Author’s response to reviews

Title: Incidence of Retinopathy of Prematurity Type 1 and Type 2 in a Regional Hospital of Social Security in the State of Queretaro, Mexico (2017-2018)

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Author’s response to reviews:

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Andreas Ebneter, M.D., Ph.D.
BMC Ophthalmology

Dear Dr. Ebneter:

I wish to re-submit the manuscript titled “Incidence of Retinopathy of Prematurity Type 1 and Type 2 in a Regional Hospital of the Social Security in the State of Queretaro, Mexico (2017-2018)”. The manuscript ID is BOPH-D-18-00981R1.

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in the BMC Ophthalmology.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers’ suggestions. The point-by-point responses to all comments have been prepared and provided below.

Sincerely,

Roger Acevedo-Castellón
Response to Comments from Reviewers to the Authors

Clare Gilbert, MB ChB., MSc., MD (Reviewer 1)

Response to General Comments

The authors are to be congratulated on publishing data from their very first screening experience. However, the paper could be improved in several ways.

First, to make the data comparable with international studies, please present data according to the eye with the most advanced disease.

Second, please can you ask someone to review the paper for language and sentence construction which are poor in places.

Thank you very much for your kind observations. To make the data comparable with international studies, as you suggested, we have changed data presentation according to the eye with the most advanced disease.

We have requested the revision of the manuscript to Editage from the grammatical point of view and language construction.

Response to Detailed Comments

Abstract

The results section of the abstract is extremely difficult to follow. Please present data as follows: immature retina 37.5%; mild ROP not reaching type I or type II 21.6%; Type 2 ROP 4.5%, type I ROP 27.3% and advanced disease 1.1%. It would be useful to present the mean birth weight and gestational age, and their ranges, of babies with Type 1 + advanced ROP as one group. Thank you very much for your observation. We have changed the manuscript and presented data as recommended to make it more easy to follow.

Data which are not presented in the manuscript is whether any of the babies with Type 1 or advanced ROP fell outside the Mexican screening criteria.
All children who were screened and identified with those two conditions were included within the results presented.

Introduction

ROP is only the main cause of blindness in children in some middle and lower middle income countries. Please use another reference for this.
Thank you very much for your observation. We have corrected the manuscript and used another reference for this statement.

Page 4 line 54: please remove the words "or unreliable" as this statement cannot be supported by what is said in the sentence.
Thank you very much for your observation. We have removed those words from the manuscript.

Methods

Readers outside Mexico need to know a bit more about hospital where neonatal care unit was located. Is it a university teaching hospital? Is it in the government sector? Does the hospital also have an eye department? Presumably the neonatal intensive care unit is a level III unit i.e., with facilities to ventilate babies? Please clarify.
Thank you very much for your observation. We have added the information requested to improve the understanding of the context by readers outside Mexico.

Page 6 lines 33 to page 7 line 33: Details of the classification system are not required for this journal.
Thank you very much for your observation. We have deleted the details of the classification system from the manuscript.

Congratulations on documenting the proportion of infants who did not complete screening (17%) as this is rarely reported. This should be commented upon in the discussion. Presumably a high proportion of these infants did not return for screening after they had been discharged from the neonatal unit?
Thank you very much for your observation. We have specified in the manuscript, as you mention, that this children did not return for screening after they had been discharged from the neonatal unit.

Page 8. The following statement appears twice on page 8 "The eyes were subclassified, assigning themselves to the lowest area found in the assessments." I am not sure what this means.
Thank you very much for your observation. We have erased that statement from the manuscript because it was confusing. What we wanted to express was that when classifying premature infants with immature retina by zone, they were assigned to the group with the highest immaturity detected in the screening assessments.

More details are required on the statistical methods used.
Thank you very much for your observation. We have added more details to statistical methods used.
Page 8. The following sentence is describing two separate points and should be two separate sentences with a full stop after Microsoft Excel. "The descriptive statistical analysis with measures of central tendency, and inferential by ANOVA test was done in Microsoft Excel®. In order to avoid potential registration errors that could affect the calculations made on the sample data, the consistency between the physical and electronic records was corroborated meticulously."

Thank you very much for your observation. We have corrected the manuscript.

Results

Page 9 first paragraph: In addition to giving the mean values for birth weight and gestational age please also give the ranges.

Thank you very much for your observation. We have added ranges as requested.

Lines 34-44. Please rewrite to improve clarity, such as "Findings among infants who completed surveillance (264 eyes) were as follows: 8% had complete retinal vascularization (i.e., mature retinal vasculature) at first evaluation; 37.5% had immature vessels and did not develop any ROP; 21.6% had mild ROP (i.e., did not develop Type 1 or Type 2 ROP); 4.5% had type 2 ROP; 27.3% had Type 1 ROP and 1.1% developed Stage 4 or Stage 5 (Table 1)."

Thank you very much for your observation. We have made the changes in the manuscript.

Please clarify whether stage 4 or 5 developed after treatment, or whether this was detected before any treatment was given.

Thank you very much for your observation. We have clarified that this was before any treatment was given.

Page 9 lines 48-58 and Page 10 lines 14-21 and lines 25-33: Many of these findings are presented in table 2 and so they do not need to be repeated in the text. Please say something like: "Infants with mature retinal vasculature at first examination were larger (mean BW 2445 +/- 383 g) and more mature (mean 36 week and 3 days +/- 6) than those who developed ROP. Infants who developed type I ROP had the lowest birth weight (mean 1310 +/- 79g) and gestational age (mean 30 weeks 4 days +/- 3 days)(Table 2)."

You can then give the findings of the different comparisons, using just two groups: those who develop Type 1 or advanced ROP, and those who had no, mild, or Type 2 ROP. Statistical comparison of the birth weight and gestational age of these two groups of babies would be helpful.

Thank you very much for your observation. We have made a single table from table 1 and table 2, because we consider it important to present the number of infants (n) of each group in order to properly interpret the confidence intervals of the presented data. Since many of the findings presented in former table 2 and now table 1 are repeated in the text we have decided to make only a comparison between the two groups suggested. Readers can make comparisons between categories using mean values, ranges and confidence intervals presented in table 1.

Page 11 Lines 16-23: You are not presenting a risk factor study which would entail exposure to oxygen, sepsis failure to gain weight etc. It is not clear in the table what data of "birth weight and" gestational age" and "Other" refer to.

Thank you very much for your observation. We have made the correction in the manuscript text and in the table; these categories (“BW only”, “GA only”, “BW and GA”, and “Other”) represent the reason why ROP screening was performed in these children, so we have changed the heading “risk factors” for
“screening indication”, to represent why the first screening examination took place.
We consider it important to present this data to discuss whether in our population the ranges defined in the ROP detection guidelines are consistent with the presentation of the disease.

Can I suggest you present the findings as was done Vinekar at el, by plotting the birth weight against gestational age of all babies screened, using the two groups suggested above (i.e., Type 1 + advanced, and all others). I have suggested these groupings as the purpose of screening is to find babies needing treatment, and this plot will show very clearly which babies are at risk in your setting, and whether any of those with type 1 ROP fall outside the Mexican screening criteria.

https://www.google.co.uk/search?q=Vinekar+KIDROP&source=lnms&tbm=isch&sa=X&ved=0ahUKEwj_gtnKmebfAhVzXhUIHRBODNQQ_AUIDigB&biw=2275&bih=1170#imgrc=r-d-A7vUC7RghM:
Thank you very much for your observation. We have changed figure 1 for another one that presents the findings as you suggested.

Comments:

Where all the babies with type I ROP treated? If so please say so explaining how they were treated.
Yes, they were treated with primary intravitreal Ranibizumab (0.25mg/0.025ml) within 24 hours after diagnosis.

Did any of the babies develop aggressive posterior ROP? If not this would be surprising given the high rate of type 1 ROP.
Yes, three children were identified with this condition, which represents the 2.3% of premature children who were screened in the year and completed surveillance. We have added this data within the results, and also presented the characteristics of this group.

Discussion

I suggest you reorder the discussion, starting with type I ROP.
Thank you very much for your observation. We have reordered the discussion as suggested.

Page 12 line 52: a comparison of your findings with those of Zepeda are only valid if the same screening criteria were used. Was this case?
Yes. The center in which Dr. Zepeda conducted her retrospective study (Hospital Civil de Guadalajara) is subject to Mexican ROP Guidelines. While it is true, Dr. Zepeda stratified their results in two large groups (less than 32 weeks of gestational age and greater than 32 weeks of gestational age) to compare the first group with the WINROP study results, you can use the data presented in tables 1 and 2 to calculate the general incidence of the different categories (ROP type 1, ROP type 2, Mild ROP, and No ROP) among screened children in that center.

A rate of 27.3% needing treatment is very high given the wide screening criteria. This implies that a lot needs to be done in this unit to improve the quality of neonatal care. For example, what are the policies for resuscitation of preterm infants? Is there enough equipment to safely deliver and monitor supplemental oxygen for all babies receiving this? Does the unit have high rates of sepsis?
Thank you very much for your observation. Although Clinical Practice Guidelines approved by the Ministry of Health of the Federal Government establishes that resuscitation should preferably be done
with ambient air instead of 100% oxygen, and that later supplemental oxygen should be administered with the use of blenders, in the case of the NICU of the center under study, blenders are not available and supplemental oxygen is 100% administered. On the other hand, the rate of neonatal sepsis reported in Mexico is much higher than the reported in the USA, and ranges between 4 and 15.4 per 1,000 live births.

The difference in findings between your study and those of Quinn and the Canadian studies almost certainly reflect a far higher mortality in very premature infants in your unit than is currently the case in the US and Canada. However, at the moment you do not present range of birth weights and gestational ages and it is not possible for the reader to see whether extremely preterm babies are surviving long enough to be examined.

Thank you very much for your observation. We have added all ranges for: gestational age, birth weight, post menstrual age in which diagnosis was done, for all groups, and can be consulted by the readers in table 1.

Conclusions:

You should not comment on treatment in the conclusions without presenting any data.

Thank you very much for your observation. We have added information regarding treatment in the methods and results section.

Once you have plotted the data as suggested above, you may want to comment on the screening criteria being used in Mexico.

Thank you very much for your observation. We have added a figure with the plotted data as suggested.

Tables and figures

The headings for the tables and figures could be simplified by removing the words "Distribution of eyes of the sample by" which are not required.

Thank you very much for your observation. We have removed the words from each table.

Table 4: Remove the word "ACTIVITY".

Thank you very much for your observation. We have removed the word.

Table 5: It is not clear what data are being presented in the columns "BW and GA" and "Other" as this is not explained in the text (in any case, you already present data on BW and GA and this table could be removed).

Thank you very much for your observation. We have changed the heading from “risk factors” to screening criteria. This is information is crucial to discuss Mexican criteria in the ROP Guidelines so we have decided not to remove the table but to explained it in the text.

Figure 1: A plot of two groups would be more informative and easier to interpret: Type 1 + advanced ROP as one group and Type 2 + mild ROP as the other.

Thank you very much for your observation. We have changed figure 1 for another one that presents the findings as you suggested.
Michael Paul Blair (Reviewer 1)

Response to General Comments
The authors present ROP characteristics in Queretaro, Mexico. It is important to characterize ROP populations outside the US and Canada so this is valuable.

Thank you very much for your kind observation.

Response to Detailed Comments

My only comment is that Table 2 presents ages with an 's' presumably for 'semana' but this should be replaced by 'w' for 'week'.

Thank you very much for your observation. We have made the correction in Table 2 which is now Table 1.