Place of the colloids in fluid resuscitation of the traumatized patient

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Purpose of review
The examination of the recent literature aimed at analysing the most recent data that could affect decisions regarding the use of colloids in trauma resuscitation.

Recent findings
Animal data have generally shown a beneficial effect of colloids in trauma resuscitation, with improvements in capillary leak demonstrated in lung, intestine and brain. In most studies, hydroxyethyl starch resuscitation was more effective than crystalloid and decreased markers of inflammatory processes were observed. Brain injury in animals was attenuated with colloids. In uncontrolled haemorrhage, resuscitation with colloid increased bleeding and mortality.
Human studies have also failed to confirm the suggestion that albumin resuscitation may be associated with a worse outcome in head injury. However, there is a strong suggestion that aggressive prehospital resuscitation, particularly with colloid, may be harmful. Studies in burns have consistently shown an improvement in the tendency to fluid overload with the inclusion of colloid in the resuscitation strategy, but so far no outcome benefit has been shown.
Two studies of general trauma resuscitation have shown apparent benefit from the use of HES in early resuscitation with reductions in mortality and in renal injury.

Summary
Recent trauma studies provide ongoing, but not conclusive, evidence of a benefit from colloid resuscitation in trauma.

Keywords
colloids, crystalloids, fluid therapy, trauma

INTRODUCTION

The place of colloids in the resuscitation of patients with trauma remains controversial. Over many years, colloids have been shown to provide faster restoration of haemodynamic parameters with the use of smaller fluid volumes, but this has not translated into improved outcomes, and has, in some instances, been associated with worse outcomes. Part of this controversy is the fact that a wide variety of pharmacological products including various types of albumin solutions, gelatins, dextrans and hydroxyethyl starches have been grouped together as a single study group, when, in reality, these are very different products, with different properties and side-effects. In the recent literature, most of the publications have focused on either albumin or hydroxyethyl starch (HES) and this review will therefore concentrate on these two colloid formulations.

ANIMAL STUDIES

In the past year, several animal studies have addressed the issue of the use of colloids, and in particular HES, in the setting of haemorrhagic shock. Resuscitation with Ringer's lactate and HES 130/0.4 was compared in a pig model of uncontrolled liver injury. In this model, several incisions were made into the liver and the animals allowed to become hypotensive through internal

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KEY POINTS

- The use of colloids remains controversial in trauma.
- Animal data provide increasing support for colloid resuscitation.
- The use of colloids in burns is being increasingly advocated.
- In general trauma recent studies have suggested improved outcomes with colloids.

haemorrhage. Although HES produced a significantly greater plasma volume effect, its use was associated with higher mortality as it provoked uncontrolled bleeding, whereas this did not occur with Ringer's lactate [1▪]. This study is consistent with clinical studies of early and aggressive resuscitation in patients with penetrating trauma and uncontrolled haemorrhage showing adverse outcomes [2].

By contrast, other animal studies of controlled haemorrhage have not shown adverse effects with colloids. In a dog study, haemorrhagic hypotension was maintained at 40–50 mmHg for 45 min and the animals then resuscitated with Ringer's lactate in a 3 : 1 ratio to shed blood, HES 130/0.4 in a 1 : 1 ratio or HES in hypertonic saline limited to 4 ml/kg. In this study, equal resuscitation with similar outcomes was found for the crystalloid and isotonic colloid groups, but small-volume hypertonic resuscitation gave worse outcomes in terms of systemic oxygenation and gastric perfusion compared to the isotonic colloid and crystalloid [3▪]. In a rabbit study of acute haemorrhagic shock, mean arterial pressure was reduced to 60% of baseline for 30 min, and then the animals were resuscitated with Ringer's lactate in a ratio of 3 : 1 to shed blood or HES 130/0.4 in a 1 : 1 ratio. This study examined cerebral perfusion as the primary endpoint. These authors concluded that HES 130/0.4 provided better haemodynamic stability with restoration of arterial pressure to baseline in this group, but not in the Ringer's lactate group. The balance of cerebral oxygen supply to consumption during resuscitation was also superior in the HES 130/0.4 group [4]. In another study in rabbits, animals were rendered hypotensive and hyperlactataemic by haemorrhage and then given no resuscitation, or resuscitation to a fixed endpoint with Ringer's lactate, HES alone, or a combination of HES and Ringer's lactate. This study examined renal effects of the various fluids and concluded that haemorrhagic shock induced tubular injury including vacuole formation, but that none of the resuscitation solutions produced any additional harmful effects on either histology or on various cytokine markers of tissue injury [5]. These studies suggest that, in controlled haemorrhage, a 1 : 1 ratio of HES to shed blood provides at least equivalent resuscitation as a 3 : 1 ratio of Ringer's lactate to shed blood, and the colloid might have some advantages in addition to the smaller volume infused.

Other studies have examined the influence of colloids on inflammatory consequences of haemorrhage in small animals. In rats, haemorrhagic hypotension was maintained for 60 min and then the animals resuscitated with Ringer's lactate, shed blood or HES 130/0.4 to the starting arterial pressure values. In this study, the primary endpoints were pulmonary capillary leakage and an array of inflammatory markers. Capillary leakage was significantly lower following resuscitation with either shed blood or HES compared to Ringer's lactate. HES and shed blood were also more effective at attenuating the increases in inflammatory markers [6]. The same group published a similar study examining intestinal permeability and inflammatory markers. Again, the conclusion was that HES prevented intestinal injury and decreased the expression of inflammatory markers [7]. A rat study investigated the combination of haemorrhagic shock and lipopolysaccharide on lung tissue damage and pulmonary oedema. Rats were resuscitated with HES, hypertonic saline or Ringer's lactate. Both hypertonic saline and HES were found to reduce lung tissue damage and pulmonary oedema [8]. A femoral fracture model in which haemorrhagic shock was induced in addition to a left femoral fracture was studied in rats, with the primary outcome of apoptosis and morphologic alterations in bone marrow mononuclear cells. Haemorrhagic shock was maintained for 30 min followed by resuscitation with Ringer's lactate, HES 130/0.4 or 5% albumin and the bone marrow examined at 24 and 48 h after resuscitation. Both albumin and HES were superior to Ringer's lactate in terms of early apoptosis, but HES was significantly better than albumin or Ringer's lactate at 48 h [9].

Finally, a study in mice subjected to traumatic brain injury and haemorrhagic shock examined the effects of resuscitation with Ringer's lactate, hypertonic saline, polynitroxylated albumin or Hextend (6% HES 670/0.75 in a balanced salt solution). Animals were resuscitated with the test solutions to an arterial pressure greater than 50 mmHg over 30 min and then further resuscitation with shed blood to a target arterial pressure greater than 70 mmHg. Total fluid requirements to achieve the targets were significantly lower with both colloids. At 7 days, the animals were sacrificed in the brains examined.

Seven-day survival was nonsignificantly greater in the albumin group. The authors concluded that the colloid groups showed more favourable resuscitation characteristics than the crystalloid groups with similar cerebral histological scores.

HUMAN HEAD INJURY STUDIES

In human studies, the issue of albumin and brain injury has again been addressed. A retrospective study of 93 patients with severe traumatic brain injury investigated the impact of a resuscitation protocol that incorporated the use of albumin [10]. These authors reported an early achievement of negative fluid balance in these patients with well maintained plasma albumin concentrations. Over the first 10 days for which the patients were studied, colloids constituted 40–60% of the total fluids given daily and fluid balance was assisted by the use of furosemide. Mortality at 28 days and 18 months was 11 and 14%, respectively. The authors contrast this with the SAFE study in which albumin usage was found to be associated with adverse outcomes in trauma and a subsequent post-hoc analysis which suggested that in critically ill patients with traumatic brain injury, fluid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline [11]. In the Scandinavian study [10], mortality was substantially lower than that in the SAFE study, but these comparisons should be viewed with caution as the resuscitation strategies, particularly the management of intracranial pressure, may well have been different between the two studies. However, a reappraisal of the use of albumin in brain injury has recently been advocated [12].

PREHOSPITAL RESUSCITATION

Prehospital resuscitation is a very important consideration in fluid therapy for trauma. A major retrospective database analysis examined the role of prehospital fluids affecting outcome in over 750 000 patients. Multivariate analysis indicated that patients receiving prehospital intravenous fluids were significantly more likely to die across nearly all subsets of trauma patients, but particularly in patients with penetrating injuries, hypotension and severe head injury [13▪]. A review of battlefield trauma management advocated limited use of crystalloids or colloids for field resuscitation with greater emphasis on plasma and other blood products for the treatment of severe haemorrhage [14▪]. The issue of the management of coagulation in trauma will be dealt with elsewhere in this edition. However, a recent publication addresses the issue of fluid therapy related to trauma-induced coagulopathy. These authors retrospectively examined a total of 1987 patients in which coagulation testing by the prothrombin time had been performed. In this study they concluded that a high prehospital colloid : crystalloid ratio was associated with coagulopathy on admission to the emergency department after adjusting for the ongoing state of shock [15▪▪]. Taken together with the recent animal data, these publications strongly suggest that prehospital resuscitation should be limited to the minimum required to achieve an acceptable peripheral perfusion given associated injury factors and that the place of colloids in prehospital resuscitation is limited.

BURNS

There have been a number of recent studies examining the use of fluids in patients suffering burns. In one publication, the role of hyperoncotic 10% HES 200/0.5 was examined in a pilot trial of 30 patients. Although the numbers are small, the study was abandoned as the hyperoncotic starch was associated with an apparent increased incidence of fatal outcome [16]. These data should be taken in conjunction with other publications that have suggested that hyperoncotic starch may be associated with harm [17,18] and emphasize the view that there is virtually no place for hyperoncotic colloids as acute resuscitation solutions. However, a number of other studies and reviews suggest that the role of colloids in the resuscitation of patients suffering burns is being re-examined.

Fluid resuscitation formulas, such as the Parkland formula, have found wide application around the world and form the basis for calculation of fluid resuscitation regimes. A recent review of this topic commented that, whereas crystalloid fluid has been the mainstay of resuscitation for the better part of four decades, there has been a progressive but as yet unexplained recent trend toward provision of resuscitation volumes well in excess of those predicted by the formula. This increased fluid load has been associated with numerous oedema-related complications. This review emphasizes that, in burns involving more than 25% body surface area, capillary permeability is increased, not only in the damaged tissue, but also in nonburnt areas. It was proposed that correction of this so-called fluid creep will likely revolve around several strategies, which may include tighter control of titration, re-emergence of colloids and hypertonic salt solutions, and possibly the use of adjunctive markers of resuscitation other than urinary output [19]. In a subsequent retrospective review, the same

author concluded that this trend had not improved and that, over an 8-year period, higher than recommended urine output had been attained as a result of increased crystalloid administration [20▪▪]. Another review concluded that HES may limit burn oedema by ameliorating capillary leak and that improved endpoints for resuscitation may help to minimize the problems of over-resuscitation [21]. A further retrospective review examined the effect of adding albumin to the resuscitation fluid strategy on fluid input/output (I/O) ratios. The administration of albumin rapidly reduced hourly fluid requirements, restored normal I/O ratios and ameliorated fluid creep [22▪]. A study in paediatric burns confirmed these findings showing that the use of albumin restored a normal I/O ratio in paediatric patients, adding further weight to the inclusion of colloid in burns resuscitation strategies [23▪].

FLUID VOLUMES

An important issue related to the use of colloids in trauma is the complex matter of trying to decide how much resuscitation fluid any given patient should receive. The data demonstrating very poor correlation between the standard measures of heart rate, blood pressure and central venous pressures to circulating volume are convincing. However, there is currently little else for the emergency care physician to use as an indicator since renal output is also a poor marker of appropriate tissue perfusion. A recent review article has examined the value of pulse waveform analysis on the management of resuscitation in burns [24]. The authors conclude that these techniques may have a future role in optimizing fluid resuscitation in burns, but that they still require validation in multicentre randomized trials. However, current data do not yet support the concept that these haemodynamic monitoring techniques influence major outcomes in critically ill burn patients [24]. Once a validated method of estimating circulating volume is established, it may be easier to find answers to the ongoing crystalloid-colloid debate.

GENERAL TRAUMA STUDIES

The first study to demonstrate a survival benefit associated with the use of colloids in trauma was published within this review period. In this retrospective study of 1714 patients admitted to a level 1 trauma centre, the authors examined the outcomes in patients who did, or did not, receive a colloid (Hextend) as part of the resuscitation strategy. Compared to the crystalloid-only standard-of-care treatment, the overall mortality analysed by univariate analysis was significantly lower in the colloid-treated patients (5.2 versus 8.9%, $P = 0.0035$). The results were similar when only patients with penetrating trauma were considered ($P = 0.0016$) and when only severely injured patients with injury severity scores greater than 26 were considered ($P = 0.0014$). More starch-treated patients survived to reach intensive care and more blood and blood products were used in this group. However, coagulation measures (prothrombin time and partial thromboplastin time) were not different between the groups. Urine output and renal function were similar between the groups, but there were more early deaths in the standard-of-care group, which introduces the possibility of selection bias. Controlling for early deaths with multivariate analysis showed similar trends, but the data no longer reached statistical significance [25▪▪].

The first randomized, double-blind controlled trial of crystalloid (0.9% saline) versus isotonic colloid (HES 130/0.4 in saline) in trauma resuscitation has recently been published (FIRST trial). In this study of 109 patients, blunt and penetrating traumas were randomized separately. In the penetrating trauma group ($n = 67$), lactate clearance was slightly faster over the first 4 h of resuscitation and lactate and acid base balance were significantly better in the HES group on day 1. The HES group had a zero incidence of renal injury (renal risk, injury, failure, loss, end stage criteria) compared to 17% in patients treated with saline ($P = 0.019$). This difference persisted even after allowance for the early deaths in both groups. Maximum Sequencial Organ Failure Assessment (SOFA) scores were significantly lower in the HES group. The colloid : crystalloid ratio in the first 24 h was approximately 1 : 1.5, resulting in a reduction of 2.5 litres of study fluid. The use of blood and blood products was similar, with a nonsignificant trend to lower product use in the HES group. The blunt trauma analysis was severely hampered by the fact that the blunt HES group was much more severely injured (median injury severity score 29.5 versus 18, $P < 0.01$). There was no significant difference in the use of study fluid between groups and the HES group required significantly more blood and blood products. Outcomes were similar in terms of renal function and organ recovery, with no differences in mortality [26▪▪].

CONCLUSION

Recent evidence and opinion has shown increasing support for the use of colloids in trauma, but the data remain scanty. Hyperoncotic colloids appear to have no place and colloids have a limited place in the prehospital setting. In burns, there is a clear

trend towards increased use of colloids in the early phases, with albumin as the main colloid receiving attention. In general trauma two studies suggest a benefit for HES in penetrating trauma. Data for blunt trauma, which is the commonest form of injury in the Western World, remain unclear.

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Conflicts of interest

The following conflicts of interest are relevant: Professor M.F.M. James has received numerous travel grants and lecture fees from a variety of fluid therapy companies including Baxter, B Braun and Fresenius-Kabi. His university also received an unrestricted educational grant for the conduct of the FIRST trial.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Zaar M, Lauritzen B, Secher NH, *et al.* Initial administration of hydroxyethyl ■ starch vs. lactated Ringer after liver trauma in the pig. Br J Anaesth 2009; 102:221–226.

This study uses a pig model of hepatic rupture to study the effect of resuscitation fluids on survival. The colloid (HES) solution provided better resuscitation, provoked uncontrolled bleeding leading to higher mortality.

2. Bickell WH, Wall MJ Jr, Pepe PE, *et al.* Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994; 331:1105–1109.
3. Barros JM, do NP Jr, Marinello JL, *et al.* The effects of 6% hydroxyethyl ■ starch-hypertonic saline in resuscitation of dogs with hemorrhagic shock. Anesth Analg 2011; 112:395–404.

In this haemorrhagic dog study, hypertonic saline in combination with HES gave worse outcomes than either Ringer's lactate in a 3 : 1 ratio to removed blood or a 1 : 1 ratio of isotonic HES.

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5. Adanir T, Aksun M, Cirit M, *et al.* The renal effect of replacement fluids in controlled severe hemorrhagic shock: an experimental study. Ulus Travma Acil Cerrahi Derg 2009; 15:423–432.
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12. Statler KD. Albumin and brain injury: time for a new approach? Crit Care Med 2011; 39:217–218.
13. Haut ER, Kalish BT, Cotton BA, *et al.* Prehospital intravenous fluid adminis- ■ tration is associated with higher mortality in trauma patients: a National Trauma Data Bank analysis. Ann Surg 2011; 253:371–377.

This massive retrospective study provides further evidence that aggressive prehospital fluid therapy is associated with worse harm. Although it does not directly address the issue of colloids, the greater efficacy of colloid resuscitation suggests that the effect may be worse where colloids are used for prehospital resuscitation.

14. Dubick MA. Current concepts in fluid resuscitation for prehospital care of ■ combat casualties. US Army Med Dep J 2011; 18–24.

This review of battlefield casualties advocates the concept of damage control resuscitation utilizing strategies that promote haemostasis rather than aggressive resuscitation with either crystalloids or colloids.

15. Wafaisade A, Wutzler S, Lefering R, *et al.* Drivers of acute coagulopathy after ■■ severe trauma: a multivariate analysis of 1987 patients. Emerg Med J 2010; 27:934–939.

This large retrospective study concluded that large volumes of prehospital fluids, the ratio of crystalloid to colloid used (high colloid being associated with greater risk of coagulopathy) and persistent shock were all significant drivers of trauma-induced coagulopathy.

16. Bechir M, Puhan MA, Neff SB, *et al.* Early fluid resuscitation with hyperoncotic hydroxyethyl starch 200/0.5 (10%) in severe burn injury. Crit Care 2010; 14:R123.
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This retrospective trial examined the trend towards excessive fluid administration and concluded that, despite the risk being emphasized in recent literature, the problem persists. Resuscitation strategies appear to be targeting excessively high urine output leading to fluid overload. Albumin administration is increasing in an attempt to lessen the problem, but fluid creep remains a major problem in burns resuscitation.

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22. Lawrence A, Faraklas I, Watkins H, *et al.* Colloid administration normalizes ■ resuscitation ratio and ameliorates 'fluid creep'. J Burn Care Res 2010; 31:40–47.

This retrospective review examined the input/output ratio of fluid therapy in burns. They concluded that the addition of colloid to the Parkland formula rapidly reduces fluid requirements and ameliorates fluid creep.

23. Faraklas I, Lam U, Cochran A, *et al.* Colloid normalizes resuscitation ratio in ■ pediatric burns. J Burn Care Res 2011; 32:91–97.

This study examined the role of colloids in decreasing fluid requirements, improving I/O ratios and minimizing fluid creep and concluded that the addition of colloid to the resuscitation strategy rapidly normalized the I/O ratios in children.

24. Lavrentieva A, Palmieri T. Determination of cardiovascular parameters in burn patients using arterial waveform analysis: a review. Burns 2011; 37:196–202.
25. Ogilvie MP, Pereira BM, McKenney MG, *et al.* First report on safety and ■■ efficacy of hetastarch solution for initial fluid resuscitation at a level 1 trauma center. J Am Coll Surg 2010; 210:870–872.

This is the first study to show an outcome benefit from the administration of colloids in trauma. This retrospective study concluded that the addition of colloid to standard resuscitation strategies was associated with a significant reduction in mortality. The study impact is a little diminished by possible confounding survival effects.

26. James MFM, Michell L, Joubert IA, *et al.* Resuscitation with hydroxyethyl starch ■■ improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (fluids in resuscitation of severe trauma). Br J Anaesth 2011. doi: 10.1093/bja/aer229.

This is the first randomized, controlled, double-blind study of crystalloid versus isotonic colloid in trauma with blunt and penetrating trauma randomized separately. The study had significant problems with randomization, in that the blunt trauma colloid group was significantly worse injured than the comparative crystalloid group. In penetrating trauma there was an apparent benefit in terms of faster resuscitation that was associated with absence of renal injury and lower SOFA scores.