Reviewer's report

Title: Efficacy of Levetiracetam for Neonatal Seizures in Preterm Infants

Version: 0 Date: 02 Oct 2017

Reviewer: Noah Cook

Reviewer's report:

Overall I found the manuscript to be well organized and well written. I think the information contained within this manuscript adds to an important body of literature that may ultimately enable us to manage neonatal seizures in the preterm population more safely and effectively, but I believe the conclusions drawn here are overstated and should be placed in proper perspective given the study design limitations. I did attach a marked-up manuscript, but per the instructions here I will also list the more substantial (vs. minor editorial) comments here:

Methods:
1- It's not clear how the decision was made to use LEV as a first line agent for these patients. Did this center have a policy or standard for selection of AEDs for such patients? Was LEV considered an acceptable first line agent or was it being administered for research purposes? If the decision was made to administer LEV for the purpose of conducting this study, was informed consent obtained? Along these lines, there is a comment in the discussion that the findings of this study "motivated [the investigators] to institute a protocol for neonatal seizures in preterm infants", which further confuses the picture - did they institute a protocol with LEV as a first line agent before conducting this study or as a result of this study (or was the use of LEV not a part of this protocol)?
2- The approach to selection/method of administering AEDs should be outlined here (vs the Results section under 'response to treatment')
3- Recommend adjusting and/or clarifying the upper age limit for study subjects. Consider limiting to those under 4 weeks of life (the typical neonatal period), or to a particular adjusted age (since they are focusing on the preterm population).
4- Investigators should explain the statistical analysis methods employed (e.g., descriptive statistics)

Results, Gestational Ages and Body Weights:
1 - define ELBW/VLBW/LBW

Results, Onset of neonatal seizures:
1- suggest adding adjusted age of seizure presentation

Results, Type of seizures:
1- This description would seem to indicate that all seizures being evaluated were detected clinically. Is that so? Even if all were identified based on clinical suspicion of seizure activity, I'd expect some subclinical seizure activity that's caught on EEG. Perhaps this categorization is meant to describe the initial presentation?

Results, Etiology:
1 - Be careful in assigning an 'etiology', as these are clinical associations
2- HIE was said to occur in 67% of infants, but this is not a typical finding among preterm infants. Age ranges for this particular population would be helpful, and I'd assume most/all of those with HIE were relatively mature. It may worth separating out the 35-36 weeker with HIE from the 26-28 weeker with IVH, as well as providing a definition for HIE.

Results, adverse reactions to LEV:
1 - Were patients being monitored systematically for any particular side effects? Whatever approach was taken for safety monitoring (whether consistent/systematic or not) should be explained in the methods section. For example, explain what labs were drawn and when, explain whether irritability/somnolence being consistently monitored and/or documented and if so, how.

Results, Follow-up:
1- provide definition for 'delayed development'

Discussion:
1 - regarding the statement on p7, lines 57-59, I know there are some more recent publications indicating/suggesting a relationship between control of seizure burden and outcome in neonates.
lines 1-6 contain contradictory statements - 'few reports' vs 'several studies' on the efficacy and safety of LEV on neonatal seizures. I believe the latter is true in light of the number of publications cited and described in table 2. This, in turn, begs the question as to what this particular study adds to the existing literature. This should be more clearly outlined. For example, this study would seem to be more (though not completely) unique in analyzing the use of LEV as a first line agent for this population.

3- page 10, last paragraph of discussion - I disagree with the statement that these results suggest that LEV can be an appropriate treatment. At best, the results are supportive of carrying out a prospective randomized controlled trial. Although using words like 'can' arguably provides some leeway, I think it is premature and potentially dangerous to even suggest such a conclusion based on these findings.

4 - I believe the authors should expand on the limitations of the small sample size and retrospective design, specifically noting that 1) any conclusions about safety or efficacy are limited, and 2) rare side effects are more difficult to detect.

Conclusion
I think it's more appropriate to conclude that these data add to the growing body of literature that LEV is safe and well tolerated when administered to neonates with seizures, and that larger, prospective studies are warranted to define the role of LEV in the management of neonatal seizures (I took those words directly from the publication #25 in the bibliography, which also needs some editing). These results also appear to be consistent with reported findings of at least 50% efficacy in controlling seizures among this population.

**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.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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