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ORIGINAL ARTICLE

Comparison of Efficacy and Safety of Injectable Levetiracetam and Phenytoin in the Management of Neonatal Seizures

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ABSTRACT

Objective: To compare the efficacy and safety between intravenous levetiracetam and phenytoin in the control of neonatal seizures.

Methodology: The current pediatric study was a randomized controlled, open-label and parallel-group designed study. This study was carried out in the Department of Pediatric Medicine (Neonatal Emergency) at The Children Hospital and Institute of Child Health at Multan duration Study was January to October 2023. One hundred and thirty infants with persistent seizures were randomly divided into two cohorts where each numbered 65. Patients that received levetiracetam were assigned to group A and those that received phenytoin were assigned to group B. The outcome of the patients was monitored in terms of the adverse reaction and time elapsed to resolve the seizures. Efficacy and safety of levetiracetam versus phenytoin were used as primary outcomes to measure.

Results: The properties of levetiracetam, namely its safety and efficacy profile proved to be superior to that of phenytoin. There were no reports of respiratory and cardiac depression in neonates treated with Levetiracetam, and on the other hand phenytoin had been associated with depression on respiration (6.15%), and cardiac (1.53 %). Fewer cases of hypotension were witnessed in the Levetiracetam group. Moreover, Levetiracetam proved to be linked with faster cessation of seizures within 30 minutes (95.38 % vs. 90.77 %) and higher efficacy (95.38 % vs. 90.77 %, p=0.0128). The safety drug was also better in the Levetiracetam group (96.92 % vs. 87.69 %, p=0.022).

Conclusion: The results of this study justify the claim that lacosamide (LEV) is safer and more effective than phenytoin in treating neonatal seizures among the preterm infants.

Keywords: Levetiracetam, Phenytoin, Neonatal Seizures, Safety, Children, Health.

INTRODUCTION

Definition Neonatal seizures include paroxysmal neurological changes that may be of a motor, behavioral or autonomic nature. They pose serious problems for the population-health, especially in poor countries since they are related to a great deal of neonatal morbidity and death[1]. Neonatal seizures occur between 1-5 per 1000 live births in high-income countries. On the contrary, it is worse to note it in the low-income nations: research carried out in Kenya pegged at 39.5 per 1000 live births, a figure that is far much higher than is reported in affluent nations[2]. It is considered that worldwide neonatal seizures cost approximately 1.6 million neonatal deaths, yearly, of which 99 percent deaths are seen in developing nations[3]. South Asia alone contributed 38.9% of the death rate associated with neonatal seizure in 2013 alone[4]. Observational studies also report the 1.7 million cases worldwide every year, and the greatest burden is amongst South Asia and sub-Saharan Africa. This is the case of countries like Bangladesh[5].

In the medical context, neonatal seizures are often the first form of clinical-neurological dysfunction, and they are highly resented by cognitive impairments in adulthood. Neonatal seizures have other etiological and phenomenological characteristics than the seizures occurring in older children and adults[6]. The most frequent cause of the seizures that occur as a direct result of childbirth belongs to hypoxic-ischemic encephalopathy (HIE) followed by an A, of sepsis, B, prematurity, C, infectious processes, and D, metabolic disturbances. In case effective diagnosis followed by treatment of the seizures are not employed, the seizures may extend longer, and the outcomes related to this may include epilepsy, cerebral palsy, and mental retardation.

Neonates weighing less than 1500g face a significantly and considerably higher chance of having seizures; the recorded ratio of one in every 1.7 assessed to have seizures is in juxtaposition with the per cent of 1 in 1000 in neonates that weigh between 2500 and 3999 g [7, 8]. There is a high level of preterm infants who are especially susceptible and the incidence rate of seizures among these newborns is about twice as much as in term babies and four times in very low birth weight children [9]. Mismanagement of the seizure still constitutes one of the core causes of adverse outcomes. Furthermore, as shown in the National Neonatal Perinatal Database (NNPD 200203), there are 10.3 complications of neonatal seizures per 1000 live births in India, with mortality having decreased to 20 percent but the short-term neurodevelopmental complications standing at 30% only [10].

In the past phenobarbitone and phenytoin were the standard of care in the treatment of neonatal seizures, but it is limited due to lack of efficacy. This study is comparing the efficacy and safety of injectable levetiracetam and phenytoin toward improving treatment of neonatal seizures.

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METHODOLOGY

The study was carried out in the neo emergency room of the children's hospital and the institute of child health Multan. It involved a randomized controlled design, and the duration Study was January to October 2023. Non-probability purposive sampling technique was employed to enroll a total number of 130 neonates (65 in each group). The inclusion criteria were 1-month-old babies with seizures that were treated at the Neonatal Emergency Room, with a notepad, of both sexes, no matter of gestational age or weight. Infants who were already given anti-seizure drugs other than benzodiazepine, those under assisted breathing, and whose seizures were triggered by correctable metabolic condition (including hypoglycemia, hypocalcemia and hyponatremia) were excluded. All neonates that presented with seizures in the Neonatal Emergency Room with the period of the study and met the inclusion criteria were recruited. The symptoms of emergency treatment required two doses of diazepam 0.3 mg/kg after informed consent was collected. If subjects were not cured during the first treatment period, they were assigned group A and group B randomly in the ratio of 1:1. The name of the antiepileptic drug assigned in the envelope was opened and indicated three potential treatments; Levetiracetam to those in group A and phenytoin to the group B patients. Levetiracetam or phenytoin was then applied. Sealed envelopes were used to do random allocation.

Group A involved the use of neonates who were all given intravenous levetiracetam at a concentration of 30 mg/ kg, and

group B had neonates who received phenytoin intravenously in loading doses of 20 mg/Kg, diluted in normal saline over a phase of 30 minutes. The two groups were followed up prospectively in terms of any adverse side effect and effectiveness of therapy in terms of time between commencement of therapy to ceasing of the seizures. Supportive care was also given simultaneously according to the existing standards in the hospital and an emergency resuscitation trolley was always available to address any situation of breathing crisis, low blood pressure, and possible cardiac arrhythmia. Each patient was observed to have potential adverse effects of both agents, hypotension, respiratory depression, CNS depression, and cardiac depression. Efficacy and safety have been the main outcome variables with all the drugs being considered problematic in case any of the adverse effects emerged. The information was recorded prospectively, on a predesigned proforma and divided according to age of neonate in days, gestational age, and etiology of seizure. The efficacy was determined using the percentages of treated neonates in whom the seizures were terminated in less than one hour after drug administration. All the data were saved in written proforma. After collection of all data, information was entered into SPSS version 20. Percentages and Frequencies were calculated for qualitative variables like gender, age, gestational age, and etiology of seizures and the duration of seizure control. Means and standard deviations of data were applied as descriptive statistics. Efficacy and safety of both drugs was determined by using chi-square test, and P-value is <0.05, which was considered significant statistically.

RESULTS

A total of 130 neonates with seizures were randomized into two equal groups of 65, receiving either Levetiracetam or Phenytoin. There was no difference in mean age of entry into the study (Levetiracetam: 7.03+/-1.97 days; Phenytoin: 6.98+/-1.43 days). Most of the subjects were between 1 and 7 days old (78.46 percent in the Levetiracetam group and 80 percent in the Phenytoin group). Both groups showed a male bias (72.31 % in the Levetiracetam and 64.62 % in the Phenytoin group). In terms of gestational age, 32.13 % neonates in the cohort of Levetiracetam and 27.69 % of the neonates in the cohort of Phenytoin were preterm and the others are the term babies. The most common causes of seizures in both groups were hypoxic-ischemic encephalopathy (HIE) (61.54 % in the Levetiracetam group and 55.38 % in the Phenytoin group) and haemorrhage/infarction, as well as CNS infections.

Table 1: Demographics and Clinical Characteristics

Characteristic	Levetiracetam (n=65)	Phenytoin (n=65)
Mean Age (days)	7.03 ± 1.97	6.98 ± 1.43
Age 1–7 days	51 (78.46%)	52 (80%)
Age 8–28 days	14 (21.54%)	13 (20%)
Male	47 (72.31%)	42 (64.62%)
Female	18 (27.69%)	23 (35.38%)
Term Neonates	44 (67.69%)	47 (72.31%)
Preterm Neonates	21 (32.13%)	18 (27.69%)

Table 2: Etiology and Adverse Effects

Parameter	Levetiracetam (n=65)	Phenytoin (n=65)
HIE	40 (61.54%)	36 (55.38%)
Hemorrhage/Infarction	13 (20%)	15 (23.01%)
CNS Infection	09 (13.85%)	11 (16.91%)
Brain Malformation	03 (4.61%)	03 (4.61%)
Respiratory Depression	0 (0%)	04 (6.15%)
Cardiac Depression	0 (0%)	01 (1.53%)
Hypotension	02 (3.08%)	03 (4.61%)

Table 3: Efficacy and Safety Outcomes

Outcome	Levetiracetam (n=65)	Phenytoin (n=65)
Seizure Cessation ≤30 min	62 (95.38%)	59 (90.77%)
Efficacy (Seizure controlled)	62 (95.38%)	59 (90.77%)
Safe (No serious side effects)	63 (96.92%)	57 (87.69%)

There is increased safety and efficacy suggestively shown by levetiracetam when compared with phenytoin. No clinical respiratory or cardiac depression was reported in neonates treated with levetiracetam, but phenytoin led to respiratory depression (6.15 %) and cardiac depression (1.53 %). Incidences of hypotension were also reduced in relation to levetiracetam administration. Resolution of seizure within less than 30 minutes was present in more of the neonates treated with levetiracetam (95.38 % vs. 90.77 %) and was much higher (95.38 % vs. 90.77 %, p = 0.0128). Safety results also cast their vote to levetiracetam (96.92 % vs. 87.69 %, p = 0.022). These results have shown that levetiracetam is therefore successful and safer in treating neonatal seizures.

DISCUSSION

Neonatal seizures are the most common neurological emergency in neonatal intensive care units, and their outcomes depend on frequency, intensity, and underlying etiology. Differentiating epileptic from non-epileptic events remains challenging. Animal and human studies have shown that neonatal seizures adversely affect cognition and learning abilities[11]. While phenobarbital remains the most commonly used first-line antiepileptic, evidence supporting its efficacy is limited. In contrast, levetiracetam has emerged as a promising alternative with better safety and tolerability[12]. In a study by Favrais et al.,[12] levetiracetam improved tone and posture in term neonates, with significant improvement in Hammersmith Neonatal Neurological Examination (HNNE) scores, unlike phenobarbitone. In a comparative trial, levetiracetam (20 mg/kg) and phenobarbitone (10 mg/kg) were used in neonates with uncontrolled seizures. Cessation of seizures occurred in 86% (43/50) of the levetiracetam group compared to 62% (31/50) in the phenobarbitone group[13]. Adverse effects like hypotension, respiratory depression, and ventilator requirement were reported in 10 neonates treated with phenobarbitone, whereas no side effects were observed in the levetiracetam group.

The commonest neurological emergency in the neonatal intensive care units is the seizure in the neonate. The prognosis of these is greatly affected by the number of seizures, their severity, and the cause of these. Diagnosis of epileptic and non-epileptic seizures is however problematic. Empirical data have shown that neonatal seizures lead to negative subsequent development of cognition and learning[11]. Though phenobarbital has hitherto been considered as the gold criterion first-line antiepileptic agent, evidence to support its effectiveness is scarce. By comparison, levetiracetam has proven to be an optimistic alternative and seems to provide better security and tolerability[12]. Favrais et al. found that levetiracetam had correspondingly elevated the tone and posture of term neonates, showing a meaningful increase in Hammersmith Neonatal Neurological Examination (HNNE) scores, but phenobarbitone did not [12]. A comparative trial was done where 20 mg/kg levetiracetam and 10mg/kg phenobarbitone were put into neonates who had volatile seizures. The seizures stopped totally in 86 % (43/50) of those in the levetiracetam group compared with 62 % (31/50) in the phenobarbitone group[13] and some adverse events such as hypotension, respiratory depression, and need to go to a ventilator were observed in ten phenobarbitone-treated babies but none was observed in the levetiracetam group.

Levetiracetam's efficacy and safety profile has also been supported by studies in animal models, suggesting it does not trigger neuronal apoptosis, unlike conventional drugs[14]. However, a UK trial found that 80% of neonates treated with phenobarbitone remained seizure-free for 24 hours, while only 28% achieved this with levetiracetam. Yet, a dose escalation of levetiracetam from 40 to 60 mg/kg improved efficacy without notable adverse effects (Sharpe et al., 2020). Levetiracetam is approved by the FDA for intravenous use when oral administration is not feasible[14]. Compared to phenytoin, levetiracetam had fewer side effects. One study showed only 2 out of 65 neonates treated with levetiracetam experienced side effects, versus 8 in the phenytoin group, which included respiratory and cardiac depression[15,16]. Phenytoin's

known adverse effects, including hypotension and arrhythmias, limit its utility[17]. In contrast, levetiracetam does not interact significantly with other drugs due to minimal hepatic metabolism and protein binding, reducing the risk of toxicity[14, 18].

Efficacy and safety of levetiracetam have been demonstrated by both clinical and pre-clinical findings. Levetiracetam was found in animal models not to cause apoptosis of neurons, an activity observed with several of the older antiepileptic drugs and therefore implied an improved neuroprotective profile [14]. However, a recent prospective single-center study in UK indicated that 80 % of neonates, who administered phenobarbitone became 24 h seizure-free compared to 28 % of those who received levetiracetam. Notably, dose escalation of levetiracetam (to 60 mg/kg) from 40 mg/kg was highly effective and did not lead to the development of adverse effects (Sharpe et al., 2020). Moreover, levetiracetam is FDA-approved in intravenous administration if the mouth treatment is not possible [15]. Levetiracetam has fewer side effects compared with phenytoin. An observational study with a retrospective cohort explained that among the 65 neonates who were treated with levetiracetam, 2 people showed adverse effects and in 38 others where phenytoin was used, 8 people showed unwanted effects, including cardiac and respiratory depression [16]. The known complications of the latter drug, hypotension, and arrhythmias, also restrict the usefulness of this drug in this patient group[17]. Additionally, levetiracetam has a low level of hepatic metabolism and protein binding, which results in reduced chances of experiencing a pharmacodynamic interaction-driven toxicity [14, 18].

According to Han et al. (2018)[19], the administration of levetiracetam as first line therapy of anticonvulsants showed a 57 % control of seizures in preterm babies without the need of using a second line anticonvulsant and no adverse effects were noted. Seizure control was better (86 %) in position levetiracetam compared to phenobarbitone (62 %) in another Indian case-control study[13] involving 100 neonates, thus highlighting the safety aspect of the agent. Sharpe et al. (2020)[14] also noted that phenobarbitone was linked to greater adverse events regardless of its superiority in the first 24 hours of antiepileptic treatment. Thanks to its pharmacokinetics, satisfactory safety strengths, and low side-effect load, there is a tendency to accept levetiracetam as an appropriate first-line treatment of neonatal seizures.

CONCLUSION

This study demonstrates that in the management of neonatal seizures LEV is more effective and well-tolerated by neonates than phenytoin.

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