Author’s response to reviews

Title: Practice variation in anti-epileptic drug use for neonatal hypoxic-ischemic encephalopathy among regional NICUs

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Guilherme Sant'Anna, M.D., PhD
BMC Pediatrics

February 16, 2018
RE: BPED-D-18-00744
Dear Dr. Sant’Anna,

Thank you for the decision to “accept after discretionary minor revisions.” Please find our responses to the reviewer comments copied below.

Sincerely,

Maria Dizon

Abstract: no issues

Introduction: no issues. Only a comment that it may be worth providing evidence from other diseases or populations that identifying ICV is the first step in improving care. The discussion of seizure management is important, but can be found in review articles.

We referenced additional neonatal diseases in which uniform treatment approaches have led to improvements in outcome.

Methods: No issues. One comment: How were aEEG results surmised from chart review? My own experience is that aEEG results are not always adequately documented in the medical chart. Is it possible that some "clinical seizures" were also detected on aEEG but not documented in the chart as such? Lack of aEEG documentation could, perhaps, explain the high rate of "clinical seizures."

The CHND Manual of Procedure instructs abstractors to, “Check seizures confirmed by EEG or aEEG >DOL3” and “Check seizures confirmed by EEG or aEEG <=DOL3” “if there is documentation in infant’s history that infant had EEG evidence of seizures prior to admission and after DOL3.” Furthermore, whether the modality was cEEG or aEEG is recorded. If the abstractor could not find documentation of an aEEG reading, it is true that this would then be classified as a “clinical seizure” only.

Results: -Page 9: Was there a standardized definition of status epilepticus across centres? -Did the proportion of babies with mild and/or moderate encephalopathy increase over time? Perhaps this could account for the reduction in AED use over time, and the stability over time of electrographic seizure rate despite increase in cEEG usage.
There was not a standardized definition of status epilepticus across centers. The CHND Manual of Procedure bases the definition of status on the neurophysiologist report and instructs abstractors to, “Check Yes, if status epilepticus was observed on EEG report.”

The rates of babies with mild to moderate encephalopathy did increase over time and we added this data to the Results.

Discussion:

Page 14: "Our data reinforce that cEEG should be obtained in all mild cases of encephalopathy as EEG seizures would indicate that the eligibility for TH had been met." Would aEEG not be sufficient? If aEEG demonstrates continuity and/or SWC, would the baby still need a cEEG? I'm not sure that the data provided here reinforces need for cEEG in all babies with mild HIE, particularly since this study looks at quaternary hospitals only. Need for cEEG in every baby with mild encephalopathy may suggest that all babies with mild encephalopathy should be transferred to a quaternary care centre.

We agree that this is a valid point. We changed the sentence to include aEEG which is consistent with our statements in the Conclusion.

Page 14: "That some clinical seizures did not have EEG correlates" may be better phrased as "That some clinical seizures occurred in the absence of electrographic seizures." Again, I would like to know if the authors were confident in their ability to discern aEEG seizures from chart review.

We changed the sentence to the one you suggested on page 13. The CHND registry data set includes the same biases as other data sets, but this is relieved somewhat by the fact that abstraction is semi-contemporaneous. In addition, data quality assurance is rigorously maintained and intermittently tested.

Page 17, last paragraph: It may not be worth speculating as to the higher unadjusted rate of seizures in neonates who were selectively head-cooled since the practice is of course centre-specific and the analysis here did not adjust for centre. Perhaps this hypothesis can be further explored in a separate analysis. Overall, I am not sure that the cost analysis of AEDs is helpful in achieving their stated objective. I understand that calculating cost is novel, but I'm not sure it adds to the paper. The cost appears to refer to the cost of the drugs only, which is minimal, and does not represent the costs associated with seizure detection and other aspects of seizure management.
We agree that this crude difference in head versus whole body hypothermia is a hypothesis that can be further explored in a separate analysis. We mention it here only as an example of potentially testable hypotheses generated in the course of this analysis. Because this is registry data, the point of the cost analysis is not really cost, but as another measure of utilization that varies consistently with other measures, and therefore collectively the different measures strengthen the conclusion.