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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)

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Editor's key points

- Opinions are divided concerning resuscitation fluids in trauma.
- This double-blind randomized controlled trial compared resuscitation with isotonic hydroxyethyl starch (HES 130/0.4) or 0.9% saline in trauma patients.
- Biochemical markers of resuscitation and renal function were better in those who received HES 130/0.4 after penetrating trauma.
- Study outcomes were similar after blunt trauma, although numbers in these subgroups were modest.

Background. The role of fluids in trauma resuscitation is controversial. We compared resuscitation with 0.9% saline *vs* hydroxyethyl starch, HES 130/0.4, in severe trauma with respect to resuscitation, fluid volume, gastrointestinal recovery, renal function, and blood product requirements.

Methods. Randomized, controlled, double-blind study of severely injured patients requiring>3 litres of fluid resuscitation. Blunt and penetrating trauma were randomized separately. Patients were followed up for 30 days.

Results. A total of 115 patients were randomized; of which, 109 were studied. For patients with penetrating trauma (n=67), the mean (SD) fluid requirements were 5.1 (2.7) litres in the HES group and 7.4 (4.3) litres in the saline group ($P<0.001$). In blunt trauma (n=42), there was no difference in study fluid requirements, but the HES group required significantly more blood products [packed red blood cell volumes 2943 (1628) *vs* 1473 (1071) ml, P=0.005] and was more severely injured than the saline group (median injury severity score 29.5 *vs* 18; P=0.01). Haemodynamic data were similar, but, in the penetrating group, plasma lactate concentrations were lower over the first 4 h (P=0.029) and on day 1 with HES than with saline [2.1 (1.4) *vs* 3.2 (2.2) mmol litre^{-1}; P=0.017]. There was no difference between any groups in time to recovery of bowel function or mortality. In penetrating trauma, renal injury occurred more frequently in the saline group than the HES group (16% *vs* 0%; P=0.018). In penetrating trauma, maximum sequential organ function scores were lower with HES than with saline (median 2.4 *vs* 4.5, P=0.012). No differences were seen in safety measures in the blunt trauma patients.

Conclusions. In penetrating trauma, HES provided significantly better lactate clearance and less renal injury than saline. No firm conclusions could be drawn for blunt trauma.

Study registration: ISRCTN 42061860.

Keywords: acute kidney injury; fluid therapy; hydroxyethyl starch; saline solutions; trauma

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Controversy persists regarding the choice of fluids for resuscitation in critically injured patients. Colloids are advocated as they are associated with rapid attainment of circulatory goals.[1] Crystalloids have been recommended since they are cheaper and no survival benefit has been shown for colloids.[2] However, resuscitation with large crystalloid volumes has been associated with complications of tissue oedema and an increased incidence of abdominal compartment syndrome.[3 4]

The medium molecular weight hydroxyethyl starch, HES 130/0.4, is a moderate duration colloid with minimal effects on coagulation.[5] There has been no extensive study of its use in resuscitation of trauma patients. The need for a well-controlled, carefully conducted, prospective, randomized, double-blind study of colloids compared with crystalloids in trauma resuscitation has been highlighted.[6 7]

We compared resuscitation with 0.9% saline against HES 130/0.4 with respect to shock reversal, coagulation, gastrointestinal and renal function in shocked trauma patients presenting to a level 1 trauma unit.

Methods

The protocol and subsequent protocol amendments were approved by the Human Research Ethics Committee of the

Faculty of Health Sciences, University of Cape Town (REF 217/2006). Deferred written informed consent was obtained from participants or their legally acceptable representatives.

This was a single-centre, randomized, double-blind, clinical trial comparing the efficacy and safety of HES 130/0.4 with saline 0.9%. Severely injured patients who had received a maximum of 2 litres of crystalloids before randomization were resuscitated with either solution (FIRST fluid) in a blinded fashion. The groups were designated Penetrating HES (P-HES), Penetrating Saline (P-SAL), Blunt HES (B-HES), and Blunt Saline (B-SAL). Inclusion and exclusion criteria are presented in Table 1.

Randomization and blinding

The resuscitation fluids were prepared by sealing identical 500 ml bags in black plastic which concealed the label and contents. Penetrating and blunt trauma were randomized separately and data for the two categories analysed independently. Randomization was by random numbers grouped in blocks of 8 for each category of trauma in a ratio of 1:1 for the study fluid. Using these numbers, the trial pharmacist pre-packed numbered boxes labelled 'Blunt' or 'Penetrating' containing blinded study fluid that were then placed sequentially into a warming cabinet in the trauma resuscitation room.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Penetrating or blunt trauma	Fluid overload pulmonary oedema
Requiring >3 litre volume resuscitation	Known allergy to hydroxyethyl starch
Aged 18–60 years	Known pre-existing renal failure with oliguria or anuria
	Patients receiving dialysis treatment before the injury
	Severe hypernatraemia or hyperchloraemia on admission
	Severe head injury from which recovery was unlikely
	Severe intracranial bleeding
	Severe crush injury
	Unrecordable arterial pressure unresponsive to 2 litre i.v. fluid loading
	Clinically obvious cardiac tamponade
	Neurogenic shock (high spinal cord injury)
	Known AIDS or AIDS-related complex
	Patients admitted >6 h after injury
	Patients who have already received any colloid before randomization
	Patients taking part in another clinical trial at the same time
	Patients refusing consent

Resuscitation and subsequent management

Data collected are indicated in Table 2. Arterial and central venous pressure catheters were placed in all patients as soon as possible.

FIRST fluid was administered using clinical indicators of shock according to a predetermined algorithm (Fig. 1). Resuscitation was deemed complete when haemodynamic and renal targets were achieved and sustained. Patients with clinical evidence of continuing bleeding underwent emergency surgery without waiting for full resuscitation. Patients undergoing surgery continued to receive appropriate i.v. fluid resuscitation according to the algorithm.

Packed red blood cells (PRBCs) were administered when the measured haemoglobin decreased below 8 g dl^{-1} with a target for transfusion of 10 g dl^{-1}. Platelets (Plt), fresh-frozen plasma (FFP), and cryoprecipitate were only administered in accordance with abnormal thrombelastography (TEG) measures and if there was clinical evidence of non-surgical bleeding (Fig. 1).

All fluids were warmed and a forced-air warmer was applied to prevent hypothermia. Where required, the only vasoactive pharmacological support used during resuscitation was epinephrine.

Resuscitation data were collected for the first 24 h and thereafter daily until exit from the study. Biochemical measurements, assessment of renal function, and calculation of sequential organ function (SOFA) scores were performed daily on all patients until study exit.

Injury severity was categorized using the injury severity score (ISS) and new injury severity score (NISS).

Study exit was defined as death or recovery of gastrointestinal function, defined as tolerance of full enteral feeding. From this point, no further FIRST fluid was administered. All surviving patients were followed up for 30 days after enrolment and a personal or telephone interview was conducted where contact with the patient could be made. Serious adverse events were recorded and reported to the Ethics Committee.

Statistical considerations

Primary outcome variables were the volumes of FIRST fluid needed in the first 24 h after enrolment and the number of patients achieving normal gastrointestinal function by day 5.

Safety was determined by 30 day mortality, serious treatment-related adverse events, and acute renal injury as defined by the RIFLE criteria evaluated through daily urine output and creatinine measures against baseline until study exit.[8]

Secondary outcome variables were the use of blood products, biochemical abnormalities, particularly lactate, chloride, and acid–base disturbances, days in intensive care, days on ventilatory support, SOFA scores, TEG measurements, and the incidence of skin itching as elucidated at the end-of-study interview.

A retrospective pilot study of trauma patients established feasibility and showed a ratio of 2:1 of penetrating *vs* blunt trauma. The power calculation for fluid requirement was

Table 2 Schedule of measurements. HR, heart rate; CVP, central venous pressure; Hb, haemoglobin; Ca^{2+}, ionized plasma calcium; FBC, full blood count; Diff, differential count; INR, international normalized ratio of the prothrombin time; PTT, partial thromboplastin time; TEG, thrombelastography; SOFA scores, sequential organ failure scores

	Day				
	Day 0			Day 1	Subsequent days
	Baseline	Resuscitation	Thereafter	9 a.m.	9 a. m.
Haemodynamic					
HR	×	15 min	As indicated	×	As indicated
Arterial pressure	×	15 min	As indicated	×	As indicated
CVP	×	15 min	As indicated	×	As indicated
Biochemistry					
Sodium	×			×	
Potassium	×			×	
Chloride	×			×	
Urea	×			×	
Creatinine	×			×	
Blood gases					
Arterial+lactate, Ca^{2+}	x	Hourly	As indicated	×	As indicated
Venous for Scv_{O_2}	×	Hourly	As indicated	×	As indicated
Hb	×	Hourly	As indicated	×	As indicated
Haematology					
FBC and Diff	×			×	
INR and PTT	×			×	
TEG	×	Hourly	As indicated	×	As indicated
SOFA scores				×	Daily

based on an assumption of a 2:1 ratio of FIRST fluid usage in the initial 24 h, with an anticipated mean of 5 litres in the crystalloid group and 2.5 litres in the colloid group with a standard deviation of 4 for each fluid type. This yielded a required sample size of a minimum of 17 in each limb of the study. This meant that a minimum number of 34 patients were required in the blunt trauma limb of the study. Since we anticipated twice the number of penetrating injuries, 68 patients would be required in the penetrating injury group, giving a minimum sample size of 102 patients in the entire study.

A power calculation for the gastrointestinal outcome was more difficult as there was inadequate information available on which to base assumptions. An anticipated incidence of full enteral recovery at 5 days of 50% was expected in the crystalloid group and of 75% in the colloid group. Using a one-sided χ^2 test at a significance level of 0.025, 66 patients per group were needed to show the difference of 25% with a power of 80%. Thus, a complete study sample size of 140 patients was planned.

Proportional comparisons between the groups within each category were conducted with Fisher's exact test. Normally distributed variables were compared between the groups within each category using Student's *t*-test. For changes in lactate over time a linear, mixed-effect regression model was used after adjustment for baseline lactate and missing data over the first 4 h of the resuscitation period. For non-parametric data or data that were not normally distributed, the Mann–Whitney *U*-test was used for between-group comparisons in each trauma category. Statistical significance was defined as $\alpha < 0.05$.

Results

Recruitment and study closure

The study was closed after 3 yr because of a change in referral patterns which led to a decline in enrolment. Consequently, the study ended after 115 of the 140 patients had been enrolled with six exclusions (Fig. 2).

Patient characteristics and mortality

Patient characteristics were similar and the mechanism of injury was comparable between the groups in each of the categories (Table 3). However, injury severity was significantly greater in the B-HES group compared with the B-SAL group. No patient in the penetrating trauma category suffered direct renal injury and the incidence of haematuria at enrolment was similar between the two groups. Mortality was 16.5% with no significant differences between the groups.

Fluid balance

Fluid utilization in the first 24 h is summarized in Table 4. Significantly, more FIRST fluid was required in the P-SAL group

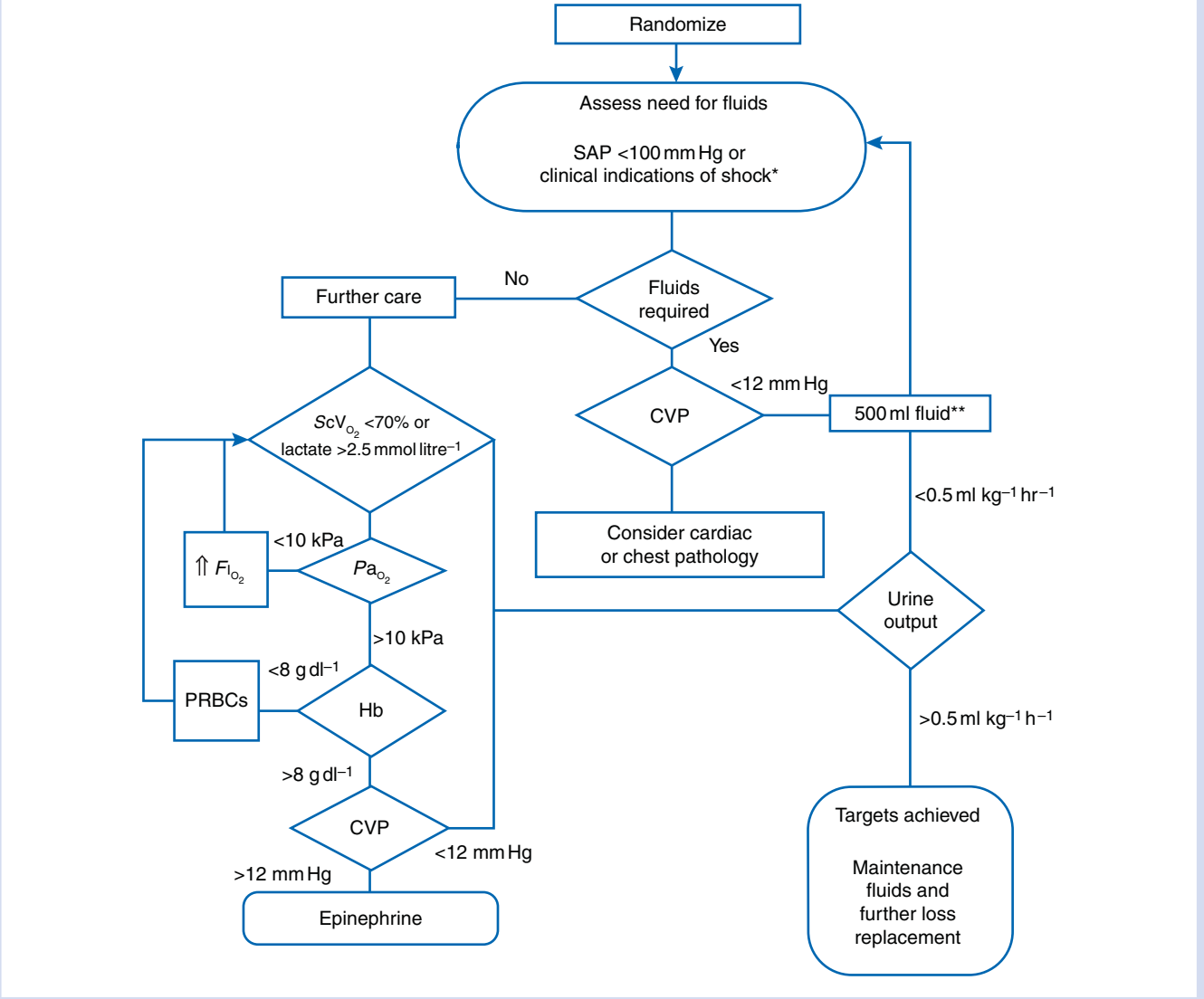

Fig 1 Study algorithm for the administration of fluids and assessment of resuscitation. *Clinical indications of shock: <estimated blood loss replaced; HR>110 beats min^{-1}; poor peripheral perfusion; poor saturation signal; cold peripheries; metabolic acidosis: pH<7.25. **Fluid choice: Hb<8 g dl^{-1}: PRBCs; if the TEG *r*-time was >12 min or the α-angle was <30°, FFP was administered. Plt were administered if the platelet count <60 000 or if the MA on the TEG was <40 mm otherwise FIRST fluid was used.

vs the P-HES group, while the volumes in B-HES and B-SAL were similar. The volumes of blood products were calculated as 350 ml for PRBCs, 320 ml for FFP, and pooled Plt as 250 ml. Blood product requirements were significantly greater in the B-HES group than the B-SAL group. Blood requirements correlated weakly with injury severity (NISS, $r=0.31$, $P<0.05$). Urine output was similar in all groups over the first 4 days of the study.

Gastrointestinal function

There was no difference in the recovery of gastrointestinal function between the groups. Similar proportions of surviving patients in both categories and in the two groups within those categories (~60%) had recovered gastrointestinal function by day 5. However, three patients in the P-SAL group developed abdominal compartment syndrome after receiving 19, 17, and 13.5 litres, respectively. The first two of these had abdominal injuries and subsequently died. The third had no abdominal injuries but required laparotomy for secondary abdominal compartment syndrome.

Coagulation

All groups apart from B-HES had near-normal TEG values on enrolment and showed similar mild deterioration in coagulation over the resuscitation period. There was little evidence of trauma-induced coagulopathy in this study. Although both HES groups showed some evidence of impaired coagulation on enrolment [decreased maximum amplitude (MA)], there was no evidence of this effect in the SAL groups, where the TEG measures all fell within the normal range. The P-HES

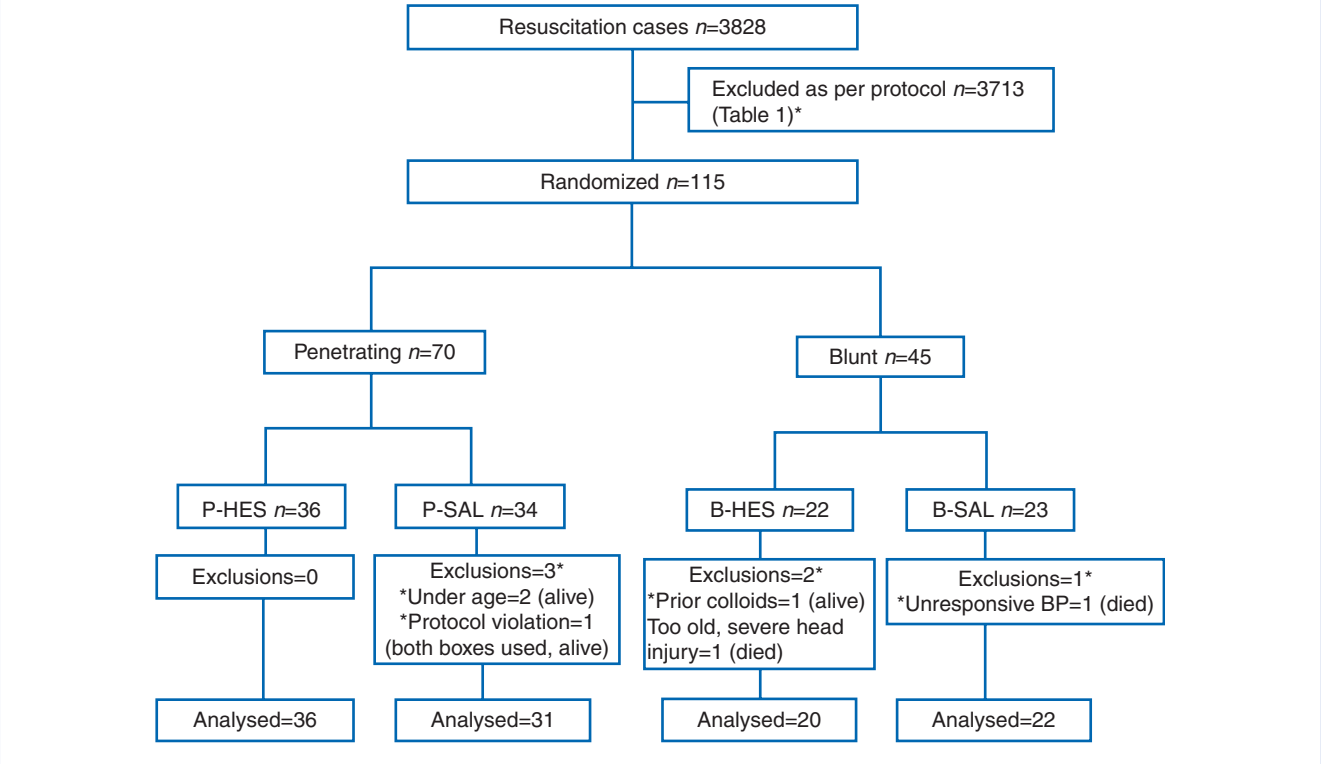

Fig 2 Flow diagram of progress through the phases of the study. B-SAL, blunt trauma allocated to the saline group; B-HES, blunt trauma, HES group; P-SAL, penetrating trauma, saline group; P-HES, penetrating trauma, HES group. *Patients were selected for inclusion by the trauma unit front room staff and not by the Trial Team except for eight patients who were referred but excluded as not meeting protocol requirements. No patient declined consent.

showed minor deterioration in the worst TEG measures compared with P-SAL, while the B-HES group showed significantly greater deterioration in coagulation during resuscitation, particularly a prolonged *r*-time. In the two penetrating trauma groups, the worst TEG measures were marginally abnormal, but not sufficient to define a coagulopathic state.

Measures of resuscitation

Heart rate, arterial pressure, and central venous pressure responded similarly in all groups but did not correlate well with improvements in lactate. All surviving patients had adequate urine output at 24 h.

Haemodynamic measures were virtually identical for all the groups, indicating that the resuscitation algorithm was well followed.

Central venous oxygen saturation (Scv_{O_2}) lagged well behind improvements in lactate and mean Scv_{O_2} did not exceed 60% during the first 4 h of resuscitation.

Initial lactate concentrations were elevated in ~60% of patients in all groups, with the exception of the B-HES group in which 100% of patients had an elevated lactate. Plasma lactate decreased during resuscitation in both categories (Fig. 3A and B). However, in the P-HES group, the plasma lactate was significantly lower over the first 4 h than in the P-SAL group (Fig. 3C). On day 1, the mean lactate concentration was significantly lower in the P-HES group compared with the P-SAL group (Table 5). The pH and bicarbonate measurements were significantly higher on day 1 in the HES groups of both trauma categories which could not be accounted for by the chloride concentrations, which were not different.

Safety measures

Using RIFLE criteria, renal risk was identified in 20 patients and renal injury in 12 patients with five of these requiring dialysis (Table 6). Of those needing dialysis, four died. There was significantly less renal injury and risk in the P-HES group. No patient demonstrated oliguria at any stage except for those patients who eventually required dialysis. One patient in the B-HES group had significantly elevated serum creatinine concentrations (323 μmol litre^{-1}) on admission and probably had renal dysfunction before injury. This patient went on to develop renal failure requiring dialysis, and eventually died.

Median (range) maximum SOFA scores were 6 (0–19) in the B-HES group and 4 (0–11) in the B-SAL group (P=NS). In the penetrating trauma category, median (range) SOFA scores were 2 (0–10) in the P-HES group and 4.5 (0–17) in the P-SAL group (P=0.012).

Table 3 Characteristics of patients analysed in the study. Data are presented as mean (SD), except for age [mean (range)], and the ISS and NISS which are given as median (range). MVA, motor vehicle accident. There were no significant differences apart from ISS and NISS where the B-HES group was significantly different from B-SAL (*$P<0.01$, Mann–Whitney *U*-test). ISS P-HES *vs* P-SAL, $P=0.52$; NISS P-HES *vs* P-SAL, $P=0.41$

	P-HES	P-SAL	B-HES	B-SAL
n	36	31	20	22
Age (yr)	27.6 (18–49)	32.6 (21–56)	33.0 (18–50)	35.7 (20–58)
Height (cm)	170.1 (6.1)	172.5 (8.0)	171.6 (6.6)	172.1 (6.6)
Weight (kg)	72.2 (7.6)	77.4 (13.7)	76.8 (14.4)	78.8 (13.6)
M/F	33/3	27/4	15/5	15/7
Injury mechanism				
Gunshot (*n*)	23	22		
Stabbing (*n*)	13	9		
MVA (*n*)			18	19
Train collision (*n*)			2	3
ISS	18 (9–45)	16 (8–34)	29.5 (9–57)*	18 (9–66)
NISS	34 (10–57)	27 (10–66)	36 (22–66)*	27 (13–66)

Table 4 Volumes of FIRST fluid, PRBCs, FFP, and Plt administered in the first 24 h (in ml) according to the group. Data presented as mean (SD), together with urine output after the first 24 and for the first 3 days. *$P=0.0002$ for the difference between P-HES and P-SAL. †$P=0.005$ for the difference between B-HES and B-SAL

Fluid type	P-HES	P-SAL	B-HES	B-SAL
FIRST	5093 (2733)*	7473 (4321)	6113 (1919)	6295 (2197)
PRBC	1553 (1562)	1796 (1361)	2943 (1628)†	1473 (1071)
FFP	503 (773)	640 (788)	1045 (894)†	349 (732)
Plt	80 (168)	85 (142)	225 (291)†	45 (125)
Urine 24	2891 (1264)	2581 (1349)	2520 (1048)	2005 (816)
Urine day 1	1556 (1080)	1273 (912)	1917 (1076)	1568 (769)
Urine day 2	2441 (1159)	2282 (1193)	1561 (900)	2045 (1043)
Urine day 3	2231 (868)	2298 (1301)	1593 (1044)	2430 (1186)

Ninety patients were available for follow-up at 30 days. In those patients receiving HES, the average total dose was 12 litres over the 30 days of the study. Skin itching was reported by seven patients in total, five in the saline group, and two in the HES group.

Serious adverse events

Apart from the deaths, 17 other patients suffered serious adverse events, including prolonged intensive care unit stay, sepsis, and multiple organ failure. There were four patients who experienced adverse events in the B-SAL group, three in the B-HES group, eight in the P-SAL group, and two in the P-HES group. Only the three secondary abdominal compartment syndromes were considered to be possibly study related. All other adverse events were attributable to the severity of the initial injuries.

Discussion

This is the first randomized, controlled, double-blind study comparing crystalloids with isotonic colloids in trauma. We found that HES130/0.4 provided more rapid and consistent resolution of increased plasma lactate concentrations in penetrating trauma up to the first post-resuscitation day, despite similar haemodynamic measurements between the groups. In penetrating trauma, a colloid to crystalloid ratio of 1:1.5 was found. However, the better lactate clearance in the P-HES group indicated superior tissue resuscitation with the colloid. The lower maximum SOFA scores and the absence of renal injury seen in the P-HES group further support the argument that this group showed better early resuscitation. These results are supported by a recent observational study, in which mortality was significantly lower when HES was included in the early resuscitation strategy, particularly in penetrating trauma.[9] In blunt trauma, it is much more difficult to draw conclusions, given the large difference in injury severity. While it could be argued that the colloid was no more effective than the crystalloid and led to a greater requirement for blood and blood products, it could equally well be argued that the requirement for blood and blood products was the consequence of greater injury severity and that the colloid provided at least equivalent resuscitation despite much more serious injury. Furthermore, the better acid–base state of the blunt

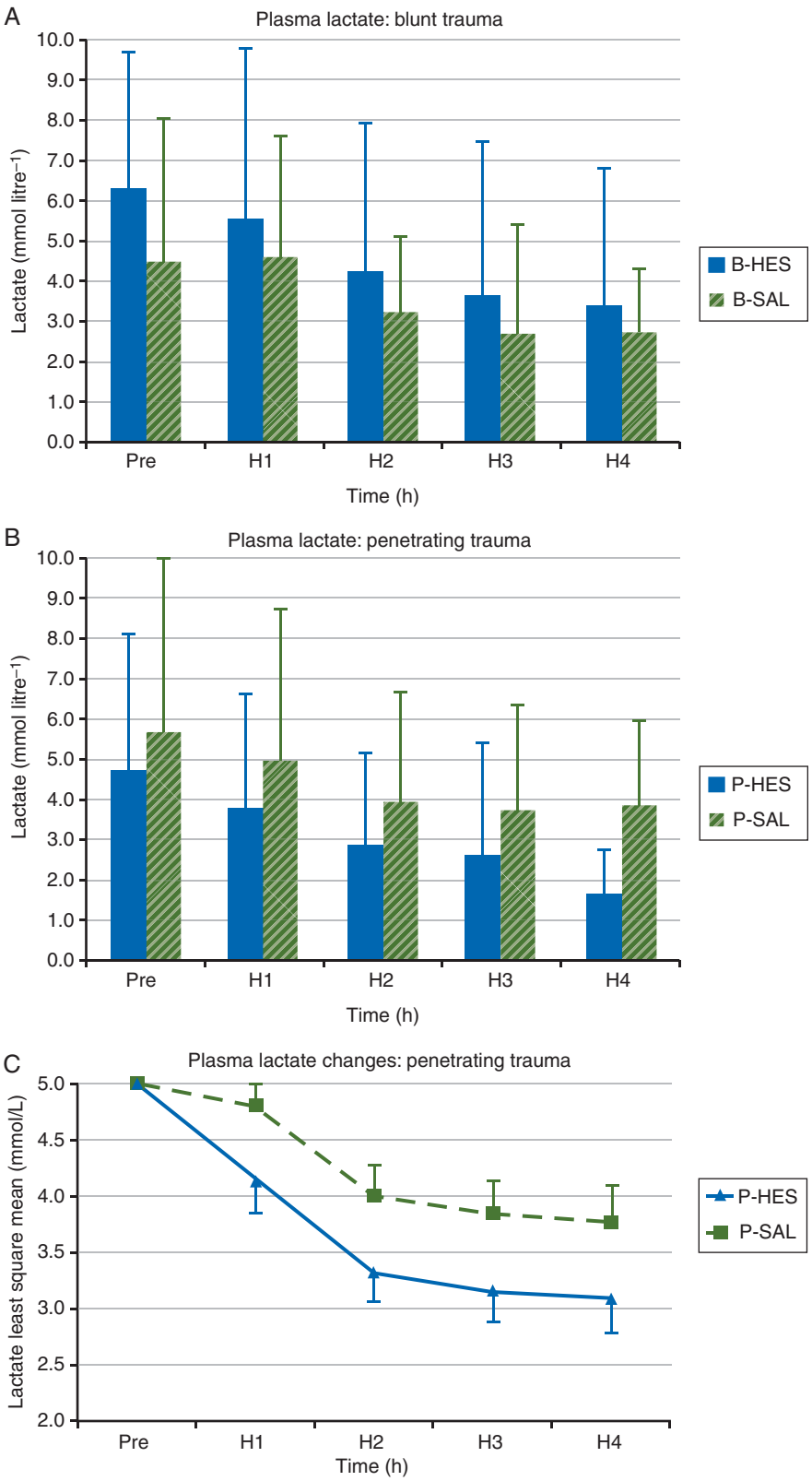

Fig 3 (A, B and C) Mean plasma lactate concentrations (SD) in the two categories of trauma patients. together with a linear, mixed effect, regression model of change in lactate over time (SEM) with baseline adjustment to 5 mmol litre^{-1}. B-SAL, blunt trauma allocated to the saline group; B-HES, blunt trauma, HES group; P-SAL, penetrating trauma, saline group; P-HES, penetrating trauma, HES group. P-HES demonstrated a small but statistically significantly greater lactate clearance than P-SAL (P=0.029).

Table 5 Laboratory data. Lactate concentrations at 4 h and on day 1, together with acid–base, chloride, and Hb values for the first 3 days after resuscitation with the numbers of patients on whom measures were recorded (*n*) on each day. *$P<0.01$ for the differences between P-HES and P-SAL. †$P<0.05$ B-HES *vs* B-SAL

	P-HES	*n*	P-SAL	*n*	B-HES	*n*	B-SAL	*n*
Lac D1	2.1 (1.4)*	26	3.2 (2.2)	23	2.4 (1.3)	16	2.9 (2.0)	17
pH 1	7.35 (0.07)*	26	7.24 (0.10)	23	7.36 (0.09)†	16	7.30 (0.06)	17
pH 2	7.40 (0.06)	20	7.36 (0.10)	18	7.37 (0.06)	17	7.39 (0.07)	17
pH 3	7.42 (0.03)	15	7.41 (0.09)	17	7.41 (0.04)	16	7.45 (0.05)	15
HCO_3 1 (mmol litre^{-1})	22.0 (3.1)*	26	17.7 (4.3)	23	22.0 (3.3)†	16	18.8 (3.0)	17
HCO_3 2 (mmol litre^{-1})	24.4 (2.6)	20	20.6 (4.0)	18	22.4 (3.7)	17	23.6 (4.1)	17
HCO_3 3 (mmol litre^{-1})	25.5 (2.4)	15	23.9 (4.9)	17	24.9 (4.7)	16	27.0 (2.7)	15
Cl^- 1 (mmol litre^{-1})	113.6 (3.9)	20	114.3 (4.5)	20	114.7 (6.7)	15	113.5 (4.6)	13
Cl^- 2 (mmol litre^{-1})	108.1 (4.3)	21	111.4 (7.2)	17	113.1 (4.9)	14	106.4 (93.5)	14
Cl^- 3 (mmol litre^{-1})	103.1 (4.1)	16	106.2 (6.9)	17	110 (4.8)	12	102.9 (3.4)	12
Hb 1 (g dl^{-1})	10.2 (1.5)*	25	11.6 (2.2)	26	9.4 (1.7)†	18	10.9 (1.9)	17
Hb 2 (g dl^{-1})	11.1 (1.5)	24	10.6 (1.8)	22	9.5 (1.2)	17	9.6 (1.4)	17
Hb 3 (g dl^{-1})	9.9 (1.5)	19	9.7 (1.3)	22	8.4 (1.0)	16	8.5 (1.3)	18

Table 6 Distribution of renal outcomes in blunt and penetrating trauma by fluid group. *$P=0.043$ for the difference between P-HES and P-SAL. †$P=0.018$ for differences between P-HES and P-SAL

	P-HES		P-SAL		B-HES		B-SAL	
	No	Yes	No	Yes	No	Yes	No	Yes
Risk	35*	1 (3%)	25	6 (19%)	13	7 (35%)	16	6 (27%)
Injury	36†	0 (0%)	26	5 (16%)	16	4 (20%)	19	3 (14%)
Dialysis	36	0	29	2 (6%)	18	2 (8%)	21	1 (5%)

HES group at day 1 further argues for better sustained resuscitation in this group.

The smaller than expected difference in the ratio of fluid volumes administered is likely to be the consequence of the inadequacy of the static haemodynamic measures (heart rate, arterial pressure, and central venous pressure) as indicators of circulating plasma volume.[10] Central venous oxygen saturation also appeared to be an unreliable marker of adequate resuscitation. Lactate was the most satisfactory marker of resuscitation, and although it was not used as a resuscitation endpoint, our results support regular lactate measurements as a useful resuscitation target. It is possible that dynamic monitoring systems measuring corrected flow times, stroke volume variation or responsiveness, or other estimates of optimal cardiac filling may have provided better endpoints for fluid resuscitation. These have some drawbacks in the acute trauma patient as an oesophageal probe is often not a feasible option and stable, positive pressure ventilation is seldom practical outside of a critical care environment. However, advantages have been described in trauma in animals[11] and post-resuscitation critical care patients[12] using these techniques and wider application of these technologies may well enhance fluid management in trauma.

This study failed to support the concept that crystalloid resuscitation is associated with a greater degree of gastrointestinal dysfunction. This is in contrast to surgical publications regarding bowel recovery[13 14] and to descriptions in trauma of intra-abdominal hypertension and abdominal compartment syndrome associated with high-volume crystalloid resuscitation.[15 16] These reports have led to calls for more restrictive approaches to crystalloid administration in trauma.[4 15 16] In our study, the volume of clear fluid administered in the first 24 h was approximately half of that given in the high-fluid group of the study by Balogh and colleagues[3] and much lower than the clear fluid use associated with secondary abdominal compartment syndrome in burns resuscitation.[16] The only patients in whom severe abdominal compartment syndrome was seen were those who received very large crystalloid loads. We did not achieve the numbers required by our power calculations for proper assessment of gastrointestinal dysfunction, but this is of little importance since the distribution of dysfunction is so even that this could not possibly change had the full number of patients been enrolled. The absence of any difference in recovery of gut function and the low incidence of abdominal compartment syndrome suggest that in trauma, reasonable fluid resuscitation is not a major risk factor.

Our results support other studies that have suggested that HES 130/0.4 is not associated with increased bleeding,[17–19] although similar minor alterations in coagulation measures have been described.[20 21] Despite the fact that very large volumes of HES were used in the first 24 h, there was no increased requirement for blood or blood products in the P-HES group. However, in blunt trauma, where there is more diffuse microvascular damage, adverse effects on coagulation may lead to a greater risk of increased bleeding. Thus, our results in the blunt trauma group may reflect a greater effect of HES on coagulation in that the B-HES patients required significantly more blood and blood products during resuscitation. This group also showed significantly greater deterioration in coagulation measures over the first 24 h. However, this increased requirement for blood and blood products could equally well be explained by the greater injury severity. The B-HES group had the worst initial coagulation screen and the greater deterioration in coagulation in this group may simply have reflected trauma-induced coagulopathy.[22 23] We cannot, therefore, draw any firm conclusions regarding the influence of HES on coagulopathy and bleeding in blunt trauma.

None of the P-HES patients developed renal injury, and only one patient exhibited transient renal risk. This is an important observation as much has been made of the potential of different HES solutions to harm the kidney in critically ill patients.[24] Non-specific renal dysfunction has been described in association with various HES products in renal transplantation[25] and sepsis.[26] This risk seems to be mainly apparent with hyperoncotic HES and other hyperoncotic colloids including albumin.[27 28] However, in a multicentre observational study involving more than 3000 intensive care patients, HES was not shown to be associated with renal dysfunction.[29] High-dose HES (up to 70 ml kg^{-1} per day) in neurosurgical patients failed to demonstrate any deterioration in renal function.[30] In patients undergoing aortic aneurysm repair, HES appeared to be protective of renal function compared with gelatin.[31]

Our results do not support the view that there is a serious risk of renal injury associated with the use of HES 130/0.4 in acute resuscitation. In the B-HES group, despite the higher ISS, there was no difference in renal outcome compared with B-SAL, although the numbers are small. The better renal outcome achieved in the P-HES group may have been related to superior tissue resuscitation as evidenced by more rapid lactate clearance. An animal study comparing HES with Ringer's lactate in haemorrhagic shock found better resolution of lactate levels with HES 130/0.4 together with less oedema which the authors attributed to reduced microvascular permeability.[32] Endothelial protection has been suggested as part of the renal protective mechanism during vascular surgery,[31] but there is no evidence in our data to support or refute this argument. A recent study[33] suggested better resuscitation of the microvascular circulation in sepsis with the use of HES compared with saline. Nevertheless, although our results support the view that there is no significant renal risk associated with large doses of HES 130/0.4 used for acute resuscitation, it does not address the issue of ongoing use of HES products in critical care and, in particular, in sepsis.

The major limitations of this study are the relatively small numbers and the imbalance of the injury severity in the blunt trauma category. Owing to fluctuating haemodynamics during the acute phase, judging the endpoint of resuscitation was difficult, hence the need to use the 24 h fluid utilization for assessment. The small numbers of investigators involved allowed reasonable consistency in judgement of volume requirements even when absolute haemodynamic measures were varying.

In conclusion, this randomized, controlled, double-blind study has demonstrated faster lactate clearance in penetrating trauma with the use of HES 130/0.4 compared with 0.9% saline without clinically relevant coagulopathy. The superior resuscitation had an outcome benefit, in that no HES patients demonstrated renal injury compared with an incidence of 16% in the saline group. No advantage could be shown for HES in blunt trauma.

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Conflict of interest

M.F.M.J. has received numerous travel grants and honoraria from various fluid therapy companies including Baxter, B Braun, and Fresenius-Kabi. W.L.M. has been a Member of Fresenius-Kabi Nutrition advisory board meetings and has received travel and accommodation support and also a honorarium. I.A.J. has received honoraria and travel support from Fresenius-Kabi. He has also received lecture fees from a variety of companies not related to fluid therapy.

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