Levetiracetam is Still Not a First-line Treatment in Neonatal Seizures

I read with interest the research article by Gowda, *et al*. [1] and the accompanying editorial by Swami and Kaushik [2]. I would first like to commend the authors for conducting a randomized study to compare levetiracetam with phenobarbital in neonatal seizures. I completely agree with two particular observations documented in the editorial *viz*, the need for future robust trials before considering levetiracetam as the first-line therapy, and the need of continuous video EEGs for confirmation of cessation of seizures.

Moreover, it would also be important to assess and document the seizure severity (seconds of seizures/hour) before the study drug administration. As most neonatal seizures are symptomatic in nature and self-resolving, administration of the study drug during decreasing seizure trend can falsely mimic improvement from the study drug rather than the natural tendency of seizures to gradually decrease in severity and stop.

The authors in the research study used 20 mg/kg of levetiracetam as the loading dose, with a further loading dose of 20 mg/kg in the presence of continuing seizures. However, the results did not mention how many neonates in the study required this second dose. Additionally, this dose may be inadequate as a loading dose; a recent phase 2b randomized controlled study (NEOLEV2) showed that a higher levetiracetam dose (increase to 60 mg/kg from 40 mg/kg) had been associated with seizure remission in 7.5% of additional patients [3]. Additionally, in this study, phenobarbital (80%) was noted to be significantly more effective than levetiracetam (28%) [3].

In general, this cohort had a very high proportion of sepsis/meningitis neonates, almost close to the incidence of hypoxic-ischemic encephalopathy and much higher than other cohorts, including NEOLEV2 cohort. Moreover, the mean age of seizures in the study by Gowda, *et al*. [1] was 8-9 days. It is important to note that the high seizure burden in HIE is in the first 3 days of life and raises an uncertainty of generalizing the conclusion of the study to use levetiracetam as a first line treatment in neonates with HIE, especially during the first 72 hours. Besides, the authors did not mention how many of these patients received therapeutic hypothermia, as that may have some effect on the seizure control.

Although clinical seizure suppression is routinely considered as a good primary outcome measure, a long term follow up to assess neurodevelopmental outcome is necessary as effects of neuronal injury secondary to seizures *vs*. apoptotic injury due to antiseizure medicines are still unknown, and might be more clinically relevant rather than acute seizure suppression.

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REFERENCES

1. Gowda VK, Romana A, Shivanna NH, Benakappa N, Benakappa A. Levetiracetam versus phenobarbitone in neonatal seizures – A randomized controlled trial. Indian Pediatr. 2019;56:643-6.
2. Swami M, Kaushik JS. Levetiracetam in neonatal seizures. Indian Pediatr.2019; 56:639-40.
3. Sharpe C, Reiner GE, Davis SL, Nespeca M, Gold JJ, Rasmussen M, *et al*. A randomized controlled trial of levetiracetam compared with phenobarbital in the treatment of neonatal seizures. (June 17, 2019). Available at: *https://ssrn.com/abstract=3405581*. Accessed on October 11, 2019.

AUTHOR'S REPLY

We thank the reader for critically evaluating our research study [1]. The queries raised are addressed below:

Video EEG was not done in our study and we have already mentioned it as a study limitation, and the same has also been highlighted in the accompanying editorial [1,2]. We agree that most neonatal seizures are symptomatic and do not require long-term medications. Our objective was to find out short-term outcome, and it was expected that randomization would have overcome any bias due to spontaneous seizure resolution or resolution due to medications, as it applies for both groups.

Following first dose of levetiracetam (LEV), seizures stopped in 30 (60%) neonates and following second dose, seizures stopped in 43 (86%) in our study [1]. The dose of LEV is not established in neonates and, we used a dose based on published studies, evidence available from off-label use, and our experience. The phase 2b randomized controlled study (NEOLEV2) was published after our study was completed [3]. As there are studies showing that both phenobarbitone (PB) and LEV are equally effective but LEV has lesser side-effects, we need more studies to find a definite answer in this regard.

Our study is on neonatal seizures in general and not specific to hypoxic ischemic encephalopathy (HIE), that may be the reason for mean age being 8-9 days. None of