
REGULAR REVIEW

Gelatin Colloids in the Resuscitation of trauma

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INTRODUCTION

Trauma of any mechanism renders a patient vulnerable to haemorrhage and intravascular volume depletion; shock may ensue, with consequences extending beyond the initial resuscitation phase. The identification and correction of circulatory dysfunction is then recognised as a fundamental priority in trauma management. Intravenously administered fluids are a basic resuscitation tool but they have generated controversy in an era of evidence driven practice. The choice of fluid – colloid or crystalloid – has been repeatedly examined and subject to shifts in the consensus view. The colloids are a heterogeneous family of fluids, differing in their composition and physiological influence and include albumin, the synthetic starches, dextrans and the modified fluid gelatins. Hypertonic saline is frequently included in this class due to its supra-physiological osmotic potential, but is not strictly a colloid. This article examines the role of the modified fluid gelatins in the resuscitation of trauma. It will provide an overview of the properties of the gelatins available to the clinician and examine the limited evidence regarding the risks and the benefits associated with their use in this setting.

SHOCK – AN OVERVIEW

Shock is a failure of tissue perfusion with resulting cellular hypoxia and the consequent metabolic derangement precipitates cellular dysfunction and organ failure. In haemorrhage there is loss of blood from the intravascular compartment, compromising oxygen carrying potential and disturbing the mechanics of flow. Reduced venous return to the heart decreases cardiac output with further impairment of circulation, oxygenation and removal of metabolic by-products from organs and tissues. Established homeostatic mechanisms attempt to ameliorate volume loss. The sympathetic nervous system, anti-diuretic hormone and the renin-angiotensin-aldosterone system serve to increase cardiac output, redistribute blood flow to vital organs (brain, heart, kidneys) and stimulate the renal retention of sodium and water. However, a redistributed circulation results in under-perfusion of tissue beds and organs of lesser priority. The physiological insult resulting from disrupted perfusion precipitates the release of vasoactive and inflammatory mediators. If unchecked, a

widely distributed inflammatory storm results in a ‘systemic inflammatory response syndrome’, multi-organ failure and death. Consideration of the shocked state as an inflammatory process has yielded new models of the endothelium as a significant component to the microvasculature. Far from acting purely as a physical barrier between the vascular and interstitial spaces, it serves a dynamic function in the critically ill. Numerous humoral mediators, including the prostaglandins and nitric oxide moderate vascular tone(1). Increased capillary permeability causes unrestrained leakage of larger molecules – notably albumin – into the interstitial space. Osmotically driven fluid shifts produce interstitial oedema and organ dysfunction – particularly the non-cardiogenic pulmonary oedema of the Acute Respiratory Distress Syndrome (ARDS)(2).

In simple terms, haemorrhagic hypovolaemia should be addressed in the short term by restoration of the circulatory volume and then definitive management of the source of volume loss – by surgical means or otherwise. Even in this respect the treatment priorities have been subject to controversy. The goals of volume therapy have been variously discussed in the ‘scoop and run’ versus ‘stay and play’ debate and will not be further addressed in this article(3).

COLLOIDS

The capillary wall is a selectively permeable membrane, across which there is transfer of water and soluble small molecules of relative molecular mass (M_r) less than 70,000 Daltons (Da). In the steady state, differences in concentration across the capillary membrane are eliminated by the process of diffusion. The presence of electrically charged species, and hydrostatic pressures within the circulation modifies the concentration differences to produce a final state representing an equilibrium between each of these factors.

The colloids are fluids comprising large molecules which do not freely penetrate the capillary membrane, as distinct from the crystalloids, which are ionic solutions of restricted molecular mass. Colloids are retained within the circulation, supporting the intravascular volume and exerting a colloid osmotic pressure which promotes fluid shifts in favour of increased intravascular volume; properties which may be manipulated in their clinical application.

Colloidal fluids may be classified as natural or synthetic, according to the process by which they are obtained. Albumin is the principal natural colloid and is derived from pooled human plasma via a rigorous sterilisation process. The synthetic colloids may be further subdivided into dextrans, modified fluid gelatins and the synthetic starches. Companion articles in this series review the properties of albumin, the synthetic starches and dextrans.

THE GELATINS

Gelatin-based plasma substitutes have existed since 1915 and are on the WHO list of essential medicines; they are derived from bovine collagen. The structure of the source collagen is manipulated in the manufacturing process to form three principal sub-classes of modified fluid gelatin: cross-linked or oxypolygelatins (Gelifundol – Amarey Nova Medical), succinylated (Gelofusine – Braun, or Volplex – Cambridge) and urea cross linked (Haemaccel – Syner-Med). The bovine collagen source material is initially broken down via a process of hydrolysis. The action of hexamethylene di-isocyanate then produces

urea-linked gelatin, and that of succinic anhydride produces succinylated gelatine. The intravascular persistence of the gelatins is contributed to by both their macromolecular nature (mean Mr of 30 kDa) and a substantial negative charge which induces a stretched conformational change, reducing their ability to pass through the pores of the capillaries(4,5). The gelatins however have the lowest Mr in comparison to other colloid preparations (Albumin 69 kDa, Dextrans 40-70 kDa and Hydroxyethylstarch preparations 70-450 kDa) and as such are comparatively rapidly excreted, largely unchanged, by the kidneys, with consequent limitation of half life to about two hours. The plasma expansion effect is only about 70% of the infused volume and they have an inferior plasma expansion profile compared to other colloids after acute haemorrhage(6,7). The limited half life mandates repeated administration in prolonged resuscitation to maintain haemodynamic stability, but in the presence of adequate renal function the gelatins do not accumulate. The profiles of representative gelatin colloids of the three groups are detailed in Table 1. Their shelf life is of order three years.

Product	Nature	Mean Molecular Weight (kDa)	Electrolyte Base (mOsm/L)	Osmolarity (mOsm/L)	Elimination Half Life (Hours)
Gelofusine	Succinylated Gelatin (4%)	30	154 – 120 <0.4	274	3-4
Volplex	Succinylated Gelatin (4%)	30	154 – 125	284	4
Haemaccel	Polygeline Urea cross linked (3.5%)	30 – 35	145 5.1 145 6.25*	301	5-8

Table 1: Physical properties of the commercially available modified fluid gelatins (8)

*The significant calcium content in urea linked gelatins precludes concomitant administration through an intravenous line being used for blood transfusion.

Adverse effects

Colloid use is not without risk. The synthetic colloids as a family are known to provoke allergic responses and may induce a coagulopathy and end-organ damage and renal dysfunction; the potential for disease transmission must also be considered. However, as a diverse group, the synthetic colloids do not pose equivalent risks.

Hypersensitivity reactions

Allergic responses to a foreign antigen, including the proteins upon which colloids are based, encompass a range from urticaria to anaphylaxis and circulatory collapse. Such a response would be catastrophic in the presence of an existing circulatory deficit in trauma. An early initial study placed the incidence of serious allergic responses to gelatin-based colloids at

0.038% (9). Similarly, Lundsgaard-Hansen reported a 20 year clinical experience of in excess of 120,000 administered units of gelatin-based colloid, citing an incidence of serious anaphylactoid reactions of 1 per 13,400 units with a single fatality(10). A multicentre French study(11) prospectively examined the incidence and severity of allergic responses to colloids. In a cohort of 19,593 patients given a variety of colloids, the overall rate of allergic reactions was 0.219% with half of them having received gelatins. The specific gelatin allergic response rate was 0.345%. Starches and dextrans induced 6 and 4.7 times respectively less anaphylactoid responses than gelatins. Ig-E dependant anaphylaxis was confirmed in 7 of 15 patients demonstrating an allergic response to gelatins. Further evidence of the

heterogeneity of colloids as a fluid group with reference to their allergic potential was reported by Barron *et al*(12). Safety data extracted from 113 studies of colloid administration demonstrated significant differences. In comparison to albumin as reference, gelatins precipitated anaphylactoid reactions with incidence rate ratio of 12.4 (95% CI 6.4-24.0), the hydroxyethyl starches 4.51 (95% CI 2.06-9.89) and dextrans 2.32 (95% CI 1.21-4.45). As a consequence gelatin use has dwindled in the USA (13). The structural similarities of Gelofusine and Haemaccel suggest a common allergenic potential. A lesser overall propensity for inducing anaphylaxis has been reported in the urea-linked compared to succinylated gelatins(14) but an Australian centre has reported cross reactivity to Gelofusine in two patients with a previously proven intolerance to Haemaccel(15). This area has yet to be fully explored.

BSE Transmission

The raw material for all the gelatins is bovine bones, raising the spectre of potential BSE transmission. However, the gelatin is sourced from BSE free regions of the EU and USA and subject to inspection by veterinary authorities and the FDA. The infective potential of these products, after manufacture and sterilisation has been examined in an animal model using transmissible spongiform encephalopathy agents and no such infective potential has been demonstrated(16).

Effects on Clotting

The use of plasma expanders may impair haemostasis beyond the haemodilutional effect on clotting factors. Whilst the starches and dextrans are the principal culprits, Mardel(17) also demonstrated a reduction in clot quality in the presence of gelatin-based colloids when compared to crystalloid in an *in vitro* study. The reduced clot strength, weight and elasticity was due to an alteration of clot architecture secondary to macromolecular binding, and not a reduction in the sequestration of platelets, red cells and fibrinogen into the clot. *In vivo* studies have further demonstrated an impairment of primary haemostasis secondary to gelofusine infusion in healthy volunteers with a reduction in Von Willebrand's Factor (VWF) in addition to a dilutional effect on thrombin generation(18), although to a lesser degree than that due to the dextrans and modified starches(19,20) and not to the extent that necessitates dose limitation as with dextrans. Impaired platelet aggregation attributable to the calcium content of Haemaccel has been demonstrated experimentally(21). The influence of the anti-haemostatic effect in the trauma setting

remains under-investigated. Gelatins do not interfere with blood cross matching.

Renal Dysfunction

Acute renal failure following trauma is a hazard of both renal hypoperfusion in shock and the nephrotoxic effects of substances administered during the resuscitation process. The gelatins are rapidly filtered at the glomeruli in comparison to other colloids and toxic accumulation has not been demonstrated. Renal toxicity in consequence to gelatin use in haemorrhagic hypovolaemia secondary to trauma has yet to be fully investigated. Gelatin fluid resuscitation may potentially be beneficial: Cittanova(22) demonstrated a relative nephron sparing effect in transplanted kidneys retrieved from brain-dead donors receiving circulatory support with gelatin products compared to hydroxyethyl starches and a sepsis based study reproduced these findings(23). The overall renal effects of the gelatins in traumatic hypovolaemia have yet to be fully investigated.

Efficacy in resuscitation of critically ill and trauma patients

The Cochrane Collaboration compared colloid and crystalloid use in all-cause hypovolaemia with mortality as the specific end point(24). The analysis was stratified to assess the effect of different colloids compared to crystalloids. Seven randomised control trials comparing gelatins to crystalloids satisfied their inclusion criteria, accounting for only 346 randomised participants. Meta-analysis yielded a pooled relative risk of death of 0.54 (95% CI 0.16-1.85) associated with plasma expansion using gelatins compared to crystalloids.

However, only two of the seven trials dealt specifically with traumatic hypovolaemia(25,26). This meta-analysis therefore contributes little to support gelatin use in preference to crystalloids and concluded that no survival advantage can be attributed to colloid rather than crystalloid use in critical illness. The American College of Surgeons Committee on Trauma advocate crystalloid as the initial non-blood infused fluid in the management of haemorrhagic shock in their guidelines on Advanced Trauma Life Support(27).

In an earlier meta-analysis, Schierhout and Roberts(28) assessed a body of randomised control trials comparing crystalloid and colloid as resuscitation tools in the critically ill. Mortality was taken as the primary end point for comparison. Trials prior to 1997 were considered and 37 suitable trials identified. The authors reported a 4% increase (95% CI 0 – 8%) in mortality associated with colloid rather than crystalloid use, concluding that continuing colloid use in this context could not be

supported. Within the analysis only 7 trials involved trauma, of which only a single trial involved a gelatin based colloid in a comparison arm(25). This study, contributed by Evans, is directed towards an assessment of coagulopathy associated with gelatin (Haemaccel) use as discussed above. The mortality data was submitted separately to the committees responsible for the described meta-analyses.

Comparison between the gelatins and other colloids in the trauma arena is similarly sparse. Allison *et al*(29) have reported a comparison between hydroxyethyl starch (HES) and a gelatin used as post-trauma resuscitation tools. The study focuses upon the influence of each fluid upon capillary leak within an initial 24 hour period following blunt trauma in human subjects, measured using the urine albumin excretion rate. It concludes that hydroxethyl starch is superior to gelatin in reducing capillary leak during this period, with a significantly lower urine albumin excretion rate recorded in the HES treated group in comparison to patients receiving a gelatin based colloid. The authors conclude that HES is superior in terms of reduction of post trauma capillary leak in comparison to gelatin-based colloid. If this finding is considered in the broader context of intravascular fluid retention and the detrimental effect of interstitial oedema upon organ function and outcome, gelatin use cannot then be favoured in this setting.

More recently, Wu and co-workers have sought to address the defect in evidence concerning gelatin use in trauma(26). They have reported a prospective randomised trial in which a modified fluid gelatin (Gelofusine) was compared to a crystalloid (lactated Ringer's solution) as a tool for volume expansion in hypovolaemic shock secondary to trauma. Adult patients without co-existing cardiac co-morbidity presenting acutely with shock of traumatic origin and a presenting mean arterial blood pressure less than 80mmHg were identified. Randomisation was to rapid infusion of 1000mls of Gelofusine or Ringer's Lactate solution at initial presentation. Invasive monitoring established at presentation permitted measurement of blood pressure, central venous pressure (CVP) and in a smaller subgroup pulmonary artery occlusion pressure (PAOP), at intervals within the first hour of resuscitation. Ventilated patients, and patients requiring blood transfusion or surgery to achieve haemodynamic stability were excluded. Mortality data was reported. 41 patients were enrolled into the study with shock of hypovolaemic or neurogenic origin and traumatic aetiology. 18 patients received Gelofusine, of which 16 presented with haemorrhagic shock and 2 presented with shock of neurogenic origin. 16 patients received Ringer's lactate, with 13 cases of hypovolaemic and 3 cases of neurogenic

shock. There were no significant differences between the age or presenting haemodynamics of patients enrolled into each study arm. The authors reported a significant early difference in response between the two treatment arms. Patients receiving Gelofusine demonstrated a significant increase in CVP and PAOP compared to baseline at 15 minutes into the resuscitation protocol. This effect became significant in the crystalloid arm only at 60 minutes. However, PAOP data could only be conclusively reported from a smaller subgroup of patients – 11 of 18 patients in the colloid arm and 8 of 16 in the crystalloid arm. Additionally, blood pressure and heart rate measurements were not significantly different between the treatment arms when assessed across the entire period of measurement. No significant mortality difference or fluid-related adverse effects were reported. The authors assert a superiority of Gelofusine over Ringer's lactate in terms of more rapid volume replacement. However, the clinical advantage that may be drawn from this is uncertain and small patient numbers make it difficult to discern significant differences in treatment efficacy.

Summary

To date, the specific role of gelatins in trauma resuscitation remains under-investigated. Their adverse affects are well described and relate principally to the provocation of allergic responses whilst their influence upon haemostasis is relatively benign in comparison to the other colloids. However, their benefits are only sparsely documented and the evidence to choose one gelatin over another virtually non-existent. As knowledge of the microcirculatory dysfunction inherent in the shocked state increases, the role of the gelatins in trauma resuscitation is being increasingly sidelined by other colloids – notably the starches. Their role beyond a basic resuscitation tool is now uncertain.

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