Effects of saline or albumin fluid bolus in resuscitation: major statistical flaws in the re-analysis of the FEAST trial

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We read with interest the article by Levin and colleagues[1], where various secondary analyses were performed on data from the FEAST trial to explore mechanisms by which fluid resuscitation therapy led to increased mortality in children with shock in Africa.

Unfortunately, the statistical methods used have major errors which invalidate their conclusion that "Hyperchloraemic acidosis and respiratory and neurological dysfunction induced by saline or albumin explained the excess mortality due to bolus". The first key error relates to the imputation of base excess, chloride and bicarbonate at one hour after randomisation for all patients (web appendix). The authors use two approaches to impute a single value at 1 hour for each patient. The first approach is based on a separate linear interpolation in each treatment group, calculated from incomplete data on these parameters for survivors at 24 hours, and applied to all patients; but 90% of deaths occurred before 24 hours[2]! In the second approach, the 1 hour values for base excess, bicarbonate and chloride were derived from changes after saline infusion reported in other studies. These errors generate false conclusions, because:

- A single value has been imputed, and then treated as 'observed' in the analysis; this statistically invalid procedure is known to hugely overestimate the information [3 – Chap 2];
- In the first approach this single value rests on the untested assumption of linear trend over 24 hours and on extrapolation from trends seen in children who survived up to that time;
- Both approaches result in a constant change from baseline within each treatment group: they impute the same value of change for all patients in the same treatment group. Thus the imputed levels at 1 hour are confounded with the treatment assignment (bolus/no bolus). Because of this confounding, it is not surprising that the Cox models fitted by the authors erroneously suggest that differences in acidosis and chloride parameters (together with physiological scores) explain the treatment difference in mortality between bolus and no bolus.

There is a further major statistical flaw. Even if these variables were measured in all children at one hour post randomisation with pinpoint accuracy, the authors' analysis is not sufficient to support their causal conclusion about the mediating role of hyperchloraemic acidosis and respiratory and neurological dysfunction. Such analyses would require controlling for confounding factors of the relationship between abnormal physiology/biochemistry and mortality (mediators-outcome relationships). We are not protected against such confounding by randomisation, because these confounders may arise post-randomisation. Besides, changes in the estimate of the hazard ratio after adjusting for a putative mediator may not be indicative of mediation even if there were no confounding issues. There is an extensive literature on methods to perform mediation analyses that can be given a causal interpretation[4,5], but none of these methods are mentioned and none of the assumptions under which the authors' conclusions hold are discussed.

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