

## Effects of Hydroxyethyl Starch Solutions on Hemostasis

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HYDROXYETHYL starch (HES) solutions are frequently used plasma expanders that are indicated to restore and maintain intravascular volume, to stabilize hemodynamic conditions, and to improve tissue perfusion. According to these clinical indications, HES is used in perioperative situations with a high risk of bleeding. Side effects of HES on hemostasis pose serious limitations to the clinical use of this artificial colloid. Recent developments have centered around designing new starch molecules by modulating their pharmacochemical characteristics to increase colloid osmotic pressure and hemodynamic efficacy while minimizing the risk of adverse reactions such as antithrombotic effects. The aim of this Clinical Concepts and Commentary article is to provide clinicians with a brief overview of the literature on potential side effects of various HES preparations, including hetastarches, pentastarches, and the novel tetrastarches, on both plasmatic and cellular hemostasis.

### Chemistry

Polymers of the natural amylopectin are chemically modified by hydroxyethylation at the glucose subunit carbon atoms C2, C3, or C6 (fig. 1). The most important physicochemical characteristics are the molar substitution (mole hydroxyethyl residue per mole glucose subunit), the C2/C6 ratio (pattern of hydroxyethylation at the carbon position C2 and C6), the spectrum of molecular weights, and the mean molecular weight. HES solutions are classified according to the manufactured mean molecular weight into high-molecular-weight ( $\geq 400$  kd), medium-molecular-weight (200–400 kd), and low-

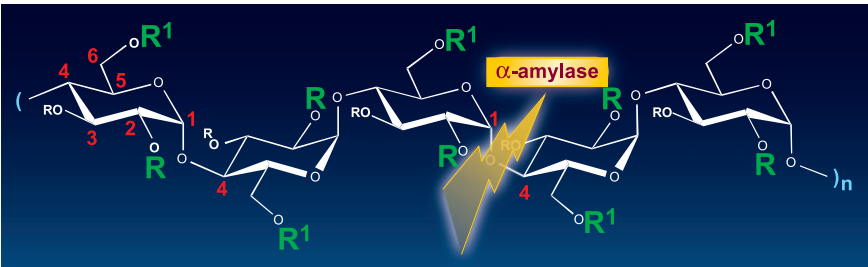
molecular-weight solutions ( $< 200$  kd) according to the molar substitution into highly substituted (hetastarch; 0.62–0.75), medium-substituted (pentastarch; 0.5), and the new generation of low-substituted solutions (tetrastarch; 0.4), and according to the C2/C6 ratio into solutions with a high C2/C6 ratio ( $> 8$ ) or a low C2/C6 ratio ( $< 8$ ). HESs are polydisperse solutions of molecules with a broad range of molecular weights. After intravenous infusion, the low-molecular-weight fraction is rapidly lost by renal elimination, and the larger molecules are progressively hydrolyzed by serum  $\alpha$ -amylase, resulting in a narrow distribution of molecular weights of a mean *in vivo* molecular weight that is lower than the mean molecular weight of the infused fluid.<sup>1</sup>  $\alpha$ -Amylase, an endo-amylase, cleaves within the polyglucose chain and not glucose-by-glucose from the ends. The resulting smaller HES fragments will be further excreted *via* urine. A minor proportion is transiently stored in tissues and ultimately excreted after redistribution. Especially molar substitution and C2/C6 ratio determine the *in vivo* behavior of specific HES types and the rate of HES degradation.<sup>1–6</sup> Plasma clearance of tetrastarch is at least 20 times higher than that of hetastarch and pentastarch.<sup>6</sup> Pharmacodynamics regarding volume efficacy are strikingly dependent on the *in vivo* mean molecular weight and the colloid osmotic pressure.<sup>6</sup> Similarly, adverse effects on hemostasis are determined by the *in vivo* degradation of a particular HES preparation. Although methods for determination of the *in vivo* mean molecular weight have already been validated (low-angle laser light scattering, high-performance liquid chromatography), this clinically relevant information is still lacking in current product information of older HES solutions. Against this background, HES products will be grouped into slowly degradable and rapidly degradable compounds in this review as a surrogate parameter for the *in vivo* mean molecular weight. High-molecular-weight HES and medium-molecular-weight HES with a high molar substitution are classified as slowly degradable HES; medium-molecular-weight HES with a low molar substitution and low-molecular-weight HES are classified as rapidly degradable HES (table 1). In Europe, a large variety of HES products are commercially available but are dominated by rapidly degradable HES preparations, whereas slowly degradable HES preparations are mainly available in the United States (table 1). Solvents for HES molecules are either saline-based or buffered, balanced electrolyte formulations. Most 6% solutions have a volume expansion of approximately 100%, whereas 10% solutions

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Fig. 1. The structural formula of HES = poly(O-2-hydroxyethyl)starch. R = -H, -CH<sub>2</sub>CH<sub>2</sub>OH. R<sup>1</sup> = -H, -CH<sub>2</sub>CH<sub>2</sub>OH, or glucose unit. 1-6 = carbon atoms in positions 1-6. Enzymatic cleavage site of serum α-amylase (yellow arrow) at carbon atoms 1 and 4.



have an expansion of 130-145% due to the movement of water from the interstitial to the intravascular space. However, statements on volume effects are valid only for selected clinical situations with defined volume status at onset, infusion time, speed, and volumes applied.

Maximum daily doses of HES solutions have been recommended to prevent potential side effects. Recent developments center around designing new starch molecules (by modulating molar substitution, molecular weight, and C2/C6 ratio) that not only increase colloid osmotic pressure but also do not interfere with renal function, splanchnic perfusion, reticular endothelial system function, and inflammatory response and do not induce pruritus after long-term and repeated infusion, e.g., in the treatment of stroke, sudden hearing loss, and intensive care patients. Other adverse effects, such as anaphylactoid reaction, are not an issue of major clinical relevance because antigenicity is lowest for HES when compared with gelatin, dextran, and albumin.<sup>7,8</sup>

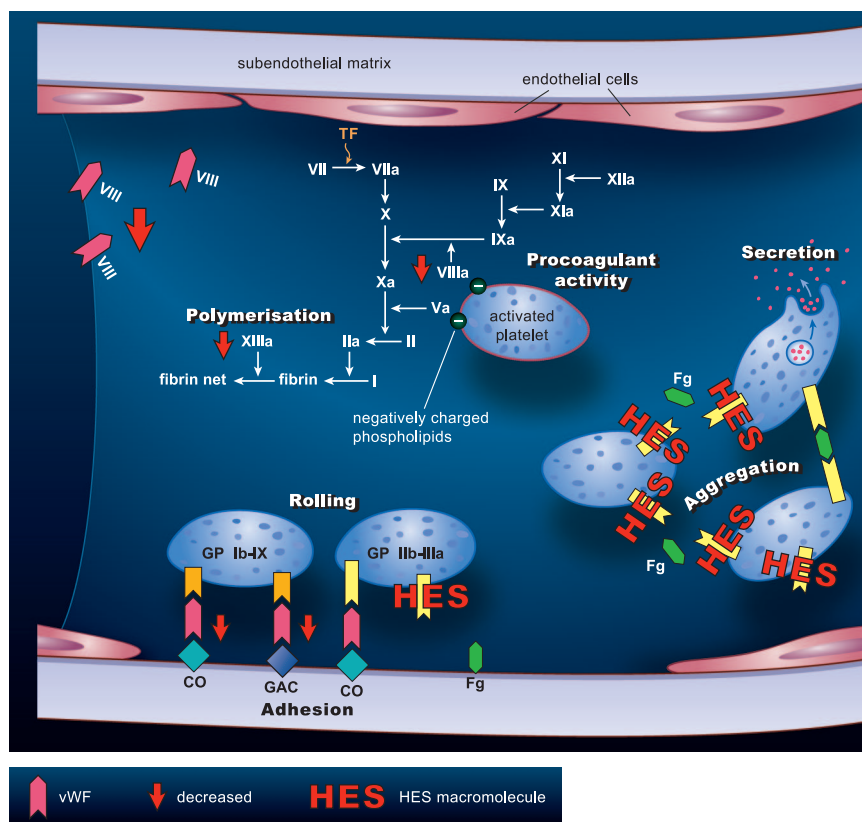
Effect of HES on Coagulation Factor VIII and von Willebrand Factor

Acquired von Willebrand syndrome and the decreasing effect on factor VIII of slowly degradable HES have been repeatedly observed since the introduction of slowly degradable HES solutions into clinical practice (fig. 2). Treib *et al.*<sup>3,4,9</sup> systematically investigated differences of HES preparations with regard to coagulation. Physicochemical differences have been shown to be important for the factor VIII/von Willebrand factor (vWF)-decreasing properties of particular HES preparations: Slowly degradable HES solutions have been consistently shown to decrease circulating plasma concentrations of coagulation factor VIII and vWF by up to 80% in healthy volunteers<sup>10-12</sup> and in patients<sup>6,13-16</sup> even when used below the recommended daily amounts of 25-50 ml/kg. The pathophysiologic consequence of the decrease in factor VIII and vWF is an impairment of functional parameters such as ristocetin co-factor activity or activated partial thromboplastin time.<sup>14</sup>

Table 1. Pharmacological profile of various hydroxyethyl starch solutions approved for volume expansion and commercially available in the European Union and U.S.A.

Degradation	Mean molecular weight (kiloDalton)	Molar substitution	C2/C6-ratio	Solvent (g/l)	Concentration (%) available in Europe (E) or U.S.A	Initial volume effect (%)	Maximum daily dose (ml/kg)
Rapid	70	0.5-0.55	3:1	NaCl (6.9), KCl (0.3), CaCl <sub>2</sub> H <sub>2</sub> O (0.22), sodium lactate (4.48)	6% E	100	20
	130	0.38-0.45	9:1	NaCl (9)	6% E	100	50
	200	0.4-0.55	5:1	NaCl (9)	6% 10% E	100 145	33 20
Slow	200	0.6-0.66	9:1	NaCl (9)	6% E	145	20
	200	0.6-0.66	9:1	NaCl (75)	6% E	400	4
	450	0.7-0.8	6:1	NaCl (9)	6% E	120	20
	670	0.75	4-5:1	NaCl (6.7), KCl (0.22), CaCl <sub>2</sub> H <sub>2</sub> O (0.37), sodium lactate (3.2), MgCl <sub>6</sub> H <sub>2</sub> O (0.1)	6% U.S.A.	100	20
	600	0.7	5:1	NaCl (9)	6% 10% U.S.A.	100	20
	480	0.7	5:3	NaCl (9)	6% U.S.A.	100	20

All statements are given by the manufacturers. Initial and duration of volume effect are valid for a defined experimental condition only and depend on volume status at infusion onset, infusion speed, infusion time, and volumes applied.



**Fig. 2.** Effect of hydroxyethyl starch molecules (HES) on hemostasis. Slowly degradable HES solutions decrease (red arrows) the plasma concentration of coagulation factor VIII and its carrier glycoprotein (GP) von Willebrand factor (pink symbols). Consequently, von Willebrand factor-mediated rolling and adhesion of platelets to subendothelial collagen (CO) and heparin-like glycosaminoglycans (GAC) involving platelet GP Ib-IX and GP IIb-IIIa (light yellow symbols) are impaired in the presence of HES. Reduced availability of activated GP IIb-IIIa by platelet surface coating of HES macromolecules (HES) impairs adhesion to surface-bound fibrinogen (Fg) and, most important, soluble fibrinogen (Fg) ligand binding between neighboring platelets causing platelet aggregation. Activated platelets expose negatively charged phospholipids (black dots) on their surface, which bind constituents of the prothrombinase (Va) and tenase complex (VIIIa; procoagulant activity). Consequently, reduced availability of the accelerator VIIIa results in diminished activation of factor X in the intrinsic coagulation pathway. HES impairs fibrin polymerization required for stable clot formation. The *in vivo* pharmacokinetic behavior of HES types, especially the *in vivo* molecular weight and HES plasma concentration, determine side effects on hemostasis: Rapidly degradable HES has fewer effects when compared with slowly degradable HES.

In contrast to slowly degradable HES, rapidly degradable HES solutions had no effects in orthopedic patients, in patients with cerebrovascular disease after chronic administration, and in volunteers<sup>6,11,16</sup> Recent trials reported the use of high tetrastarch doses of up to 50–70 ml/kg without deterioration of VIII.<sup>17,18</sup> In parallel to the lower *in vivo* molecular weight of tetrastarch, factor VIII and vWF returned to almost normal up to 5 h postoperatively, but not in hetastarch-treated orthopedic patients.<sup>6</sup> There is a physiologic increase in acute phase parameters such as coagulation factor VIII and vWF in the postoperative period starting at the time of arrival in the recovery room,<sup>13</sup> which plays a role in the postoperative hypercoagulability. Slowly degradable HES<sup>15,19</sup> but not rapidly degradable HES diminished the postoperative increase in factor VIII and vWF.<sup>20,21</sup>

#### Pathophysiology

The pathogenetic mechanism responsible for the adverse effects on plasmatic coagulation is not yet understood.

Although passive hemodilutional effects are observed immediately after infusion (such as the decrease in hemoglobin and fibrinogen concentration), vWF reaches its minimum 1–2 h afterward and exceeds the degree of decrease (20% *vs.* 47%) indicating additional mechanisms responsible for the decrease beyond the dilutional effect.<sup>11</sup> Nondilutional mechanisms, however, remain hypothetical. While each *in vivo* study found a decrease in factor VIII (although the decrease did not reach statistical significance in some studies<sup>19,22</sup>), *in vitro* studies did not reproduce the decreasing effect of HES on factor VIII (except for one recent experimental study<sup>23</sup>). This result may indicate the absence or blockade of the pathogenic mechanism in the *in vitro* testing milieu.

A decreased release is unlikely considering the half-life of vWF of 8 h. Antibody-mediated mechanisms also seem to be unlikely because of the rare occurrence of pre-formed HES antibodies.<sup>8</sup> Increased proteolytic degradation is unlikely because both small and large vWF multimers decrease similarly after HES infusion.<sup>3</sup> Association

of vWF with collagen has been suggested to regulate GP Ib binding function. Similarly, association with larger HES molecules may occur, and accelerated elimination after complexing has been considered as a pathogenic mechanism responsible for the adverse effect on factor VIII/vWF complex. In this context, it remains to be determined whether its association with HES molecules modulates vWF function and whether the interaction of vWF with platelet receptors blocked by HES molecules modulates vWF-cleaving protease secretion or activity.

### Effect of HES on Platelet Function

While focusing on the decrease in factor VIII and vWF, side effects of HES on platelet function have remained a blind spot until recently. Although the decrease in platelet volume observed after HES hemodilution<sup>5</sup> does not allow conclusions to be drawn about platelet function, the introduction of near-patient coagulation monitoring such as platelet function analyzer PFA-100 and thrombelastography and novel platelet testing techniques such as whole blood flow cytometry advanced our understanding of HES-dependent platelet effects. Similar to the plasmatic coagulation changes, physicochemical differences were found to be important for the platelet-inhibiting properties of particular HES preparations: Slowly degradable HES solutions have been found to prolong PFA-100 closure times significantly,<sup>24,25</sup> whereas rapidly degradable HES had minimal specific effects, if any, in healthy volunteers.<sup>24</sup> PFA-100 measures global platelet function that is dependent on the interaction of GP IIb-IIIa and GP Ib with their ligands, such as fibrinogen and vWF. HES-induced prolongations in PFA-100 closure times have been confirmed in the majority of studies,<sup>10,24,26</sup> but not in one study in which surgery *per se* may have counteracted the effect of HES on platelet function.<sup>20</sup> Platelet inhibition by HES molecules has been further investigated at the cellular level using flow cytometry, which permits evaluation of surface receptor expression and intracellular messenger status on individual platelets.<sup>24,25</sup> Our own recent experiments suggest that not only their physicochemical differences but also the composition of the solvent determines side effects of HES preparations on platelet function: The novel high-molecular-weight HES (670 kd, molar substitution 0.75) exerts platelet-stimulating effects which may be, at least in part, due to the high calcium concentration in the solvent.<sup>27</sup>

Fitting into the above elaborated picture, rapidly degradable HES did not decrease platelet aggregation,<sup>20</sup> whereas slowly degradable HES impaired platelet aggregation.<sup>28</sup> The aforementioned effects of HES on hemostasis have been further confirmed in multiple studies using either conventional or platelet inhibitor-modified thrombelastography: Changes in the speed and the quality

of clot formation have been documented extensively.<sup>11,19,22,29-31</sup> Thrombelastography confirmed that physicochemical characteristics of HES preparations significantly modify their side effects on blood coagulation and on thrombelastographic parameters indicative of platelet function (including angle  $\alpha$ , maximum clot firmness, and coagulation time), with slowly degradable HES having the most pronounced effect.<sup>11,29,30</sup> Thrombelastometric coagulation analysis, however, proved insensitive to detect the modest impact of molar substitution of two different rapidly degradable HES preparations in *in vitro* hemodilution.<sup>31</sup> The increasing understanding of the crucial importance of the *in vivo* molecular weight and the specific *in vivo* pharmacokinetic behavior of a particular HES preparation suggests that some experimental *in vitro* study designs may be inadequate to detect HES-dependent hemostatic side effects due to altered metabolic degradation and absent elimination *in vitro*.

### Pathophysiology

Platelet activation transforms the extracellular portion of platelet membrane GP IIb-IIIa complex into a conformational state that is competent for binding its ligands, such as soluble fibrinogen and vWF. This reaction is a prerequisite for platelet aggregation and irreversible adhesion to the subendothelium (fig. 2). Slowly degradable HES induces cellular abnormalities with a decreased agonist-induced expression and activation of platelet surface GP IIb-IIIa.<sup>24,25</sup> Reduced activated GP IIb-IIIa availability in turn leads to impaired platelet adhesion and aggregation and prolongs PFA-100 closure times. Slowly degradable HES molecules seem not to exert their inhibitory effect on platelet function by interfering with intracellular signal transduction because the agonist-induced increase in cytoplasmic calcium, the key second messenger in platelets, was unchanged in the presence of HES.<sup>32</sup> Platelet secretion is a downstream platelet function dependent on intracellular calcium. Supporting the independence of platelet-inhibiting HES effects on intracellular signal transduction, platelet secretion assessed by the expression of P-selectin, was not decreased<sup>24</sup> or was only slightly decreased<sup>33</sup> by slowly degradable HES. Further *in vitro* experiments investigated unspecific binding of fluorochrome-coupled HES molecules to the platelet surface as another potential mechanism of HES-induced platelet inhibition.<sup>34</sup> These flow cytometric experiments visualized extracellular coating of human platelets by HES macromolecules as proposed by early studies. HES may inhibit platelet reactivity by blocking the access of ligands to surface receptors (fig. 2) or by an unspecific modification of cytoplasmic membrane structures, and a consecutive inhibition of the conformational change of GP IIb-IIIa. It remains to be determined whether extracellular coating impairs platelet procoagulant activity by modifying the binding of constituents of the prothrombinase and tenase



complex to the negatively charged phospholipids exposed on activated platelets.

### Fibrinolysis

The effect of colloids on fibrinolysis has been discussed controversially. Some studies showed increased fibrinolysis *in vivo* and *in vitro* in the presence of HES,<sup>29,30,35</sup> whereas others found no effect.<sup>12,14,28</sup> Although a definite conclusion cannot be drawn from the available data, the effect of HES on fibrinolysis seems not to be of predominant clinical importance.

### Fibrin Formation and Fibrin Polymerization

Mild to moderate hemodilution with HES has been reported to accelerate the onset of clotting.<sup>11,22</sup> This phenomenon may be an *in vitro* artifact, or HES may serve as an additional surface able to activate coagulation factors, thus accelerating the conversion of fibrinogen to fibrin. In contrast to crystalloid-induced hypercoagulability, an imbalance between thrombin generation and antithrombin concentration is not suggested to be involved in HES-induced hypercoagulability.<sup>22</sup> Polymerization of fibrin monomers is impaired in the presence of HES macromolecules.<sup>22,36</sup>

### Clinical Aspects: Perioperative Blood Loss

Side effects of HES on the coagulation system have been accused of worsening clinical outcome.<sup>37</sup> A meta-analysis involving 16 trials and 653 randomized patients showed a significant higher postoperative bleeding in cardiopulmonary bypass patients exposed to slowly degradable HES than in those exposed to albumin.<sup>38</sup> The percentage of patients with excessive bleeding (> 1,000 ml) after cardiopulmonary bypass was significantly higher in the HES group.<sup>38</sup> This may increase costs of care because excessive bleeding triggers blood transfusion, prolonged mechanical ventilation, or reexploration for bleeding in many centers.

In contrast to slowly degradable HES, patients receiving rapidly degradable HES were not different with respect to blood loss and transfusion requirements after cardiac, major abdominal, and orthopedic surgery when compared with patients receiving gelatin or albumin.<sup>10,18,20,21,29</sup> In trials comparing various HES solution usage, there was a statistically significant difference favoring rapidly degradable HES. Mediastinal drainage was lower in recipients of pentastarch than in recipients of hetastarch.<sup>39</sup> Rapidly degradable HES, as compared with hetastarch, reduced the reoperation rate in cardiac surgery patients<sup>40</sup> and reduced requirements for transfusion of blood products in orthopedic surgery.<sup>16</sup> Decreased interaction with VIII, vWF, and platelet function of rapidly

degradable HES might translate to a smaller blood loss.<sup>6,31</sup> Even after repetitive large-dose infusion up to 70 ml · kg<sup>-1</sup> · d<sup>-1</sup> for up to 28 days, blood loss and transfusion of packed erythrocytes were lower in patients treated with rapidly degradable HES.<sup>17</sup> The increased therapeutic safety index of the tetrastarch HES 130/0.4 has recently been acknowledged by the European regulatory authorities by increasing the maximum daily dose to 50 ml/kg body weight per day.

### Clinical Aspects: Coagulation Monitoring

A growing body of evidence points to a reduction of transfusion requirements during various surgical settings when coagulation management algorithms are based on point-of-care tests instead of clinician discretion.<sup>41</sup> Clinically relevant monitoring options for the detection of side effects of HES on hemostasis include routine coagulation monitoring, such as activated partial thromboplastin time, coagulation factor VIII, and ristocetin cofactor activity, as well as near-patient monitoring, such as thrombelastography and PFA-100. Unfortunately, only the extent of change separates specific HES-dependent effects from dilutional coagulopathy *per se*, and this differentiation may become infeasible in bleeding patients who require massive transfusion.

### Clinical Aspects: Volume Efficacy

Hydroxyethyl starch solutions are used clinically as plasma expanders to restore and maintain intravascular volume, to stabilize hemodynamic conditions, and to improve tissue perfusion. Before giving recommendations on the use of slowly or rapidly degradable HES types in these specific clinical settings, the question about the extent and duration of their volume efficacy must be addressed. Residual plasma concentrations of slowly degradable HES are higher when compared with rapidly degradable HES.<sup>6</sup> Lower plasma concentrations, however, do not mean a lower number of osmotically active particles, because a given weight of HES contains more molecules in the case of lower molecular weight. Rapidly degradable tetrastarch and hetastarch were equally effective volume expanders because colloidal volume requirements for hemodynamic stabilization were similar.<sup>6,21,42</sup> Moreover, a recent study in major orthopedic surgery showed not only comparable osmotic pressure values but also a similar duration of volume efficacy of tetrastarch compared with hetastarch despite higher residual plasma concentrations of hetastarch and a higher *in vivo* molecular weight.<sup>16</sup> In volunteers undergoing acute hypovolemia, the volume effect sustained even longer after rapidly degradable tetrastarch than after hetastarch infusion.<sup>43</sup> Together, these results show that degradation rate does not correlate with the degree and duration of the volume effect.<sup>6</sup>

Pharmacodynamics regarding volume effect do not directly mirror HES pharmacokinetics. The plasma concentration half-life of HES must not be interpreted as efficacy half-lives.<sup>6</sup>

No considerable volume effects have been proven beyond 24 h despite substantial residual plasma concentrations, especially of slowly degradable HES. For maintaining volume expansion at this time point, repetitive doses are required for any HES type. Accumulation and tissue storage of HES molecules exert no therapeutic volume effect but rather induce side effects such as pruritus, organ dysfunctions, and modified inflammatory response. Prolonged persistence of HES in plasma and tissue can be avoided by using rapidly degradable HES types.<sup>44</sup>

## Practical Recommendations

Rapidly degradable HES seems to be a suitable volume expander in the routine perioperative setting because of the adequate volume efficacy and the low risk of hemostatic derangements. Restrictive use of slowly degradable HES types is recommended whenever hemostatic competence is critical (such as in neurosurgery) and potential bleeding sites are lethally dangerous, in patients with preexisting coagulopathies (such as von Willebrand disease and hemophilia), in an older population with increased susceptibility for HES-induced hemostatic side effects,<sup>26</sup> in critically ill patients who require repetitive HES infusions, or in patients with overt bleeding. In this clinical situation, replacement by rapidly degradable HES or by second-line colloidal infusions is recommended,<sup>22</sup> and general prothrombotic therapy is indicated. It is important to note that second-line colloidal infusions such as gelatin and dextrans share the same factor VIII- and vWF-decreasing potency and affect platelet function.<sup>45,46</sup> Even the natural colloid albumin has been reported to induce platelet dysfunction. Studies comparing the effects of different plasma substitutes (without the new generation of tetrastarch) on coagulation have previously been reviewed.<sup>45</sup> The effect of modified gelatin is similar to that of low-molecular-weight HES and albumin. The administration of desmopressin has been reported to reverse the decreasing effect of HES on factor VIII and vWF and to shorten bleeding times.<sup>14</sup> Other prothrombotic options for correction of specific hemostatic alterations induced by slowly degradable HES may include the substitution of a factor VIII-vWF concentrate or platelet transfusion that distributes HES macromolecules to an increased pool of platelets.

Hydroxyethyl starch-induced hemostatic changes may be either beneficial or unwanted, depending on the status of a given patient. Attenuation of the postoperative hypercoagulability as a physiologic component of the acute phase reaction after surgery by slowly degradable HES

solutions may be beneficial in patients at risk of thrombotic episodes. Long-term repeated infusion of slowly degradable HES *e.g.*, in patients with cerebral perfusion disorders who are at an increased risk of thrombosis may benefit from the HES-induced antithrombotic and platelet-inhibiting effects.

## Conclusion

This article is not intended to discourage the perioperative use of HES solutions, but it should alert clinicians to the potential for hemostatic alterations associated with HES resuscitation. The current data support the recommendation to differentiate between HES specifications and their corresponding pharmacokinetic characteristics. The low-molar substitution is the main determinant of increased metabolic degradation, which determines side effects of particular HES preparations on hemostasis. Slowly degradable HES (high- and medium-molecular-weight hetastarch HES) decrease plasma concentrations of coagulation factor VIII and vWF and impair platelet reactivity by reducing the availability of the platelet fibrinogen receptor glycoprotein IIb-IIIa and by decreasing platelet-linking properties of vWF. Rapidly degradable HES solutions (medium- and low-molecular-weight pentastarch HES and tetrastarch HES) have minimal influence, if any, on hemostasis. Proven volume efficacy and the beneficial risk difference for hemostatic derangements, postoperative blood loss, and reoperation rate favor rapidly degradable HES *versus* slowly degradable HES.

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