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ORIGINAL ARTICLE

Effect of levetiracetam on cerebral oxygenation in neonates

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ABSTRACT

Objective: To assess the effect of levetiracetam on cerebral oxygenation in the newborn period, whether it was used as first-line or add-on treatment for neonatal seizures.

Material and Methods: A prospective, cross-sectional study was performed. Neonates who were treated with levetiracetam because seizures were suspected clinically were included in the study. The included neonates were clinically stable and preparing for discharge during the study period. Baseline regional cerebral oxygenation (rSO_2-C) and cerebral fractional oxygen extraction (FTOE) were recorded one hour before levetiracetam administration; three additional measurements of rSO_2-C and FTOE were recorded during levetiracetam administration, and one and two hours after administration.

Results: Eighty-one doses of levetiracetam were administered to 22 neonates, and nine (40.9%) of the neonates were receiving phenobarbital together with levetiracetam. The median gestational age and birth weight of the neonates were 37.5 (25–41) weeks and 2755 (720–3740) g, respectively. The levetiracetam dose ranged from 10 mg/kg to 60 mg/kg, with a median value of 20 mg/kg. There were no significant changes in the measurements of rSO_2-C and FTOE associated with levetiracetam doses.

Conclusion: The impact of levetiracetam on NIRS findings suggests that levetiracetam is safe in the neonatal period in terms of cerebral oxygen metabolism.

Keywords: Cerebral oxygenation, levetiracetam, near infrared spectroscopy, neonatal seizures.

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INTRODUCTION

Seizures are more common in the newborn period compared to any other time of life, with an incidence of approximately 1 to 3.5 per 1,000 live births.[1,2] Early detection and treatment of seizures and their underlying causes in newborns are essential to have better neurodevelopmental outcomes in this vulnerable group.[2–5] Although neonatal seizures have potentially devastating consequences, there is still important controversy about the degree of seizure control which is required to optimize outcomes among survivors and there are still many clinical questions about the necessity for treatment, the kind of treatment and the length of treatment.[2]

Phenobarbital (PB) is still the most frequently used drug for the first-line treatment of seizures in newborns.[2,6] But PB usage is decreasing because of concerns about little proof of efficacy for seizure control and possible neurodevelopmental side effects.[7,8] Such concerns about PB force clinicians to search for new antiseizure medications (ASMs). Levetiracetam (LEV) is now increasingly used off-label as a second-line therapy for seizures in newborns without Food and Drug Administration approval.[6,9] There are many studies that assess the effects of LEV in the neonatal period, and the results of these studies are both conflicting and promising that this drug is safe and at least as efficient as PB in seizure control even among premature infants with lower incidence of side effects compared to PB.[10–18] In studies that compared the long- and short-term neurodevelopmental outcomes of LEV with PB, it was found that LEV was associated with better outcomes compared to PB.[11–13]

Video-electroencephalography (EEG) is the gold standard for detection and quantification of seizures in newborns, and when video-EEG monitoring is not possible, serial routine-length EEGs or continuous amplitude-integrated electroencephalography (aEEG) may be utilized as adjunct diagnostic instruments.[19] Recently, additional cerebral monitoring, near infrared spectroscopy (NIRS), provides continuous, noninvasive surveillance of tissue oxygenation in newborns. Cerebral oxygenation monitoring allows for a continuous dynamic evaluation of autoregulation at the bedside and provides the opportunity to commence adequate actions to preserve adequate cerebral blood flow.[20,21] The change in cerebral oxygenation after PB administration was investigated with NIRS in newborns, and it was shown that cerebral oxygenation deteriorated after a PB loading dose.[22] As a result of all these conditions, LEV, which is the first-line candidate drug instead of PB, came to the fore in seizure control, and it was considered necessary to investigate whether LEV administration had a similar unfavorable impact on cerebral oxygenation. In the light of the current literature, we intended to assess the effect of LEV on cerebral oxygenation in the neonatal period, whether it was used as first-line or add-on treatment for seizures in the neonatal period.

MATERIAL AND METHODS

A prospective, cross-sectional study was performed in a tertiary level NICU at the University of Health Sciences in a Maternity and Children's Training and Research Hospital.

Ethics and Consent

Approval for the study was obtained from the institutional review board and the study was conducted according to the institution's ethical guidelines (date: 24.06.2020, number: 130). The study was completed in accordance with the Declaration of Helsinki as revised in 2013. Patients were enrolled in the study from June to December 2020. Detailed information about the study was given to the parents who allowed their babies to participate, and informed consent forms were obtained.

Study Design and Interventions

The neonates who were given LEV either as first-line or add-on treatment due to seizure activity on aEEG were included in the study. Neonates were enrolled when they reached at least postmenstrual 36th week and became clinically stable enough for discharge. Therefore, none of the neonates included in the study needed ventilation support or inotrop treatment, had clinical seizures, or anemia requiring erythrocyte transfusion; all neonates could tolerate full enteral feeding and had normal renal and liver function tests during the study period. Neonates who required another ASM besides LEV and PB for seizure control, or who had major congenital anomalies, were excluded.

Seizures in the neonatal period were clinically described as abnormal, stereotyped, and paroxysmal dysfunctions in the central nervous system, arising in the first 28 days after birth in full-term infants or before 44 weeks of gestational age in preterm infants.[14,15] All clinical seizures were confirmed by aEEG. Phenobarbital was used as first-line treatment for neonatal seizures in our NICU for stable and fully enterally fed patients.[19] Levetiracetam was used as the first choice only in cases where oral drug intake was contraindicated for any reason, such as necrotizing enterocolitis and septic ileus. Subjects suspected to have seizure and who could tolerate oral medication received treatment with PB at a dose of 20 mg/kg, with 15 minutes allowed for the drug to take effect. If clinical seizures continued or reappeared 15 minutes after the first dose, a further 10 mg/kg dose of PB was given. We did not always have intravenous (IV) form of PB available in our unit and could only obtain it via a drug report for the neonate who would use it. Therefore, subjects suspected to have seizure and who could not tolerate oral medication received treatment with LEV infusion over 15 minutes at a dose of 20 mg/kg as the first-line ASM, with 15 minutes allowed for the drug to take effect. If clinical seizures continued or reappeared 15 minutes after the first infusion was completed, a further 20 mg/kg dose of LEV was given. If clinical seizures continued or reappeared after a further 15 minutes, the last 20 mg/kg dose of LEV was given. If clinical seizures continued or reappeared 15 minutes after the total dose of 30 mg/kg PB and/or 60 mg/kg LEV was completed, the neonate was then treated with an alternate ASM.[19] If the first-line ASM was PB and failed to stop seizures, we used LEV as an add-on treatment for seizure control, and the LEV dosages were administered as mentioned above.

Patients who used any PB loading dose were given maintenance PB (5 mg/kg/day, orally once a day). Patients were given maintenance LEV doses at the same doses at which it was started and given by IV route once a day. As soon as the patients could

tolerate oral medication, we switched the IV route of LEV to oral form at the same doses. The availability of both oral and IV formulations of LEV rendered the drug very functional as an off-label ASM in the treatment of neonatal seizures in our unit.

If we used LEV as an add-on treatment, we left at least a 6-hour time interval between the LEV and PB maintenance dosages, as the time to peak serum concentration after oral administration of those ASMs are; 1.4±0.9 hours for LEV among fasting infants and children aged <4 years (neonatal data was not available), and 1.5 to 6 hours for PB among newborns.[23,24] We intended to assess the effects of LEV on cerebral oxygenation without mixing with the effect of PB on cerebral oxygenation.

Near Infrared Spectroscopy Measurements

The regional cerebral oxygenation (rSO_2-C) was estimated using NIRS (INVOS 5100; Covidien Somanetics, Troy, MI). The NIRS probes were applied to the skin on the forehead to measure rSO_2-C when the neonates met the inclusion criteria for this study. We began to record the data 60 minutes before the ASM administration and proceeded with recording at least two hours after the ASMs. The NIRS data were kept for off-line analyses. Simultaneously measured venous oxygen saturation (SPO_2) via pulse oximetry was utilized to quantify the cerebral fractional oxygen extraction (c-FTOE), which is the percentage of the delivered oxygen utilized by the tissue ($FTOE=[SPO_2–rSO_2\text{-}C]/SPO_2$).[25] The baseline rSO_2-C and c-FTOE were recorded one hour before levetiracetam, and the other three measurements of rSO_2-C and calculations of c-FTOE were recorded during, one, and two hours after levetiracetam administration. The NIRS recordings were continued whole days during the study period in order to assess the day-long effects of LEV on rSO_2-C and c-FTOE. At the time of inclusion in the study, all patients were receiving LEV treatment orally.

Data Collection

Comprehensive medical history was recorded including the etiologies and types of seizures, weight and hemoglobin values of the babies during enrollment in the study, and dose of LEV. The prospective data was collected by qualified research assistants and transferred electronically to the network for confirmation and examination.

Statistical Analyses

Descriptive statistics were given as median with minimum–maximum values for continuous variables dependent upon the distribution. Numbers and percentages were used for categorical variables. The normality of the numerical variables was checked by the Kolmogorov–Smirnov, Shapiro–Wilk, and Anderson–Darling tests. The Friedman test was used to examine the changes of numerical variables (SPO_2, peak heart rate, rSO_2-C, and c-FTOE) over different study intervals (pretreatment, during treatment, post-treatment-1 hr, and post-treatment-2 hr). For statistical analyses, Jamovi project (2020), Jamovi (Version 1.6.16.0) (Computer Software) (Retrieved from https://www.jamovi.org) and JASP (Version 0.14.1.0) (Retrieved from https://jasp-stats.org) were used. A p value of <0.05 was considered significant in all statistical analyses.

Table 1: Clinical characteristics of newborns with neonatal seizures (n=22)

Etiologies of neonatal seizures, n (%)	
Hypoxic-ischemic encephalopathy	6 (27.2)
Intracranial bleeding	6 (27.2)
Fetal anemia	1 (4.5)
Sepsis	2 (9)
Unknown	7 (31.8)
Type of seizure, n (%)	
Subtle	9 (40.9)
Myoclonic	7 (31.8)
Focal clonic	5 (22.7)
Apneic	1 (4.5)
Weight during study (gr), median (min–max)	3066.5 (2015–4000)
Dose of levetiracetam (mg/ kg), median (min–max)	20 (10–60)
Levetiracetam dose per patient recorded for the study, n (%)	
3 doses	7 (31.8)
4 doses	15 (68.2)
Hemoglobin during study (g/dl), median (min–max)	11.2 (8.4–19.5)

Min: Minimum; Max: Maximum.

RESULTS

There were 81 doses of LEV administered to 22 neonates during the study period. Nine (40.9%) of the neonates were receiving 5 mg/kg/day PB treatment together with LEV, and 34 doses of PB were given to those neonates throughout the study period. The median gestational age and birth weight of the neonates were 37.5 (25–41) weeks and 2755 (720–3740) g, respectively. Eight (36.4%) of the cases were girls and 14 (63.6%) were male. The features regarding etiological factors and the type of neonatal seizure, and other clinical variables are summarized in Table 1.

The changes in SPO_2, peak heart rate, rSO_2-C, and c-FTOE during LEV treatment are given in Table 2. There were no significant changes in the measurements of SPO_2, peak heart rate, rSO_2-C, and calculations of c-FTOE associated with LEV doses, even if LEV was used as first-line (n=46 doses of LEV) or add-on treatment (n=35 doses of LEV) (Table 2). The changes during PB treatment in SPO_2, peak heart rate, rSO_2-C, and c-FTOE were also analysed and are given in Table 3. There were also no significant changes in the measurements of SPO_2, peak heart rate, rSO_2-C, and calculations of c-FTOE depending on the course of PB treatment.

Table 2: Changes in clinical and cerebral oxygenation parameters depending on the timing of levetiracetam treatment

	Pre–treatment Median (min–max)	During treatment Median (min–max)	Post–treatment– 1 hr Median (min–max)	Post–treatment–2 hr Median (min–max)	p†
Levetiracetam treatment in all group (patient n=22, dose n=81)					
SPO_2 (%)	97.75 (94–99)	97.38 (94–99)	97.5 (94–99)	98 (94–99.67)	0.073
Peak heart rate (pulse/min)	135 (110–145)	135 (110–145)	135 (110–145)	135 (110–145)	0.145
rSO_2–C (%)	65.67 (55.5–86.67)	66 (54.75–87.67)	66.375 (55.5–86.33)	67.125 (55.75–87.25)	0.195
FTOE	0.32 (0.11–0.43)	0.32 (0.1–0.44)	0.32 (0.12–0.42)	0.3 (0.09–0.43)	0.418
Levetiracetam as add on treatment (patient n=9, dose n= 35)					
SPO_2 (%)	97.48 (94–99)	97.5 (94–99)	97.32 (94–99)	97.6 (94–99.52)	0.072
Peak heart rate (pulse/min)	135 (115–145)	135 (115–145)	135 (115–145)	135 (110–145)	0.14
rSO_2–C (%)	65.52 (55.52–85.41)	65.6 (54.93–88.52)	66.47 (55.7–86.65)	67.14 (55.6–87.4)	0.201
FTOE	0.32 (0.1–0.43)	0.32 (0.11–0.42)	0.32 (0.12–0.40)	0.31 (0.1–0.42)	0.407
Levetiracetam as first line treatment (patient n=13, dose n= 46)					
SPO_2 (%)	97.1 (94–99)	97.38 (94–99.3)	97.27 (94–99.2)	97.5 (94–99.4)	0.07
Peak heart rate (pulse/min)	135 (116–145)	135 (116–145)	136 (115–145)	136 (110–145)	0.139
rSO_2–C (%)	65.47 (55.5–85.39)	65.5 (54.87–88.42)	66.47 (55.5–86.5)	66.85 (55.62–87.35)	0.197
FTOE	0.32 (0.11–0.40)	0.32 (0.1–0.39)	0.32 (0.11–0.40)	0.32 (0.1–0.40)	0.402

FTOE: Fractional (cerebral) tissue oxygen extraction; rSO_2–C: Regional cerebral oxygenation; SPO_2: Venous oxygen saturation; †: Friedman Test.

Table 3: Changes in clinical and cerebral oxygenation parameters depending on the timing of phenobarbital treatment (patient n=9, dose n=34)

	Pre–treatment Median (min–max)	During treatment Median (min–max)	Post–treatment– 1 hr Median (min–max)	Post–treatment–2 hr Median (min–max)	p†
SPO_2 (%)*	96 (94–99)	96 (94–99)	96 (94–99)	96 (94–99)	NaN
Peak heart rate (pulse/min)	135 (118–145)	135 (118–145)	135 (118–145)	135 (118–145)	NaN
rSO_2–C (%)	64 (54–85.25)	65.75 (55–83.25)	63.67 (58–81.5)	64.5 (57.5–89)	0.678
FTOE*	0.33 (0.11–0.43)	0.33 (0.13–0.41)	0.33 (0.16–0.39)	0.35 (0.07–0.39)	0.674

FTOE: Fractional (cerebral) tissue oxygen extraction; rSO_2–C: Regional cerebral oxygenation; SPO_2: Venous oxygen saturation; NaN: Not a number; †: Friedman Test.

DISCUSSION

We found that cerebral oxygen metabolism did not change after LEV treatment in neonates. As far as we know, this is the first study to evaluate variations in NIRS-measured cerebral oxygen metabolism linked with LEV dosing for seizures occurring in the neonatal period. In a study, Sokoloff et al.[22] found that the absolute changes in rSO_2-C and c-FTOE associated with PB dosing are small, typical PB loading doses are associated with prolonged decreases in cerebral oxygen extraction, and seizures in the neonatal period may be associated with transient increases in oxygen metabolism. They concluded that it should be specified if the effect of PB on cerebral oxygenation has clinical consequences. Similar to their findings, as an additional result, we did not find any important variations in cerebral oxygen metabolism after PB maintenance dose administration. In our study, the fact that SpO_2, heart rate, rSO_2-C, and cerebral c-FTOE did not change even when LEV was administered at a high dose of 60 mg/kg/dose in clinically stable newborns suggests that LEV is safe in terms of vital signs and brain oxygenation in newborns.

Although there is not enough data to recommend the use of LEV as first-line ASM for seizures in the neonatal period, there are many

studies suggesting that LEV might replace PB in the near future.[10–15, 26–31] In a recent systematic review, it was declared that LEV had promising anti-epileptic characteristics for the control of seizures in the neonatal period with better effectiveness and fewer adverse effects when compared to PB.[26] It was found that LEV had a better effect on short-term neurodevelopmental outcome compared to PB,[12,13] and the long-term effects of LEV persisted throughout the first year follow-up.[27] On the other hand, some studies found LEV less effective than PB and unsuccessful in seizure control in 74% of extremely preterm babies.[17,18] In the NEOLEV2 study, it was shown that PB was more successful compared to LEV in terms of eliminating all seizure activity for 24 hours, but elevated rates of sedation, respiratory suppression, and hypotension were reported with PB in this study.[18] Therefore, it was concluded that a medication less efficient in providing seizure cessation but resulting in more favourable neurodevelopmental outcome through neuroprotective action or lack of neurotoxicity might be the first-line treatment choice.[18]

There are limited data in the literature evaluating cerebral oxygen metabolism during seizures and ASM administration in neonates.[22,32] Near infrared spectroscopy monitoring may have a very significant function in neonatal care, and the assessment of neonatal brain oxygenation can be extremely useful in clinical settings to recognize both seizure activity and termination of seizure by ASM administration.[20] This issue should be highlighted with the support of new studies.

Our study has some limitations. Firstly, we could not make a remark about the influence of LEV blood levels on NIRS results, because we could not monitor LEV blood levels. Secondly, the relationship between cerebral oxygenation and LEV dose was not examined due to the wide dose range and lack of standardization in dosing. Finally, all of the neonates included in our study were clinically stable and were preparing for discharge, and none had clinical seizures during the enrollment period. Therefore, the effect of LEV on cerebral oxygenation during seizures could not be evaluated.

This study had significant strengths. We only analyzed data from one and two hours after medication administration, but we had at least 72 hours lasting NIRS recordings per patient; thus, we were able to comment on the day-long effects of LEV on cerebral rSO_2-C. As we did not find any effects of LEV on rSO_2-C, we did not interpret the whole day NIRS recording. All the neonates who were included in the study were clinically stable during the study period; thus, we thought that cerebrovascular autoregulation was also stable and did not affect the results.

CONCLUSION

Neonatal seizures require immediate medical attention, with quick diagnostic and therapeutic interventions, as the seizure burden increases the possibility of development of epilepsy and disability.[2,3] The impact of LEV on NIRS findings made us think that LEV is safe and does not disturb brain oxygen metabolism, but our data are not sufficient to suggest routine NIRS monitoring for neonates receiving LEV or using LEV as first-line ASM. Further prospective studies are needed to find out the principal therapeutic choice for seizures in the neonatal period, and studies are needed on the long-term neurodevelopmental effects of LEV use in the neonatal period.

Statement

Ethics Committee Approval: The University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Ethics Committee granted approval for this study (date: 24.06.2020, number: 130).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Conflict of Interest: The authors have no conflict of interest to declare.

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