

Correspondence

Inadequate Evidence to Support Phase III Studies of Albumin in Severe Malaria

Charles J. Woodrow, Timothy Planche

The study on severe malaria by Akech et al. [1] found no significant difference between albumin and Gelofusine in any outcome measure, yet the authors reject further investigation of Gelofusine and propose phase III studies of albumin as a neuroprotective agent potentially capable of reducing mortality in severe malaria by over 80% [2]. Several issues related to study design and interpretation require reconsideration of the authors' main conclusions.

Study design did not incorporate allocation concealment, a major omission that can influence patient recruitment at all stages from case finding strategy to consent [3]. Figure 1 gives the impression that patients were randomised after eligibility assessment, whereas in reality their treatment was known in advance. Comparison of baseline data for albumin and Gelofusine groups is an insensitive way to detect enrolment bias with these numbers of patients. An additional problem arises from a separate interventional study with phenytoin conducted simultaneously in comatose children, but no information is provided about possible interactions with fluid interventions. The task of undertaking two independent interventions in the same population would have benefited from prospective evaluation, for example, using a factorial design to minimise confounding.

Both intention to treat (ITT) and per protocol (PP) analyses are presented, with ITT including patients enrolled as an emergency who did not meet inclusion criteria. In isolation, this approach may appear reasonable but in similar previous studies Newton's group excluded such patients from all analyses. Given that two of four patients not meeting inclusion criteria but entering the Gelofusine arm subsequently died (versus zero of four in the albumin arm), has the decision to include such patients on this occasion been taken post hoc since it favoured albumin? The ITT analysis is quoted selectively at certain points, e.g., while Table 4 shows a mortality rate of 10% with Gelofusine (PP analysis), the ITT figure of 16% is reported in the text and press release. Table 3 describes deaths (eight for Gelofusine, not seven as reported throughout the text) without reference to patients failing inclusion criteria; we assume that these "out of criteria" deaths are cases 2 and 10. If so, the short time between admission and death (1 h and 3 h) suggests that these patients were moribund at presentation. The potential for bias to influence enrolment of these patients (see above), or the decision to include such patients in the ITT analysis, is evident.

Unfortunately, the editorial commentary compounds interpretative difficulties by incorrectly stating: "Death rates in hospital were lower in the group given albumin, and this was statistically significant." Gelofusine was not associated with a significant increase in mortality compared to albumin (even by ITT analysis). Justification for albumin's superiority over Gelofusine is instead based on a small "meta-analysis" of studies of albumin versus "other fluids", the

dominant study of which enrolled 150 patients with 11 saline and two albumin deaths [4] (an alternative interpretation that large volumes of saline are hazardous has been discussed [5]). With only 80 patients enrolled in the Gelofusine versus albumin study, the "meta-analysis" was highly likely to generate the same result as its dominant study. We calculate that this albumin versus Gelofusine study could have had equivalent mortality in the two arms (up to 10 deaths per arm), yet the "meta-analysis" would still have showed significant benefit for albumin. Furthermore, there are discrepancies between the original studies and the "meta-analysis" both in total number of patients and deaths attributed to saline/Gelofusine (described, along with other inconsistencies, in our e-letter on the *PLoS Clinical Trials* Web site [<http://clinicaltrials.plosjournals.org/perlserv/?request=read-response&doi=10.1371/journal.pctr.0010021#r1317>]).

Based on these data, as well as preliminary studies of albumin as a neuroprotective agent in stroke, the authors now propose a phase III study with albumin, saline, and maintenance-only arms. This would again test two separate hypotheses simultaneously (volume resuscitation and brain protection), and ignores the possibility that saline may be dangerous [5]. If the authors are committed to studies of albumin as a neuroprotective agent, an appropriate development plan should include a prospective, randomised phase II trial of albumin versus maintenance-only fluid in patients with cerebral malaria, with specific monitoring for adverse events (particularly pulmonary oedema), as for studies of albumin in stroke [6].

The accompanying article providing support [7] for the authors' call for phase III studies has not clarified these issues. Complicated and important fields of research demand corresponding rigour. Phase III mortality studies ought to be based on appropriately designed and adequately powered phase II trials with close regard to safety. ■

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Phase III Trials Required to Resolve Clinical Equipoise over Optimal Fluid Management in Children with Severe Malaria

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There is a consensus among paediatricians that outcome of children presenting with life-threatening infections, irrespective of the infecting pathogen, can be improved by timely recognition and prompt intervention to correct disordered physiology using simple approaches to resuscitation [1–3]. These approaches include the provision of oxygen and the correction of fluid, electrolyte, and glucose deficits [4,5]. Indeed, studies have shown that most of the recent gains in survival of children with severe infections have come through the application of this approach by non-specialists during the initial hours of management [6,7]. Correction of hypotension and volume depletion through fluid administration is a fundamental component of resuscitation in most critically ill children [8,9], but its role in severe malaria remains uncertain and thus represents one of the most important theoretical gaps in our understanding of supportive treatments in this condition.

Many children with severe malaria have signs of cardiovascular compromise or compensated shock on presentation to hospital and a smaller proportion are hypotensive [10]. One of the major unresolved aspects of management is whether volume expansion should be undertaken in children displaying signs of compensated shock, as is recommended in other paediatric disorders. Intravascular volume depletion (hypovolaemic shock) results in impaired cardiovascular function and inadequate tissue and organ perfusion, and would usually be corrected rapidly. Simple dehydration, predominantly affecting the intracellular compartment, can be safely corrected gradually. The choice of the optimum fluid for resuscitation is also unclear. Colloidal solutions, although more costly, are less likely to precipitate cerebral and pulmonary oedema due to their oncotic properties.

Recognising the importance of adequate fluid management to the outcome of the critically ill child, the group at Kilifi has conducted a staged series of studies over the last 15 years to address each of these questions. In a collaboration that included specialists in paediatric intensive care, neurology, and clinical trials, the group demonstrated the importance, prognostic implications [11], and clinical correlates of

metabolic acidosis in children with severe malaria [12] and provided clear evidence of intravascular hypovolaemia by using standard methods for studying critical illness [13]. We have undertaken two randomised trials to assess the safety of and response to volume expansion, and to determine whether colloid replacement offers any advantage over crystalloid replacement [13,14]. We hypothesised that administration of colloids such as human albumin solution with volume expansion would help to retain fluid in the intravascular compartment and may also improve endothelial function. In each of these trials we observed that albumin administration was associated with a lower mortality than saline. Although this data suggested the need for a large clinical trial of albumin, in view of the cost of albumin we thought that cheaper synthetic colloids should be assessed before embarking on a phase III trial. The intention in the small phase II trial, recently published in *PLoS Clinical Trials* [15], was to provide sufficient physiological data on succinylated gelatin to inform the design of the next phase, rather than to establish statistical superiority of one colloid over the other. For this purpose the trial was most instructive. Again we observed the same benefits of albumin: only one child who received albumin died, out of a group of participants that included children treated as emergencies who were subsequently found to be ineligible for the trial. The results for Gelofusine, however, were not encouraging. The combined findings that death, severe allergic reaction, and acute neurological events were more common in the Gelofusine group suggested that albumin, rather than a cheaper substitute, should be taken forward into the next phase. This was supported by the analysis of the combined data from three trials, including 238 children receiving volume expansion. While this small phase II study was not powered to prove that Gelofusine was superior to saline or albumin, the results suggest that Gelofusine is unlikely to offer any advantage over the cheaper saline solution.

Given the continued controversy over the use of resuscitation fluids in the management of severe malaria, we suggest that this can only be resolved through a definitive clinical trial. Woodrow and Planche [16] have chosen a different interpretation. The evidence presented from two studies conducted in Gabon, one which assessed volume depletion in only 12 survivors [17] and the other larger study conducted in less critically unwell children [18], supports a position of equipoise—the basis which usually prompts the need for a definitive clinical trial. ■

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Phase III Trial of Albumin in Malaria Still Lacks Scientific Justification

Charles J. Woodrow, Timothy Planche

We wrote to *PLoS Clinical Trials* [1] following the publication of the article by Akech et al. [2] in order to highlight specific

problems in the design and analysis of the study presented, point out errors in the presentation of the data, and seek clarification over certain details. As a consequence of this letter an erratum [3] to the editorial commentary has been issued confirming that no difference was found in death rate or any other outcome measure between the two arms of this study.

The authors' follow-up letter [4] reiterates claims concerning the benefit of albumin over other fluids, including Gelofusine. Unfortunately, this letter missed an opportunity to clarify a number of issues and perpetuates a number of inaccuracies. For example, the notion of albumin's superiority over Gelofusine (groundless given the lack of statistical evidence for this; see erratum) persists in the statement beginning: "The combined findings that death, severe allergic reaction, and acute neurological events were more common in the Gelofusine group..." Similarly, the erroneous total patient number included in the meta-analysis (238) is still used in preference to the correct number (239).

Phase III studies must be based on specific and relevant phase II studies. These preferably assess intervention versus standard treatment ("maintenance-only" fluids in most African hospitals) and optimise dosing strategy while rigorously and proactively noting adverse events (e.g., pulmonary oedema by chest radiography [5]). However, none of the studies on albumin performed in Kilifi have incorporated these elements into their design and reported adverse events in a standardised fashion [5]. Even the amounts of fluid actually received by patients in the most recent study are not provided [2]. Comparison of case fatality rates with historical controls cannot provide the required safety data to underpin a phase III study. Additionally, given the lack of a clear hypothesis (the authors discuss albumin acting in both volume expanding and neuroprotective capacities), the group of patients who might benefit from albumin remains uncertain.

Failure to address any of the specific points in our letter impairs the ability of readers to review primary data for themselves. Repeating arguments for phase III studies on albumin in severe malaria does not make them more compelling. ■

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