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Hydroxyethyl starch in severe sepsis: end of starch era?

Carlos A Estrada[1] and Raghavan Murugan[1,2]*

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Expanded abstract

Citation

Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group: **Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.** *N Engl J Med* 2012, **367:**124-34.

Background

Hydroxyethyl starch (HES) is widely used for fluid resuscitation in ICUs, but its safety and efficacy have not been established in patients with severe sepsis.

Methods

Objective: To assess the effects of HES 130/0.4 compared with a balanced crystalloid solution on mortality and end-stage kidney failure in patients with severe sepsis.
Design: Multicenter, parallel-group, blinded, randomized clinical trial, in patients with severe sepsis.
Interventions: Patients with severe sepsis admitted to the ICU received fluid resuscitation with either 6% HES 130/0.42 (Tetraspan) or Ringer's acetate at a dose of up to 33 ml per kilogram of ideal body weight per day.

Results

Of the 804 patients who underwent randomization, 798 were included in the modified intention-to-treat population. The two intervention groups had similar baseline characteristics. At 90 days after randomization, 201 of 398 patients (51%) assigned to HES 130/0.42 had died, as compared with 172 of 400 patients (43%) assigned to Ringer's acetate (relative risk, 1.17; 95% confidence interval (CI), 1.01 to 1.36; P = 0.03); 1 patient in each group had end-stage kidney failure. In the 90-day period, 87 patients (22%) assigned to HES 130/0.42 were treated with renal replacement therapy versus 65 patients (16%) assigned to Ringer's acetate (relative risk, 1.35; 95% CI, 1.01 to 1.80; P = 0.04), and 38 patients (10%) and 25 patients (6%), respectively, had severe bleeding (relative risk, 1.52; 95% CI, 0.94 to 2.48; P = 0.09). The results were supported by multivariate analyses, with adjustment for known risk factors for death or acute kidney injury at baseline.

Conclusions

Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal replacement therapy compared with those receiving Ringer's acetate.

Commentary

Fluid resuscitation is the cornerstone of treatment for patients with hypovolemia due to severe sepsis [1]. Colloids are used as they are thought to remain in the intravascular space longer, achieve faster circulatory stabilization [2], and require less amount of fluid for resuscitation compared with crystalloids [3]. Hydroxyethyl starches (HESs) are synthetic colloids composed of amylopectin obtained from maize or potato starch and vary in their molecular weight, hydroxyethyl moieties, and in the ratio of C2 to C6 substitutions [4].

Results of clinical trials comparing resuscitation with colloids and crystalloids have been conflicting. Compared to modified Ringer's lactate solution, resuscitation with HES 200/0.5 has been associated with increased risk of acute kidney injury (AKI) and requirement of renal replacement therapy [5]. Another recent study (CRYSTMAS) found that resuscitation with low molecular weight HES 130/0.4 was associated with less time to hemodynamic stabilization and no difference in

*Correspondence: muruganr@ccm.upmc.edu
[1]Department of Critical Care Medicine, 642A Scaife Hall, 3550 Terrace Street, University of Pittsburgh, Pittsburgh, PA 15261, USA
Full list of author information is available at the end of the article

AKI, renal replacement therapy, and mortality compared to resuscitation with 0.9% saline [2]. However, this study was underpowered to detect differences in mortality and establish safety of low molecular weight HES [6].

In this trial, Perner and colleagues [7] elegantly demonstrate that patients with severe sepsis who received fluid resuscitation with HES 130/0.42 had increased mortality, increased risk of renal replacement therapy, a trend for increased bleeding, and increased blood product transfusion when compared to resuscitation with Ringers acetate. Interestingly, the study did not find that patients who received colloids require less amount of fluid when compared to crystalloids. Strengths of the study include being well-designed and adequately powered with broad inclusion criteria and low risk of bias due to double-blinding and the multicenter nature of the trial. Importantly, the study measured patient-centered long-term clinical outcomes, such us 90-day mortality and renal replacement therapy. Since Ringers acetate was a vehicle for HES in the intervention arm and was also the fluid in the control arm, it allows one to examine the causal effect of HES on outcomes.

The few limitations of the study include a lack of a control for co-interventions and protocol violation. Of 69 patients with protocol violation, 28 patients in the HES group and 41 patients in the Ringers acetate group received trial fluid at doses higher than the maximum specified in the protocol. Moreover, the criteria for initiation of renal replacement therapy were not pre-specified in the study protocol, and the determination of requirement of fluid for resuscitation was based on clinician judgment rather than more objective hemodynamic parameters.

Several important points related to the mechanisms of harmful effects of HES deserve further consideration. First, the study showed that resuscitation with HES was associated with increased risk of AKI requiring renal replacement therapy compared to resuscitation with Ringer's acetate (22% versus 16%, $P = 0.04$). This study adds to the growing body of literature that suggests that HES, independent of the molecular weight or molar substitution, increases the risk of AKI in an at-risk population [8]. Although not well understood, potential mechanisms by which HES might cause AKI include increased uptake of the starch into the proximal renal epithelial cells inducing 'osmotic nephrosis-like lesions', tubular obstruction caused by the production of hyperviscous urine, and renal interstitial inflammation [9].

Second, more patients receiving HES compared to Ringers acetate received blood product transfusions (relative risk, 1.20; 95% confidence interval (CI), 1.07 to 1.36; $P = 0.002$) with higher volumes (cumulative median blood product volume, HES versus Ringers acetate, 1,340 versus 1,055 ml; $P = 0.003$). Multiple studies have demonstrated that HES molecules were associated with platelet dysfunction, interact with the coagulation cascade, and decrease factor VIII and von Willebrand factor levels [4] and fibrin polymerization [10]. Importantly, increased bleeding tendency has also been observed with use of low molecular weight starches [11].

Maize-derived and potato-derived HESs (as used in the study by Perner and colleagues) have structural differences due to differences in the percentage of amylopectin (98% versus 75%) and C2/C6 substitution ratio (9:1 versus 6:1) [4]. However, there is conflicting evidence regarding whether this structural difference has a clinical impact. For instance, while molecular studies demonstrate biochemical differences between these two starches [12], *ex vivo* studies show no difference in bleeding effects [10]. These findings suggest that the risk of AKI and increased bleeding diathesis associated with HES is a class effect of starches rather than its molecular weight or molar substitution [8].

Another recent large (n = 7,000) clinical trial (CHEST) found no difference in 90-day mortality between HES 130/0.40 and 0.9% saline in a heterogeneous group of critically ill patients [13]. However, the need for renal replacement therapy was higher among patients who received HES (7.0% versus 5.8%; relative risk, 1.21; 95% CI, 1.00 to 1.45; $P = 0.04$) compared to saline. Moreover, patients in the CHEST trial were less severely ill than patients in the study by Perner and colleagues, and in the subgroup analysis of patients with severe sepsis, there was a trend towards increased AKI and mortality in those who received HES.

More recently, when taking into consideration the absence of significant clinical benefit and the potential harmful effect of starches based on the above studies, the 2013 surviving sepsis campaign [14] recommended against using any HES in patients with severe sepsis. Another recently completed large (n = 3,000) clinical trial (CRYSTAL) [15] comparing crystalloids and colloids will provide additional insight into HES fluid resuscitation on clinical outcomes.

Recommendation

Fluid resuscitation with HES 130/0.4 increases risk of AKI requiring renal replacement therapy and mortality in patients with severe sepsis. Given evidence of harm and lack of significant clinical benefit, HES 130/0.4 should not be used for fluid resuscitation for critically ill patients with severe sepsis.

Abbreviations

AKI, acute kidney injury; CI, confidence interval; HES, hydroxyethyl starch.

Competing interests

The authors declare that they have no competing interests.

Author details
[1]Department of Critical Care Medicine, 642A Scaife Hall, 3550 Terrace Street, University of Pittsburgh, Pittsburgh, PA 15261, USA. [2]The Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

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References

1. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut J-F, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent J-L: **Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008.** *Crit Care Med* 2008, **36:**296-327.
2. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A, Van Aken H: **Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study.** *Crit Care* 2012, **16:**R94.
3. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R: **A comparison of albumin and saline for fluid resuscitation in the intensive care unit.** *N Engl J Med* 2004, **350:**2247-2256.
4. Westphal M, James MFM, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H: **Hydroxyethyl starches: different products--different effects.** *Anesthesiology* 2009, **111:**187-202.
5. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K: **Intensive insulin therapy and pentastarch resuscitation in severe sepsis.** *N Engl J Med* 2008, **358:**125-139.
6. Hartog CS, Reinhart K: **CRYSTMAS study adds to concerns about renal safety and increased mortality in sepsis patients.** *Crit Care* 2012, **16:**454.
7. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard A-L, Fabritius ML, Mondrup F, Pott FC, Møller TP, *et al.*: **Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.** *N Engl J Med* 2012, **367:**124-134.
8. **National Heart, Lung, and Blood Institute (NHLBI) and Food and Drug Administration (FDA) Public Workshop: Risks and Benefits of Hydroxyethyl Starch Solutions** [http://www.nhlbi.nih.gov/meetings/workshops/Hydroxyethyl.htm]
9. Claus RA, Sossdorf M, Hartog C: **The effects of hydroxyethyl starch on cultured renal epithelial cells.** *Anesth Analg* 2010, **110:**300-301.
10. Godier A, Durand M, Smadja D, Jeandel T, Emmerich J, Samama CM: **Maize- or potato-derived hydroxyethyl starches: is there any thromboelastometric difference?** *Acta Anaesthesiol Scand* 2010, **54:**1241-1247.
11. Navickis RJ, Haynes GR, Wilkes MM: **Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials.** *J Thorac Cardiovasc Surg* 2012, **144:**223-230.
12. Lehmann G, Marx G, Förster H: **Bioequivalence comparison between hydroxyethyl starch 130/0.42/6 : 1 and hydroxyethyl starch. 130/0.4/9 : 1.** *Drugs R D* 2007, **8:**229-240.
13. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SAR: **Hydroxyethyl starch or saline for fluid resuscitation in intensive care.** *N Engl J Med* 2012, **367:**1901-1911.
14. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent J-L, Moreno R: **Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012.** *Crit Care Med* 2013, **41:**580-637.
15. ClinicalTrials.gov: **Efficacy and Safety of Colloids Versus Crystalloids for Fluid Resuscitation in Critically Ill Patients** [http://clinicaltrials.gov/ct2/show/NCT00318942]

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