Commentary

The promise of next generation colloids

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See related research by Martini *et al*., http://ccforum.com/content/12/2/R54

Abstract

The aim of perioperative haemodilution is to reduce loss of red blood cells during elective surgery. The oncotic and molecular characteristics of the various plasma substitutes employed determine how effectively normovolaemia is maintained, and their non-oncotic effects include alterations in microvascular perfusion. In the previous issue of *Critical Care*, Martini and colleagues assessed the effects of haemodilution with either polyethylene glycol (PEG)ylated albumin or a commercially available hydroxyethyl starch-based colloid in a hamster haemorrhage model. PEGylated albumin was superior to hydroxyethyl starch, as reflected by survival, haemodynamic parameters and assessment of the microcirculation using intravital microscopy.

In the previous issue of *Critical Care*, Martini and colleagues [1] assessed the effects of haemodilution with either polyethylene glycol (PEG)ylated albumin or a commercially available hydroxyethyl starch-based colloid in a hamster haemorrhage model. The aim of perioperative haemodilution, also termed acute normovolaemic hemodilution (ANH), is to reduce loss of red blood cells during elective surgery. It involves the collection of several units of blood from the patient before the operation and substitution of an equivalent volume of plasma expander. Although surgical blood loss remains unchanged, the lost blood contains relatively fewer red blood cells and clotting factors. The patient's blood is returned to them once haemostasis is achieved. Some regard ANH to be an underused technique that can significantly reduce exposure to allogeneic blood [2]. The oncotic and molecular properties of the various plasma substitutes employed in ANH determine how effectively normovolaemia is maintained. Fluid resuscitation using colloids typically requires one-quarter to one-half the infusion volume of crystalloids [3]. Whether the advantages of colloid use in elective surgery apply equally to the critically ill, and in all such populations, is less certain. Thus, on the basis of a prospectively defined subset of trauma patients in one large-scale clinical trial of albumin versus crystalloid resuscitation [4], the former was associated with an increased risk for death. By contrast, in *post hoc* analysis, patients with sepsis might have benefited from albumin.

The microcirculation is the primary site for gas and nutrient exchange. Perturbations in capillary perfusion may have more adverse prognostic significance [5] than traditional markers of oxygen utilization, and are implicated in the pathogenesis of organ failure in human sepsis [6]. The physicochemical attributes of the colloids determine their nononcotic effects, which include alterations in microvascular perfusion and integrity, and modulation of inflammation and coagulation. Martini and colleagues [1] explored these effects further by examining the consequences of slow replacement of 50% of the circulating volume in hamsters with either PEGylated albumin or a commercially available hydroxyethyl starch (HES)-based colloid, namely Voluven® (Fresenius Kabi, Austria), followed by removal of 60% of circulating volume over 1 hour. Blood was removed in an exponential manner in order to simulate surgical haemorrhage, and the surviving animals were observed using intravital microscopy in their shocked state for a further hour.

Animals receiving PEG-albumin all survived the experiment. By contrast, none of the HES animals completed the 1-hour hemorrhage stage. Other end-points also favoured PEG-albumin, in that for the first 30 minutes of experimental haemorrhage mean arterial blood pressure and heart rate were better supported than with HES. Moreover, from baseline the PEG-albumin group had a lower haematocrit, implying that more of the study solution remained within the vascular compartment. Furthermore, significantly more arteriolar and venular constriction was detectable during haemorrhage in the HES group. More convincingly, the arteriolar and venular flow had already begun to diminish after haemodilution and fell further during haemorrhage. Finally, these changes were mirrored by the reduction in functional capillary density, which

ANH = acute normovolaemic haemodilution; HES = hydroxyethyl starch; PEG = polyethylene glycol.

decreased in both groups during haemorrhage, but more so when HES was administered.

How robust are these data? The group concerned has a wealth of experience in employing these techniques. Additionally, although performed in animals, clinically relevant end-points were used. However, the study does have some limitations. First, only five animals were studied in each group. Second, blood loss was excessive and allowed only limited data for the HES group to be provided; a less severe protocol might have been more revealing. Third, the microcirculatory bed studied sits within the superficial connective tissue; the changes observed may not reflect changes in more clinically relevant organs, such as the viscera. Fourth, although the data indicate beneficial effects of PEG-albumin as a colloid, they may not pertain equally to the perioperative situation, in which the extent of haemodilution and severity of the blood loss are less. Finally, the authors rightly draw attention to the effects of the suspending fluid. It could be argued that the excess chloride load administered in the HES group might have contributed to their trend toward acidosis that occurred before onset of haemorrhage.

Where does this work lead us? In models of extreme haemorrhage, microvascular perfusion appears to be better maintained if plasma expanders of greater viscosity are employed. Viscous drag is thought to stimulate local nitric oxide production and vasodilatation. Despite not being a highly viscous solution, PEG-albumin has been shown to sustain microvascular perfusion. Although this may be a result of direct physical interaction of the PEG with the endothelium, its potential role as a nitric oxide distributor deserves further investigation. Use of techniques applicable to humans, such as orthogonal polarization spectral imaging, sidestream dark field imaging, or near-infrared spectroscopy, has been reported in this hamster skinfold model [7] but not under conditions of extreme haemorrhage. Confirmation of the equivalence of these methods in haemorrhage or sepsis would be valuable before moving on to the clinical arena.

PEG-albumin holds promise as the next generation of 'super-colloids' emerge, both as an effective plasma volume expander and potentially as an ameliorator of microvascular dysfunction. Watch this space!

Competing interests

The authors declare that they have no competing interests.

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