Reviewer's report

Title: Enteral vitamin A for reducing severity of bronchopulmonary dysplasia in extremely preterm infants: a randomised controlled trial

Version: 2 Date: 23 Jun 2017

Reviewer: Namasivayam Ambalavanan

Reviewer's report:

The well-written manuscript addresses a planned RCT of enteral water-soluble vitamin A in extremely preterm infants to reduce neonatal chronic lung disease (as determined by improvement in the SpO2-PiO2 curve). The study is important, clinically relevant, and would advance the field. The authors should be commended for evaluating this important intervention using sophisticated techniques including lung and diaphragm functions, in addition to clinical outcomes. There are some opportunities for improvement as listed below:

1) The dosing frequency (daily) is not indicated in the Abstract.

2) The supplementation is planned until 34w PMA...In the view of this reviewer, this would most likely lead to high (potentially toxic) concentrations in infants. It may be better to limit the supplementation until postnatal day 28 or a maximum of 42 days. We have done plasma retinol levels in infants who get retinol supplementation after day 28 when they are on full feeds (getting an additional ~2000 IU/day in feeds), and continuing the supplementation after the first month (when infants are on full feeds and usually less sick) often leads to very high serum levels. Most infants with established BPD have adequate retinol levels.

3) The expected improvement (20% in the SpO2-PiO2 curve) is probably a bit too optimistic. It is most likely that the actual improvement will be in the range of 10% (max 15%), and the study may be under-powered. Enrolling in an additional center (or centers) and increasing sample size would be preferable - it is important to remember that the NICHD Vit A trial (Tyson et al) enrolled >800 infants and showed only a 7% benefit in reducing BPD/death.

4) It is probably necessary to evaluate safety more often than once per week in a masked fashion by a clinician, at least for the first third of infants. In our previous study of
different vitamin A doses (Ambalavanan et al. J Pediatr 2003), we evaluated infants as often as 9 times per week.

5) The rationale for the study is that enteral administration is more convenient and more acceptable, and that water-soluble vit A may be better absorbed as compared to fat soluble form, which may have been used in the study by Wardle et al. However, even when we administered twice the dose (10,000 IU given IM 3/week), a substantial proportion of infants were still biochemically deficient (Ambalavanan et al. J Pediatr 2003). We later showed that the reason preterm infants had lower vit A concentrations (Ambalavanan et al. J Perinatol 2005; PMID 16208398) was that inflammation reduces TTR and RBP (the vitamin A transport proteins). Hence, lower concentrations of vitamin A are not because these infants are given less vitamin A (even if given IM, they still have lower levels), but because they do not have sufficient transport capacity. Therefore, it may be useful to also measure markers of inflammation such as CRP and transport proteins such as RBP and TTR in a subset of infants.

6) Not clear how the competing outcome of death is being considered...if mortality is increased in the Vit A group (e.g due to toxicity), these infants would also be the ones at highest risk of BPD.

7) The outcome of SpO2-PiO2 is not a commonly used one, and it will be difficult for clinicians to interpret this result if there is no difference in the rate of BPD. While convenient and allowing for a lower sample size (due to being a continuous variable), this is an outcome that may not be optimal. It may be better to consider an outcome such as Physiologic BPD (with an oxygen reduction test at 36w PMA) to reduce inter-clinician variation.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal