Is 6% tetrastarch 130 kDa (hydroxyethyl starch 130/0.4 or 130/0.42) suitable for severe sepsis?

Fluid resuscitation is an essential part of initial sepsis management. Hydroxyethyl starch solutions are used to maintain or achieve volume expansion, but their safety and efficacy remains controversial, particularly for critically ill patients with severe sepsis, where a mortality of 35–50% at 90 days might be expected. Specification of hydroxyethyl starch products has moved away from higher molecular weight compounds to 6% tetrastarch products (mean molecular weight 130 kDa ±20 kDa). Tetrastarches have overlapping molar substitutions of 0.38 to 0.45 (from where the term tetrastarch is derived), and are often abbreviated as 6% hydroxyethyl starch 130/0.4 or 130/0.42.

The case for 6% tetrastarch 130 kDa in severe sepsis

Four studies have reported improvements in multiple surrogate end points with 6% tetrastarch 130 kDa exposure of 9–37 ml/kg/day for 1–5 days. Two single centre randomized controlled trials compared tetrastarch to 20% albumin. Palumbo et al (2006) (n=20) and Dolecek et al (2009) (n=56) observed improved arterial:inspired oxygen ratio, along with other physiological parameters in the tetrastarch group.

Dolecek et al (2009) did not detect a difference between groups and extravascular lung water reduction was greatest in the albumin group (P<0.05). Improvements in some sublingual microcirculation parameters were found in a dual-centre randomized controlled trial (n=24) with tetrastarch rather than crystalloid (Dubin et al, 2010). CRYSTMAS, a 24-centre double-blind randomized controlled trial (n=196), reported a 2.4-hour reduction in the time to achieve haemodynamic stability with 6% tetrastarch exposure than that with crystalloid (Guidet et al, 2012).

A direct relationship between surrogate and clinically meaningful end points, including mortality, is questionable. Statistically significant excess mortality or adverse effects in the 6% tetrastarch groups were not reported, although point estimates tended to favour control groups in most randomized controlled trials. Variable length of follow up may explain the heterogeneity in overall mortality. None of these studies were designed to assess mortality (all were underpowered for this), and most were at risk of biases (Patel et al, 2013).

The case against 6% tetrastarch 130 kDa in severe sepsis

The primary outcome was 90-day mortality in the 26 centre 6S (Perner et al, 2012) and 32 centre CHEST (Myburgh et al, 2012) randomized controlled trials which compared 6% tetrastarch 130 kDa to crystalloid in well-conducted pragmatic double blind protocols. 6S (n=798) reported excess intervention group mortality (relative risk=1.17, 95% confidence interval=1.01–1.36; P=0.03) and requirement of renal replacement therapy (relative risk =1.35; 95% confidence interval=1.01–1.80; P=0.04) in their severe sepsis population that received 14 ml/kg/day tetrastarch for 3 days (Perner et al, 2012).

CHEST did not report excess mortality in the pre-defined sepsis sub-group (n=1937), or the enrolled mixed population of critical care patients (n=7000). Although not specifically reported for the sepsis group, excess intervention group renal replacement therapy use (relative risk 1.21; 95% confidence interval = 1.00–1.45; P=0.04) was reported for the mixed population that received 8 ml/kg/day tetrastarch for 4 days (Myburgh et al, 2012). The risk of type II error cannot be excluded given the lower daily dose of tetrastarch, mortality rate (24%), observed power (16%), and patients with severe sepsis or septic shock (although exact figures were not reported), compared to 6S.

A meta-analysis specifically addressing the safety and efficacy of 6% tetrastarch 130 kDa in critical care severe sepsis patients found tetrastarch was associated with excess 90-day mortality (relative risk 1.13; 95% confidence interval 1.02–1.25; P=0.02; number needed to harm 29), requirement of renal replacement therapy (P=0.01; number needed to harm 15.7), and allogeneic transfusion (P=0.001; number needed to harm 9.9) (Patel et al, 2013).

Conclusions

There is an emerging picture of potential harm associated with hydroxyethyl starch. The safety or efficacy of 6% tetrastarch 130 kDa cannot be demonstrated when used for volume resuscitation in critical care patients with severe sepsis (Patel et al, 2013). The authors believe that alternatives should be used in these patients. BJHM

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