Author's response to reviews

Title: Hypoglycaemia in severe malaria, clinical associations and relationship to quinine dosage

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Author's response to reviews: see over
11th October 2010

To
The editor,
BMC Infectious Diseases

Dear Sir/Madam,

Ref: Hypoglycaemia in severe malaria, clinical associations and relationship to quinine dosage.

Very many thanks for the positive feedback on the manuscript. We thought the comments were excellent and have improved the overall interpretation of our findings and directed us to clarify areas where the some lack of detail or confusion.

You had asked about consent. This study is an audit of clinical practice. However, all children included in the study had the general informed consent and for those included in trials additional informed consent was taken.

We have made the appropriate changes suggested in bold and highlighted in yellow.

Please thank the reviewers for their insightful appraisal of our manuscript.

We are kindly looking forward to a favourable response from you and your team.

Yours sincerely,

Gilbert Ogetii
Kathryn Maitland
Responses to reviewer comments

Reviewer: Merlin L. Willcox

Reviewer’s report:

Major Compulsory Revisions

1. Table 1: Please add a row to show the proportion of children with severe hypoglycaemia (<2.2mmol/l) in both groups.
   
   This has been added

2. Table 2: Please add rows to show deaths in those with / without hypoglycaemia AT admission (as well as the data already shown for hypoglycaemia AFTER admission). Presumably post admission means “post treatment” – please confirm this is the case.
   
   This has been added. Post admission means post initiation of treatment.

Minor Essential Revisions

1. Methods 2nd paragraph: “three different definition thresholds; <2.2 mmol/l (severe hypoglycaemia), <2.5 mmol/l (moderate hypoglycaemia), and <=3 mmol/l (any hypoglycaemia)” – it only becomes apparent in the penultimate paragraph of the discussion why these cut-offs were chosen. It would be better to give the explanation with references here in the methods section.
   
   Explanation and references on hypoglycaemia cut offs moved to methods section

2. Results line 1: a total OF; THE old regimen
   
   Typo corrected

3. Line 3: bracket needs to appear before “median age” or after “28 months” otherwise it doesn’t make sense
   
   Typo corrected

4. 2nd para: insert “the” before “2002-2006 cohort” and “2006-2009 cohort” (on all occasions)
   
   Suggested corrections made

5. Line 4 : insert “cohort” after 2002-6
   
   Suggested corrections made

6. Timing and distribution of hypoglycaemia episodes: Delete the 2nd and 3rd sentences of this paragraph which simply reiterate data which is clearer to see in table 2. Refer to table 2 instead.
   
   Suggested corrections made

7. Predictors of hypoglycaemia: please explain what is meant by “temperature gradient” and how this was calculated (either here or in the methods section).
   
   Explanation added in results section

8. Discussion para 3: “These observations concur with our earlier studies indicating that whilst glucose production is increased in severe malaria gluconeogenesis fails to compensate, in the
presence of decreased glycogen flux to glucose (glycogenolysis), putting children at risk of developing hypoglycemia [27].” – this sentence is difficult to read and comprehend. Please reword and re-punctuate to improve clarity.

We have done this. I hope the revision provide more clarity.

9. Discussion para 4: “careful monitoring is recommended to facilitate early diagnosis and prevent poor outcome and neurological sequelae [31-33].” – do the authors have any data on the prevalence of neurological sequelae in the patients in their two cohorts? If so it would be useful to include this in table 2.

Incomplete data on prevalence of neurological sequelae at discharge for the two cohorts is available therefore not included. We mention this in the methods.

10. The WHO guidelines, on the other hand, recommends <2.5 mmol/l threshold for treatment of hypoglycaemia in children with severe malaria.” – please quote reference. The guidelines I have recommend <2.2 as the threshold.

Reference quoted

11. “Another recent study conducted in Mali by Willcox and colleagues demonstrated that low glycaemia (2.2-4.4mmol/l) was significantly associated with odds of mortality in children with a clinical diagnosis of severe malaria [38]. The authors concluded that an optimum threshold of 6.1mmol/l for intervention which is much higher than currently recommended.” The first of these sentences is accurate but the second is not. I suggest rewording as follows: “The authors concluded that the optimum threshold is 6.1mmol/l for predicting mortality which is much higher than current definitions.” We were not able to comment on the effect of intervention but instead concluded that “There is a need to conduct a randomized controlled trial to assess whether treatment with intravenous glucose or sublingual sugar is beneficial to those with low glycaemia, above the current treatment threshold.”

Sentence re-phrased as suggested

12. Discussion para 5: “patientS with moderate to severe anaemia”

Typo corrected

**Discretionary Revisions**

1. Results:
   “42% (78/187) of episodes occurred during a blood transfusion or a period of inadequate glucose supply” – can you separate out the transfusions from the other interruptions? If so it would be useful to quote these separately so that the reader can judge which is likely to be the bigger problem.

Results for transfusions and other interruptions now reported separately

2. Discussion: “We found a coincidence of hypoglycaemic episodes during transfusions or periods of disruption of intravenous glucose infusion”.

What implications does this have for treatment? Would the authors suggest that i-v glucose or sublingual sugar is given simultaneously with blood transfusions to prevent these episodes of hypoglycaemia?
The answer is complex—transfusions should ideally contain sufficient dextrose in their dextrose/citrate to prevent the possibility of hypoglycaemia. It may possibly due to the ‘metabolic stress’ of transfusion in a child with critical glycaemic control or inadequate procedures in the transfusion services to ensure sufficient dextrose/citrate is included in the transfusion. Many paediatric transfusions are prepared from adult packs that supply multiple small volume transfusions—so this really opens a can of worms. I would prefer not to suspect poor practice rather than advising stringent surveillance. I think the suggestion of sublingual glucose is a very good one—but I think that a poll of 100 hospitals in malaria endemic Africa would find few if any had this available. Nice little future project I think.

Reviewer: Marcus Lacerda

Reviewer's report:

**Minor essential revisions**

1. In the introduction of the manuscript, the authors state that hypoglycaemia is probably related to depletion of glucose stores, parasite utilisation of glucose, cytokine-influence and hyperinsulinaemia, this last restricted to adults. The references cited point to the absence of hyperinsulinemia triggered by quinine in children, therefore, it is highly expected that no dose-dependent effect on the glucose level would be seen anyway. The authors should clarify their hypothesis in the introductory section.

We have added the following sentence – which supports the fact that there is some confusion and anxiety over whether the evidence for no association is strong…. ‘However, considerable concern still exists and intravenous dosing is strongly recommended in solutions containing dextrose to avert the risk of hypoglycaemia by international treatment guidelines.

2. Apparently only those with cerebral and/or pulmonary malaria were enrolled, but the authors do not mention if children exclusively with hypoglycaemia pre-treatment were also analysed and if there was any. From what they present, we conclude that hypoglycaemia presenting during the hospitalization was much more a prolonged effect of hypoglycaemia pre-treatment therefore not related to quinine itself.

Respiratory distress and impaired consciousness is our standard criteria for defining severe of malaria (Marsh et al 1996). Hypoglycaemia alone was not a criterion for severe malaria. We have added the Marsh reference for this

Children with hypoglycaemia at admission had hypoglycaemia corrected. In the results section paragraph 2 we have shown the proportion of children who presented with hypoglycaemia who went on to develop hypoglycaemia post treatment.

3. The higher dose of quinine should clear parasitaemia faster, and therefore, lead to less hypoglycaemia post-treatment if parasite consumption of glucose is actually a relevant mechanism for hypoglycaemia. The authors do not discuss this point of view. In the multivariate
analysis, parasitaemia should be added because the inhibitory effect of a higher dose of quinine on hypoglycemia could be masked by the statistically significant higher parasitaemia in the second group (from 2006 to 2009). The authors also neglect to analyse if parasitaemia was an independent factor associated to hypoglycaemia on admission.

Parasitaemia now added to the logistic regression model.

4. In table 2, authors do not analyse the level of hypoglycaemia (pre and post-treatment) with fatality, which is discussed in the discussion section, but not based on the analysed data.

   Table 2 now show analysis of pre and post treatment hypoglycaemia with fatality

5. In table 3, I do not agree that the second column is a univariate analysis, because age was also used to correct the OR. Maybe it would become clearer if they present in each column which variables were considered for that model.

   This has now been corrected. The univariate analysis is now not adjusted for age.

Discretionary revisions

1. It should be emphasized that the dosage of glucose during the admission and every 4 hours thereafter is a routine in the service and how many patients were excluded due to the lack of this information in the retrospective analysis, which is a weak point of the manuscript, despite of being useful for the literature.

   No children were excluded. Children in both cohorts were admitted to a paediatric high dependency unit were standard treatment protocols are used.

2. The authors do not mention if the drug used during the two periods is from the same source or any attempt to let us believe that quinine suppliers did not change over time.

   The quinine used for both periods was obtained from same supplier (Indus Pharma, Pakistan). This has now been included in under the methods section.

3. It is not described how the nutritional status was assessed in the children in the methods section, since this is a major characterization for the discussion of hypoglycaemia. In table 3, only visible wasting is used for the statistical analysis.

   Nutritional status was assessed using MUAC, visible wasting and oedema– this is now included in the methods section and reference to paper examining pragmatic anthropometric definitions of children included. In table 3 only parameters with a significant difference at baseline were adjusted for in the multivariate model. MUAC did not have a significant P-value and so not included.

4. Time of disease and the time between diagnosis and treatment were not presented. Peripheral parasitaemia could somehow estimate these variables, but that would also be dependent on the immune status of children, which was not discussed.

   The following statement has been added to methods section: “Appropriate treatment was started immediately after admission. The study did not include children that deteriorated after admission, albeit relatively few”.

5. It is referred that oral treatment was used, but no clear criteria for its use is presented for those not familiar with the antimalarial policy in Kenya.
Oral antimalarial treatment policy clarified i.e. period when sulfadoxine pyrimethamine (2002-2005) or artemether-lumefantrine (2006-2009) was used added.