Hydroxyethyl starch in patients with trauma

Editor—The Fluids in Resuscitation of Severe Trauma (FIRST) randomized trial conducted by James and colleagues compared hydroxyethyl starch (HES) 130/0.4 with 0.9% saline in the resuscitation of 115 patients with severe blunt or penetrating trauma at a single centre in South Africa. In blunt trauma, which accounts for 86–97% of all traumatic injuries in Europe,1,2,3 no differences were found between HES 130/0.4 and 0.9% saline in either of the two primary study endpoints: fluid volume needed during the first 24 h and number of patients achieving normal gastrointestinal function by day 5. In penetrating trauma, HES 130/0.4 reduced fluid requirement significantly but less than generally expected and showed no effect on normalization of gastrointestinal function. In the published report of the trial, the FIRST investigators emphasized improvement in renal function (P = 0.018) and lactate clearance (P < 0.05) among patients with penetrating trauma receiving HES 130/0.4. Conversely, they downplayed an observed increase in transfusion of blood products among HES130/0.4 recipients with blunt trauma. For that type of trauma, mean transfusion of packed red blood cells was twice as great in the HES 130/0.4 as the 0.9% saline group (P = 0.005), fresh-frozen plasma (FFP) three times as great (P = 0.005), and platelets five times as great (P = 0.005). Two primary endpoints and seven secondary endpoints were pre-specified (www.controlled-trials.com/ISRCTN42061860/42061860). However, there is considerable discrepancy between the predefined study endpoints and those published in the report. Three safety endpoints were defined in the publication, which were not included in the register entry. Among the non-pre-specified study and safety endpoints are acute kidney injury (AKI) and lactate clearance, which are highlighted as the main results in the title of the paper. However, the post hoc analyses of the data for those endpoints presented in the publication should be considered exploratory and not conclusive. Furthermore, the FIRST trial was not powered to assess differences in AKI. The baseline data that were presented make it clear that the study groups in the FIRST trial were not well matched. Among patients with blunt trauma, both Injury Severity Score and New Injury Severity Score (NISS) were significantly higher in the group allocated to HES 130/0.4 (P < 0.01 for each comparison). The small P-values indicate that the imbalances were unlikely to have arisen by chance, suggesting the possibility of flawed randomization. Although not statistically significant, substantial imbalances were also present in other baseline characteristics. Thus, the penetrating trauma group allocated to HES 130/0.4 (P-HES), that is, the group with apparently improved renal function and lactate clearance, was >5 yr younger on average than any other group and weighed >5 kg less. Furthermore, the mean baseline plasma lactate level was ~40% higher in the group with blunt trauma allocated to HES 130/0.4 than 0.9% saline, but ~20% lower with penetrating trauma. The pervasive baseline imbalances in this trial raise doubt as to whether observed between-group differences were due to study fluid or confounding variables. Interpretation of the trial results is further complicated by the absence of key data such as site of injury, pre-study crystalloid volume, baseline SOFA score, and the time to resuscitation targets, that is, mean arterial pressure, heart rate, central venous pressure and oxygen saturation, serum creatinine, and the mortality by group. No analysis was reported on the influence, if any, of baseline imbalance in blunt injury severity on blood product transfusion. The finding of only 31% correlation between baseline NISS and blood product usage suggests that the higher transfusion requirement of HES 130/0.4 recipients with blunt trauma may have persisted after adjustment for injury severity. Appropriate statistical analysis should have been performed to resolve this important question. The claim that HES 130/0.4 resulted in more effective resuscitation by increased lactate clearance remains highly questionable for several reasons. First, as shown in Figure 3c of the publication, the mean plasma lactate level was higher at baseline in the P-SAL than in the P-HES group, and mean levels in the two groups closely paralleled each other over the first 3 h of resuscitation. Those observations are not consistent with a significant between-group difference in plasma lactate. However, such a difference is reported in Figure 3c based upon a mixed-effect linear regression analysis. No details are provided about that analysis, which assumes that the data are normally distributed. However, since the coefficients of variation shown in Figure 3c exceed 50%, the normality assumption is clearly violated. No assurance is provided in the FIRST publication that the mixed-effect linear regression analysis is valid. Secondly, plasma group difference with respect to epinephrine use, which can cause hyperlactaemia, might also account for the perceived differences in lactate clearance. The maximum SOFA score was significantly higher in the P-HES group than the corresponding control group (P-SAL), but this observation would only be meaningful if baseline scores were closely matched. Without baseline SOFA data, the fidelity of matching with respect to that score remains indeterminate. AKI was scored in accordance with the RIFLE criteria which are based on serum creatinine or urine output. Differences in urine output were not found in the FIRST trial, so the AKI results were evidently derived from serum creatinine measurements. However, serum creatinine data were not reported, and so the basis for a difference in AKI is difficult to assess. Thrombelastography (TEG) data were assessed, but data were not provided;
given that this is the first time that TEG was measured in a trial comparing HES 130/0.4 with crystalloids in trauma patients, it would have been informative to see the data, especially since transfusion of FFP or platelets was triggered by TEG and three times more FFP and five times more platelets were given to the patients in the blunt trauma group who received HES 130/0.4 than those receiving saline. A higher frequency of pruritus is reported among 0.9% saline recipients in the FIRST trial. HES-related pruritus is typically severe, protracted, and refractory to treatment. Pruritus due to HES is also frequently delayed in onset by 1–6 weeks. Since follow-up in the FIRST trial was limited to 30 days, some cases of HES-induced pruritus may have been missed. The discrepancies between pre-specified and actually evaluated endpoints, the poor matching at baseline of the study groups, the small sample size, the failure to report key data, and some deficits in the statistical analysis make it difficult to draw firm conclusions about the efficacy and safety of HES 130/0.4 for trauma resuscitation.

**Declaration of interest**

K.R. was the principal investigator of the VISEP (Intensive insulin therapy and pentastarch resuscitation in severe sepsis) trial which received partial funding by an unrestricted grant from B. Braun, Melsungen, Germany. In the past, K.R. received honoraria and travel fees from B. Braun, Melsungen, Germany.

K. Reinhart
C. S. Hartog
Jena, Germany
*E-mail: konrad.reinhart@med.uni-jena.de*

1 James MF, Michell WL, Joubert IA, Nicol AJ, NavaSaria PH, Gillespie RS. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 2011; 107: 693–702


doi:10.1093/bja/aer467

**Reply from the authors**

Editor—We thank Drs Reinhart and Hartog for their interest in our paper. We fully agree that these results cannot be extrapolated to blunt trauma, given the inherent problems in that limb of the study. These authors raise an issue regarding data entered into the ISRCTN register. The registration states that physiological endpoints would be targeted, and this obviously includes S\textsubscript{cvO2}, lactate, and acid–base balance. The reason the safety data endpoints were not included is quite simply that they were not asked for and space was not provided in this abbreviated study presentation. It is inconceivable that a study of this nature would have received ethical committee approval without pre-specified safety endpoints. As part of the study and analysis plan, interim efficacy and safety analysis was required for 64 patients, with particular emphasis on renal data. This analysis was performed by an independent statistician and suggested a strong trend towards an increased incidence of renal dysfunction associated with one of the fluid groups (at this stage, the researchers were blind as to which fluid this was). In the opinion of the statistician, if this trend was sustained, statistical significance was likely to be achieved after 104 patients were enrolled. Ethics committee approval was obtained to continue the study in the face of this possible evidence of adverse events. When the study was finally unblinded, it was revealed that the interim adverse renal events were associated with saline and this gives us reasonable confidence that the AKI data reported are sound and appropriately powered. The data in the penetrating trauma group showed substantial internal consistency that further raises confidence in the conclusions. The lactate, acid–base, renal function (including the fact that the P-HES group had the highest urine output on day 1 in the face of the lowest administered fluid volume), and SOFA scores all show considerable agreement. The input/output balance for the first 24 h very strongly favours P-HES with a positive balance of 4.2 litre as opposed to a positive balance for P-SAL of 7.4 litre (obviously blood loss cannot be included as there was no way to measure it).

We agree that the imbalance of injury severity in the blunt trauma group was unfortunate, but that is the risk of this kind of study with relatively small numbers. We disagree with the rather contentious argument that the penetrating trauma group was unbalanced. These differences are neither statistically nor clinically significant in a population of relatively young adults. It is inappropriate to make assumptions regarding the imbalance within these groups using non-significant data. Given the higher injury severity scores (ISSs) in the B-HES group, it is hardly surprising that the lactate was higher in this group, even though this difference did not reach statistical significance. We therefore strongly dispute that there are ‘pervasive baseline imbalances’ in the study other than the imbalance in ISS reported. A study such as this is dependent on patients who meet inclusion criteria presenting for management. Obviously, it is impossible to predetermine the nature or the severity of the injuries sustained. The implication of a flawed randomization process is rejected. The randomization sequence was planned by an independent, professional organization and based on random numbers in blocks of eight to minimize time-based variations. This sequence was sent independently to the hospital pharmacy which prepared the boxes of bags in the specified order. It is hard to conceive of a