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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Author’s response to reviews:

Guilherme Sant’Anna, M.D., PhD

BMC Pediatrics

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

Thank you for the opportunity to revise our manuscript, “Practice variation in anti-epileptic drug use for neonatal hypoxic-ischemic encephalopathy among regional NICUs,” further. We hope we have addressed Dr. Van Meurs remaining concerns adequately, especially with regards to the conclusion. We have responded to each of her points below and highlighted changes within the revised manuscript.

Sincerely,

Maria Dizon, MD

Abstract

1. I’m surprised that one of your conclusions is not to harmonize use of neuromonitoring across centers since this definitely drives AED use and will discourage the treatment of clinical seizures without an electrographic correlate. I would suggest referencing the 2 articles about treating clinical versus electrographic seizures (van Rooij Pediatrics 2010 and Srinivasakumar Pediatrics 2015).

We changed the Conclusion within the Abstract to include neuromonitoring in addition to AED practices as targets for QI processes. (Increased neuromonitoring by cEEG was previously mentioned in the Conclusion of the manuscript.) We also mentioned the importance of treating subclinical seizures (van Rooji and the Srinivasakumar articles) in the Introduction.

Introduction

1. I would suggest adding a sentence about the use of aEEG in the NICU as you mention that cEEG is resource intensive and not available in all centers.

We added a sentence noting that aEEG is easily interpretable and is routinely used in many but not all centers. Within this study, aEEG was obtained in fewer than 1/3 of cases and cEEG was obtained in greater than 2/3 of cases.
2. You state that the field lacks randomized trials of AEDs, I would reference the trials that do exist (include Pressler Lancet 2015) and that have recently completed enrollment (NeoLev NCT 00461409).

We referenced the bumetanide study and the recently completed levetiracetam study.

3. The last paragraph of the Introduction belongs in the Methods section.

We moved this sentence to the Methods.

4. I would clearly state your objective for this study and mention the plan to identify opportunities for quality improvement as you do in the abstract.

We stated our objective and plan at the end of the Introduction.

5. You mention how head cooling precludes cEEG monitoring. I note that 20% of TH was head cooling. Since the Olympic device is not longer being sold in the US, has this rate significantly decreased in more recent years?

Our data show an abrupt decline in aEEG use between 2014 and 2016 (Figure 4); we mentioned this in the Discussion.

Methods

1. No further suggestions.

Results

1. I would mention that another reason for underestimation of seizures is that initiation of aEEG or cEEG is delayed (page 12).

We included delayed monitoring as a possible explanation for underestimated seizures.

2. I would give the range of incidences. You reference a single article which is not the best citation for this statement. It discusses the impact of seizures on outcome in HIE.
We corrected this sentence and referenced seizure rates for the CoolCap, NICHD and TOBY trials and removed the previous reference.

3. Did the incidence of seizures change as the rate of neuromonitoring increased?

We previously stated that the incidence of seizures did not change as the rate of neuromonitoring increased in Results, Practice Changes Over Time, first paragraph and Figure 4D.

4. On page 13 you state "Our data reinforce… as EEG seizures would indicate TH." I would change "would indicate" to "would indicate that the eligibility for TH had been met."

We changed this sentence as you suggested.

5. It would be interesting to report the variation by center in AED use at discharge in patients treated with AEDs during hospitalization.

Sites with the lowest any AED exposure were the same sites with lowest AED at discharge rates (Figure 3A and 3C).

6. I'm confused by the added sentences on page 15. You attribute the use of AED use in neonates without electrographic seizures to neuroprotection or seizure prophylaxis at referral sites and then suggest increased outreach education. Why wouldn't the receiving hospital discontinue the AED use if used for neuroprotection or even for seizures that did not recur? I suggest modifying this sentence.

You are correct that the practice of outreach sites should not affect the practice at the referral site and so it does not make sense that this could explain continued AED use. Therefore, we have changed these sentences to reflect a need to identify CHND sites that use AEDs for seizure prophylaxis or neuroprotection and to stop these practices.

Conclusions

1. Again, I suggest that focusing on not only AED utilization but also on use of "timely" neuromonitoring, optimally with cEEG but if not possible with aEEG.
We added the goal of timely neuromonitoring to the Conclusion. We also allowed for aEEG diagnosis of EEG seizures in addition to cEEG.