CME

Intravenous Starches: Is Suspension the Best Solution?

Karthik Raghunathan, MD, MPH,*† Timothy E. Miller, MB ChB, FRCA,* and Andrew D. Shaw, MB, FRCA, FCCM, FFICM*†

IV fluid therapy may be the most common intervention in operating rooms (ORs) and intensive care units (ICUs) worldwide, yet the notion that "fluids are drugs" is underappreciated.[1] There is significant arbitrary variation in the choice of IV fluids typically used to maintain euvolemia and correct overt or presumed hypovolemia.[2,3] Fluid therapy may also be initiated preemptively to maximize blood flow as part of an intraoperative goal-directed therapy (GDT) protocol in moderate- and high-risk patients.[4–6] In all these contexts, the specific type of IV fluid used may potentially influence outcomes.

For decades, fluid choice has been a crystalloids versus colloids debate,[7] although there is tremendous heterogeneity within and across these groups. Despite physiologic expectations of significantly greater intravascular volume expansion with colloids,[8] clinical trials have found modest hemodynamic benefits in critically ill patients.[9,10] These differences in volume efficacy have not consistently translated into major differences in patient-centered outcomes,[7,11–14] and because colloids are more expensive, crystalloids have been recommended for resuscitation in ICUs.[15] In contrast, intraoperative GDT protocols often use synthetic hydroxyethyl starch (HES) colloid solutions for preemptive intravascular volume optimization[16] rather than albumin, and multiple studies have shown an improvement in outcomes with this goal-directed approach.[17] With the Food and Drug Administration (FDA) issuing a "black box" warning on the use of HES solutions in some settings (http://www.fda.gov/Safety/MedWatch/default.htm accessed June 24, 2013), clinicians may be uncertain about the risks versus benefits of HES in different clinical contexts. We offer perspective on the question of whether suspension of HES from clinical practice is the best solution to safety concerns.

How Did We Get Here?

Surveys over the last few years suggest that HES is widely used in Europe but less so in the United States.[2,3] In 2011, several articles on HES were retracted after investigations that received widespread press coverage.[18] The FDA convened a public workshop on the Risks and Benefits of HES in September 2012 as results from the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial on the safety of modern HES (tetrastarch solution) among critically ill patients with severe sepsis were reported.[19] The Crystalloid versus HydroxyEthyl Starch Trial (CHEST) that examined tetrastarch use in a heterogeneous group of ICU patients needing fluid resuscitation was reported subsequently.[10] By June 2013, the FDA had issued the safety advisory citing increased mortality and risk for severe renal injury in sepsis. Presently, the FDA recommends avoiding HES in patients with preexisting renal dysfunction, monitoring renal function for at least 90 days in all patients receiving HES, and discontinuing HES at the first sign of renal injury or coagulopathy among those undergoing cardiac surgery with cardiopulmonary bypass. The FDA announcement also cited a recent review of 6% tetrastarch (HES 130/0.4) among patients undergoing surgery[20] where, in contrast to the ICU findings, the authors concluded that there is no evidence of harm associated with tetrastarch when used intraoperatively or in the immediate postoperative period. Hence, while some clinicians support the use of tetrastarch among surgical populations,[20,21] others reject it in all settings.[22] Recently, the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial, an open-label randomized comparison of crystalloids against colloids early during resuscitation, reported a possible benefit for colloids when used during the resuscitation phase for acute hypovolemia.[23] However, fluid choice was not blinded in this study, and the fluids being compared were not specified because each site was allowed to choose a local alternative. Of note, most patients in the crystalloid group received saline while most in the colloid group received HES. Before addressing this discrepancy between randomized controlled trials (RCTs), we briefly review the pharmacology and toxicities of HES.

HES Pharmacology and Toxicities

Recent reviews have described the pharmacology of modern HES in detail.[24,25] In brief, HES is derived when amylopectin in potato or waxy maize is modified by the substitution of hydroxyl groups with hydroxyethyl residues on the glucose subunits.[24,26] The average number of hydroxyethyl residues per glucose unit defines the degree of molar substitution and has been decreasing from the older hetastarch to the newer tetrastarch solutions (from an average of 7 down to 4 residues per glucose subunit). In the plasma, HES is enzymatically hydrolyzed by α-amylase, and hydroxyethylation slows this process. The plasma elimination half-life is longer for highly substituted hetastarch (46 hours)

From the *Department of Anesthesiology, Duke University Medical Center; and †Durham VAMC, Durham, North Carolina.

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Address correspondence to Karthik Raghunathan, MD MPH, Department of Anesthesiology, Duke University Medical Center/Durham VAMC, DUMC 3094, Erwin Rd., Durham, NC 27710. Address e-mail to Karthik.Raghunathan@duke.edu.

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compared with the less substituted tetrastarch solutions (12 hours). FDA-approved product inserts recommend a higher maximal daily volume limit for tetrastarch (50 mL/kg per 24 hours) when compared with hetastarch (20 mL/kg per 24 hours).[25] In addition to these differences, HES products also differ based on the carrier fluid,[27] and 4 solutions are currently licensed in the United States: 2 hetastarch solutions suspended in saline (Hespan™ (B. Braun Medical Inc., Bethlehem, PA) and a generic hetastarch), a hetastarch in a balanced electrolyte solution (Hextend™, Hospira, Inc., Lake Forest, IL), and the modern 6% tetrastarch (Voluven™, Hospira, Inc., Lake Forest, IL) suspended in saline.[25] There may be such heterogeneity in the effects of different HES products in different situations that a summary aggregate measure of effects may be inappropriate. The recent FDA communication on the risks of HES does not draw any distinction among these different preparations.

Reviews have noted increased acute kidney injury and impaired coagulation with HES solutions that have higher degrees of molar substitution (hetastarch and pentastarch), particularly among septic and cardiac surgery patients, respectively.[11–14] There may be important differences between these and the modern tetrastarch formulations.[28,29] Tetrastarches (lower molar substitution) were promoted based on faster plasma clearance even with repeated administration.[25,30,31] However, the data on tissue uptake of modern HES are conflicting with reports of both increased and reduced tissue accumulation (mathematical models from human studies[26] versus 14C tracer-based animal studies).[30] Increased concentration in renal tissue has been described,[32,33] and histological findings may be consistent with those reported in clinical reports of impaired function.[33,34] However, the renal effects of exposure to limited amounts of intraoperative HES remain unclear. Perioperative studies, in contrast to the recent ICU trials, have generally had limited follow-up (not typically to 90-day outcomes) and have been small (i.e., underpowered to detect differences in renal-replacement therapy as an outcome).[20]

Risks of bleeding may differ depending on the formulation of HES[28] and the clinical situation (e.g., repeated use in cardiac surgery patients versus restricted use during GDT).[35] In vitro hemostatic impairments appear multifactorial involving impaired fibrin polymerization, decreased levels of factor VIII, vWF, and XIII,[28] and decreased availability of fibrinogen-binding sites on platelets.[36] However, clinical studies have shown reduced transfusion with modern tetrastarch when compared with the older starches during major surgery.[29,37] In post hoc analyses of trials 6S and CHEST,[10,19] receipt of blood products in the ICU appeared marginally larger in the HES group. The clinical relevance of such differences remains uncertain (e.g., an increase in use of blood products of 0.057 mL/kg/d in CHEST), but clinicians need to be aware of these findings when considering intraoperative HES therapy.

RCTs in the ICU

The CHEST (*n* approximately 7000)[10] and 6S (*n* approximately 800)[19] trials were primarily powered for safety outcomes among critically ill patients (Table 1). These large trials have informed the debate on use of modern HES in the ICU and account for most of the total sample size in current pooled meta-analyses.[34,38] They are relevant to clinicians as long-term patient-centered outcomes are emphasized, and although there are important similarities in results, there are also significant differences that may be masked in pooled estimates (Table 2). Even within ICU populations, differences in context appear to affect outcomes. First, death by 90 days was significantly more likely in the 6S trial but not in CHEST. A possible interpretation is that sicker ICU patients with a high baseline mortality risk (45% in 6S) are more likely to die when treated with large quantities of HES (aggregate dosage up to 44 mL/kg) when compared with patients at lower mortality risk (18% in CHEST) receiving lower aggregate doses (5 mL/kg).[39] Second, the 6S trial only recruited patients with severe sepsis, compared with the heterogeneous group of ICU patients in CHEST. Thus, it is possible that the increase in mortality with HES occurs

Table 1. Key Features of the 6S and CHEST Trials

Characteristic	6S	CHEST
Fluids contrasted	HES in Ringer's acetate versus Ringer's acetate (RA)	HES in saline versus saline
Number included in final analysis	HES (n = 398) versus RA (n = 400)	HES (n = 3358) versus saline (n = 3384)
Primary outcome	Composite of death or dialysis dependence 90 d after randomization	Mortality 90 d after randomization
Secondary outcomes	Several including the development of acute kidney injury	Mainly acute kidney injury and failure/treatment with renal-replacement therapy
Predicted baseline mortality rate for sample size estimation (APACHE II/SAPS II)	45%	26%
Observed mortality differences	HES (51%) versus RA (43%)[a]	HES (18%) versus saline (17%)
Relative risk for 90-d mortality	17% increase with HES[a]; 21% increase in shock subgroup[a]	No difference in 90-d mortality
Maximal study HES volume allowed	33 mL/kg/d	50 mL/kg/d
Net fluid balance on day 1[b]	HES (2206 mL) versus RA (2200 mL)	HES (1100 mL) versus saline (1200 mL)
Relative increase in use of renal-replacement therapy	35% (relative risk 1.35 [1.01 to 1.80])[a]	21% (relative risk 1.21 [1.00 to 1.45])[a]
Difference in blood products (post hoc analysis)	HES group (58.3%) received more packed red blood cell transfusions than RA group (45.5%)[a]	HES group received more blood products over 4 d[a]

Primary outcome (90-day mortality) was significantly worse in 6S, and there was no mortality difference in CHEST. The group randomized to receive hydroxyethyl starch (HES) saw a relative increase in the use of renal replacement therapy in both studies. Differences in the receipt of blood products may not be clinically relevant.

[a]Statistically significant difference.

[b]After randomization, difference in net fluid balance on day 1 was not significantly different.

Table 2. Relative Risk for Death in Prespecified Selected Subgroups of the 6S and CHEST Trials

Mortality in subgroups (%)	HES, %	Comparator, %	Mortality HES – comparator (risk difference), %
CHEST			
Trauma	7.0	6.8	0.2
APACHE II score <25	13.8	12.7	1.1
Acute renal injury present at randomization	19.1	18.9	0.2
Sepsis	25.4	23.7	1.7
APACHE II score ≥25	36.8	35.9	0.9
6S			
Acute renal injury present at randomization	50.7	45.0	5.7
Acute renal injury absent at randomization	50.7	42.3	8.4[a]
Shock at randomization	53.2	43.9	9.3[a]

Only the highest risk subgroups in 6S showed a statistically significant increase in the risk of death.
HES = hydroxyethyl starch.
[a]Statistically significant difference.

only in severe sepsis as even the sepsis subgroup in CHEST did not show a difference in mortality. Third, relative risks depend on event rates in the control group. Saline (used in CHEST) may be harmful in its own right when compared with balanced fluids like Ringer's acetate solution (used in the 6S trial).[40,41] Therefore, the hazard from HES may be harder to discern when comparing it with saline (CHEST) rather than with balanced fluids (6S trial). Last, renal morbidity was not entirely consistent in CHEST. Based on predefined criteria, HES appeared to improve certain renal outcomes compared with saline. Yet HES was more harmful in post hoc analyses based on changes in serum creatinine, and the use of renal-replacement therapy was also higher in patients randomized to HES, OR 1.20 (1.00–1.44).

It is important to note that the pragmatic study design in trials 6S and CHEST meant that clinicians used fluids without explicit algorithms. The concept of volume responsiveness is critical because fluid therapy administered to "volume nonresponders" is potentially harmful.[42] In both CHEST and 6S trials, initial resuscitation had occurred before randomization. Hence, the quantitative harm from receipt of unnecessary fluids may have been compounded by the qualitative harm from fluid type (in this case, HES). Recently, the CRISTAL trial reported a practical randomized comparison of crystalloids versus colloids among patients with acute hypovolemia[23] but had potential for bias due to a lack of blinding. The primary 28-day mortality outcome was equivalent, while the secondary 90-day mortality outcome showed an advantage for colloids (0.88; 95% confidence interval, 0.77–0.99). The colloid group also had more days alive and more days without vasopressor therapy and mechanical ventilation at 7 and 28 days. Proponents of HES may cite the lack of a mortality difference in CHEST and highlight better mortality outcomes among acutely hypovolemic patients in the CRISTAL trial, emphasizing the importance of volume context during administration of HES. However, the possible benefits in secondary outcomes observed in CRISTAL need to be confirmed in further studies.

Perioperative HES: Context Is Key

What inferences regarding use of HES in the intraoperative period can one make based on RCTs conducted on ICU populations? We believe that context is crucial: the population at-risk; interventions being compared; and outcomes being evaluated need to be carefully contrasted in order for clinicians to weigh the situational risks and benefits of therapy in the OR versus in the ICU.[43] More than 2800 patients randomized in CHEST were in the ICU postoperatively (after emergent or elective noncardiac and nonliver transplantation surgery). As subset results are not yet available, it is unclear whether outcomes in this subset were similar to that of the entire cohort. Regardless, these data may not adequately inform clinicians about the risks versus benefits of intraoperative volume optimization with HES. The traditional Starling model of forces governing IV fluid disposition is being revised with increasing insight into the role of the endothelial glycocalyx layer and volume context,[44,45] and physiologic appraisal suggests that traditional colloid-crystalloid distinctions may be of less importance than previously thought. The risk of using modern tetrastarch in the setting of an intact glycocalyx in the patient undergoing intravascular volume optimization early during major surgery may be potentially different than risks associated with severe sepsis where there is significant glycocalyx shedding and disruption. From a clinical standpoint: first, patients presenting for preemptive volume optimization (the population-at-risk) have a lower predicted mortality at baseline (compared with ICU patients). Assessment of mortality risks associated with use of HES during GDT would require a very large RCT (rare outcome). Second, HES during GDT is restricted to those instances where flow improves with fluid administration.[4,5] As suggested by the CRISTAL trial, safety outcomes may be equivalent or favor colloids when patients are volume responsive. Third, safety risks from HES might not be relevant if the alternative is potentially harmful such as the empiric use of large volumes of saline.[40,46] It is possible that the risk of harm could actually increase when albumin or saline boluses are used.[47] By addressing occult hypovolemia early during major surgery, GDT could improve outcomes and lower the risk of harm from HES.

As the trend in perioperative fluid therapy moves toward a more restrictive approach, it may become even more difficult to appreciate outcome differences between different fluid types. The total administered volume may be more important than the type of fluid given.[48] We suggest that Bellamy's[49] as well as Kehlet and Bundgaard-Nielsen's[50] descriptions of the relationship between toxicity (risk) and fluid dose (or volume status) may help clinicians conceptualize these potential differences. This dose-toxicity curve may be modified by patient characteristics (cardiovascular disease and other comorbidities,

critical illness), surgical factors (inadequate modulation of the surgical stress response), and fluid choice. Curves may be U shaped in the OR and V shaped in the ICU, reflecting narrow physiologic reserves in the critically ill and a greater safety margin in the OR. Individualized goals target the augmentation of preload to achieve euvolemia. In contrast, a traditional arterial blood pressure and urine output-guided approach may be associated with increased risks. For example, the clinician's response to low blood pressure or oliguria may be fluid therapy although vasopressors (in distributive shock states like neuraxial blockade) or inotropes/diuretics (cardiogenic shock state) may be indicated.

The Gap in the Evidence and Where Do We Go from Here?

RCTs powered for short-term efficacy outcomes may not offer any insight into safety. For instance, in the CRYSTMAS trial that was conducted to fulfill a postmarketing regulatory requirement, Guidet et al.[51] compared Voluven™ with saline in patients suffering from severe sepsis, and the primary outcome was the fluid amount required to achieve initial hemodynamic stability. Investigators found that slightly less HES was needed but also concluded that there was no evidence of long-term harm, which was inconsistent with the results of the larger 6S trial where long-term harm was demonstrated. Similarly, Feldheiser et al.[52] compared balanced tetrastarch with balanced crystalloids within a GDT context, finding a modest and proximal efficacy advantage. There is no GDT trial large enough with a follow-up period long enough, to draw definitive conclusions regarding the risks of intraoperative HES. There is a significant likelihood of type II errors for safety outcomes. Benefit may be modest and plateau early, while toxicity may be cumulative and occur late. Rather than draw conclusions about intraoperative safety from underpowered studies, we believe that clinicians should ask if an adequately powered trial should be designed for that specific clinical context. As shown by Yates et al.,[53] crystalloids can be used for GDT, but more volume will be needed. For patients in whom this excess in volume may need to be avoided, HES might offer benefits potentially without (measurable) harm. Hence, the gap in the literature, the relationship between use of colloid during GDT and long-term patient-centered outcomes, needs to be filled. We recommend that future RCTs focus on safety outcomes over an extended postoperative period as suggested by Myles and Devereaux[54] (disability-free survival at 1 year). In addition, we also suggest that future studies on fluid choice examine the effects of variable chloride content and strong ion difference.

CONCLUSIONS

Careful consideration of quantitative and qualitative toxicities is needed. Timing of therapy, volume context, fluid type, patient comorbidities, mortality risk, and the type of surgical procedure (effects on the endothelial glycocalyx) are all relevant but beyond the scope of this discussion. There may yet be a role for perioperative HES but precisely who will benefit and how much is unclear. To work within the recent regulatory restrictions placed on HES, clinicians may find the following considerations helpful:

- Define the problem that IV fluid therapy is intended to solve. For example, volume responsiveness does not equal volume deficiency. Conversely, volume deficiency should be assessed by testing for volume responsiveness rather than assumed based on changes in blood pressure or urine output.
- Define the goal of therapy. This may vary according to the clinical setting. With active bleeding, for example, the goal may be to allow moderate hypotension until surgical control is established rather than to volume load with crystalloids. In contrast, the goal with preemptive GDT is to fluid load for maximal stroke volume.
- Determine the type of fluid to use. We believe that balanced crystalloid solutions may be a safe default for most situations. Colloids may be indicated in specific settings such as to avoid large crystalloid volumes during the management of acute hypovolemia or in preemptive GDT.
- Delineate starting and stopping points with monitoring for response during treatment. This implies measuring end-organ perfusion, recognizing that this varies by organ.

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Contribution: This author helped in manuscript preparation.
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Name: Timothy E. Miller, MB ChB FRCA.
Contribution: This author helped in manuscript preparation.
Attestation: Timothy E. Miller approved the final manuscript.
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Name: Andrew D. Shaw, MB FRCA FCCM FFICM.
Contribution: This author helped in manuscript preparation.
Attestation: Andrew D. Shaw approved the final manuscript.
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This manuscript was handled by: Steven L. Shafer, MD.

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