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:

We thank the reviewers for their comments that have helped us craft a much improved manuscript. We have highlighted changes in the resubmission in yellow.

Sonia Bonifacio (Reviewer 1): This is a well designed and well written manuscript. It is important information that is needed to improve the quality of care provided to this group of patients.
I think there is an opportunity within this data set to also evaluate if over the course of time there has been change in practice across centers. Specifically related to the question of use of AEDs without EEG seizures, especially in the several centers that expose patients to AEDS who do not have EEG seizures > 40% of the time. These centers may have changed practice between 2010 and 2016 (hopefully).

-We did look at all the centers as a group before and after ACNS guidelines were published and found an overall increase in the use of cEEG that we now include in our Results as well as our Discussion.

In addition figure 1a could also be done by removing patients with 'clinical seizures only' and then we can see if the variation by center is related to clinical only vs EEG confirmed seizures.

-We changed the figure (now Figure 2A) to include No Seizures, EEG Seizures and Clinical Seizures by center.

Only by looking at the data over time can we then take the data to inform a CHND QI project because what is happening now or in the last year of data that you have may be very different from what was happening in 2010.

-We added a Results section and a new Figure 4 that addresses practice changes over time.

A few other areas that I suggest you evaluate and present in this manuscript:

1. Can you present the size of each center in terms of number of critical care beds?

-We added the median number of beds and range to the Results.

2. What is the average number of babies per center that is treated with TH per year? Is this changing over time? Is the number of babies with diagnosis of seizures changing over time? As we educate and improve our use of EEG or aEEG are there fewer babies being diagnosed with clinical seizures only?

-We now report the number of babies treated with TH per center for the study period in the Results and added a new Figure 4 showing cEEG, aEEG, no seizures, clinical seizures and EEG seizures by year.
3. Of the 20 centers reported included how many actually have some sort of a NEURONICU or a team dedicated to providing neurocritical care?

Is the presence of a NeuroNICU team or daily involvement of a neurologist associated with decreased variation in care?

- We added to the Results that all centers have a NeuroNICU program and/or daily availability of Neurology and that no center provides peophylactic phenobarbital as usual practice.

4. In the background I am not sure that you can say there is a lack of consensus about the order of AEDS - from your data and from others it appears that most places still use PHB as first line agent. When we write in manuscripts that there is a 'lack of consensus' then it encourages others to try Lev as a first line agent when we don't actually know that it is any better than PHB and it is as you have shown far more costly.

- We removed the sentence referred to and replaced it with, “the field lacks randomized trials in neonates proving safety or efficacy of one AED over another.” We are aware of, but did not allude to, the not yet published results of the Keppra v. Phenobarbital trial.

5. On page 6 line 51 Data Analysis section - there is an 'in' or 'in AED' missing after you write "ICV (should insert either in or in AED) duration was evaluated..."

- We inserted “in AED” duration.

6. In section labeled AED selection - there were only 757 patients who received any AED - therefore it is not possible to say that 452 received only 1, 317 received 2, and 483 received 3 or more AEDs.

We apologize for this error. We corrected the total number of patients receiving 1, 2 or 3 or more AEDs; this analysis includes exclusions for midazolam, lorazepam and clonazepam.

7. In the discussion you mention trends over time - should also evaluate if there was a trend over time in Exposure to AEDs without EEG seizures.

- We added Figure 4F that shows exposure to AEDs without EEG seizures by year.
8. In the discussion - should also mention staggering cost of Lev when there is no evidence that it is any better than PHB, especially as first line and also in general. One way to drill down on LEV use would be to see how many patients of those that only received 1 AED received LEV - this way you know if it is being used as first line in which case this is another opportunity for QI.

We included the phrase, “2.9-fold greater than fosphenytoin/phenytoin,” to emphasize the cost of levetiracetam over other AEDs, and added the number of patients who received only levetiracetam which is 10.

9. Discussion - since you are proposing this as data to be used in a QI project one would wonder and should postulate - do we have an idea about what amount of AED exposure without EEG seizures we should accept - clearly 81% in center 18 is too high - but should the goal be 20%?

We think it should approach 0% (not including lorazepam), and have mentioned this in a description of the QI project we propose.

10. You could also mention that the AAP has made recommendations for what services should be available at centers that provide TH. In California, the governing body that certifies NICUs has mandated which services must be available in order to be a TH center. Those centers that can not comply with the requirements must close there programs until they can provide the services, education, training that is needed to be a TH center. Can google - CCS numbered letter therapeutic hypothermia. This set of requirements was developed by key stakeholders and providers at regional NICUs. https://urldefense.proofpoint.com/v2/url?u=https-3A__www.dhcs.ca.gov_services_ccs_Documents_ccsnl061116.pdf&d=DwIGaQ&c=yHlS04HhBraes5BQ9ue5zKhE7rtNXt_d012z2PA6ws&c=r=7sGkB6BWCE8izW-GSI5BgJ0tBi_zNuMRiL54j-e4SE&m=sYJlQqaMFuSYFZIHAK5fpgzohnkhw-2jSwOB-cdWpiU&s=AOQ2KHU29VZ49yf9qWT3UZ-h29pZkcEhzihUWqB6TJg&e=

- We added to the Discussion that, “All CHND centers involved in this study met recommendations by the American Academy of Pediatrics Committee on Fetus and Newborn for centers that provide TH, including Level III or higher NICU care, neurologic consultation, neuromonitoring with aEEG or cEEG, neuroimaging by MRI, systems for monitoring longitudinal neurodevelopmental outcome, training programs and infrastructure including written protocols and monitoring of outcomes as well as outreach to community hospitals.”

11. Please review numbers in table 1. In particular row "treated with AED" the % listed under column of EEG seizure can not be 59%. 447/472 is 95%, 310/1186 is 26% not 40.9%
We apologize for this mistake. We changed the rate of treated with AED and no EEG seizures to 26.1% and the rate of treated with AED and EEG seizures to 94.7%.

12. Another possible analysis - how many of the 'mild HIE' patients received AEDs and then broken down by EEG seizures or not. This is another important QI topic - why are we cooling so many milds - clearly part of this is a definitional problem using the VON definition is probably not accurate - and are we causing them harm.

-We added to the Results, “Eighteen percent of the cohort (308 of 1658) had mild encephalopathy; of these 5.8% had clinical seizures.”

Krisa Van Meurs (Reviewer 2): 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.

-We clarified in the Abstract, that 26% without electrographic seizures received AEDs.

Introduction

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

-We referenced in the Introduction, the work on protocolized management of seizures by these groups.
Methods

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

   - We added a flow diagram as Figure 1 and added a Figure 1 legend.

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.

   - We provided more information on clinical seizures in the Results and Tables and discussed them in the Discussion. There were 239 cases of clinical seizures not confirmed by cEEG or aEEG which amounted to 20% of all cases of HIE treated with TH analyzed. Of these, 200 occurred at or before 3d of life and 39 occurred after 3d of life. Clinical seizures without EEG correlates might include the following scenarios: clinical movements might not be due to epileptiform activity; seizures noted prior to transport might have spontaneously resolved or resolved following AED given; the threshold to treat clinical seizures during TH might be higher if patients are not on cEEG or aEEG for the entire period of hypothermia and rewarming; even if they were, cEEG reading might not be immediately available.

Results

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

   - We looked at rates of cEEG use and observed an increase after ACNS guidelines were published as compared to before, and mentioned this in the Discussion. We also added Figure 4 showing cEEG use, aEEG use, clinical seizures and EEG seizures by year.

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.
- We clarified in the Results that, “The exam timing of initiation of cEEG or aEEG monitoring was not known although it was known if studies were done before or after 3d of life; almost all studies were done by 24h of life.”

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?

- We moved this sentence to the Discussion.

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.

- We added a clinical seizures column to Table 1.

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?

- We added to the Results the information that, “Phenobarbital was the first-line AED throughout the entire study period. The most common second drug changed over the course of the study from fosphenytoin/phenytoin to levetiracetam.” We also added a graph illustrating this change (Figure 4).

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?

- We added to the Results, “The rate of cEEG monitoring was lower in the selectively head-cooled baby,” and added rates of cEEG and aEEG. We added to the Discussion, “We speculate that delay in obtaining cEEG may result in delay in treatment and a higher rate of seizures at first cEEG.”
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?

-We would recommend that the referring hospital or transport team give lorazepam for clinical seizures prior to cEEG.

2. Another reason for underestimation of seizure burden with aEEG is seizure focus being not central or parietal.

-We added this reason for underestimation of seizure burden with aEEG.

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.

-We discussed seizure prophylaxis and AED toxicities in both the Introduction and the Discussion.

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.

-We do have data on length of AED exposure (see page 5, “AED exposure was defined as >= AED CTC code during the initial hospitalization in a given patient.” What we do not have is timing of AED exposure in relationship to EEG.

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.

-We added a discussion of adherence to Best Practices for babies with HIE.
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.

- We specified that the practices that will be the targets for our initial QI include: “1) observation or use of lorazepam for clinical seizures without EEG confirmation, 2) cEEG on admission for all neonates transported for TH (metrics will also include time from admission to placement of cEEG), 3) cEEG confirmation of seizures prior to phenobarbital, 4) time from cEEG confirmation of seizures to infusion of phenobarbital.”

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?

- We clarified at the bottom of the table that “VON or NICHD definitions of HIE were used depending on each site’s practice; for the NICHD definition, infants with mild encephalopathy on Sarnat exam and seizures qualify for TH.” We discussed seizures in mild HIE in the Discussion.

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.

- We changed the legend to clarify that these were babies with EEG seizures versus No seizures.

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.

- We added (n, %) and bolded these within the table.

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?
-We clarified at the bottom of the table that aEEG was not consistently displayed on full EEG across centers. aEEG reflects cerebral function monitor output.