

HYDROXYETHYL STARCH FOR RESUSCITATION OF TRAUMA PATIENTS

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Introduction

Haemorrhage control and the infusion of fluid are fundamental components of trauma resuscitation. The aim of fluid resuscitation is to restore tissue perfusion and cellular oxygenation and to maintain end organ function. It requires **both** an appropriate volume and type of fluid. Nearly all resuscitation rooms in the NHS follow Advanced Trauma Life Support® (ATLS®) guidelines, compiled by the American College of Surgeon's Committee on Trauma. This group advocates the use of crystalloid as the initial non-blood fluid for treating haemorrhagic shock (1). In the initial stages of trauma patient resuscitation, the precise fluid used is not critical, as long as an appropriate volume is given (2). However, as the systemic response to hypovolaemia evolves the choice of fluid may be more important. Any final year medical student will state that colloids are beneficial as they remain in the intravascular space for longer than crystalloids, but this may be overly simplistic. Consideration of the most appropriate fluid for resuscitation requires an understanding of all the pros and cons of existing fluids. This paper reviews these options and then focuses specifically on the hydroxyethyl starches, their benefits, adverse effects and current role in resuscitation. Other fluids are covered in detail in companion articles in this series.

Options for Fluid Replacement

In an ideal world, the optimal fluid for resuscitation would combine the volume expansion and oxygen carrying capacity of blood, without the need for cross-matching or the risk of disease transmission. It would also retain and restore the normal composition and distribution of the body fluid compartments

(3). As no such fluid exists, the options are either crystalloid, colloid or the blood substitutes.

Crystalloid

The crystalloids are solutions of water that are classified in respect to plasma as hypotonic, isotonic and hypertonic. The most commonly used solutions are listed in Table 1. Glucose-based solutions rapidly become hypotonic following metabolism of the glucose. This leaves free water, which distributes throughout all compartments providing no expansion of the intravascular space. These fluids are not suitable for trauma resuscitation. (4)

The most commonly used fluids are isotonic – examples are 0.9% Saline and Hartmann's solution. The latter contains calcium, potassium and lactate to ensure it is closer to the composition of plasma. The lactate is indirectly converted to bicarbonate. Ringer's Lactate, which is used in the United States, is almost identical (5). These fluids are inexpensive and readily available but they distribute relatively quickly into the interstitial compartments, resulting in peripheral oedema. A 1L infusion results in an expansion of about 200ml meaning the volume of fluid used for adequate resuscitation would be 3-4 times that of the estimated blood loss (6). It has been shown that 30 minutes after infusion, 16% of infused crystalloid remains in the intravascular space, however this is information obtained in healthy volunteers rather than in the hypovolaemic patient (7). A massive transfusion drives the cycle of hypothermia, acidosis and coagulopathy, and has been linked with increased risk of abdominal compartment syndrome (8). Normal saline can cause hyperchloraemic metabolic acidosis (9).

Table 1. Composition of common crystalloid solutions for intravenous administration

Solution	Osmolarity (mOsmol/l)	pH	Na ⁺ (mmol/l)	Cl ⁻ (mmol/l)	K ⁺ (mmol/l)	Ca ²⁺ (mmol/l)	Glucose (mg/l)	Lactate (mmol/l)
Glucose 5%	252	3.5- 6.5	-	-	-	-	50	-
Glucose 50%	2520	3.5-6.5	-	-	-	-	500	-
N. Saline 0.9%	300	5.0	154.0	154.0	-	-	-	-
Glucose-Saline	262	3.5-6.5	30.0	30.0	-	-	40	-
Hartmann's Sol ^a	278	5.0-7.0	131.0	111.0	5.0	2.0	-	29.0
Hypertonic Saline	1025	5.0	513	513	-	-	-	-

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Hypertonic saline has the benefit of requiring small volumes for restoration circulating volume but an outcome advantage has yet to be defined. A Cochrane review assessed the use of hypertonic versus isotonic crystalloid in resuscitation in trauma, burns and surgery (10). The authors concluded that hypertonic was useful in trauma and surgery but not in burns; the wide confidence intervals indicated that the results were not significant. Hypertonic saline reduces intracranial pressure in head-injured patients but this has not been shown to improve outcome (11).

Colloid

A colloid is a homogenous non-crystalline substance consisting of large molecules or ultramicroscopic particles of one substance dispersed through a second substance. The particles do not settle and cannot be separated out by filtration or centrifugation unlike the components of blood (12). Colloids can be subdivided into two major groups - protein and non-protein (also described as plasma derivatives and semi-synthetics.).

Naturally occurring colloids include human albumin solutions and fresh frozen plasma. Albumin is the only one used in resuscitation and solutions (4.5% or 20%) are derived from human plasma. It is a monodisperse colloid with a plasma half-life of 16 h. Controversy arose in 1998 when authors of a meta-analysis concluded that use of albumin was associated with an increase in mortality of 6% (13). This controversial conclusion was proven wrong with the publication of the SAFE study in 2004 (14). This was a large multi-centred, randomised double-blind trial comparing 4% albumin with normal saline for intravascular resuscitation. The study found no difference in mortality, ICU or hospital days. However, albumin is expensive and has a small risk of disease transmission, and is therefore not used routinely for fluid resuscitation.

The non-protein or synthetic colloids are classified into dextran solutions, the modified fluid gelatins and the synthetic hydroxyethyl starches. These are dissolved in a crystalloid carrier solution which is commonly isotonic saline. The gelatins, which are not available in the US, are derived from hydrolysis of bovine collagen and have a half-life of up to 3.5 – 4hrs in the intravascular space (15). The dextrans are groups of branched polysaccharides of manufactured by the bacterial action of *Leuconostoc mesenteroides* on a sucrose medium. The products available are Dextran 40 and 70 (Molecular Weight (MW) of 40,000 and 70,000 respectively), with only the latter being used in resuscitation (12).

The hydroxyethyl starches (HES) are produced by hydroxyethyl substitution of amylopectin, a D-glucose polymer, obtained from sorghum or maize (16). They are the youngest generation of artificial colloids after gelatin and dextrans. These solutions were first introduced 20 yrs ago. They have evolved greatly and recent solutions have a wider range of indications and fewer complications.

Pharmacokinetics of HES

HES is a polydisperse solution meaning it contains particles of varying size. The first HES solutions were of relatively high molecular weight in order to attempt to prolong their vascular persistence. The molecular structure of HES is a branched amylopectin polymer and is broken down by serum amylase in the blood. The resulting components are smaller than the renal threshold allowing them to be removed from the circulation by glomerular filtration. The polymer can undergo etherification which results in substitution of hydroxethyl groups for hydroxide. This occurs at the position C2, C3 and C6 of the glucose molecule and increases the resistance of degradation by the amylases; meaning that higher degrees of substitution

increase intravascular persistence (5, 17). The majority occur at position 2, with the C2:C6 ratio also influencing the enzymatic degradation.

The starch products are described by their molecular weight, followed by their degree of molar substitution – i.e. a solution of hetastarch 450/0.7 has a MW of 450kDa and a molar substitution of 0.7. It is the latter which contributes most to the physiological and physicochemical characteristics. The higher the molar substitution and C2/C6 ratio, the slower the starch is metabolised (18). All starch preparations are stable at room temperatures and have long shelf lives.

In Europe, until recently, the most commonly used starch was hydroxyethyl starch 200/0.5. In the United States, hetastarch – hydroxyethyl starch 450/0.7 was the only starch available for blood volume therapy (with hydroxyethyl starch 250/0.5 being for leukapheresis) (18). With the development of hydroxyethyl starch 130/0.4 (Voluven®; Fresenius Kabi AG, Bad Homburg, Germany), there has been a rapid increase in the interest in the uses of this starch and its profile *in vivo*.

A small proportion of hydroxyethyl starch is known to be transiently stored in tissues and finally excreted in the urine after distribution. Side effects of hydroxyethyl solutions include impaired coagulation, altered renal function and pruritus and are more common with the higher molecular weight solutions (19, 20). As it is not physically possible to measure the transiently stored HES in the tissue in humans, it has been studied in animals. Two studies have looked at levels in tissue after multiple infusions of starches 130/0.4, 200/0.5 and 450/0.7 (21, 22). Both groups looked at organ-specific ¹⁴C activity as percentage of infused dose. Radioactivity in the animal carcass after 28 days since the last dose of 450/0.7 starch was 5-fold higher than 24 days after the last dose of 200/0.5 HES and 11-fold higher than 24 days after the last dose of 130/0.4 (18).

In humans, it is necessary to measure either plasma concentration (only possible with experimental conditions) or urine clearance. Studies have looked at both single dose and repeated dose administration. Waitzinger et al (23) showed that after 500ml of HES 130/0.4 infusion the plasma clearance was 31.4mL/min for 6% solution, which is considerably higher than shown for hetastarch which had a clearance of less than 1 mL/min (24). The mean half life of the latter was 6.3hrs compared to that of the former which had a half life of 1.39hrs.

Authors of an earlier paper (25) measured plasma concentrations of hetastarch after infusions on three consecutive days in repeated infusions. It was found that the residual plasma concentration 24hrs after the third infusion was higher than the peak concentration after the first infusion. Multiple administrations of HES 130/0.5 (10%) showed that no relevant plasma accumulation occurred over 10 days despite high accumulative amounts given (26). A very recent prospective randomised, double-blind study (27) using healthy volunteers looking at 500 ml infusions of either HES 130/0.4 or HES 200/0.5. These were given on five consecutive days with a 7hr daily observation for blood sampling. This was accompanied by a 30 day follow-up. Each volunteer then returned five weeks later and the other solution was infused with the same protocol. Serum concentrations of HES were calculated to allow the calculation of the area under the concentration curve, maximal concentration and elimination half-life. The number in the study was small (n=9), but results were significant, showing a lower concentration of HES 130/0.4 after the first day and increased much less than HES 200/0.5 for the initial 5 days. This trend was reflected in the elimination half-time for HES 130/0.4 which was much shorter on both the first day - 0.37h vs 1.02h for HES 200/0.5 and over the following 5 days. At this stage the elimination half-

time was 0.41h for HES 130/0.4 vs 2.97h for HES 200/0.5. This data verifies that HES 130/0.4 accumulates less in serum than HES 200/0.5.

These results have been mirrored in patients as well as healthy volunteers. Jungheinrich (28) looked at plasma concentrations after giving HES 130/0.4 and 200/0.5 during orthopaedic surgery. After similar doses were given intra-operatively and to a maximum of 2L in the first 24hr post-operative period: plasma concentrations were found to be significantly different from 5hrs post-surgery until the last measurement was taken at the end of the first post-operative day. Results at that stage were found to be 2.6mg/ml for HES 200/0.5 vs 1.0mg/ml for HES 130/0.4 ($p < 0.01$). It is postulated that both the reduced molecular weight and the molecular substitution result in the lack of accumulation and this in turn alters the adverse effects that have been described with starches.

Pros and Cons of HES

The first hydroxyethyl starch solutions that were of relatively high molecular weight and high degree of substitution were associated with increased risk of bleeding, renal failure, anaphylaxis and itching. The introduction of the lower molecular weight generation of starches have shown an improved pharmacological profile with fewer negative effects on coagulation, renal function and, as described, less plasma/tissue accumulation (17, 29, 30).

Inflammatory Response

Starches have been shown to be beneficial in septic patients and acute inflammation (31). At a cellular level inflammation is characterised by pan-endothelial injury causing increased endothelial permeability, loss of proteins and interstitial oedema. The subsequent extra-cellular fluid accumulation appears to be a major factor in the pathogenesis of organ failure. A number of studies have shown benefit in animal studies. Feng et al (32) used a rat model of caecal ligation and perforation; each rodent was then resuscitated using either HES or gelatin solutions. Results showed a reduction in inflammatory modulators in the HES group allowing a conclusion to be drawn that HES attenuates capillary leakage by modulating the inflammatory response. These results have been reiterated with similar findings from a septic-porcine model (35) which showed significant decrease in capillary leakage when resuscitated with HES 130/0.4. This all builds on previous animal studies where the use of HES was shown to firstly cause an attenuation of hypoxia-induced increases in vascular leakage and in acute inflammation (33). Secondly, in mice with trauma-haemorrhage (34), HES resuscitation restored macrophage integrity, thus preventing an increase in release of interleukin-6 (IL-6). Although it can be difficult to extrapolate results from animal studies to humans, and a dampened inflammatory response may not necessarily translate into a clinical benefit, these are still encouraging trends in the argument for the use of HES in both trauma and sepsis.

Improved Intraoperative Lung Function

Restoration of blood flow to ischaemic tissue, as in the case of aortic surgery, results in an increase in vascular permeability, interstitial oedema and in the lung culminates in non-cardiogenic pulmonary oedema. Rittoo et al (36) looked at pulmonary function after aortic aneurysm surgery with resuscitation with either HES or gelatin solution. Results showed that perioperative and postoperative lung function was better in patients treated with HES infusion.

Renal Dysfunction

Cittanova and colleagues published a comparison trial where organ-donating brain dead patients were given either HES or

gelatin solutions (37). After kidney donation, 9 out of the 27 recipient patients required haemofiltration in the HES-treated group, whereas only 1 of 20 needed this in the gelatin group. On renal biopsy, 3 of the HES treated group demonstrated osmotic-nephrosis-like lesions which had since been described in case reports of acute renal failure in the post-operative phase in a patient given HES (38).

The adverse effect on renal function was further highlighted by Schortgen and colleagues (39) who studied the effects of HES and gelatin on renal function in severe sepsis in a multicentred randomised study. A total of 159 patients were randomised to be given either HES (200/0.6) or gelatin as a volume expander. In comparison with gelatin, use of HES increased the incidence of acute renal failure (odds ratio = 2.57). Further studies have failed to show an association with renal failure (40, 41), especially when using the lower MW starches.

Two publications from this year (42, 43) add further weight to the argument that HES does not impair renal function. Mahmood et al (42) have reported a prospective, randomised trial comparing the effects of two different types of starch solution (MW of 200/0/62 kDa and 130/0.4 kDa) and gelatin on renal function during elective aortic aneurysm surgery. Sixty-two patients were randomised to receive an initial intra-operative bolus and then an infusion given to maintain a mean arterial pressure of 80mmHg or greater. Serum creatinine concentrations were taken as a marker of glomerular filtration rate and were measured pre-, peri- and post-operatively for five days. Urine immunoglobulin G (IgG) was also measured as a marker of glomerular and tubular injury. The median serum urea increased significantly in the gelatin group compared to the starch group ($p = 0.010$). There was no difference in the two starch groups. Urinary IgG increased in all three groups but significantly lower in the HES group than the gelatin ($p = 0.030$) showing that both glomerular and tubular function was better maintained with starches. Although this study was small, considering the relatively high incidence of renal dysfunction in this surgical sub-group (up to 13%), its findings should be looked at in a positive light.

A recent paper has addressed the common criticism of small study numbers. Sakr and colleagues (43) have reported on a multicentred, pan-European, prospective, observational study involving 3147 patients looking at the effect of hydroxyethyl starch on renal function in critically ill patients. They studied fluid requirement, urine output, sequential organ failure assessment (SOFA) score, serum creatinine and the need for renal replacement therapy (RRT). 34% (1075) of the patients received HES and even though more of these patients actually required RRT, in a multivariate analysis this subgroup was not associated with a subsequent risk for RRT (odds ratio: 0.417). Unfortunately the MW or degree of substitution of HES infused was not recorded, nor were the sensitive markers of renal function used. Despite this, the fact that there seems to be no impact on renal function after HES administration is an important finding in the on-going debate of HES use (44). However, evidence regarding fluid replacement in patients with altered kidney function is lacking and thus cannot be recommended in this group of patients (45).

Unfortunately, the results of the recently completed VISEP Study, so far published in abstract form only, indicate that HES 200/0.5 may well cause renal failure in septic patients. Many clinicians are awaiting publication of the detailed results before deciding on the continued use of HES.

Effect on Coagulation

Haemostatic alterations that are associated with the use of intravenous fluid can be related to either non-specific and/or

specific effects (46). The former is related to the progressive dilution of the plasma and cellular coagulation factors. The latter is from the direct action of the substitute on coagulation factors, fibrinolysis and platelet function (47). HES interferes with platelets in two ways, the first resulting in a dysfunction as seen in von Willebrand's disease (abnormal platelet aggregation) (48). After the administration of up to 1000ml of HES, a decrease in factor VIII:C and von Willibrand's factor (vWF) was recorded that was greater than expected by simple dilution (49). The second effect is altered platelet aggregation where it is thought that HES modifies the platelet membrane and results in a longer bleeding time (46). The HES macromolecules are also known to decrease plasma levels of coagulation factor VIII and this is especially related to solutions of high MW and raised plasma concentrations (18, 50). This trend is not mirrored to such an extent with use of the lower MW solutions, as described by Langeron who looked at HES 200/0.5 vs 130/0.4 in patients undergoing major orthopaedic surgery (51). Significantly less allogenic transfusions were required ($p=0.042$) and less interference with factor VIII ($p<0.05$) was noted in the 130/0.4 group. This trend was corroborated by two further papers studying patients undergoing major abdominal surgery (52, 53).

The current daily dosage of HES 130/0.4 is currently 50ml/kg/day and is higher than the volume recommended for the other starches because the faster excretion time and lower plasma accumulation. The studies to date have included relatively few subjects and have yet to address fully the variables such as initial level of vWF, speed of infusion and the clinical parameters such as acidosis, hypothermia and state of shock which can all alter haemostasis in their own right (46).

Pruritis

The higher MW starches accumulate in plasma more than the lower MW starches and cause pruritus. With the lower MW starches, these effects appear to be attenuated (27, 54, 55).

Efficacy of HES in Resuscitation of Critically Ill and Trauma Patients

In 2004, the Cochrane Collaboration published two large reviews on fluid resuscitation in critically ill patients. The first of these was to address the on-going debate of whether or not the use of crystalloids versus colloids is better (56). The authors' objective was to assess the effects on mortality of colloids compared to crystalloids for fluid resuscitation in critically ill patients; one subset they compared was hydroxyethyl starch. In this group, ten trials with a total of 374 patients were reviewed. The pooled relative risk (RR) of death was 1.16 (95% confidence interval [95% CI] 0.68 to 1.96). The overall conclusion of the reviewers was *"There was no evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery."*

The second review looked at the benefits of the available colloid used in resuscitation (57). The main outcome considered were death, amount of whole blood transfused and incidence of adverse reactions. Out of the 36 trials reviewed, 20 compared albumin versus HES and 11 compared gelatine versus HES. The pooled RR of death in these sub-groups was 1.17 (95% CI 0.91 to 1.50) for the former group and RR= 1.00 (95% CI 0.78 to 1.28) in the latter. Overall, there is no significant difference in mortality rates and as such there was insufficient evidence to determine if one colloid solution is any more effective or safer above its competitors.

Allison and colleagues (58) looked at the use of gelatin compared to HES in patients with blunt trauma. Building on

the evidence that had shown that an increase in capillary permeability is one element that activates the cascade leading to multi-organ failure, they looked primarily at the presence of low level urine albumin excretion (microalbuminuria) as a method of monitoring changes in the capillary permeability. Secondary outcomes measured were pulmonary function, inflammatory response and markers of haemostasis.

Forty-five patients that had been admitted within 2hrs of blunt trauma were randomised to receive either HES (250/0.45) or gelatin as their colloid in the first 24hrs. The patients were followed for a maximum of 5 days. Injury Severity Score (ISS), overall fluid requirement, volumes of infused blood products, daily bloods including C-reactive protein (CRP), clotting times, and the PO_2/FiO_2 ratio were recorded. Microalbuminuria was measured for only the first 24hrs. HES was given to 24 patients and gelatin to 21. There were three deaths in the HES group and none in the gelatin group, with no significant difference in the initial ISS. Capillary permeability was significantly lower in the first 24hrs in those patients given HES compared with the gelatin group. The HES group also showed significantly lower mean CRP levels in this period. Over the complete observation period there were no differences in the mean clotting times, mean serum creatinine level, infused volumes of blood products, volumes of crystalloid administered and the urine output. Interestingly, patients in the HES group had an average intensive care stay of 8.8 days vs 11.1days in the gelatin group, even though it was not statistically significant. The authors acknowledged that the power of the study was insufficient to ascertain if use of HES is linked with increased mortality due to uncontrolled bleeding. The paper is a good pilot to instigate further work at initial resuscitation using HES, even more so if a lower MW (HES 130/0.4) was given.

Work in animal studies continues to fuel the debate of HES use in sepsis and trauma (59). Preliminary studies have shown that early use of HES in pigs that had undergone a controlled haemorrhage results in prompt recovery of tissue perfusion equal to that seen with crystalloids (60). In the resuscitation of septic shock from faecal peritonitis in sheep (61), fluid resuscitation was given to maintain pulmonary artery occlusion pressure at baseline levels, without antibiotics or inotropic support. The group given HES and albumin showed a significantly higher stroke volume, cardiac index and oxygen delivery when compared to either Ringer's lactate or gelatin. The HES group also showed a significantly lower lactate concentration. Despite this, the researchers found the choice of resuscitation fluid did not affect overall outcome.

Looking at studies focusing on patients undergoing major abdominal surgery as a mimic to the physiological insult encountered with trauma, Boldt et al observed the outcomes of the use of albumin-based volume replacement in the elderly (62). In the USA, albumin is more widely accepted in trauma and critically ill than in Europe (5) and the elderly population was selected as it was assumed that older patients have a poorer prognosis secondary to pre-existing disease. This group undergoing major abdominal surgery was taken to experience a significant inflammatory response as noted in trauma. Measurements of CRP, IL-6 and plasma levels of adhesion molecules were recorded (the latter to indicate the degree of endothelial activation and injury). The increase in these markers was less in patients who received HES compared with those given albumin. This attenuation of inflammatory response in similarly stressed patients undergoing abdominal surgery was recorded with use of HES 130/0.4 intra-operatively in comparison to crystalloid (63).

Even though these studies show some benefit from HES (especially low MW; 130/0.4) these findings should not be

extrapolated to the setting of the initial resuscitation of trauma patients. Given that trauma remains the leading cause of death in the young (64), a large multicentred trial, looking primarily at mortality, with randomisation to either crystalloid or HES 130/0.4 would be essential in resolving the current controversy.

Conclusion

There is no evidence justifying the use of colloid in the initial resuscitation of a trauma patient. However, as the inflammatory response and its physiological sequelae evolve the choice of fluid may be more critical. Low molecular weight hydroxyethyl starch may offer some benefits in these critically ill patients but its precise impact on renal function must be elucidated. If low MW HES is proven safe, the current UK predilection for using gelatin in this period is likely to change. Further human studies using HES in both the resuscitation room and during emergency surgery are needed to ascertain its role in these settings.

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