Gelatin solutions for critically unwell septic adults

Fluid resuscitation and volume expansion are essential for initial sepsis management. Critically unwell septic adults have a high hospital mortality of 25–50%. Gelatin solutions are the most frequently used colloid fluid in the UK. Despite global use, the safety and efficacy of this synthetic colloid remains uncertain, and the Surviving Sepsis Campaign 2012 guideline (Dellinger et al, 2013) does not provide clear direction.

Five (one described across two articles) randomized clinical trials published between 1994 and 2010 reported the outcome of mortality in 230 adults diagnosed with sepsis, severe sepsis or septic shock in Europe. They were mechanically ventilated (84%) and managed in the critical care setting. A total of 113 patients were randomized to receive 3–4% modified fluid gelatin 30–35 kDa, and 117 to receive control fluid: 6% hydroxyethyl starch 200–400 kDa 0.45–0.7 molar substitution (n=105), 0.9% saline (n=6), and 5% human albumin (n=6). All the studies were single blinded, open label to fluid type, parallel group non-crossover randomized clinical trials. Importantly, none of these studies were designed to assess mortality, all were underpowered for this endpoint and were at risk of biases.

The case for gelatin use

A three-centre French trial (n=129) of mechanically ventilated (71%) and non-ventilated adults with severe sepsis and septic shock (34%) reported less acute kidney injury (P=0.02; number needed to treat=5.5, 95% confidence interval=2.9–44.5) associated with 3% gelatin 35 kDa exposure of 43 ml/kg for a median of 9 days compared to 6% hydroxyethyl starch 200 kDa 0.60–0.66 (Schortgen et al, 2001). However, renal toxicity with hydroxyethyl starch is well recognized (Patel et al, 2013).

In a smaller Dutch single centre trial (n=24) of mechanically ventilated adults, 4% gelatin 30 kDa exposure of 18.8 ml/kg over 90 minutes led to improved colloid osmotic pressure and cardiac output despite baseline myocardial depression with all studied colloids, including 6% hydroxyethyl starch 200 kDa 0.45–0.55 and 5% human albumin, compared to 0.9% saline (van der Heijden et al, 2009; Trof et al, 2010).

The case against gelatin use

UK (n=13) and French (n=34) trials both reported a reduction in haemoglobin of 10 g/litre 30 minutes after exposure to 500 ml (7.1 mg/kg) 4% gelatin 30–35 kDa (P=0.0003) (Beards et al, 1994; Asfar et al, 2000). A subsequent Hungarian (n=30) trial, comparing up to 1000 ml (14.3 ml/kg) 4% gelatin 35 kDa and 6% hydroxyethyl starch 200 kDa 0.6 (Molnar et al, 2004) in adults with septic shock over 60 minutes, did not detect a difference between fluid groups for a range of cardiopulmonary parameters and oxygen delivery, consistent with similar studies in mechanically ventilated patients (Beards et al, 1994; Asfar et al, 2000; van der Heijden et al, 2009; Trof et al, 2010). However, Asfar et al (2000) did report increased gastric pH, a surrogate marker of improvement in hypovolaemia, compared to 6% hydroxyethyl starch 200 kDa 0.6. A robust direct relationship between these surrogate end-points and mortality is questionable.

Data synthesis and conclusions

Pooling (Mantel–Haenszel) of mortality data from the five randomized trials above revealed heterogeneity was not present (I^2=0%). Although the risk of type II error is high, the random effects 0.98 (95% confidence interval 0.77–1.26; P=0.89) or fixed effects 1.02 (95% confidence interval 0.79–1.33; P=0.86) point estimates and wide 95% confidence intervals cannot confirm safety or efficacy of gelatin solutions for fluid resuscitation and volume expansion in critically ill septic adults. However, only one randomized clinical trial (discussed in two articles) managed patients after the initial Surviving Sepsis Campaign launch (van der Heijden et al, 2009; Trof et al, 2010).

More problematic, most control group patients received hydroxyethyl starch, another synthetic colloid, which is unsuitable and is associated with harm (Patel et al, 2013) and European Medicines Agency suspension (EMA/349341/2013). Thus further studies specifically assessing the end-point of mortality are urgently required. In the authors' view, as alternative fluids are available, perhaps gelatin should be avoided in these septic patients. BJHM

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