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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)

M. F. M. James[1*], W. L. Michell[2], I. A. Joubert[1], A. J. Nicol[2], P. H. Navsaria[2] and R. S. Gillespie[1]

[1] Department of Anaesthesia and [2] Department of Surgery, Groote Schuur Hospital and Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town, Western Cape 7925, South Africa

* Corresponding author. E-mail: mike.james@uct.ac.za

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