Reviewer's report

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

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Reviewer: Krisa Van Meurs

Reviewer's report:

Thank you for the opportunity to review the manuscript by Dizon et al. entitled "Practice variation in anti-epileptic drug use for neonatal HIE among regional NICUs". This is a multi-center study of 20 quaternary NICUs belonging to CHND using linked CHND and PHIS data on babies ≥ 36 weeks with HIE. The objective was to examine practice variation in anti-epileptic drug use.

Abstract

Overall a good summary of the manuscript. In the Results section you state that 26% without seizures received AEDs however you do not specify if you are referring to electrographic seizures or clinical seizures. It would helpful to be specific.

Introduction

I would suggest referencing the work done at UCSF, University of Calgary, and Riley Children's on protocolized management of seizures.

Methods

1. A CONSORT diagram would be useful to better understand the cohorts being compared and the various reasons patients were excluded.

2. Did the authors consider separating out the group with clinical seizures from the "No EEG seizure" group. This way it would be easier to understand if the use of AEDs in the NO EEG seizure group was because clinical seizures were witnessed prior to use of neurophysiologic monitoring versus AEDs were used for seizure prophylaxis. It is unclear now how many of the No EEG seizure group had clinical seizures? At the time of the clinical seizure, were they undergoing EEG or aEEG? Also, how many of the No EEG seizure group without EEG or aEEG monitoring were treated with AEDs.
Results

1. Since you are evaluating a 6-year period, it may be of interest to look at changes in practice over time.

2. I would specifically state that the timing of initiation of EEG or aEEG monitoring was not known in the second sentence of second paragraph since this greatly impacts interpretation of the results.

3. The sentence "these rates were lower than expected and may be related to the application of TH to mild HIE cases in real practice" belongs in the discussion not in the results section. I think you could answer this question with data analysis instead of speculating. Was the incidence of status lower in babies with mild HIE?

4. You state that clinical seizures without electrographic seizures were seen in 21%. How many of the group with electrographic seizures also had clinical seizures? This information should be included in one of the Tables.

5. It would be useful to provide information about the order of AED selection if this information is available. Is there as much ICV in the first drug used? Which is the most common second drug?

6. On page 8 you mention that there was a higher rate on seizures in neonates who were selectively head cooled; however, you state in the introduction that head cooling often precludes cEEG monitoring. How do you explain your findings? Was the rate of EEG or aEEG monitoring lower in babies who received head cooling? Was the initiation of monitoring delayed until after the cooling period?

Discussion

1. You state that a future QI collaborative targeting babies with HIE but without seizures is warranted. I believe that some of the AED use may be happening before, during or shortly after admission when EEG or aEEG monitoring has not yet been initiated. What recommendation do you have for those babies with clinical seizures prior to monitoring?

2. Another reason for underestimation of seizure burden with aEEG is seizure focus being not central or parietal.
3. More discussion of literature regarding use of AEDs for seizure prophylaxis and toxicities of AEDs is warranted given the results seen in this study.

4. On page 13 you stated that you showed ICV in "other measures of AED utilization, including any exposure and duration of exposure…” I thought you did not have specific data on the length of AED exposure.

5. A concise summary of best practices around neuromonitoring in babies with HIE and use of AEDs might be helpful especially given the data presented.

Conclusion

1. I would suggest that your conclusion should state that evidence based practices should be implemented in the member hospitals of CHND and state what specific practices you would target based on the analysis you have performed.

Tables and Figures

1. Table 1. I noted that 6% of EEG seizure group were classified as mild HIE. Were you using the NICHD severity classification which states that babies with seizures are classified as moderate independent of the Sarnat exam? Did these babies have seizures after classification as mild HIE?

2. Figure 1. The wording used in the series of bar graphs in Seizure versus No seizure. Do you mean No EEG seizure? It is clear that many centers are using AEDs in babies without seizures; however, it is not clear if they are treating clinical seizures seen prior to initiation of EEG/aEEG or if they are using AEDs for seizure prophylaxis.

3. Table 2. I suggest including N for your 3 populations and also specifying N available for various analyses. This information should be in footnotes.

4. Table 2. From the way aEEG at 24 hours and full EEG within 24 hours are separated, I suspect that aEEG was not displayed on full EEG. Is this correct?
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?
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Yes

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