CJEM Journal Club

Pentastarch resuscitation in severe sepsis and septic shock

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Clinical question
Does resuscitation with pentastarch reduce mortality when compared with resuscitation using Ringer lactate in patients with severe sepsis or septic shock?
Article chosen
Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125–39. (The VISEP trial)
Study objective
The authors of this study sought to assess the safety and efficacy of intensive insulin therapy compared with conventional insulin therapy in patients with severe sepsis or septic shock. In addition, they evaluated the safety and efficacy of hydroxyethyl starch (HES) compared with Ringer lactate in patients in the same patient population. We will discuss only the comparison of HES with Ringer lactate.

BACKGROUND

Few data are available to guide the choice of colloid or crystalloid for fluid resuscitation in patients with severe sepsis or septic shock.[1,2] A large randomized controlled trial of 4% albumin versus 0.9% saline in a heterogeneous group of critically ill patients found no differences between the solutions, although a subgroup analysis suggested a potential benefit of albumin use in severely septic patients.[3] Hydroxyethyl starch (HES) solutions are an alterative colloid solution, and have been increasingly used for intravascular volume resuscitation.[4] However, definitive clinical evidence to support the use of HES solutions in severe sepsis or septic shock is lacking.

STUDY DESIGN AND PATIENT POPULATION

The study was a prospective, multicentred, randomized, open-label trial with a 2 × 2 factorial design. Patients were recruited from multidisciplinary intensive care units (ICUs) at 18 academic tertiary care hospitals in Germany. Patients 18 years of age or older with severe sepsis or septic shock were eligible for enrolment. Patients were eligible for inclusion if the onset of severe sepsis or septic shock was less than 24 hours before admission to the ICU, or less than 12 hours after admission if the condition developed in the ICU. For the purpose of outcome measurement, the treatment period ended 21 days after randomization, or at discharge from the ICU or at the time of death. Patients were ineligible for inclusion if they

- received more than 1000 mL of HES in the 24 hours before randomization;
- had pre-existing renal failure requiring dialysis or a serum creatinine greater than 320 µmol/L;
- required an inspired oxygen fraction greater than 0.7;
- had an intracerebral hemorrhage;
- had New York Heart Association class IV heart failure;
- had immunosuppression with cytotoxic chemotherapy; or
- had AIDS or were taking high-dose steroids.

Patients were randomly assigned to receive 10% pentastarch, a low molecular weight HES or Ringer lactate. During the 96 hours after randomization, a resuscitation protocol was employed to achieve a central venous pressure of 8 mm Hg. If, during that period, the mean

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arterial pressure was less than 70 mm Hg, and mixed venous oxygen saturation was under 70%, the treating physician decided on further measures (fluid repletion, vasopressors and/or inotropes) to raise mean arterial pressure and mixed venous oxygen saturation to prespecified ranges. Decisions on further fluid resuscitation for sepsis-related volume depletion after 96 hours was left to the discretion of the treating physician; however, the study arm assignment resulted in some stipulations in this regard. In the HES group, HES was given until a limit of 20 mL/kg/d, then, preferentially, Ringer lactate or other noncolloid fluid was to be administered after this threshold was reached. In the Ringer lactate group, only additional Ringer lactate could be administered.

OUTCOME MEASURES

The co-primary outcomes were death from any cause at 28 days and morbidity as measured during the intervention by the mean score on the Sequential Organ Failure Assessment (SOFA).[5] Secondary outcomes included acute renal failure (defined as a doubling of the baseline serum creatinine level or need for renal replacement therapy), time to hemodynamic stabilization, use of vasopressor therapy, mean SOFA subscores, red-cell transfusions, duration of mechanical ventilation, length of ICU stay and 90-day mortality rate.

RESULTS

After a preplanned interim analysis of 600 patients, the Data and Safety Monitoring Board terminated the trial because of an increased rate of acute renal failure and a trend toward greater 90-day mortality among patients who received HES.

Among the 537 patients who could be evaluated, there was a higher rate of acute renal failure (34.9% v. 22.8%, absolute risk increase [ARI] 12.1%, number needed to harm [NNH] 8, $p = 0.009$), and an increased requirement for renal replacement therapy (31% v. 18.8%, ARI 12.2%, NNH 8, $p = 0.001$) in the HES group. The rate of death at 28 days was not different between the HES and the Ringer lactate groups (26.7% v. 24.1%, $p = 0.48$). However, there was a trend toward a higher rate of death at 90 days in the HES group (41.0% v. 33.9%, $p = 0.09$). The adverse effects appeared to be dose-related, as patients who received higher doses of HES (> 22 mL/kg for at least 1 day) had a higher 90-day mortality when compared with patients who received lower doses (< 22 mL/kg) (59.6% v. 30.9%, ARI 28.7%, NNH 3, $p < 0.001$). The mean SOFA scores did not differ significantly between the HES group and the Ringer lactate group (8.0 v. 7.5, $p = 0.16$). For patients in the intensive insulin group, there was a trend toward an interaction with HES, based on the renal SOFA score (odds ratio 2.65, 95% confidence interval 1.51 to 4.68, $p = 0.06$) suggesting that the combination of HES and intensive insulin control may affect renal dysfunction in a manner that was not anticipated before the study design. Patients in the HES group also had a lower median platelet count ($p < 0.001$) and received more units of packed red blood cells ($p < 0.001$).

COMMENTARY

Severe sepsis and septic shock are commonly encountered in emergency departments (EDs), and are associated with high patient mortality.[4,6–8] Optimal management includes early recognition, broad spectrum antimicrobial administration and aggressive resuscitation.[9,10] Rapid intravenous fluid administration is a resuscitation priority to correct hemodynamic instability and tissue hypoperfusion associated with these conditions.

Various fluid solutions are available in the ED for the restoration of intravascular volume.[11] Traditionally, fluids have been classified as crystalloids (0.9% saline, Ringer lactate) or colloids (albumin, HES, dextrans or gel solutions). The relative merits of each class of solution have been debated for decades.[12–14] Systematic reviews on resuscitation fluids have resulted in conflicting conclusions.[1,2,15–18] Recently, a prospective, randomized, double-blind study of 6997 patients requiring intravascular volume resuscitation in an intensive care setting compared normal saline and 4% albumin (the Saline Versus Albumin Fluid Evaluation [SAFE] trial). The use of 4% albumin was found to have no benefit over 0.9% saline, as there was no difference in 28-day mortality, ICU length of stay or hospital length of stay.[3]

Hydroxyethyl starch solutions were developed as an alternative colloid for intravascular volume expansion, and are now the dominant colloid used for resuscitating critically ill patients.[19,20] Synthetic HES solutions are modified polysaccharides and are similar to human glycogen.[19] Numerous HES fluids are available and possess different physiochemical characteristics based on molecular weight, molar substitution, and the ratio of hydroxyethyl substitution at the C2 or C6 position (C2:C6 ratio).[11,19,21] Currently, 3 HES solutions (Pentaspan, Voluven and Hespan) are available in Canada, although little data are available of their use in the ED.

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Concerns with the administration of HES have been voiced by various authors.[2,10,12,18,21] Recently, adverse events associated with HES use has been increasingly documented in the literature. Adverse events associated with HES include coagulopathy, renal failure, peripheral tissue deposition resulting in puritis, hyperamylsasmia, anaphylactoid reactions and neurologic dysfunction.[11]

The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial is important to emergency physicians, as the results raise concerns about the use of HES solutions in patients with severe sepsis or septic shock. Patients resuscitated with HES solutions had more acute renal failure, a greater need for renal replacement therapy and a trend toward increased 90-day mortality. In addition, there seems to be a dose-response relationship, as patients who received higher doses of HES had a greater 90-day mortality rate compared with patients who received lower doses. This trial was terminated early for predetermined safety reasons based on harm deemed attributable to the use of HES. The results of the VISEP trial build on the growing body of evidence from randomized controlled trials that suggests these products are harmful in the setting of sepsis.[22]

A balanced appraisal of this study must consider potential limitations before a change in Canadian emergency medicine (EM) use of HES can be advocated. Patients enrolled in the VISEP study were recruited from the ICU, and therefore may differ from ED patients with severe sepsis or septic shock. Although the groups had similar baseline characteristics, the trial was not blinded; hence, it is possible that co-interventions that impacted the results may have differed between the study groups. In addition, 38% of patients in the HES group exceeded the daily HES dose limit by 10% or more, and this occurred within the initial 24 hours 75% of the time, an occurrence that may not reflect current Canadian EM fluid resuscitation practices.

One potentially important consideration of the VISEP study is its factorial design, which allows for individual treatment effects to be evaluated for more than 1 intervention in a single trial. In this study, patients were essentially randomly assigned to groups twice; first to the HES or Ringer lactate group and then to a second "tight" or "conventional" glucose control group. The benefits of factorial design trials include cost savings when compared with the funding required to complete separate studies and reduced sample size requirements. However, the potential for interactions between the study interventions in factorial design trials is an important limitation that must be carefully considered. Interactions between trial interventions may result in an erroneous inflation or reduction of the treatment effect estimate of either intervention. The investigators of the VISEP trial found a trend toward an interaction in patients who received intensive insulin therapy and HES, as compared with intensive insulin therapy and Ringer lactate, based on the renal SOFA score. This interaction means the independent harm effect associated with HES in the severe sepsis and septic shock setting is potentially lower than estimated in the study, especially since a randomized controlled trial of tight versus conservative insulin control in the critically ill found tight control was associated with an increase in 90-day mortality.[23]

So where does this leave the Canadian emergency physician caring for a critically ill patient with septic shock who requires immediate resuscitation? The VISEP trial does not support the use of pentastarch for the early treatment in this patient population, and therefore alternative resuscitation fluids should be administered. Should these results be generalized to the use of other HES solutions in severe sepsis or septic shock? Little evidence is available to support the benefit of HES solution use in the EM setting. However, in severe sepsis or septic shock, the VISEP trial has demonstrated concerning adverse events in patients. Until further clinical trials with definitive clinical outcomes clearly determine the safety and efficacy of other HES solutions, emergency physicians should avoid their use in patients with severe sepsis or septic shock.

CONCLUSION

Pentastarch use in patients with severe sepsis or septic shock has been associated with increases in renal failure and, possibly, mortality. Although other HES solutions are available in Canada, unless future research demonstrates safety and improved efficacy in severely septic ED patients, crystalloids should remain the solution of choice for this population.

Competing interests: None declared.

Keywords: sepsis, resuscitation, pentastarch, factorial clinical trials

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