically relevant problem when using HES preparations with a M_w of 130 kD and a MS <0.5. Dissolving modern HES preparations in a plasma adapted, balanced solution has further improved safety with regard to changes in hemostasis.

There is no evidence that timely, limited use (e.g., intraoperatively or in acute trauma care) of modern HES preparations has negative effects on kidney function in patients with normal kidney function. The propensity of HES to negatively influence kidney function in patients with preexisting renal disease depends on the HES preparation and its proper use. The importance of using substance specific, recommended doses for each HES preparations cannot be overemphasized: "Dosis sola veneum facit"—the dose is poisoning (Paracelsus 1493–1541). The "critical" serum creatinine level below which HES preparations should not be used is still unknown. By accepting a sCr of >2.5 mmol/L as an exclusion criterion, modern HES preparations with a M_w of 130 kD and a MS <0.5 appear to be safe with regard to kidney function. Unfortunately, current evidence in this area is lacking.

Whether the choice of fluid has an impact on patient outcome is still not clear but appears to be unlikely.[60–62] Conflicting results with regard to patient outcome are most likely due to variations in clinical protocols, selection of patients, criteria for volume administration, and the type of plasma substitute administered. More than 10 yr ago, Warren and Durieux[63] asked "HES: safe or not." They concluded that "HES should be used with caution . . .." like all other drugs. Medical therapy has developed rapidly over the last few years, and safety issues have become increasingly important. When respecting its limitations, there seems to be no good reason to avoid modern HES preparations for correcting hypovolemia. There also appears to be no argument against using HES dissolved in a balanced solution instead of unphysiological saline solution. Modern ("third-generation") HES preparations dissolved in a balanced solution have added another piece in the puzzle of finding a safe, nonblood volume replacement strategy.

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