In neonates requiring intravascular volume resuscitation is the use of Gelofusine safe and efficacious?

Report by

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A neonate born at 26 weeks and weighing 930 g underwent laparotomy on day 21 of life for perforation secondary to necrotising enterocolitis (NEC). He required fluid resuscitation during the procedure and Gelofusine was given rather than normal saline or blood products. We reviewed the evidence for the use of Gelofusine for volume replacement in neonates.

Structured clinical question

In neonates requiring intravascular volume replacement/resuscitation [patient] is use of Gelofusine [intervention] efficacious and safe [outcome]?

Search strategy and outcome

Search terms: "Gelofusine", "Gelatin" and "Synthetic Colloids".

Search literature: PubMed and Medline 1966–2005, EMBASE 1974–2005, Cinahl 1982–2005 using Dialog Data Star, Google Scholar, Proquest journals.

Search limit: To human studies and English literature.

Neonatal and paediatric studies

See table 1.

Adult studies

See supplemental table 1 available at <http://adc.bmj.com/supplemental>.

Commentary

Gelofusine is a synthetic colloid, which, in recent years, has been increasingly used for volume replacement. The advantages of Gelofusine are that it is less expensive than other synthetic colloids, is readily available and can be stored for long periods without degradation.^{3 4} The increased usage is also, perhaps, secondary to perceived increased risk associated with albumin infusions and other blood products.^{5–7}

The effects of Gelofusine or alternative volume expansion in preterm infants have been subjected to a systematic review which included seven randomised controlled trial (RCTs).¹ Out of these only one RCT investigated the use of Gelofusine for volume expansion in neonates. The Northern Neonatal Nursing Initiative (NNNI) Trial Group in this multicentre study compared the effects of prophylactic administration of fresh frozen plasma (FFP), gelatine and glucose on early mortality and morbidity in preterm infants. We did not find any evidence in the literature regarding objective evaluation of the efficacy of Gelofusine for volume resuscitation/replacement in neonates. With regard to safety, the NNNI trial did not demonstrate any adverse short term outcomes related to Gelofusine use.⁸ Developmental outcome at 2 years was also similar in the three groups.⁹ However, the Cochrane review by Osborn *et al* noted that Gelofusine use or no treatment was associated with increased risk of developing NEC (relative risk (RR) 4.92) when compared to FFP.¹ Although no significant differences in mortality or disability were found in this study and a wide confidence interval suggests an underpowered study, this finding warrants further research.

Table 1 Neonatal and paediatric studies

Citation	Study group	Methods	Study type	Outcomes	Key results	Level of evidence, comments
Osborn <i>et al</i> (2004) ¹	<32 weeks, <1.5 kg, n=940	Seven randomised trials comparing the effects of early volume expansion with normal saline, fresh frozen plasma, albumin, plasma substitutes or blood compared to no treatment or another form of volume replacement. Only 1 RCT evaluated use of gelatine based plasma substitute with FFP or no treatment	Systematic review	Gelatin vs no treatment: No significant differences were found in mortality (RR 1.22, 95% CI 0.86 to 1.72), ultrasound abnormalities and death or severe disability (RR 1.05, 95% CI 0.82 to 1.34) Gelatin vs FFP: No significant difference was found in mortality (RR 1.17, 95% CI 0.83 to 1.64) and death or grade 3–4 P/IVH (RR 1.22, 95% CI 0.89 to 1.67)	The rate of NEC was significantly higher (RR 4.92, 95% CI 1.44 to 16.80) and sepsis significantly lower (RR 0.57, 95% CI 0.39 to 0.83) in infants who received the gelatin based plasma substitute compared to FFP	1a - Relevant, highlights possible adverse outcome with gelatine use in neonates, although wide confidence interval suggests study was underpowered in this regard
Akech <i>et al</i> (2006) ²	Children, n=88	Children admitted with severe falciparum malaria were allocated to receive albumin or Gelofusine. Primary outcome: resolution of shock Secondary outcome: mortality and neurological sequelae	Controlled trial	There was no significant difference in the resolution of shock or acidosis between the groups. Mortality was lower in patients receiving albumin (1/44; 2.3%) than in those treated with Gelofusine (7/44; 16%) by intention to treat (Fisher exact test, p=0.06), or 1/40 (2.5%) and 4/40 (10%), respectively, for those treated per protocol (p=0.36)	In children with severe malaria, there was a consistent survival benefit of receiving albumin infusion compared to other resuscitation fluids	2a - Paediatric age group, not randomised

CI, confidence interval; FFP, fresh frozen plasma; NEC, necrotising enterocolitis; P/IVH, peri-intraventricular haemorrhage; RCT, randomised controlled trial; RR, relative risk.

In view of the lack of appropriate studies in neonates and to further elucidate our clinical question, we extended our search to studies in the paediatric and adult population. One RCT has compared volume expansion with Gelofusine and albumin in children with severe malaria.² Akech *et al* noted no significant difference in the resolution of shock or acidosis between the two groups, but fatal neurological events were more common in the group receiving Gelofusine. Five RCTs have reported on the use of Gelofusine in adults^{10–14} (see supplemental table 1 available at <http://adc.bmj.com/supplemental>). Allison *et al* compared the use of gelatine and HES for resuscitation in patients with blunt trauma and suggested that Gelofusine was associated with a worse post-trauma capillary leak.¹⁰ This may be important in newborns with capillary leak syndrome such as sepsis and NEC, but relevance at present is conjectural. Schortgen *et al* investigated the effects of gelatine and HES on renal function in adults with severe sepsis and suggested that gelatine is safer in terms of renal function.¹² No impairment of haemostasis was noted by Haisch *et al* following Gelofusine use in adults undergoing major abdominal surgery.¹³ Rittoo *et al* in an RCT in adults undergoing abdominal aortic aneurysm surgery noted inferior gas exchange and lung compliance and poorer small lung injury score in the Gelofusine group compared to HES.¹¹ Whether this has any implications in neonates with unstable lung function and in worsening lung damage needs to be elucidated.

Adult studies suggest that Gelofusine has less antigenic properties and thus a lower chance of hypersensitivity reactions. The other potential disadvantages include the possibility of altered haemostasis^{15 16} and proteinuria.^{17 18} The relevance of these findings to the neonatal population has not been explored.

Although Gelofusine is readily available and cheap, and less monitoring is required during infusions, there is no evidence to support its efficacy for use in volume expansion in neonates. Moreover, considering the potential side effects in preterm neonates, it should be used with caution until further studies are available to prove its safety and efficacy. This is especially pertinent considering the lack of evidence of any potential superiority of various colloids over normal saline for volume replacement.¹⁹

CLINICAL BOTTOM LINE

- There is lack of evidence for the efficacy of Gelofusine for volume resuscitation in neonates.
- There is insufficient evidence to support or refute the use of Gelofusine over fresh frozen plasma or dextrose or no fluid therapy in the context of prophylactic volume replacement in neonates. (Grade B)
- Weak evidence suggests an increased risk of necrotising enterocolitis with the use of Gelofusine in neonates. (Grade B)
- Gelofusine use should be restricted to a clinical trial setting. (Grade A)
- A large RCT is needed to evaluate the efficacy and safety of Gelofusine for volume replacement in neonates.

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Should critically ill patients be routinely transfused to a normal haemoglobin level?

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Joseph, a 4-year-old boy with septic shock, lactic acidosis and multi-organ failure has been admitted to the paediatric intensive care unit. Mechanical ventilation, vaso-active support and renal replacement therapy (CVVHD) are initiated. His haemoglobin level is 8.8 g/dl (5.5 mmol/l).

The senior consultant decides to order a red cell transfusion in order to optimise oxygen delivery, but the junior fellow argues that there is no evidence that transfusion improves outcome and that it may potentially be harmful.

Structured clinical question

In critically ill children [patient] does red cell transfusion to normal haemoglobin levels [intervention] improve survival and reduce incidence of complications or duration of mechanical ventilation [outcome]?