Hydroxyethyl starch in patients with trauma

Editor—James and colleagues are to be congratulated on their contribution to the literature on resuscitation fluids. Their randomized trial comparing hydroxy ethyl starch with saline for the resuscitation of severely injured trauma patients was designed to examine two primary outcomes: first, the volumes of fluid administered in the first 24 h and, secondly, the number of patients achieving normal gastrointestinal function by day 5. The volume of saline administered was 1.5 times that of hydroxyethyl starch, a ratio very similar to that seen when saline was compared with albumin 4% in a broader population of patients in the SAFE study. The authors state that similar proportions of surviving patients recovered gastrointestinal function by day 5, but the exact numbers of patients are not reported and this seems an inappropriate way to report a primary outcome measure. The CONSORT authors recommend that for each primary and secondary outcome, the estimated effect size and its precision, for example, 95% confidence interval, are reported, for proportions both the numerator and denominator should be given; James and colleagues have not done this. Outcome-reporting bias is an increasingly recognized problem which may distort the medical literature; authors, journal reviewers, and editors should all insist that the pre-stated primary outcome measures are appropriately reported and emphasized. The title of the paper and much of the manuscript focuses on safety and secondary outcome measures without any allowance for reporting multiple outcome measures. The authors conclude that hydroxy ethyl starch improves renal function and lactate clearance. While these are important considerations, additional information is required to assess these conclusions. The authors assessed renal function using the RIFLE criteria and report a significant increase in renal injury in the patients with penetrating trauma assigned to receive saline. The authors also state that no patients developed oliguria other than those who were subsequently treated with dialysis. As the RIFLE diagnosis of renal injury requires either a doubling in baseline creatinine concentration or oliguria, I conclude that the diagnosis of renal injury was made on the basis of a doubling of creatinine concentration from baseline which in the context of a randomized controlled trial means creatinine concentration measured before randomization. Assessing both the statistical and clinical importance of this finding is hampered as the authors have reported neither the creatinine concentrations of the patients before randomization nor their peak creatinine concentrations. Reporting these data would assist readers to decide whether the diagnosis of renal injury is clinically significant. A further concern is that the diagnosis of renal injury is subject to competing risk; that is to say, patients may have died before they had the opportunity to develop renal injury and this may have biased the results. The authors state that mortality was 16.5% with no significant difference between the groups; however, they have not reported the number of patients who died in each group and this not only makes interpretation of their report difficult but also hampers the inclusion of these data in future meta-analyses. It would have been helpful if the authors had been asked to report the number of patients dying in each group and how they handled the question of competing risk as part of the review process for their paper. The significance of the rate of change of the serum lactate concentrations is also unclear. Epinephrine was the only vasopressor or inotropic agent used during resuscitation and as administration of epinephrine can increase lactate production causing a transient hyperlactataemia, it would be very useful if the authors also reported the number of patients treated with epinephrine in each group and the doses administered. James and colleagues have conducted an important trial and it may be that their conclusions and interpretation are valid. Clinical trials should be analysed and reported in the same systematic and rigorous manner in which they should be conducted; without the missing information highlighted above, a proper evaluation of the clinical significance of James’ trial is not possible.

Declaration of interest

S.F. was the principal investigator for the Saline vs Albumin Fluid Evaluation (SAFE) study which was part funded by CSL Ltd. (CSL manufactures albumin in Australia). CSL has acted as a sponsor for scientific meetings of the Australian and New Zealand Intensive Care Society and its clinical trials group which S.F. previously chaired. CSL has paid travel expenses for S.F. to present the results of the SAFE study at scientific and industry-sponsored meetings. Fresenius Kabi paid travel and accommodation expenses for S.F. to travel to Germany during the design of the Crystalloid vs Hydroxy Ethyl Starch Trial (CHEST) (Fresenius Kabi manufactures Voluven in Germany).

S. Finfer*
Sydney, Australia
E-mail: sfinfer@georgeinstitute.org.au

1 James MFM, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Resuscitation with hydroxethyl 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


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**Reply from the authors**

Editor—We are grateful to Prof. Finfer for his interest in, and comments on, our paper.1 We will attempt to answer his queries as briefly as possible. The data he requested were omitted from the final paper due to space limitations and we are pleased to provide the information. The nature of the submission format only allows two tables, so some of the data have to be presented as text. The details of recovery of gastrointestinal function on day 5 (the specified endpoint) data have to be presented as text. The nature of the recovery of gastrointestinal function on day 5 (the specified endpoint) data have to be presented as text.

Mortality data are as follows:

<table>
<thead>
<tr>
<th></th>
<th>P-HES</th>
<th>P-SAL</th>
<th>B-HES</th>
<th>B-SAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived</td>
<td>30</td>
<td>28</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Total deaths</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Early deaths</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ICU deaths</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Post-ICU deaths</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>After exit</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

As is typical of trauma, the majority of deaths occurred early either in the trauma unit or in the operating theatre within the resuscitation period. The survival time after enrolment in those who died early ranged between 2 and 18 h (the last being in theatre at the time of death). These deaths were all the result of unsurvivable injuries as classified before unblinding. Three deaths in intensive care unit (ICU) give an ICU mortality of 2.7%, which is similar to that reported for trauma in the SAFE trial (2.5%).2 All of the ICU patients who died suffered renal failure. The remaining four deaths occurred after ICU discharge and there was only one death before study exit in those leaving ICU (B-HES). In terms of the survivor effect, analysis of renal injury in those surviving the initial period shows a slightly increased proportion of renal injury (17%) in the P-SAL group from that reported in the paper in which all patients were considered. The difference between the penetrating trauma groups in terms of renal injury remains significant (P=0.024) after adjustment for the early deaths. Only one other patient died within the study period (B-HES) and this could not have affected the result in the penetrating category of the study.

Similar numbers of patients were exposed to epinephrine at some point during the first 4 h of resuscitation and on day 1 in each group in the two arms of the study. During initial resuscitation, the following numbers received epinephrine: P-HES 3/36, P-SAL 3/31, B-HES 2/21, and B-SAL 1/22. Those patients who only received inotropes in theatre did not necessarily receive epinephrine as this was in the control of the anaesthetist and not the resuscitation team. In theatre: P-HES 5/33, P-SAL 3/30, B-HES 2/19, and B-SAL 1/21. We thus cannot be precisely sure which patients received epinephrine in the 24 h resuscitation period. In ICU, the inotrope was epinephrine, but the numbers were insignificant. Obviously, epinephrine could influence the lactate level independently of tissue perfusion, but given the relatively low incidence and similarity of usage between the groups, it seems unlikely that this is a significant confounder. We did not record the exact dose given in each patient as this varied on a minute-to-minute basis in most cases.

**Declaration of interest**

M.F.M.J. has received numerous travel grants and honoraria from various fluid therapy companies including Baxter,