Randomized Controlled Trial Evaluating Levetiracetam as First-line Therapy for Seizures in Neonates

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SUMMARY

This multicenter, randomized, blinded, controlled, trial investigated the efficacy and safety of levetiracetam compared with phenobarbital as a preferred treatment for neonatal seizures of any cause. The primary outcome variable was complete seizure freedom for 24 hours, assessed by independent review of the EEGs by 2 experts. Eighty percent of patients randomly assigned to phenobarbital remained seizure free for 24 hours, compared with 28% of patients randomly assigned to levetiracetam (P, .001; relative risk 0.35 [95% confidence interval: 0.22-0.56]; modified intention-to-treat population). A 7.5% improvement in efficacy was achieved with a dose escalation of levetiracetam from 40 to 60 mg/kg. More adverse effects were seen in subjects randomly assigned to phenobarbital (not statistically significant). The authors concluded that phenobarbital was more effective than levetiracetam for the treatment of neonatal seizures and higher rates of adverse effects were seen with phenobarbital treatment.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: A group of investigators undertook a multi-centre randomized controlled trial (RCT), designated NEOLEV2, to study the efficacy and safety of using levetiracetam as first-line therapy for seizures in neonates [1]. ***Box* I** presents an outline of the trial [1] and ***Web Table* I** presents a summary of the results.

Critical Appraisal

Randomization: The method of preparing the randomization sequence was not described, however it was done by an independent team. The sequence was generated so as to allocate 60% participants to levetiracetam. The reason for this should have been specified considering that trial efficiency is maximal with a 1:1 allocation ratio. Block randomization was used, though block sizes were not described. Randomization was stratified by site.

Allocation concealment: The random sequence was communicated to pharmacies of the participating institutions, who prepared identical appearing levetiracetam and phenobarbital injections (such that the same volume would be injected, whichever drug was used). However, it is not clear whether sequentially numbered injections were provided to treating physicians, or they had to use other means such as opening sealed envelopes to identify the allocation.

Blinding: The pharmacies prepared both medications so that identical volume would be injected in both treatment arms. However, the method of ensuring similar appearance of the medication was not specified. The investigators mentioned that all investigators, clinical personnel, neurophysiologists interpreting the EEG, and parents of enrolled neonates, were blinded.

Strengths and Limitations: A major strength of this study is that the occurrence of seizures was defined by cEEG, rather than identifying convulsions clinically or indirectly through changes in vital sign parameters detected electronically. An elaborate protocol was developed for real-time reading and interpreting of cEEG recordings by trained technicians. Additional inputs by automated software were also used. This ensured high sensitivity for seizure detection (so that no seizure episode was missed). This is perhaps one of very few clinical trials wherein elaborate measures were taken to define and document seizures. However, it is unclear whether heightened sensitivity could compromise specificity or trigger administration of medications for episodes that would have been otherwise missed or ignored. The investigators also have acknowledged the latter point.

Another important strength is that the EEG recordings were also reviewed by at least two expert neurophysiologists working independently. Although this was done retrospectively, it is as near as the gold-

Box I Summary of the Trial [1]

Clinical question

The research question of this RCT could be expressed as follows: "In term-infants with neonatal seizures (*P=Population*), what is the effect of levetiracetam as first-line therapy (*I=Intervention*), compared to phenobarbital (*C=Comparison*), on seizure control and development of adverse effects (O=Outcomes), within 48 hours of treatment (*T=Time frame*)?"

Study design: Multi-centre, blinded RCT with allocation of individual participants to the trial arms.

Study setting: Six neonatal units; five located in California (USA) and one in Auckland (New Zealand).

Study duration: March 2013 to October 2017 (55 months)

Inclusion criteria

Neonates having seizures or at risk for having seizures, were eligible if they were <2 weeks old, born at term with corrected gestation ranging from 36 to 44 weeks, and weighed ≥2200g. Such neonates underwent continuous EEG (cEEG) recording to determine the occurrence of seizures. This was defined as "abrupt electrical activity for ≥10 seconds with change in 2 or more of the following EEG characteristics: frequency, amplitude and spatial distribution". The cEEG recordings were read by trained personnel in real-time and also processed using automated software. In addition, retrospective review by specialist neurophysiologists was used for confirmation.

Exclusion criteria

Neonates were ineligible if they had already received anti-convulsant medication, had serum creatinine >1.6 mg/dL, seizures were related to hypocalcemia or hypoglycaemia, and if EEG recording could not be started before treatment. Neonates in whom mortality was imminent were also excluded.

Recruitment procedure

Neonates fulfilling the eligibility criteria underwent cEEG recording and were enrolled if seizures occurred.

Intervention and Comparison groups

Neonates with seizures (defined by cEEG recording) received loading with either 40 mg/kg levetiracetam, or 20 mg/kg phenobarbital, infused over 15 minutes. This was followed by maintenance dose of levetiracetam 10 mg/kg TDS for 5 days; or phenobarbital 1.5 mg/kg TDS for 5 days. If seizures persisted after an observation period of 15 minutes after the loading dose (or recurred within 24 hours), additional loading was done with 20 mg/kg levetiracetam, or 20 mg/kg phenobarbital, infused over 15 minutes. If seizures persisted after another 15 minutes of observation (or recurred within 24 hours), those who had received 60 mg/kg levetiracetam were given 20 mg/kg phenobarbital, whereas those who had received 40 mg/kg phenobarbital were given 40 mg/kg levetiracetam. These were infused over 15 minutes, followed by an observation period of another 15 minutes. If seizures persisted or recurred within 24 hours, the groups received additional 20 mg/kg phenobarbital, or 20 mg/g levetiracetam, respectively. Thus each neonate could potentially receive a maximum total loading dose of 40 mg/kg phenobarbital plus 60 mg/kg levetiracetam. Persistence of seizures despite this was managed as per individual institution protocols (not described by the authors).

Follow-up protocol

EEG recordings were analysed for the first 24 hours after starting therapy, in real-time by technicians based at a remote site as well as by using commercial computerized algorithms designed to detect neonatal seizures. In addition to these protocols to detect seizures (and trigger administration of medications), seizure cessation/control was retrospectively confirmed by at least two neurophysiologists. Where available, cEEG recordings were analysed at the end of 48 hours of treatment. Adverse events were identified by observing recognized events, and also monitoring vital signs including heart rate, blood pressure, respiratory abnormality, sedation, inability to feed, oxygen therapy, vasopressor therapy, and need for respiratory support. Complete blood cell count and metabolic profile were evaluated at 48 hours after treatment.

Outcomes

Primary outcome:

- Seizure control for 24 hours.

Secondary outcomes:

- Seizure control for 48 hours
- Seizure control for one hour
- Seizure control for 24 hours in neonates receiving therapeutic hypothermia for hypoxic ischemic encephalopathy (HIE).
- Proportion of neonates with seizure control for 24 hours after receiving an additional loading dose (of the originally used medication).
- Adverse events
- Serious adverse events
- Death
- Discontinuation from the study
- Complete blood cell count at 48 hours

- Panel of metabolic parameters at 48 hours

Sample size

The investigators reported that a sample size of 60 (randomized to levetiracetam group) and 40 (randomized to phenobarbital group) would have 80% power to detect an absolute increase of seizure control by ≥28% from the assumed 50% control in those receiving phenobarbital, taking alpha error 0.05. Presumably this calculation was done *a priori* and not *post hoc*.

Data analysis

Modified intention-to-treat (mITT) analysis was performed (for efficacy parameters) wherein only those neonates were included in the denominator, who had seizures confirmed by neurophysiologist, and seizure control evaluation at 24 hours. *Post hoc* analyses included sensitivity analyses (using two scenarios to handle missing data), primary outcome assessed by a neurologist at the bedside, and a covariate-adjusted model based on severity of seizure, therapeutic hypothermia and etiology of HIE. Safety analysis was done by a routine intention-to-treat (ITT) model wherein all randomized participants were included in the denominator of the arm they were randomized to Additional per protocol analyses were performed.

Comparison of groups at baseline

The groups were comparable at baseline in terms of gestational age, birth weight, gender, proportion with HIE as the cause for seizures, proportion receiving therapeutic hypothermia, Apgar score at 5 minutes, cord blood pH and pre-treatment severity (although the method of calculating severity was not specified).

Box I Summary of Results (Levetiracetam *vs* Phenobarbital Groups)

Primary outcome

- Seizure control for 24 hours: 15/53 *vs* 24/30 (RR 0.35, CI: 0.22, 0.56)

Secondary outcomes

- Seizure control for 48 hours: 8/47 *vs* 18/28 (RR 0.26, CI: 0.13, 0.53)
- Seizure control for one hour: 26/53 *vs* 28/30 (RR 0.53, CI: 0.39, 0.70)
- Seizure control for 24 hours in neonates receiving therapeutic hypothermia for HIE: 6/17 vs 9/10 (RR 0.39, CI: 0.20, 0.77).
- Proportion of neonates with seizure control for 24 hours after receiving a second loading dose: 4/53 vs 3/30 (RR 0.75, CI: 0.18, 3.15).
- Proportion of neonates who had to be given two loading doses of the medication used in the other arm: 37/53 vs 6/30. Among the 37 in the levetiracetam arm (who received two loading doses of phenobarbital), 20 (54%) were seizure free for 24 hours. Among 6 in the phenobarbital arm (who received two loading doses of levetiracetam), 1 (17%) became seizure free for 24 hours.
- Death within 5 days : 2/64 *vs* 1/42 (RR 1.31, CI: 0.12, 14.02 (RR 4.63, CI: 0.24. 87.43))
- Death beyond five days and any time during the neonatal period: 3/64 vs 0/42
- Serious adverse events (SAE): Not shown separately
- Grade 4 or 5 SAE or AE: 4/64 *vs* 5/42 (RR 0.53, CI: 0.15, 1.84)
- Hypotension: 3/64 *vs* 7/42 (RR 0.28, CI: 0.08, 1.03)
- Abnormal heart rate: 3/64 *vs* 1/42 (RR 1.97, CI: 0.22, 18.30)
- Abnormal respiration: 8/64 *vs* 11/42 (RR 0.48, CI: 0.21, 1.09)
- Sedation: 7/64 *vs* 8/42 (RR 0.57, CI: 0.23, 1.47)
- Inability to feed: 6/64 *vs* 7/42 (RR 0.56, CI: 0.20, 1.56)
- Infection: 2/64 *vs* 3/42 (RR 0.44, CI: 0.08, 2.51)
- Oxygen supplementation: 38/64 vs 24/42 (RR 1.04, CI: 0.75, 1.45)
- Ventilation: 24/64 *vs* 19/42 (RR 0.83, CI: 0.52, 1.31)
- Vasopressor support: 10/64 *vs* 13/42 (RR 0.50, CI 0.24, 1.04)
- Discontinuation from the study: Data not shown
- Complete blood cell count at 48 hours: Data not shown
- Panel of metabolic parameters at 48 hours: Data not shown

Post hoc analysis of primary outcome

- Efficacy defined by assessment of neurologist at the bedside: 23/64 *vs* 35/42 (RR 0.43, CI: 0.30, 0.61)
- Best-worst scenario (*i.e* among those with missing data, those in intervention group were assumed to have seizure control and those in the comparison arm were assumed to have no seizure control): 26/64 *vs* 33/42 (RR 0.52, CI: 0.37, 0.72).
- Worst-best scenario (*i.e* among those with missing data, those in intervention group were assumed to have no seizure control and those in the comparison arm were assumed to have seizure control): 18/64 *vs* 36/42 (RR 0.33, CI: 0.22, 0.50)

standard for reading EEG. However, it is important to note that there were differences in interpretation by the paired experts in 22 cases, necessitating arbitration by a third expert. This raises a concern about the validity of the elaborate arrangements for defining and recording seizures. It is also unclear whether the 22 cases pertain to 22 enrolled neonates, or 22 episodes (among an unknown number of neonates).

The investigators chose the dose of levetiracetam on the basis of pharmacokinetic profile of the drug in the target age group. The dose was chosen so that levels higher than the maximum trough concentration could be achieved.

A total of 23 (of 106 randomized) neonates *i.e.* 22% were excluded from the analysis of the primary outcome. Thus, the intended sample size was not achieved, compromising power. A total of 11/64 (17%) were excluded in the levetiracetam arm, and 12/42 (29%) in the phenobarbital arm. These exclusions were because 8 and 3 neonates respectively did not have the data for the primary outcome. These were handled statistically using methods to impute data. Neurophysiologist cEEG review did not confirm seizures at the start of treatment in 3 and 9 neonates respectively. In a sense, excluding these 12 infants is justified because the distribution between the groups was uneven (5% *vs* 21%). Inclusion of a greater proportion of neonates without seizures at the start of treatment, into the phenobarbital arm would have falsely improved the efficacy and safety profile of the drug. On the other hand, it raises the concern that the sophisticated methods used in this study (to detect seizures), labelled it incorrectly in 12/106 (11%) of the randomized neonates.

The original plan was to measure seizure control at 48 hours as the primary outcome; however, this had to be revised to 24 hours because cEEG recordings were discontinued before 48 hours in many neonates (for various reasons). However, the change in primary outcome was duly approved by the United States Food and Drug Administration (US FDA). The investigators acknowledged that some clinically relevant and patient-centric outcomes, notably neuro-developmental outcome (short-term and long-term) were not measured in this study.

Conclusion: This RCT (1) showed that levetiracetam first-line therapy was inferior to phenobarbital for seizure control. There was no statistically significant difference in the safety profile either. A second loading dose of the original medication resulted in a modest beneficial effect in both arms. In children who were not seizure free despite two loading doses of levetiracetam, more than half became seizure free with two additional loading doses of phenobarbital.

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Pediatric Neurologist's Viewpoint

Neonatal seizures are altogether different from pediatric seizures. The risk for neonatal seizures is highest in the first week of life and especially in the first 48 hours of life. The immature neonatal brain has the highest propensity for seizure development because of excessive neuronal excitation and less inhibition. Neonatal seizures are subtle and have electroclinical dissociation, making them difficult to recognize and intervene. While managing neonatal seizure, not only short-term seizure control is desirable, but also protection of long term cognitive outcome is of paramount importance. Several of the anti-epileptic drugs (AEDs) in neonates are known to cause neuronal apoptosis and brain atrophy.

Levetiracetam is an efficacious AED with a favorable safety profile in pediatric status epilepticus [1]. It has been increasingly used to treat neonatal seizures with variable efficacy, despite limited safety and efficacy data [2,3]. Thus, this study [4] on efficacy and safety of levetiracetam in comparison to phenobarbitone for management of neonatal seizures is a welcome addition to the literature on the topic. It has several strengths such as use of continuous video electroencephalography (VEEG) monitoring for seizure identification and cessation, verification of VEEG findings by neurophysiologist, documentation of baseline seizure severity in both the arms (mean 11 min electrographic seizures/h), and levetiracetam drug level monitoring and maintenance of trough levels >20µg/mL for 3 days.

The primary efficacy endpoint of this study was seizure freedom for first 24 hours following the therapeutic intervention, 28% neonates in the levetiracetam group and 80% neonates in the phenobarbitone group remained seizure-free for 24 hours. Response to levetiracetam was not sustained, only 17% neonates remained seizure-free for 48 hours, while 64% neonate remained seizure-free for 48 hours in pheno-barbitone group. Among 53 neonates in the

levetiracetam group, 69% required phenobarbitone for seizure control. Secondary efficacy of phenobarbitone was 54%, while only 12% neonates who did not respond to 40 mg/kg phenobarbitone responded to 60 mg/kg levetiracetam.

The other important observation in this study was the effect of delay in achieving seizure cessation. It is well known that delay in achieving seizure cessation increases neuronal damage, and seizures become less responsive to subsequent AEDs. Hence it is vital to have quick seizure cessation. It was observed in this study that 30% neonates in the levetiracetam group remained unresponsive to all study drugs in comparison to 16% in the phenobarbitone group. It suggests that delayed seizure cessation reduces the likelihood of response to subsequent AEDs.

The primary etiology for neonatal seizures in this study were hypoxic ischemic encephalopathy (HIE), intraventricular haemorrhage and infracts. Neonatal seizures in HIE persist for a longer duration, hence sustained remission is desirable to prevent late recurrences. In this regard also pheno-barbitone worked better with sustained seizure remission in 64% neonates.

Authors have used 40mg/kg followed by additional 20mg/kg levetiracetam if no response. Among 53 neonates, 28% responded to 40 mg/kg, and 7.5% more neonates responded to 60mg/kg dose levetiracetam. It suggests that neonates may benefit from a higher dosage of levetiracetam. The authors should have reported whether trough levels of >20 μg/mL was achieved with 60 mg/kg levetiracetam.

Seizures are often subtle and difficult to recognize in neonates, and many of these neonates are sick requiring sedation and neuromuscular paralysis. Bedside seizure evaluation and seizure cessation assessment remain difficult. Though VEEG monitoring is the ideal method for neonatal seizure monitoring, however, it reduces the generalizability of the study. In the post hoc analysis of the study, neurologist at the bedside could determine seizure termination in 83% neonates in phenobarbitone group and 36% in the levetiracetam group suggesting marked electroclinical dissociation in the levetiracetam arm.

Gowda, *et al.* [2] from India in a randomized controlled trial reported 83% cases of neonatal seizures responded to levetiracetam and 62% responded to phenobarbitone. This dramatic difference in response rate to levetiracetam (83% *vs* 28%) in these two studies could be related to the differences in the methodology. Continuous VEEG monitoring allowed better seizure quantification, and electrographic seizures might persist even after clinical cessation. Neonates in the levetiracetam arm were sicker (cord PH 7.07, APGAR score 0-10) and had higher pre-treatment seizures frequency [4]. It might be possible that acute symptomatic seizures in the neonates due to HIE, infract, hemorrhage are less responsive to levetiracetam.

Thus, this study provides class 1 evidence for first-line AED for treatment of neonatal seizures. Phenobarbitone has superior efficacy for seizure control in comparison to levetiracetam. Further studies with a higher dosage of levetiracetam with drug level monitoring are required for neonatal seizure. Till then, phenobarbitone remains the gold standard for neonatal seizure.

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Neonatologist's Viewpoint

Immature brain is hyper-excitable, and it is no surprise that seizures are more common in neonates than in other age groups. Unlike older children and adults, there is a limited choice to treat seizures in this age group, as newer antiepileptic drugs have not been adequately tested on this unique population. Although phenobarbital is used as first line agent in neonatal seizures, it is effective in fewer than half of the neonates [1], and there are concerns of its short- and long-term toxicity, particularly on developing brain [2,3]. Despite these shortcomings, phenobarbital is still in vogue due to its availability in parenteral and oral formulations and lack of better alternative anticonvulsants to treat neonatal seizures.

In recent years, levetiracetam has emerged as an alternative to phenobarbital to treat neonatal seizures due to its reported effectiveness in retrospective studies [4] and favorable safety profile [5]. However, there is no high-quality evidence to support its use in neonates. The study under review [6], a phase IIb randomized controlled trial compared levetiracetam with phenobarbital for neonatal seizures. Authors used continuous electroencephalographic (cEEG) monitoring rather than clinical impression to assess primary outcome – cessation of seizures for 24 hours after medication use. cEEG monitoring, the gold standard for detecting seizures, is an important tool to avoid both under- and over-diagnosis of neonatal seizures. The study found that phenobarbital was more effective but also more toxic than levetiracetam for the treatment of neonatal seizures. This well designed randomized controlled trial has established the superiority of phenobarbital over levetiracetam in terminating neonatal seizures acutely. Although levetiracetam appeared safe, the study was not powered to compare adverse events. There is no information on neurodevelopmental outcomes, a major limitation of this study.

This study presents a difficult choice to the treating physician and parents: to use more effective but toxic drug versus less effective but safer drug for controlling neonatal seizures. Only long-term neurodevelopmental outcome of study cohort can settle this issue. The primary efficacy of phenobarbital was better (80%) than secondary efficacy (54%), suggesting that early use of phenobarbital is better in controlling seizures. The requirement of cEEG monitoring and trained neurophysiologists to interpret the records is a challenging task for most neonatal units in India. In the absence of these facilities we continue relying on our imperfect clinical acumen to diagnose and treat neonatal seizures.

In the light of present study, phenobarbital has re-established itself as a first line anti-seizure medication in newborns, notwithstanding its adverse safety profile. However, the story of levetiracetam is not yet over. High dose levetiracetam has been found to be effective in children with intractable epilepsy when standard dosages have failed [7]. Studies are needed to confirm the efficacy and safety of this approach in neonates. Further, the search continues for a better and a safer alternative anticonvulsant available in parenteral and oral formulations to control neonatal seizures.

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