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Fluid resuscitation for the trauma patient

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Abstract

Attempts at prehospital fluid replacement should not delay the patient's transfer to hospital. Before bleeding has been stopped, a strategy of controlled fluid resuscitation should be adopted. Thus, the risk of organ ischaemia is balanced against the possibility of provoking more bleeding with fluids. Once haemorrhage is controlled, normovolaemia should be restored and fluid resuscitation targeted against conventional endpoints, the base deficit, and plasma lactate. Initially, the precise fluid used is probably not important, as long as an appropriate volume is given; anaemia is much better tolerated than hypovolaemia. Colloids vary substantially in their pharmacology and pharmacokinetics and the experimental findings from one cannot be extrapolated reliably to another. We still lack reliable data to prove that any of the colloids reduce mortality in trauma patients. In the presence of SIRS, hydroxyethyl starch may reduce capillary leak. Hypertonic saline solutions may have some benefit in patients with head injuries although this has yet to be proven beyond doubt. It is likely that one or more of the haemoglobin-based oxygen carriers currently under development will prove to be valuable in the treatment of the trauma patient.

Keywords: Fluid resuscitation; Trauma patient; Bleeding; Haemorrhage

1. Introduction

Having secured the airway and ensured adequate oxygenation and ventilation, the focus for resuscitation of the severely injured patient moves to stopping haemorrhage and restoring the circulation. Severe hypovolaemia is associated with cardiovascular decompensation, reduced cellular perfusion and oxygen delivery, and the development of profound lactic acidosis [1]. If oxygen delivery is not restored quickly, cell membrane pumps fail irreversibly. Depending on the number of cells sustaining irreversible damage, organ failure or death will follow. In the trauma patient, the aim of fluid replacement is to minimise the number of cells damaged irreversibly by restoring adequate tissue perfusion and oxygen delivery as rapidly as possible. While both intravascular volume and oxygen carrying capacity must be addressed, the former takes priority, because acute anaemia is better tolerated than hypovolaemia. Factors to be considered when addressing fluid replacement for the trauma patient are the assessment of hypovolaemia, when to give fluid, which fluid, and how much fluid to give.

2. Assessment of hypovolaemia

The advanced trauma life support (ATLS) classification of haemorrhage is now well established and is taught to doctors throughout the world (Table 1) [2]. Unfortunately, the physiological responses (heart rate, blood pressure, skin perfusion, respiratory rate, urine output, conscious state) to injury and haemorrhage are not as consistent as is commonly believed. Heart rate may be as poor as systolic pressure as a warning of hypovolaemia. Haemorrhage and injury elicit fundamentally different responses. The response to pure haemorrhage is often one of relative bradycardia [3]. In trauma patients this is usually masked by the response to injury, which is tachycardia and in-

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creased blood pressure [4]. Nonetheless, relative bradycardia may occur even in the presence of significant tissue injury [5]. Two recent studies have shown no significant increase in heart rate in volunteers who underwent haemorrhage of between 20 and 30% of their circulating volume [6,7].

3. When to give fluid

It would seem sensible to start rapid fluid infusion as soon as possible after trauma so that adequate perfusion is restored quickly. This implies starting fluid replacement at the scene; however, attempts to replace fluid may delay the patients arrival in hospital. Furthermore, under some circumstances, increasing the patients blood pressure before control of haemorrhage may be detrimental.

4. Permissive hypotension

The goal of rapid restoration of normal blood pressure in haemorrhagic shock was derived originally from animal studies of controlled haemorrhage (e.g. Wiggers' model), in which bleeding was stopped before starting fluid resuscitation. However, these early models do not reproduce accurately the pathophysiology of fluid resuscitation in the presence of ongoing haemorrhage. Recent animal studies of uncontrolled haemorrhage have demonstrated that aggressive fluid resuscitation will increase blood pressure but will also reverse vasoconstriction, dislodge early thrombus, increase blood loss, cause a dilutional coagulopathy, and reduce oxygen delivery causing a metabolic acidosis [8,9]. In these animal studies, survival was improved by allowing the blood pressure to stay low until haemorrhage was controlled (permissive hypotension).

The animal research was taken into the clinical setting in a prospective, controlled study of patients with penetrating torso injury and a prehospital systolic blood pressure of <90 mmHg [10]. Patients received either standard intravenous fluid therapy at the scene or were cannulated but received no fluid until arrival in the operating room. Of 289 patients receiving delayed fluid resuscitation, 203 (70%) survived to discharge from hospital, compared with 193 of the 309 patients (62%) who received immediate fluid resuscitation ($P = 0.04$). Methodological flaws in the study have led some clinicians to disagree with the authors' conclusions [11]. Furthermore, the study was conducted under very specific circumstances; all patients were injured within the city limits of Houston, only those with penetrating injuries to the torso were included, the mean age of the patients was only 31 years, and prehospital times were extremely rapid. The findings of this study should not be extrapolated to include patients with blunt trauma, elderly patients with chronic illness, those with head injuries, or to other emergency medical services (EMS) where prehospital time may not be as short [12].

5. Controlled fluid resuscitation

When there is profound initial blood loss or when there is likely to be a long delay until the patient can get to an operating room, significant hypovolaemia will cause a severe metabolic acidosis. The bowel is particularly vulnerable to hypovolaemia and bowel ischaemia may fuel sepsis and multiple organ failure. In these cases, the risk from organ ischaemia may far outweigh the risk of provoking more bleeding with fluid resuscitation and the best approach may be judicious fluid infusion. Recent animal models have confirmed the potential benefits of this middle-ground

Table 1
Classification of hypovolaernic shock in the adult according to blood loss (adapted from ATLS [2])

	Class 1	Class 2	Class 3	Class 4
Blood loss (%)	<15	15–30	30–40	>40
Blood loss (ml)	750	750–1500	1500–2000	>2000
Systolic BP	Unchanged	Normal	Reduced	Very low
Diastolic BP	Unchanged	Raised	Reduced	Very low or unrecordable
Heart rate	<100	>100	>120	>140

Table 2
Composition of common crystalloids

Crystalloid	Osmolality (mOsm kg^{-1})	PH	Na^+ (mmol l^{-1})	K^+ (mmol l^{-1})	HCO_3^- (mmol l^{-1})	Cl^- (mmol l^{-1})	Ca^{2+} (mmol l^{-1})
0.9% Saline	300	5.0	150	0	0	150	0
Hartmann's	280	6.5	131	5.0	29[a]	111	2
PlasmaLyte 148	299	5.5	140	5	50[b]	98	0
5% Dextrose	278	4.0	0	0	0	0	0
4% Dextrose in 0.18% Saline	286	4.5	31	0	0	31	0
7.5% Saline	2400		1250			1250	

[a] HCO_3^- is provided as lactate
[b] 27 mmol l^{-1} as acetate and 23 mmol l^{-1} as gluconate

approach; this has been termed controlled resuscitation for uncontrolled haemorrhagic shock [13]. In the clinical setting, this means tolerating a low blood pressure before haemorrhage is controlled, while watching closely for indicators of severe ischaemia (see below) [14].

6. Prehospital fluid therapy

The practice of routine prehospital fluid therapy for trauma patients is changing. Attempts to cannulate the patient and give fluids at the scene may delay the delivery of definitive care in hospital [15]. In the UK, paramedic interventions result in an additional 12 min at the scene and intravenous cannulation contributed significantly to this time [16]. Conversely, cannulation en route does not add extra time and may be as successful as when attempted at the scene [17]. In the UK, 68% of trauma patients given fluid before arrival at hospital receive less than 500 ml [16]. Prehospital studies from the United States have also shown that ineffective volumes of fluid are given to trauma patients [18,19].

A policy of minimal or no prehospital fluid resuscitation is likely to be extremely detrimental to patients with severe head injury. Hypotension will increase substantially the morbidity and mortality following severe head injury and attempts must be made to maintain an adequate cerebral perfusion as soon as possible [20]. In a patient with even slightly raised intracranial pressure, this implies the need for a mean arterial pressure (MAP) of at least 90 mmHg.

7. Which fluid for trauma resuscitation?

Once haemorrhage has been controlled there is consensus on the fact that intravascular volume should be restored as quickly as possible in an effort to reverse tissue ischaemia. There is considerable controversy surrounding which fluid or fluids are the most appropriate for achieving these goals and whether the specific choice of fluid has any impact on morbidity or mortality.

8. Crystalloids

A crystalloid is a solution of small non-ionic or ionic particles (Table 2). Solutions containing approximately isotonic concentrations of sodium (e.g. 0.9% saline, Hartmann's solution) will distribute rapidly across most of the extracellular space. A number of recent studies have contributed usefully to our understanding of the volume kinetics of crystalloids [21–24]. In normovolaemic volunteers, an intravenous infusion of isotonic saline will expand the intravascular space by a maximum of one-third of the volume infused [23,24]. After just 30 min, only 16% of the volume infused remains in the circulation [24]. Subsequent infusions of crystalloid are cleared even more quickly [23]. In the presence of hypovolaemia, there is a reduction in the elimination rate constant for Ringer's solution and its volume effect increases [21,22]. It has been estimated that 1500–2000 ml of crystalloid is needed to replace an acute blood loss of 450 ml over 1 h, depending on how fast normal blood volumes are reached

[21]. Thus, when replacing blood loss with crystalloid, a volume 3–4 times greater than the blood lost is required. This is consistent with traditional teaching but, as only 50–70% of the extracellular water volume is expanded by infused crystalloid, the reason for this requirement is not explained totally by the even distribution of fluid across the extracellular space; it is due also to the rapid elimination of crystalloid from this space [21].

The ATLS manual [2] recommends lactated Ringer's (LR) rather than saline as the initial fluid for trauma patient resuscitation. The rational for this is that large volumes of saline will induce a hyperchloraemic acidosis [25–28]. This is because saline contains 154 mmol l^{-1} of chloride ions, substantially more than the normal plasma content of 98–101 mmol l^{-1}. The excess chloride ions reduce the strong ion difference, thus inducing a temporary metabolic acidosis. Many authorities, such as the American College of Surgeon's Committee on Trauma, regard this as potentially harmful but this has yet to be determined with certainty. Harm is most likely to be caused by aggressive treatment of a hyperchloraemic acidosis, while under the misconception that it is caused by a lactic acidosis secondary to organ hypoperfusion [27].

In comparison with plasma, LR has a lower osmolality (273 mOsm l^{-1} versus 285–295 mOsm l^{-1}). Large volumes of LR will reduce serum osmolality and may contribute to cerebral oedema. This effect is likely to be small but is enough to encourage the use of normal saline or PlasmaLyte, with an osmolality of 300 mOsm l^{-1}, rather than LR in head-injured patients [28].

9. Crystalloids versus colloids

The colloid–crystalloid controversy has continued for at least 50 years [29] and is fuelled by the lack of quality data on this subject. There are no prospective randomised controlled trials with adequate power to detect a difference in survival as the primary end point. The only two indisputable facts are that in comparison with colloid, larger volumes of crystalloid are required to restore intravascular volume, and colloids, but not crystalloids, can cause anaphylaxis.

Depletion of the interstitial fluid volume as well as the intravascular space following severe trauma may be a reason to use crystalloids, which will restore volume to both spaces [30]. This view is supported by evidence that pulmonary function is not affected adversely by crystalloid resuscitation [31]. Lymphatic flow can increase by up to 20 times, which explains why the additional fluid given during crystalloid resuscitation does not normally cause pulmonary oedema [32]. Other studies have shown that in comparison with crystalloid resuscitation, colloids will increase extravascular lung water (EVLW) and worsen pulmonary function [33]. This could be because in the presence of leaky capillaries, associated with the systemic inflammatory response syndrome (SIRS) following severe trauma, colloids will pass into the interstitium. Those preferring to use colloids tend to emphasise the concept of targeting the intravascular space specifically [29] and cite studies that show that, in comparison with crystalloids, colloids reduce the incidence of pulmonary oedema [34,35].

The crystalloid–colloid controversy has attracted a number of meta-analyses [36–39]. One of these systematic reviews concluded that resuscitation with colloid solutions was associated with an absolute increase in the risk of mortality of 4% [37]. This analysis included a very heterogeneous group of critically ill-patients. The studies were very different in their design and used a wide range of resuscitation fluids, and had different resuscitation goals. None of the individual studies were powered to detect mortality as an end point and in many cases the strategies for fluid resuscitation were not consistent with modern intensive care practice. Another review from the Cochrane Database concluded that as colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to justify their use outside of randomised controlled trials [39]. A systematic review from Canada concluded that overall, there is no apparent difference in pulmonary oedema, mortality, or length of stay between isotonic crystalloid and colloid resuscitation [38]. However, in a subgroup of trauma patients, these authors concluded that crystalloid resuscitation is associated with a lower mortality. This conclusion was based on just five studies enrolling a total of 302 patients. The most recent of these studies was completed in 1983 and, by today's standards, all of them are methodologically very weak.

The pragmatic approach to fluid resuscitation of the trauma patient is to use both crystalloid and colloid. After haemorrhage there will be some movement of interstitial fluid into the intravascular space while intracellular volume remains unchanged [40]. The replacement of interstitial fluid as well as intravascular fluid would seem rational. The better intravascular retention of colloids in comparison with crystalloid may make it easier to interpret the results of a colloid fluid challenge. Patients with severe injuries will quickly develop SIRS and with it, a leaky microcirculation [41]. A significant proportion of any colloid solution will enter the interstitial space, the precise quantity being determined by the in vivo molecular weight, molecular charge and extent of capillary leak.

10. Colloids versus colloids

The crystalloid–colloid debate has evolved into a colloid-colloid debate [42]. Colloids contain particles that are large enough to exert an oncotic pressure across the microvascular membrane. In comparison with crystalloids, they have greater intravascular persistence. The pharmacological and pharmacodynamic properties of the various colloids differ widely. The duration of intravascular persistence depends on molecular size, shape, ionic charge, and the porosity of the capillary endothelium. Albumin is the only colloid containing particles of uniform molecular weight (monodisperse). The other colloids are polymers and contain particles with a wide range of molecular weights. This makes it difficult to predict the intravascular persistence on the basis of the weight average molecular weight (MW_w). The number average molecular weight (MW_n) is a better indicator of intravascular persistence as it takes into account the distribution of molecular weights. The composition of various colloids is shown in Table 3.

10.1. Gelatin solutions

Gelatin polypeptides are derived from bovine collagen [43]. They are modified chemically to increase molecular size and intravascular retention. Urea-bridged gelatin [e.g. Haemaccel MW_n 24 500 kilodaltons (kDa)] is derived from cattle bone and succinylated gelatin (e.g. Gelofusine MW_n 22 600) is produced by the thermal degradation of calf skin collagen and the addition of succinic acid anhydride. Approximately 80% of the molecules in urea-bridged gelatin are smaller than 20 kDa and are excreted rapidly through the kidneys. Thus, the intravascular persistence of gelatin solution is relatively low (2–3 h) with urea-bridged gelatin being less than succinylated gelatin.

Data from a large French study indicate that gelatins are the colloid most likely to induce an anaphylactoid reaction (Table 4) [44]. Gelatins are considered generally to have little effect on clotting in the clinical setting. Recent studies of the effect of gelatins have produced apparently conflicting results. Two in vitro studies have shown that gelatin may impair clotting [45,46]. Both Haemaccel and Gelofusine prevent platelet aggregation induced by ristocetin [46]. Haemaccel appeared to be the more potent inhibitor of platelet aggregation, possibly because of its high Ca^{2+} content. In vitro haemodilution with gelatin does not appear to impact significantly on thromboelas-

Table 3
Physicochemical properties of colloids

Colloid	MW_w (kDa)	MW_n (kDa)	pH	Na^+ (mmol l^{-1})	K^+ (mmol l^{-1})	Cl^- (mmol l^{-1})	Ca^{2+} (mmol l^{-1})
4.5% Albumin	70	70	7.4	150	2	120	0
Haemaccel	35	24.5	7.4	145	5.1	145	6.2
Gelofusine	35	22.6	7.4	154	0.4	154	0.4
Dextran 70 in saline	70	39	3.5–7.0	150	0	150	0
Hydroxyethyl starch (450/0.7)	450	70	5.5	154	0	154	0
Hydroxyethyl starch (200/0.5)	200	60	5.0	154	0	154	0

Table 4
Incidence of anaphylactoid reactions caused by colloid solutions (1994) [44]

Colloid	Infusions	Anaphylactoid reactions	Incidence (%)
Gelatins	9424	32	0.345
Hydroxyethyl starch	5231	3	0.058
Dextrans	1861	5	0.273
Albumin	3073	3	0.099
Total	19 593	43	0.219

tograph (TEG) variables [47]. In contradiction to these in vitro studies, the postoperative TEG of patients who received gelatin to replace blood loss showed significant hypercoagulability compared with control tracings and with those of patients who had received albumin or HES [48]. The considerable usage of gelatin in the UK in comparison with the rest of the world is probably dictated more by marketing prowess rather than by science [49]. In the UK, gelatin has been a popular choice for fluid resuscitation in the trauma patient. This practice has been based on a rather optimistic estimate of its intravascular retention and on the belief that it is safer than other colloid solutions. As these misconceptions are being realised by the trauma community in the UK, the popularity of gelatin is falling and initial fluid resuscitation is becoming increasingly crystalloid based.

10.2. Dextrans

Dextrans are produced by the action of dextran sucrase during the growth of the bacteria *Leuconostoc mesenteroides* on a sucrose medium. Currently available dextran solutions are 6% dextran 70 and 10% dextran 40. Dextran 40 is hyperoncotic but is more rapidly excreted than dextran 70. Dextran reduces blood viscosity, reduces platelet adhesiveness, and enhances fibrinolysis [50]. These properties make dextran useful for prophylaxis against thromboembolism, however, doses above 1.5 g kg^{-1} will increase bleeding. Dextran 40 has been associated with renal failure, particularly in the presence of hypovolaemia and pre-existing renal dysfunction. Roleaux formation and interference with blood cross-matching was a feature of the very high molecular weight dextrans which were first used in the 1940s [51]. Modern dextran solutions do not interfere with the cross-matching of blood.

Severe anaphylactic reactions are relatively uncommon and are caused by naturally occurring dextran reactive antibodies (DRAs). These reactions are caused by immune complex (type III) anaphylaxis. Giving an injection of 20 ml of dextran 1 (monovalent hapten dextran) will block the reactive sites of the antibodies. This prevents the formation of immune complexes when an infusion of dextran 40 or 70 is given and has reduced significantly the incidence of serious reactions to dextran [51]. Unfortunately, in a number of countries (e.g. the UK), dextran 1 is unavailable. Dextran is not used in the UK for trauma patient resuscitation; this reflects the concern about increased bleeding and a perceived, though unsubstantiated, high incidence of anaphylaxis.

10.3. Hydroxyethyl starch

Hydroxyethyl starch (HES) solutions are modified natural polymers of amylopectin [52]. They are broken down by amylase. Substitution of hydroxyethyl groups into the D-glucose units increases the resistance to degradation by amylase and extends the intravascular persistence. The degree of substitution is determined by dividing the number of substituted glucose molecules by the total number of glucose molecules. Hydroxylation can occur at carbon positions 2, 3 or 6 of the glucose molecule and individual glucose molecules can have from zero to three hydroxyethyl groups. The higher the number of glucose molecules hydroxylated at the C2 position versus the C6 position, the greater the resistance to breakdown by amylase. A high degree of substitution (>0.6), a high C2/C6 ratio (>8), and a high initial molecular weight (>450 kDa) will maximise the intravascular half-life. On this basis, HES solutions can be divided into high, medium, and low molecular weights (Table 5) [53]. Polymers with a molecular weight less than about 50 kDa are eliminated rapidly by glomerular filtration and larger polymers are hydrolysed by amylase into smaller molecules. Thus, soon after infusion of HES, the molecular weight distribution of the circulating molecules becomes narrower and the average molecular weight smaller than that of the infused solution. A HES solution with an initial weight averaged molecular weight of 200 kDa decreases to 72 kDa in the first few hours following infusion.

Some of the HES is extravasated into the interstitial space where a proportion is taken up by the reticulo-endothelial system. Hydroxylethylstarch deposits have been shown in skin, liver, striated muscle, spleen, and intestine [54]. In patients who receive more than 3 g kg^{-1} within a few days, accumulation of HES in the skin causes pruritis [54,55]. The HES deposits are eliminated slowly but can still be seen a number of years after administration of large doses [54]. A randomised, controlled study comparing small volumes (less than 1 g kg^{-1}) of medium molecular weight starch with LR showed no difference in the incidence of pruritis [56].

High molecular weight HES reduces factor VIII and von Willebrand factor and will cause a coagulopathy [47,53]. For these reasons, high molecular weight HES is probably inappropriate for trauma patient resuscitation. Recently, a high-molecular starch (550 kDa) mixed in a balanced electrolyte solution has become available in the United States. There is some evidence that this has less effect on coagulation than HES of similar molecular weight in saline [57]. Further studies to confirm these claims are awaited. Medium molecular weight starch (e.g. 200/0.5) has significantly less effect on coagulation; the precise impact depends also on the degree of substitution and the C2/C6 ratio of the HES. Those with low substitution ratios (e.g. 200/0.5) have a lesser effect on bleeding except at high doses [58]. On a rather empirical basis, the datasheet advises a maximum daily volume of HES 200/0.5 of 33 ml $kg^{-1}d^{-1}$. In reality, these volumes are often exceeded without inducing a clinical problem. Low molecular weight HES may have minimal effect on coagulation [59].

Table 5
A classification of hydroxyethyl starch solutions [52]

Concentration	High	10%
	Low	6%
Weight average MW	High	450–480 kDa
	Medium	130–200 kDa
	Low	40–70 kDa
Degree of substitution	High	0.6–0.7
	Low	0.4–0.5
C2/C6 ratio	High	>8
	Low	<8

Some animal studies imply that fractionated HES solutions with a molecular range of 100–1000 kDa (e.g. Pentafraction) may be capable of plugging leaky capillaries in inflammatory states [60–63]. This potential effect of starch has been demonstrated in trauma patients recently [41]. In a randomised trial of HES (250/0.45) versus Gelofusine in trauma resuscitation, the degree of microalbuminuria was used as a marker for the capillary leak syndrome. Capillary permeability was lower in the HES-treated patients during the first 24 h after admission. The results of this study indicate that HES may have a useful role in reducing the capillary leak associated with major trauma. Hydroxyethyl starch also encourages the restoration of macrophage function after haemorrhagic shock [64]. A recent study of trauma and sepsis patients showed that 10% HES (200/0.5) resulted in significantly better systemic haemodynamics and splanchnic perfusion than volume replacement with 20% human albumin [65]. Although the incidence of significant anaphylactoid reactions associated with HES appears to be low [44], some anaphylactic reactions have been reported [66].

In theory, manufacturers can create 'designer-HES' solutions to suit the needs of the clinician and, of all the colloids, HES shows the most potential as a resuscitation fluid for the trauma patient. If the preliminary evidence showing a reduction in capillary leak is confirmed, HES may prove very valuable in the trauma population. At the moment, the concern surrounding the effects of HES on coagulation is the main factor preventing its more extensive use in the severely injured patient.

10.4. Albumin

Human albumin is a single polypeptide with a molecular weight of between 65 and 69 kDa [67]. In health, it contributes about 80% of oncotic pressure but in critically ill patients serum albumin concentration correlates poorly with colloid oncotic pressure [68]. The use of albumin in critically ill patients does not improve outcome and it is expensive [69]. Although recent claims that it increases mortality in critically ill patients are unproven [70], there is no reason to use it in adult trauma patients. It is still used by many paediatri-

Table 6
Haemoglobin-based red cell substitutes

Company	Product	Type	Comments
Baxter	Diaspirin cross-linked HemAssist™	Human	Development ceased
Northfield	Glutaraldehyde polymerised PolyHeme™	Human	Phase III trials
Hemosol	O-raffinose polymerised HemoLink™	Human	Phase II trials
Apex	Pyridoxylated, polyoxyethylene	Human	Phase II trials
Bioscience	Glycol conjugated		
Inc	PHP		
Enzon Inc	Polyoxyethylene glycol conjugated PEG-Hb	Bovine	Phase II trials
Biopure	Glutaraldehyde polymerised Hemopure™	Bovine	Phase III trials
	Oxglobin™	Bovine	Approved for veterinary use
Somatogen	Recombinantly cross-linked Optro™	Recombinant	Acquired by Baxter

cians, partly because HES is not licensed for use in children.

11. Hypertonic fluids

Hypertonic 7.5% sodium chloride has an osmolality of 2400 mOsm $l^{-1}$and produces a transient increase in intravascular volume of many times the volume infused [71]. This may be an advantage in the prehospital setting where storage volume and the ability to carry weight are limited. An infusion of hypertonic saline causes an increase heart rate and contractility, and a reduction in peripheral vascular resistance. Hypertonic saline may improve microcirculatory haemodynamics [72]. The addition of colloid extends its intravascular persistence [e.g. NaCl 7.5% and dextran 70.6%, known as hypertonic saline dextran (HSD)].

A significant increase in blood pressure before haemorrhage is controlled may not be an ideal goal and, for this reason partly, the role of hypertonic solutions in trauma resuscitation has yet to be defined. Several prehospital trials of HSD have shown a trend toward increased survival in those receiving HSD, but in none of these was the overall difference in survival statistically significant [73]. In a subgroup of head-injured patients with a Glasgow Coma Scale score of eight or less, survival to hospital discharge was higher in patients receiving hypertonic saline compared to those receiving LR [74]. Despite the lack of convincing data, hypertonic solutions are used in some neurosurgical centres but more robust data are required before these solutions can be recommended for widespread use in trauma patients.

12. Haemoglobin-based oxygen carriers

Haemoglobin is essential for oxygen transport [75]. Currently, the only reliable method of giving haemoglobin to trauma patients is in the form of blood. Human donor blood is expensive, in short supply, antigenic, requires cross matching, has a limited shelf life, requires a storage facility and carries a risk of disease transmission [76]. Homologous blood transfusion is immunosuppressive and may independently increase the risk of infection after trauma [77]. Having overcome a number of problems related to toxic stroma, short intravascular half-life, and high colloid osmotic pressure, a number of haemoglobin-based oxygen carriers (HBOC) are now at advanced stages of development [78–80]. The main sources of HBOCs currently under development are bovine blood, out of date human blood, and biotechnological methods (Table 6). The products currently under investigation do not require cross-matching, have similar oxygen dissociation curves to blood, and are apparently free from risk of transmitting viral or bacterial infections. Many of the HBOCs have a significant vasopressor effect, which is thought to result from scavenging endothelial nitric oxide [80]. In comparison with blood, HBOCs may improve oxygen delivery to ischaemic tissue; the acellular fluid may perfuse capillaries that are compressed by oedema that would prevent the passage of red cells, and haemoglobin polymer is able to filter from the circulation [80].

In a phase-II randomised study of 44 trauma patients, up to six units of PolyHeme (human polymerised haemoglobin) was given to 21 patients without serious complications [81]. Opti-

mism about the impending availability of a HBOC for use in trauma patients has been tempered somewhat by the results of a recent randomised controlled trial of diaspirin cross-linked haemoglobin (DCLHb) in trauma patient resuscitation [82]. Up to 1000 mL of DCLHb was infused during initial resuscitation of severely injured patients; the primary end point was 28-day mortality. The study was suspended after the enrolment of 112 patients. At 28 days, 24 (46%) of the 52 patients infused with DCLHb died, and 8 (17%) of the 46 patients infused with saline died ($P = 0.003$). The precise reason for this increase in mortality in the study group is unknown but the pressor effect of DCLHb may be partly to blame.

For the immediate future, human donor blood will remain the only method with which to provide an increase in oxygen carrying capacity for the trauma patient. In due course, it is quite possible that one or more of these HBOC will take over this role.

13. Fluid warming

When resuscitating the seriously-injured patient all intravenous fluids should be warmed. Hypothermia (core temperature less than 35°C) is a serious complication of severe trauma and haemorrhage and will increase mortality [83]. Adverse effects from hypothermia include [84–86]:

- The oxyhaemoglobin dissociation curve is shifted to the left, thus impairing peripheral oxygen delivery.
- Shivering compounds the lactic acidosis associated with hypovolaemia.
- Hypothermia increases bleeding [87].
- Hypothermia increases the risk of infection [88].
- Hypothermia increases the risk of cardiac morbid events [89].

Table 7
Goals for resuscitation of the trauma patient before haemorrhage has been controlled (modified from [14])

Parameter	Goal
Blood pressure	Systolic 80 mmHg. Mean 50–60 mmHg
Heart rate	<120 beats min^{-1}
Oxygenation	SPO_2 $>96\%$ (peripheral perfusion allowing oximeter to work)
Urine output	>0.5 ml kg^{-1} h^{-1}
Mentation	Following commands accurately
Lactate level	<1.6 mmol l^{-1}
Base deficit	>-5
Haemoglobin	>9.0 g dl^{-1}

14. Goals of fluid replacement

Before haemorrhage has been controlled, the fluid resuscitation strategy is one of balancing the risk of organ ischaemia in the presence of hypovolaemia against the risk of increasing bleeding with aggressive volume loading. Clinicians at the Shock Trauma Center in Baltimore have recommended some goals for early resuscitation before control of haemorrhage has been achieved (Table 7) [14].

Patients with severe injuries have high oxygen requirements immediately, and will rapidly accumulate a significant oxygen debt, as indicated by high blood lactate levels and an increasing base deficit [1]. Once haemorrhage control has been achieved, the goals of fluid resuscitation are to optimise oxygen delivery, improve microcirculatory perfusion, and reverse tissue acidosis. At this stage, traditional end points of resuscitation, such a normal blood pressure, heart rate, central venous pressure, and urine output, are inadequate and fail to differentiate survivors from non-survivors [90,91]. A significant number of trauma patients will achieve these end points and yet have evidence of hypoperfusion as assessed by raised lactate levels and/or low gastric intramucosal pH (pHi) [91]. Patients with evidence of this 'occult hypoperfusion' 24 h after admission, not surprisingly, have a significantly increased risk of death [92].

In the past, trauma patients were routinely resuscitated aggressively with a combination of fluid and high doses of inotropes in an attempt to achieve 'supranormal' goals for oxygen delivery (DO_2I) and consumption (VO_2I) [93]. Failure to achieve supranormal values of DO_2I andVO_2I is a strong predictor of multiple organ failure and death, however, with the exception of one study [94], there is no evidence that striving hard to achieve these empirical goals improves outcome. On the contrary, there is some evidence from a heterogeneous group of critically ill patients that this approach may be harmful [95]. The current strategy for resuscitation is rather more pragmatic; DO_2I is elevated with appropriate fluid

resuscitation, as assessed by CVP or pulmonary artery occlusion pressure (or non-invasive cardiac output monitoring), urine output and peripheral perfusion), with or without moderate doses of inotrope, while tracking the base deficit and/or blood lactate. The use of gastric tonometry to monitor splanchnic perfusion may have some benefit in guiding trauma patient fluid resuscitation and indicating prognosis [96,97]. Despite simplification of the technique with gas tonometry [98], gastrointestinal tonometry is not yet part of routine clinical practice.

15. Transfusion trigger

Although a haemoglobin of 10 g dL^{-1} is generally thought to provide optimal oxygen delivery, normovolaemic humans with good cardiopulmonary function will tolerate haemoglobin levels down to as low as 5 g dL^{-1} [99]. As long as normovolaemia is achieved the reduction in viscosity results in a significant increase in cardiac output and tends to improve tissue oxygenation [100]. The 30-day mortality amongst 838 critically ill patients was no different between those assigned to a restrictive transfusion strategy (haemoglobin level maintained at 7–9 g dL^{-1}) and those treated with more liberal blood transfusion (haemoglobin maintained in the range 10–12 g dL^{-1}) [101]. There was no significant difference in 30-day mortality between treatment groups in the subgroup of patients with trauma ($n = 165$). In subgroups of patients less than 55 years of age, or with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of less than 20, mortality was lower in those assigned to a restrictive transfusion strategy. It is difficult to extrapolate these data to the management of the haemorrhaging trauma patient. This is because the status of the patient's pre-existing cardiopulmonary function is often unknown, and also because the haemoglobin concentration of a trauma patient undergoing resuscitation will be changing rapidly. Under these conditions, the margin of safety is very small if the haemoglobin concentration is reduced as low as 6 or 7 g dL^{-1}, even if the patient is previously healthy. Until more data is available from studies on acute trauma patients, the haemoglobin concentration of the severely injured patient should probably be targeted at greater than 8–9 g dL^{-1}. However, in the trauma patient with only moderate injuries who is known to be cardiovascularly fit, and where bleeding has been controlled, a haemoglobin value as low as 7 g dL^{-1} is acceptable.

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