Update of use of hydroxyethyl starches in surgery and trauma

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Fluid management for trauma and surgery, at times, includes administration of asanguinous fluids. The past 2 years or 3 years have witnessed substantial controversy regarding the safety of intravenous hydroxyethyl starch (HES) preparations. In this short article, we review briefly the crux of the controversy, its applicability (if any) to surgery and trauma, and the data for the latter two clinical circumstances.

It is of substantial importance to recognize and understand differences among the many HES intravenous preparations. HESs vary by source material, average molecular weight (MW) as produced (in vitro), MW distribution as produced (in vitro), MW distribution in vivo (which differs from the in vitro values owing to metabolism and elimination), degree of molecular substitution, and ratio of C2 to C6 substitution (Table 1). HES compounds are generally labeled according to the MW and degree of substitution; for example, a molecule with an average MW of 200,000 with 62% substitution would be indicated as HES 200/0.62. They are also named commonly according to degree of substitution, using Greek terms, such that approximately 0.4 (40%) substitution is named as a "tetrastarch," while approximately 0.7 (70%) substitution is called a "hetastarch." In most of the world, the newer tetrastarches are used preferentially, while in the United States, the older hetastarches have the predominant use.

The molecular differences among HES molecules result in important pharmacokinetic and pharmacodynamic differences. Lower MW and lesser degree of substitution result in greater clearances and consequently shorter intravascular half-lives.[1,2] These differences are also reflected in the greater intravascular cumulative concentrations after multiple doses[3] and tissue concentrations after 24 days to 28 days of repetitive administration[4] with the larger and more substituted HES molecules. Tissue accumulation may be of some importance because it has been attributed by some as the possible cause of any putative adverse safety effects of HES. The effects of HES on tests of coagulation have been well reviewed[5,6] and are not be repeated here, other than to observe that the more modern tetrastarches have lesser effects. Of note, a randomized, blinded clinical trial comparing a hetastarch with a tetrastarch in major orthopedic surgery found a lesser effect on coagulation and lesser red blood cell transfusion with administration of a tetrastarch compared with administration of a hetastarch.[7] Colloids composed of large molecules, such as albumin, dextrans, and HES when administered, are used mainly because of their greater intravascular retention[8] owing to the function of the endothelial glycocalyx.[9] In this brief article, we address primarily the safety concerns regarding HES, with an emphasis on use in surgery and trauma. Some additional perspectives may be gained from other recent publications.[10–13]

Two large randomized "pragmatic" trials in the intensive care unit (ICU)[14,15] have fueled a controversy regarding HES use, in that some have sought to apply the findings in ICU patients to other clinical populations. These two reports have been the impetus, in large measure, for the US Food and Drug Administration (FDA) to issue a "safety update" including a warning to "…not use in critically ill adults, including those with sepsis… owing to increased risk of mortality and renal injury…" and that the "FDA considers increased mortality and renal injury a class effect" and because of "excess bleeding in cardiac surgery with CPB…"[16] and the European Medicines Agency declaring that HES solutions "must no longer be used in patients with sepsis or burn injuries or in critically ill patients… but may be used to treat hypovolaemia caused by acute blood loss where treatment with… crystalloids alone are not considered to be sufficient…" and that "HES solutions should not be used for more than 24 hours and patient's kidney function should be monitored after HES administration."[17]

An examination of the two reports[14,15] and a third ICU trial[18] is important to gain an appreciation why those results are not likely applicable to a surgical or trauma population. The relative merits and relevance of these trials have been more fully discussed elsewhere, and the reader is referred to that publication for a more full appreciation.[11] Briefly, "6S"[15] compared HES 130/0.42 with crystalloid and "CHEST"[14] compared HES 130/0.4 with crystalloid, in ICU patients, with 90-day mortality as primary end points. 6S studied HES 130/0.42 in only severely septic patients, finding a statistically significantly increased 90-day (50.5% vs. 43.0%, $p = 0.040$), but no statistically differences in 28-day mortality (38.7% vs. 36.0%, $p = 0.46$) or in the per-protocol analyses at 90 days (what we believe to be the correct and more informative analysis). CHEST studied HES 130/0.4 in a more general ICU population and found no mortality difference at 28 days (13.8% vs. 13.1%, $p = 0.42$) or 90 days (18.0% vs. 17.0%; $p = 0.28$) or in any of the analyzed subpopulations. The difference between the results of the two trials could be related to the different HES compounds studied or to the population differences, severely septic patients versus a general ICU population, with the former having a degraded endovascular glycocalyx[10] and thus an inability to retain large molecules solely in the intravascular space. Importantly, these trials seem to have used HES as volume maintenance over many days, rather than for acute resuscitation, as patients were enrolled many hours after ICU admission, at a time when it seems that intravascular volume was replete as reflected by central venous pressure values.

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TABLE 1. HES Products

Product	Concentration	Mean MW, kD	Molar Substitution	C2/C6 ratio
HES 670/0.75*	6%	670	0.75	4.5:1
HES 600/0.75*	6%	600	0.75	5:1
HES 480/0.7	6%	480	0.7	5:1
HES 200/0.62	6%	200	0.62	9:1
HES 200/0.5	6%, 10%	200	0.5	5:1
HES 70/0.5	6%	70	0.5	3:1
HES 130/0.4*	6%, 10%	130	0.4	9:1
HES 130/0.42	6%, 10%	130	0.42	6:1

*Available in the United States.

Frequently overlooked is the lesser incidence of new cardiovascular failure in CHEST in the HES group (36.5% vs. 39.9%, $p = 0.03$).

The observed renal effects defy logical physiologic interpretation in that the marginally statistically significant (p value just less than 0.05 for unadjusted data, 0.0495 in CHEST, 0.047 in 6S, or just greater than or at 0.05 for adjusted data, and not significant when combined with a SOFA [Sequential Organ Failure Assessment] score of ≥3) findings of increased use of subjective renal replacement therapy (RRT; without defined criteria for diagnosis or therapy, in these "pragmatic" trials) was not supported by the objective RIFLE data. In both trials, none of the reported analyses of the RIFLE criteria showed a worse result for the HES groups; the HES group had a lesser incidence of meeting RIFLE-R criteria in 6S and a lesser incidence of meeting RIFLE-R and RIFLE-L criteria in CHEST.[10] It is difficult to explain why the objective RIFLE results conflict with the subjective RRT results. One possibility is that clinicians unaware of the fluid administered and thus not understanding the differing pharmacokinetics of the fluid, interpreted the persisting intravascular HES as unresolving "fluid overload" prompting a more frequent use of RRT, despite equivalent or better RIFLE results in the HES-treated patients.[10]

Neither study reported usual data referable to hepatic injury. Substantial incidences of major protocol violations confound the interpretation of both trials.

In a somewhat different but important and relevant randomized, nonblinded clinical trial (CRISTAL), Annane et al.[18] compared colloids with crystalloids for true resuscitation, not maintenance, in 2,857 patients, including trauma, hypovolemic shock, and sepsis, but importantly, not septic shock. Judging from the location of the 57 sites, most of the HES administered was likely HES 130/0.4. There was no difference in the primary end point of 28-day mortality (p= 0.26), but as in 6S, mortality differed at 90 days ($p = 0.03$), *favoring colloid* in CRISTAL. There were no differences at 7 days or 28 days for RRT or organ failure, but those receiving colloids had a statistically significant lesser use of vasopressor therapy and mechanical ventilation. At 90 days (but not 28 days), those given HES had a lesser mortality than those given 0.9% NaCl (28.1% vs. 33.4%; $p = 0.023$ by our calculation using Fisher's exact test).

Nevertheless, some intensivists have argued (erroneously in our view) that these data support elimination of use of all HES compounds not only in all ICU patients but also in the general surgical and trauma populations—that is, they advocate that removal of all HES from clinical availability is warranted.

Surgery

There have been three recent reviews/meta-analyses of the safety of use of HES in surgery[19–21] (Table 2). In the first of these, Van Der Linden et al.[19] reviewed 59 publications of randomized clinical trials that tested any tetrastarch (only three trials reported data with HES 130/0.42) against any comparator in 4,529 patients undergoing surgery. Following carefully delineated a priori criteria, they found no hint of increased mortality, blood loss, incidence of allogeneic red blood cell transfusion, adverse renal effects (as assessed by change of or peak postoperative serum creatinine concentration or use of RRT) relative to all comparators. To the contrary, there was a strong suggestion in the 20 studies reporting transfusion data that patients given a tetrastarch had a lower incidence of red blood cell transfusion (386 [38.8%] of 995 vs. 479 [46.6%] of 1,027; odds ratio, 0.73; 95% confidence interval [CI], 0.61–0.87; $p = 0.0004$).

In a meta-analysis published shortly after the review of Van Der Linden et al.,[19] Martin et al.[20] examined 17 surgical trials of 1,230 patients randomly allocated to be given HES 130/0.4 or a comparator. They found no difference in worst postoperative serum creatinine concentration ($p = 0.65$) or acute renal failure ($p = 0.98$).

More recently, Gillies et al.[21] provided a meta-analysis of 19 surgical randomized trials of 6% HES that included 1,567 patients. They did not find any differences between HES and comparators for the examined end points of mortality (p = 0.91), RRT ($p = 0.62$), and acute kidney injury ($p = 0.34$). Similarly, there were no differences between groups for these end points for the trials in cardiac surgery. However, it should be noted that the mortality results of three categories (all surgical with all HES products, all surgical with tetrastarches only, and noncardiac surgery) are confounded by the inclusion of a trial conducted in critically ill postoperative patients, strictly in ICUs, with 47% of patients having severe sepsis at enrolment with a mortality of 49% and with an overall trial mortality of 26%[22] compared with cumulative trial mortality of less than 1% in all other studies analyzed. Exclusion of this single trial[22] by our calculations changes the probability values but does not change the result that mortality with HES did not differ from that of the comparators (p values of 0.26, 0.75, and 0.51,

TABLE 2. Summary of Recent Reviews/Meta-analyses of HES in the Perioperative Period

Review/Meta-analysis	Population	HES Examined	No. Trials	HES		Comparator		End Points	*p*
				n	Events (%)	n	Event (%)		
Van Der Linden et al.[19]	All Surgical	Tetrastarches	59	2,139	2,390			Total	
			21	956	11 (1.2)	982	22 (2.2)	Mortality	0.079
			38	1,602		1,678		Blood loss	*
			18	995	386 (38.8)	1,027	479 (46.6)	Transfusion	0.0004**
			21	1,005		1,051		Peak creatinine	†
			7	388	7 (1.8)	402	12 (3.0)	RRT	0.35
Martin et al.[20]	All surgical	HES 130/0.4	17		1,230‡			Total	
			14		1,005‡			Peak creatinine	0.65
			8		701‡			ARF	0.98
			§		531‡			RRT	0.85
			§		834‡			Mortality	NSD¶
Gillies et al.[21]	All surgical	6% HES		19	1,567			Total	
			18	685	19 (2.8)	776	46 (5.9)	In-hospital mortality	0.91‖
			17††	635	4 (0.6)	626	8 (1.3)	In-hospital mortality	0.26††
			5	204	11 (5.4)	197	7 (3.6)	AKI	0.34
			6	233	4 (1.7)	212	4 (1.9)	RRT	0.62
	All surgical	Tetrastarches	8	311	19 (6.1)	436	44 (10.0)	In-hospital mortality	0.83‖
			7††	261	4 (1.5)	289	6 (2.1)	In-hospital mort	0.75††
			5	192	3 (1.6)	190	4 (2.1)	RRT	0.73
	Noncardiac surgery	6% HES	8	271	19 (7.0)	318	43 (13.5)	In-hospital mortality	0.87‖
			7††	221	4 (1.8)	168	5 (3.0)	In-hospital mortality	0.51††
			3	106	10 (9.4)	99	7 (7.1)	AKI	0.43
			4	135	3 (2.2)	114	4 (1.0)	RRT	0.38
	Cardiac surgery	6% HES	10	414	0 (0.0)	458	3 (0.7)	In-hospital mortality	0.56
			2	98	1 (1.0)	98	0 (0.0)	AKI	0.56
			2	98	1 (1.0)	98	0 (0.0)	RRT	0.56

*Mean ratios of blood loss with HES/comparators: 0.75–1.01; upper 95% CIs of less than 1.0 for comparison with other HES or HSA, and inclusive of 1.0 for gelatin and crystalloid.
**Favors HES
†Mean ratios of peak creatinine with HES/comparators: 0.86–1.08 with all 95% CIs inclusive of 1.0.
‡Total number of patients reported; not separated by HES versus comparator.
§Data not reported.
¶NSD, described as not statistically different but no data reported.
‖Authors' analysis including that of Gondos et al.,[22] conducted in ICUs with 47% having severe sepsis with 49% mortality, with an overall trial mortality of 27%, compared with an overall mortality of approximately 1% in all other trials analyzed. See text.
††Not as reported, excludes that of Gondos et al.[22] Our recalculated approximate *p* values using a two-sided Fisher's exact test. These should be regarded as approximations because they are the synthesis of many trials rather than a single trial.
p indicates statistical probability, as reported by the authors, unless indicated otherwise
Following acceptance of this article, an additional meta-analysis examining HES use in cardiac was published online.[23] Those results have not been added to the tables, but they are consistent with the other reviews and analyses, that is, less blood loss and transfusion with tetrastarches compared with older starches; lack of adverse safety signals for blood loss, transfusion, and length of stay versus comparators; and lesser replacement volume than with crystalloids. In addition during this period, Kancir et al.[24] reported the results of a randomized blinded trial in 38 patients undergoing elective hip arthroplasty, finding no adverse renal effects of HES 130/0.4 compared with saline, as evidenced by urinary NGAL, serum creatinine, or creatinine clearance.
AKI, acute kidney injury; ARF, acute renal failure; transfusion, fraction of patients transfused.

respectively, are approximate as they result from a synthesis of the many trials, rather than a single trial). The authors concluded that while they could not find any adverse signal induced by HES use in surgery, they could not recommend the use of HES because of a lack of demonstrated benefit of any of these end points. We would note that the intended benefit of the various HES preparations has not been for those analyzed end points but for a more reliably persistent intravascular expansion than can be achieved with salt solutions.

In their analysis, Van Der Linden et al.[19] did not evaluate any surgical subgroup, thinking a priori that there would be insufficient data for any one subgroup to provide a meaningful analysis. We have reviewed the data for the 21 cardiac surgery trials examined in that publication that included 1,974 patients randomly allocated to receive either a tetrastarch or a comparator. There was no hint of greater blood loss with HES (but a suggestion that it was less with HES), fraction of patients transfused, peak postoperative serum creatinine, or mortality with HES compared with other fluids (Table 3). There were too few reports of RRT analysis to permit a meaningful analysis).

These three reviews/meta-analyses each found no adverse safety signal for the use of tetrastarch in surgery. Some have criticized the safety findings of nearly all surgical trials with HES in that follow-up was almost uniformly short (≤1 week). However, in this relatively more healthy population (compared with those critically ill in an ICU), severe adverse events (such as death

TABLE 3. Analysis of the Trials in Cardiac Surgery Used in the Analysis of Van Der Linden et al.[19]

Population	HES Examined	No. Trials	HES		Comparator		End Points	*p*
			n	Events (%)	n	Event (%)		
Cardiac surgery	Tetrastarches	21	902		1,072		Total	
		6	269	1 (0.4)	279	3 (1.1)	Mortality	0.62*
		19	762		792		Blood loss	**
		7	265	152 (57.4)	281	174 (61.9)	Transfusion	0.30*
		9	373		373		Peak creatinine	†

*These values should not be regarded as definitive because they are estimates based on the data from several studies.

**Formal statistical analysis not performed; ratio of blood loss, HES/comparator: 0.941; 95% CI, 0.885–0.997. These values should not be regarded as definitive because they are estimates based on the data from several studies

†Formal statistical analysis not performed; ratio of peak creatinine, HES/comparator: 1.018; 95% CI, 0.905–1.130. These values should not be regarded as definitive because they are estimates based on the data from several studies

Data not reported in the original publication but analyzed from the original data set.

Transfusion, fraction of patients transfused.

or need for RRT) would occur early and would be known to the physicians caring for the patients.

Trauma and Acute Hypovolemia

Current concepts in trauma management have centered on damage-control resuscitation with an emphasis on early provision of coagulation support in those patients requiring massive transfusion. However, the proportion of patients requiring massive transfusion is relatively low at less than 5% in the civilian population. Thus, the majority of trauma patients require asanguinous resuscitation, either alone or in support of transfusion with blood and blood products.

The evidence that the high-volume crystalloid resuscitation used in the past may be harmful is now conclusive, with clear evidence that crystalloid overload leads to an increased incidence of complications and even death.[25,26] One of the major concerns, particularly in burns resuscitation, is the development of secondary abdominal compartment syndrome[27] with excess crystalloid having been highlighted as the major factor in the development of this complication.[28] More recently, there has been an increased interest in the early use of colloid solutions in trauma resuscitation, and the evidence in favor of this has been reviewed recently.[29] However, there is a paucity of good-quality, randomized, controlled clinical trials comparing colloids and, in particular, HES with crystalloid for trauma resuscitation.

Several recent laboratory studies have consistently demonstrated that HES is superior to crystalloid in resuscitation from hemorrhage, particularly in terms of volume sparing, and this evidence has been recently summarized.[29] The pragmatic ICU studies referred to earlier have questioned the classical concept that colloid provides three to four times the volume effectiveness of crystalloid in the presence of hypovolemia. However, these studies did not examine hypovolemic patients, and it has been well shown that colloids are far more effective for volume expansion in the presence of hypovolemia than during normovolemia.[30] A recent, carefully controlled study of hemorrhagic resuscitation in piglets clearly demonstrated that in acute hypovolemia, HES is four to five times more effective than crystalloids in terms of both volume and rapidity of resuscitation.[31] It should be noted that not all HES restores blood volume equally after hemorrhage. In normal volunteers, a tetrastarch restored blood volume better than did a hetastarch.[32]

There have been three recent studies examining the role of HES solutions in trauma resuscitation (two retrospective chart reviews and one prospective randomized trial). In the first of these, a chart review assessed HES in a balanced salt solution (HES 650/0.7, Hextend) added to standard in-hospital resuscitation with crystalloids at the discretion of the attending medical staff.[33] Of 1,714 admissions to a Level 1 trauma center, 805 received HES, while 909 did not. The overall mortality in the HES group was 5.2% versus 8.9% in the standard-of-care group ($p = 0.0035$) on univariate analysis. On multivariate analysis, this difference no longer achieved statistical significance but remained favorable to the HES group (odds ratio, 0.63; 95% CI, 0.35–1.12; $p = 0.12$). There was no difference in the incidence of renal failure between the groups.[33]

The first randomized, controlled, double-blind study of crystalloids versus HES in trauma provided further evidence of the potential value of HES, with no evidence of harm. In this study, blunt trauma and penetrating trauma were randomized separately, and no real conclusions could be drawn regarding blunt trauma because the patients in this group receiving HES were substantially more seriously injured than their saline comparators. However, in the penetrating trauma patients (n= 67), there were clear-cut advantages for HES, with significantly more rapid lactate clearance in the first 4 hours of resuscitation. At Day 1, acid-base balance favored the HES patients in both blunt trauma and penetrating trauma, and for the penetrating trauma group, the lactate levels were significantly lower in the patients receiving HES. Importantly, in view of the controversy regarding HES and renal injury, there was no evidence that HES was associated with renal injury. On the contrary, the incidence of renal injury by RIFLE criteria was zero in the HES-treated penetrating trauma patients compared with 16% in the saline comparators ($p = 0.018$), despite these patients receiving an average of 70 mL/kg in the first 24 hours. Even in the blunt trauma group, there was no difference in the incidence of renal injury between HES and saline, despite the much more serious nature of the injuries in the HES group. The study not only demonstrated the efficacy of HES in acute hypovolemia but also

provided clear evidence that acute HES administration, even in very high doses, was not associated with renal injury in patients followed up for 30 days.[34]

The most recent publication in this area was a retrospective review of all patients admitted to a Level 1 trauma center who required massive transfusion. These patients were analyzed according to the type of asanguinous fluid support they received, either crystalloid or HES 650/0.7 (Hextend). Higher volumes of crystalloid were associated with an overall decrease in survival, while lower volumes of HES were associated with increased survival. The odds ratio for 10-day mortality of crystalloid compared with colloid was 8.41 (95% CI, 1.65–42.76; $p = 0.01$). The authors concluded that damage-control resuscitation combined with higher volumes of crystalloid was associated with a significantly higher mortality than damage-control resuscitation combined with the use of HES.[35]

There has been increasing interest in the use of colloids for burns resuscitation, and in this regard, albumin has been the most widely studied and, in recent publications, has been associated with a decrease in the incidence of "fluid creep" and of secondary abdominal compartment syndrome.[29] HES has been less well studied in burns, but one recent randomized, small (n = 26) trial compared a crystalloid-only regimen with one in which one third of the crystalloid was replaced with HES. In this study, HES-supplemented fluid resuscitation resulted in less fluid requirement, less interstitial edema, and decreased inflammatory response compared with patients receiving crystalloid alone. There was no evidence of an increased incidence of renal injury.[36]

Overall, there is growing evidence that HES provides favorable volume resuscitation in trauma patients, with a decrease in the volumes of crystalloid requirements and no evidence of harm either in terms of renal dysfunction or increased requirements for blood and blood products.

Summary/Conclusion

Independent of the important methodological and interpretative flaws of two trials of HES in ICU populations (exclusively or with a substantial fraction of septic shock), there are well-established physiologic and pharmacologic principles strongly indicating that it is inappropriate to apply those data to a surgical or trauma population. In addition, there are important therapeutic differences regarding HES use in these populations (multiple doses given over several days or weeks vs. administration only for several hours). Regulatory warnings and prohibitions do not adequately address these issues. The data derived from 59 randomized clinical trials in surgery that enrolled nearly 5,000 patients, with approximately half given a tetrastarch, do not suggest an adverse safety signal (mortality, blood loss, transfusion, renal) in these populations but rather point to lesser blood loss and transfusion in patients given a tetrastarch. Two meta-analyses in these populations confirmed the mortality and renal findings (blood loss and transfusion not evaluated). In hypovolemic volunteers, a tetrastarch restores blood volume better than does a hetastarch. The single randomized trial evaluating an HES (a tetrastarch) in trauma found greater lactate clearance and lesser renal injury in those with penetrating trauma who were given a tetrastarch rather than crystalloid. We conclude that there is an absence of adverse safety signals for the use of a modern HES in surgery and trauma and a possible indication of benefits in these clinical contexts.

AUTHORSHIP

Both authors wrote the manuscript. Both authors approved the final manuscript.

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R.B.W. has a current relationship with or consults for the following companies and organizations: US Food and Drug Administration; US National Heart, Lung, and Blood Institute/National Institutes of Health; US Department of Defense; Octapharma USA; HbO_2 Therapuetics; and TerumoBCT. In the past year, he has consulted for CSL Behring Sangart and OPK Biotech. He was also project/corp VP, Chief Medical Officer Biopharmaceuticals, and Executive Scientific Advisor at Novo Nordisk A/S 2005–2007. No one from any of these organizations influenced or participated in the writing or had any knowledge of this article.
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