Author's response to reviews

Title: Intraventricular hemorrhage in asphyxiated newborns treated with hypothermia: A look into incidence, timing and risk factors

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Author's response to reviews: see over
To: Professor C Anthony Ryan
Editor of BMC Pediatrics

Re: Manuscript # 5676764931429305 «Intraventricular hemorrhage in asphyxiated newborns treated with hypothermia: A look into incidence, timing and risk factors»

Dear Professor C Anthony Ryan,

Following are our responses to your comments and to those of the reviewers.

We would like to thank you and the reviewers for the careful review of our manuscript and for providing us with valuable comments and suggestions to improve the quality of the manuscript. The following point-by-point responses have been prepared to address all of the reviewer’s comments as well as yours. Your comments and those of the reviewers are formatted in bold, and our answers are provided in italic, including the location where the changes in the revised manuscript can be found.

Dear Dr Wintermark,

Thank you for considering BMC Pediatrics for your manuscript (above). Peer review of your manuscript is now complete and, in the light of the reports, I am sorry to say that we cannot consider the manuscript for publication and are closing your file. The reviewers' comments are accessible in PDF format via the links at the bottom of this email. Please contact systemsupport@biomedcentral.com if you have any problems opening the files.

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Editor's comment:
"Unfortunately we are unable to accept your manuscript as currently presented. Please see reviewers comments. We would be prepared to look at your paper again after revision, but would require it to be reviewed once more. There is no guarantee that it would be accepted for publication."
Please note that we think it may be possible to revise your manuscript to address these comments but that this would require longer than our standard revision period. However, we are willing to consider your manuscript further once all the concerns have been addressed. Therefore, if you are able to address all of these concerns, please do submit a new manuscript to BMC Pediatrics. If you are able to do this, a full covering letter, explaining the revisions made, should accompany the submission.

We followed the recommendations of the editor and addressed all of the comments of the reviewers. Especially, we included a neuroradiologist as a co-author and added her valuable comments about imaging, and we also had all our statistics corrected by a statistician. We modified the Methods section to clarify the prospective design of our study; only the review of additional imaging was retrospective. We also added a limitation paragraph in the Discussion section. In addition, the manuscript was proofread by an English editor to improve its English grammar and style.

Corrections in the manuscript: Throughout the manuscript.

Please note that this decision applies across the BMC-series of journals (http://www.biomedcentral.com/info/authors/bmcseries#journalist). Therefore, if you were to submit your revised manuscript to another journal within the BMC-series, your submission should also be accompanied by a full covering letter.

Thank you for your interest in BMC Pediatrics.

Best wishes,
Catherine Olino
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on behalf of Prof C Anthony Ryan
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Referee 1:
This study addresses an important and and as yet not completely understood question in the field of neonatal neurology, namely the complications of cooling for hypoxic-ischemic encephalopathy. While the large RCTs addressing complications of cooling followed a large number of complications, some such as fat necrosis and (more crucially) IVH as addressed here have only become apparent since cooling has become widespread. More information is needed to guide management. Clearly it would be ideal to address this question via a RCT. As cooling is now the standard of care, it is no longer possible to randomize infants to cooling in order to assess whether the incidence of IVH is increased, and as such this cohort study is the most feasible means of addressing the question. The data and figures are sound. The discussions and conclusions are well-supported and the supporting research is appropriately referenced. The abstract and title are also appropriate.

I would suggest that the authors spend some time addressing limitations of the study,
such as the fact that it is a cohort study, and the small number of patients (15) with IVH. We followed the recommendation of the reviewer and added a paragraph in the Discussion section mentioning the limitations of the study.

Corrections in the manuscript: Page 13, lines 20-25; Page 14, lines 1-16.

I would also suggest some language editing, as the language at times is unclear and/or cumbersome and there are spelling errors. An English editor reviewed all the manuscript to improve its grammar and style. In particular, we corrected the abovementioned sentences.

Corrections in the manuscript: Throughout the manuscript.

Lastly and most importantly, I feel that it is necessary for a statistician to review this. According to the methods stated, Chi-squared and Mann-Whitney tests were used. I would imagine Fisher’s Exact Test as well given the small sample numbers in some areas, which should be mentioned or the data reconfigured accordingly. Also, the analysis as to the significance of the combined factors of coagulopathy, thrombocytopenia, hypotension, and PPHN should most likely be performed via multivariate analysis, which if it was done was not stated.

We followed the recommendations of the reviewer and we had all our statistics corrected by a statistician (Dr. Xianming Tan). Fisher’s exact tests were used instead of Chi-square tests considering the low frequency of certain categories. Relevant revised p-values were corrected in the manuscript; significance and non-significance were not modified by this adjustment. A multivariate regression analysis of IVH (yes/no) versus relevant factors was not performed due to the limited number of IVH cases. This explanation was added as a limitation in our Discussion section.

Corrections in the manuscript: Page 8, line 7 and lines 12-14; Page 9, line 19; page 10, lines 11 and 16; Page 13, line 25; Page 14, lines 1-3.

Despite the small number of patients and the initial need for validation of statistical methods before publication, I feel that it is important that this study ultimately be published. The major RCTs did not address this issue, and if in truth there is a threefold increase in IVH risk in infants undergoing hypothermia it could impact management, especially as regards maintenance of hemodynamic stability and rewarming.

As previously mentioned, we added a paragraph discussing the limitations of the study in the Discussion section. We also had all our statistics corrected by a statistician (Xianming Tan). Despite these limitations, this study showed that the incidence of IVH was 9% (95% CI: 5.3-15.0%) in our cohort of asphyxiated newborns treated with hypothermia, which is significantly higher than the reported incidence of 3% in term asymptomatic newborns. As mentioned by the reviewer, this is of interest, since the major randomized controlled studies about hypothermia in asphyxiated newborns did not address this issue, and, if in truth a threefold increase of IVH risk exists for infants undergoing hypothermia, this risk could impact management, especially regarding the maintenance of hemodynamic stability and rewarming.

Corrections in the manuscript: Page 8, line 7 and lines 12-14; Page 9, line 19; page 10, lines 11 and 16; Page 13, lines 20-25; Page 14, lines 1-16.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published An English editor reviewed all the manuscript to improve its grammar and style. In particular, we corrected the abovementioned sentences.

Corrections in the manuscript: Throughout the manuscript.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
We followed the recommendations of the reviewer and we had all our statistics corrected by a statistician (Xianming Tan). Fisher's exact tests were used instead of Chi-square tests considering the low frequency of certain categories. Relevant revised p-values were corrected in the manuscript; significance and non-significance were not modified by this adjustment. A multivariate regression analysis of IVH (yes/no) versus relevant factors was not performed due to the limited number of IVH cases. This explanation was added as a limitation in our Discussion section.

Referee 2:
The authors have studied a cohort of newborns who suffered from a hypoxic ischemic event and underwent subsequent whole body cooling. In particular, the authors wanted to collect information about incidence and multiple clinical characteristics related to occurrence of intraventricular hemorrhage (IVH). They showed/concluded that in 15/146 (15%) of cases an IVH was noted and that it appears that these hemorrhages predominantly occurred during late hypothermia and rewarming. Consequently they recommend that efforts should be directed towards maintaining hemodynamic stability in these patients.

The study is not novel but extends on a previous study by studying a larger number of patients and collecting a greater wealth of clinical and imaging data.

Previous major randomized controlled studies about hypothermia in asphyxiated newborns did not address complications of cooling such as IVH. The only study that addressed the problem of IVH in asphyxiated newborns treated with hypothermia was a case report reporting the course of one such patient and reviewing the literature. As cooling is now the standard of care, it is no longer possible to randomize infants to cooling or not to assess the complications of cooling for neonatal encephalopathy such as IVH. As such, this cohort study is the most feasible means of addressing the question.

Major limitation is that this study is basically a retrospective study in which patients have been studied who received a neuroimaging study based upon either the standard protocol of the NICU or because the attending taking care of the newborn decided to order additional imaging. This results in a significant selection bias and does not allow to determine the exact incidence of IVH in this patient population.

We clarified the Methods section. This was a prospective cohort study of term asphyxiated newborns admitted to our neonatal intensive care unit from August 2008 to June 2013, who met the criteria for induced hypothermia. As per the current standard protocol in our neonatal intensive care unit to evaluate for brain injury in these newborns, only a brain magnetic resonance imaging (MRI) is performed after the hypothermia treatment is completed, except for the very sick newborns who may die from the complications of neonatal encephalopathy for whom a head ultrasound is requested at the bedside during hypothermia treatment. Neuroradiologists, who were blind to the clinical condition of the newborns, interpreted the brain imaging studies of the asphyxiated newborns treated with hypothermia. They reported the severity of intraventricular hemorrhage, the presence and extent of brain injury as per the previously described magnetic resonance imaging scoring system, and other intracranial bleeding. Intraventricular hemorrhage was categorized as either a hemorrhage limited to the choroid plexus in the lateral ventricle, an IVH without ventricular dilatation, or an IVH with ventricular dilatation or a parenchymal hemorrhage. For the newborns with IVH, we then retrospectively reviewed if they had other brain imaging studies performed during their neonatal hospitalization stay, since the attending physician caring for the newborn may have decided to
In addition, the neuroimaging appears to be diverse apparently partially including head ultrasound and MRI and/or CT of the brain, likely at different time points. This study would benefit from having a prospective design with an uniform imaging protocol.

As per the current standard protocol in our neonatal intensive care unit to evaluate for brain injury in these newborns, only a brain magnetic resonance imaging (MRI) is performed after the hypothermia treatment is completed, except for the very sick newborns who may die from the complications of neonatal encephalopathy for whom a head ultrasound is requested at the bedside during hypothermia treatment. In addition, since 2010, when possible (i.e., when the parents consented for their newborns to have additional MRIs, when the newborns were hemodynamically stable, and when a team of a nurse and a respiratory therapist was available to go to the MRI), newborns were enrolled in an MRI research study, and MRI scans were performed on day 1 of life, day 2-3 of life, around day 10 of life and/or around 1 month of life. These time-points were chosen to ensure that no antenatal brain injury was present (day 1 of life), to assess early patterns of injury (day 2-3 of life) and to define the extent of definitive brain injuries (around day 10 of life and around 1 month of life). In addition, for the newborns with IVH, we then retrospectively reviewed if they had other brain imaging studies performed during their neonatal hospitalization stay, since the attending physician caring for the newborn may have decided to order additional imaging.

As suggested by the reviewer, we added as a limitation that our study did not use a uniform protocol for repeated imaging (magnetic resonance imaging and/or head ultrasounds) during the hypothermia - except in the newborns enrolled in the MRI research study - that was used prospectively to determine the timing of IVH. It may be worthwhile to develop such a protocol to determine if the incidence of IVH was underestimated in our study.

Corrections in the manuscript: Page 5, lines 18-25; Page 6, lines 1-25; Page 7, lines 1-7; Page 14, lines 5-11.

In addition, it is unclear how the imaging was done in detail, no reference is made to the exact imaging technique, e.g. was SWI or DWI applied? How was the head ultrasound done. Furthermore the image evaluation is not described in detail, was a standard evaluation performed?

As suggested by the reviewer, we added the details of the imaging. The MRI scans were performed using a 3T clinical system (Achieva X, Philips Healthcare, Best, The Netherlands). Each MRI study included a 3D T1-weighted gradient-echo (TR/TE, 24/4.6 ms; matrix size, 180 x 180; FOV, 180 mm; flip angle, 30 degree; 104 sagittal slices, with a section thickness of 1.0 mm and multiplanar reformations in axial and coronal planes), a turbo spin-echo (TSE) high resolution T2-weighted (TR/TE, 5000/90 ms; TSE factor, 15; matrix size, 300x300; FOV, 150 mm; flip angle, 90 degree; 27 axial sections, with a section thickness of 3.0 mm), a single shot echo-planar imaging (EPI) diffusion-weighted imaging sequence (DWI) (TR/TE, 2424.4/69 ms; matrix size, 200 x 117; FOV, 240 mm; b values 600 and 1200 s/mm²; flip angle, 90 degree; 21 axial sections, with a section thickness of 4.0 mm) and a gradient echo (GRE) T2*-weighted sequence (TR, shortest; TE, 16 ms; matrix size, 384 x 384; flip angle, 18 degree; 21 axial sections, with a section thickness of 4 mm). In addition, since 2010, when possible (i.e., when the parents consented for their newborns to have additional MRIs, when the newborns were hemodynamically stable and when a team of a nurse and a respiratory therapist was available to go to the MRI), newborns were enrolled in an MRI research study, and the MRI scans were performed on day 1 of life, day 2-3 of life, around day 10 of life and/or around 1 month of life. These time-points were chosen to ensure that no antenatal brain injury was present (day 1 of life), to assess early patterns of injury (day 2-3 of life) and to define the extent of definitive brain injuries (around day 10 of life and around 1 month of life). Patients receiving hypothermia had their therapy maintained during the MRI scan without any adverse events [14]. Any ventilation,
pressor support, or sedation was maintained during the MRI scanning process; additional sedation was avoided. A similar imaging protocol was used with these newborns at the different time-points. The head ultrasound scans were performed at the bedside in the neonatal intensive care unit according to standard protocols using a Toshiba Applio 2D multifrequency 4.2-9.0MHz pediatric head probe.

Looking at the only image included it becomes apparent that the author interpreted a coronal image as a sagittal image?
We corrected the mistake in the legend of the figure.

Maybe the list of authors would benefit from the support and inclusion of a dedicated pediatric neuroradiologist.
We followed the recommendation of the reviewer, and we included a neuroradiologist (Dr Christine Saint-Martin) as co-author and added her valuable comments about imaging.

The grading and classification of the IVH has not been summarized. It is just been discussed as IVH, with possible parenchymal extension. It is currently well known that an IVH does not extend into the brain but that the intraparenchymal hemorrhage is a complication of a periventricular venous ischemia with secondary hemorrhagic transformation. The authors should address this issue and explain in detail how they classified the observed hemorrhages.

“Intraventricular” hemorrhage (IVH) was categorized as either a hemorrhage limited to the choroid plexus in the lateral ventricle, an IVH without ventricular dilatation, an IVH with ventricular dilatation, or a parenchymal hemorrhage. We also added in the manuscript a figure representing each type of described IVH.

The authors also discuss a significant hemodynamic instability. How is this defined and measured. Please explain.
The combination of persistent pulmonary hypertension, hypotension, thrombocytopenia, and coagulopathy was considered as hemodynamic instability. We added this in the Methods section.

Brain MRI's after hypothermia were obtained to define other neuroimaging findings?
What is meant with other neuroimaging findings?
As suggested by the reviewer, we clarified this part of the Results section. The last paragraph of the Results section described the brain injury according to the typical brain injury pattern described in asphyxiated newborns (watershed injury pattern and total cortical injury pattern), as well as the intracranial bleeding.

Minor detail, line 8, page 4, reference 9 should be in brackets.
We added the brackets around reference 9.

Line 12, page 4: they are the most prone it. Please rephrase.
We modified the sentence for "when they are the most at risk for it"
Page 6, line 6. What is the meaning of reference 14 in this sentence?
They reported the severity of intraventricular hemorrhage, the presence and extent of brain injury as per the previously described magnetic resonance imaging scoring system [15]. Reference 15 is the previously described magnetic resonance imaging scoring.
Corrections in the manuscript: Page 6, line 25; Page 7, lines 1-2.

Line 15, page 6, compared should be compare
We removed the d
Corrections in the manuscript: Page 7, line 15.

Level of interest: An article of limited interest

Quality of written English: Acceptable
An English editor reviewed all the manuscript to improve its grammar and style. In particular, we corrected the abovementioned sentences.
Corrections in the manuscript: Throughout the manuscript.

Statistical review: No, the manuscript does not need to be seen by a statistician.
We had all our statistics corrected by a statistician (Xianming Tan). Fisher's exact tests were used instead of Chi-square tests considering the low frequency of certain categories. Relevant revised p-values were corrected in the manuscript; significance and non-significance were not modified by this adjustment. A multivariate regression analysis of IVH (yes/no) versus relevant factors was not performed due to the limited number of IVH cases. This explanation was added as a limitation in our Discussion section.
Corrections in the manuscript: Page 8, line 7 and lines 12-14; Page 9, line 19; page 10, lines 11 and 16; Page 13, line 25; Page 14, lines 1-3.

We are available for any additional information you may need.

Thank you once again for your review and your suggestions to improve this manuscript.

Sincerely,

Ghalia Al Yazidi
Pia Wintermark