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Efficacy of Levetiracetam as Add-On Therapy in the Treatment of Seizures in Neonates

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Keywords
Amplitude-integrated electroencephalography · Antiseizure medication · Levetiracetam · Lidocaine · Midazolam · Seizures in neonates · Seizure reduction

Abstract

Introduction: There is no consensus regarding the efficacy of add-on therapy with levetiracetam (LEV) in the treatment of seizures in neonates. The aim of this study was to evaluate the efficacy of add-on therapy with LEV for achieving >80% seizure reduction after phenobarbital (PB) treatment. ***Methods:*** Retrospective cohort study of near term neonates admitted to the neonatal intensive care unit with EEG-confirmed seizures despite treatment with PB as first-line therapy and using LEV as 2nd-, 3rd- or 4th-line treatment. Antiseizure medication was administered according to national guidelines. All neonates were monitored with 2-channel amplitude-integrated electroencephalography. The total seizure burden in minutes, 2 h before and 4 h after administration of LEV, was calculated using raw EEG. Primary outcome was the efficacy of LEV in achieving >80% seizure reduction. The efficacy of additional midazolam (MDZ) and lidocaine (LDC) was also calculated. ***Results:*** A total of 47 full-term neonates were included. The mean total loading dose of LEV was 40 mg/kg (36–44 mg/kg). Seizure etiology consisted of hypoxic-ischemic encephalopathy ($n = 11$), hemorrhagic or ischemic stroke ($n = 16$), central nervous system infection ($n = 8$), genetic ($n = 8$), metabolic disorders ($n = 3$), and unknown ($n = 1$). Following LEV administration, >80% seizure reduction was observed in 17% (8/47) of neonates, whereas it was 23% (6/26) after MDZ and 92% (23/25) after LDC administration. ***Discussion:*** Although the cumulative loading dose of LEV was low and the group of infants studied was heterogeneous, the efficacy of LEV as add-on therapy for the treatment of seizures in neonates was limited. The highest seizure reduction rate was seen after LDC administration.

Introduction

Seizures in neonates are the most frequent manifestation of neurological disturbances in the neonatal period with an incidence of 1–5/1,000 newborns [1–5]. Underlying causes include hypoxic-ischemic encephalopathy (HIE), focal cerebral hemorrhage or infarction, metabolic disturbances, genetic disorders, infectious diseases, and cerebral malformations [6, 7]. Seizures in neonates are associated with adverse neurodevelopmental outcomes,

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including epilepsy, cerebral palsy, developmental delay, and psychomotor deficits [8–10]. The gold standard for assessing brain function in a critically ill neonate is continuous video-electroencephalography [11]. However, recording and interpretation require specialized training and staff around the clock which are not universally available. Amplitude-integrated electroencephalography (aEEG) is a widely used tool for diagnosing seizures and assessing brain function in neonates in the neonatal intensive care unit (NICU) [12]. Management with antiseizure medication (ASM) is dependent on the underlying etiology [6]. The International League Against Epilepsy (ILAE) recently published guidelines for the treatment of seizures in neonates, recommending phenobarbital (PB) as the first-line ASM (evidence-based recommendation) regardless of etiology (expert agreement) [6]. For neonates with seizures not responding to first-line ASM, phenytoin, levetiracetam (LEV), midazolam (MDZ), or lidocaine (LDC) may be used as a second-line ASM (expert recommendation). Recently, a phase IIb randomized controlled trial reported that the sequence with first PB instead of LEV was more effective for the treatment of seizures in neonates due to hypoxia-ischemia [1]. If PB has no effect other therapies can be used, including LEV, MDC, LDC, carbamazepine, phenytoin, vigabatrin, pyridoxine-5-phosphate, or pyridoxine [13–15]. Seizure cessation within 24 h after administration of LEV varied in studies from 17 to 82% [1, 16–20]. MDZ has been reported to be effective in achieving >80% seizure reduction in, respectively, 32% and 57.5% of neonates as second- and third-line treatment [21]. LDC appears to be an effective drug for second- and third-line treatment of seizures in neonates, with seizure reduction in 60–92% of cases [22, 23]. However, there is no agreement about the efficacy and order of add-on therapy with LEV, MDZ, and LDC in the treatment of seizures in neonates on top of PB therapy.

Therefore, the primary aim of this retrospective cohort study was to evaluate the efficacy of add-on therapy with LEV, in neonates with (a)EEG-confirmed seizures treated with PB, for achieving >80% seizure reduction within 4 h after start of treatment. Secondary aims were to describe seizure etiology in neonates who did or did not respond to LEV and the efficacy of the use LDC and MDZ as 2nd- or 3rd-line ASM.

Patients and Methods

This single-center retrospective observational cohort study was conducted at Leiden University Medical Center (LUMC), Leiden, the Netherlands. All full-term neonates with EEG-confirmed seizures admitted to the NICU between January 2012 and January 2023, treated with PB and LEV and monitored with aEEG were included. The Ethics Committee (non-WMO Committee LUMC, Division 3) stated that this retrospective study did not apply to the Medical Research Involving Human Subjects Act (reference 22–3,078) and informed consent was deemed unnecessary. This study was conducted according to the guidelines for human studies and the principles of the World Medical Declaration of Helsinki.

Patients

Neonates with a gestational age ≥35 weeks who were admitted to the NICU within 28 days after birth with persistent seizures in neonates despite three loading doses of PB (total 40 mg/kg) as first-line therapy, treated with a single or multiple loading doses of LEV as add-on therapy and monitored with continuous 2-channel aEEG were eligible for inclusion. Exclusion criteria were incomplete or of insufficient quality aEEG registration, no monitoring during administration of ASM, no seizures on aEEG within 12 h before and after the administration of LEV, MDC, and LDC, and/or the administration of a lower dose of LEV or MDC as maintenance medication.

aEEG/EEG and ASM

All newborns received ASM (PB, LEV, MDZ, and/or LDC) according to national guidelines. MDZ dosage was adjusted in response to the occurrence of persistent or recurrent seizures (maximum of 0.3 mg/kg/h). The LDC dosage is administered following a tapering schedule, without adjustments in case of persistent or recurrent seizures (shown in online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000535499). They were continuously monitored using a 2-channel aEEG (NicoletOne, Natus Medical, Pleasanton, USA) or Brainz Monitor (Natus Medical, Pleasanton, USA). Data were extracted from electronic aEEG databases and reviewed offline by two neonatologists (L.V. and S.S.) with more than 15 years of experience. They assessed the presence of aEEG-confirmed seizures, calculated the seizure burden in seconds throughout the 2 h before and 4 h after LEV using raw EEG, and assessed the seizure-free period (24, 48, and 72 h) after the administration of ASM (LEV, MDZ, or LDC). We compared the total seizure duration in seconds per hour over a 2-h period before LEV, MDZ, and LDC administration and a 4-h period following LEV, MDZ, and LDC administration and calculated the reduction in percentages. The total dose of LEV was calculated by adding all loading doses (maximum of three doses) within the half-life of ASM, except for maintenance dosing. The need for another ASM included recurrence of seizures requiring a newly administered ASM or an increase in dose of an already administered ASM. This applied to the following medications: LEV, MDZ, LDC, carbamazepine, phenytoin, pyridoxine-5-phosphate, or pyridoxine. Clinical data were obtained from electronic medical records, HiX (version 6.1, Chipsoft, Amsterdam, The Netherlands) and MetaVision (version 6.9, Itémedical, Leuven, Belgium) and included: sex, gestational age (GA), birth weight (BW), mode of delivery, Apgar Score, cord pH, lactate, Thompson score, neonatal mortality, seizure etiology, type and dose (mg/kg) and number of ASM and timing of LEV, MDZ, or LDC.

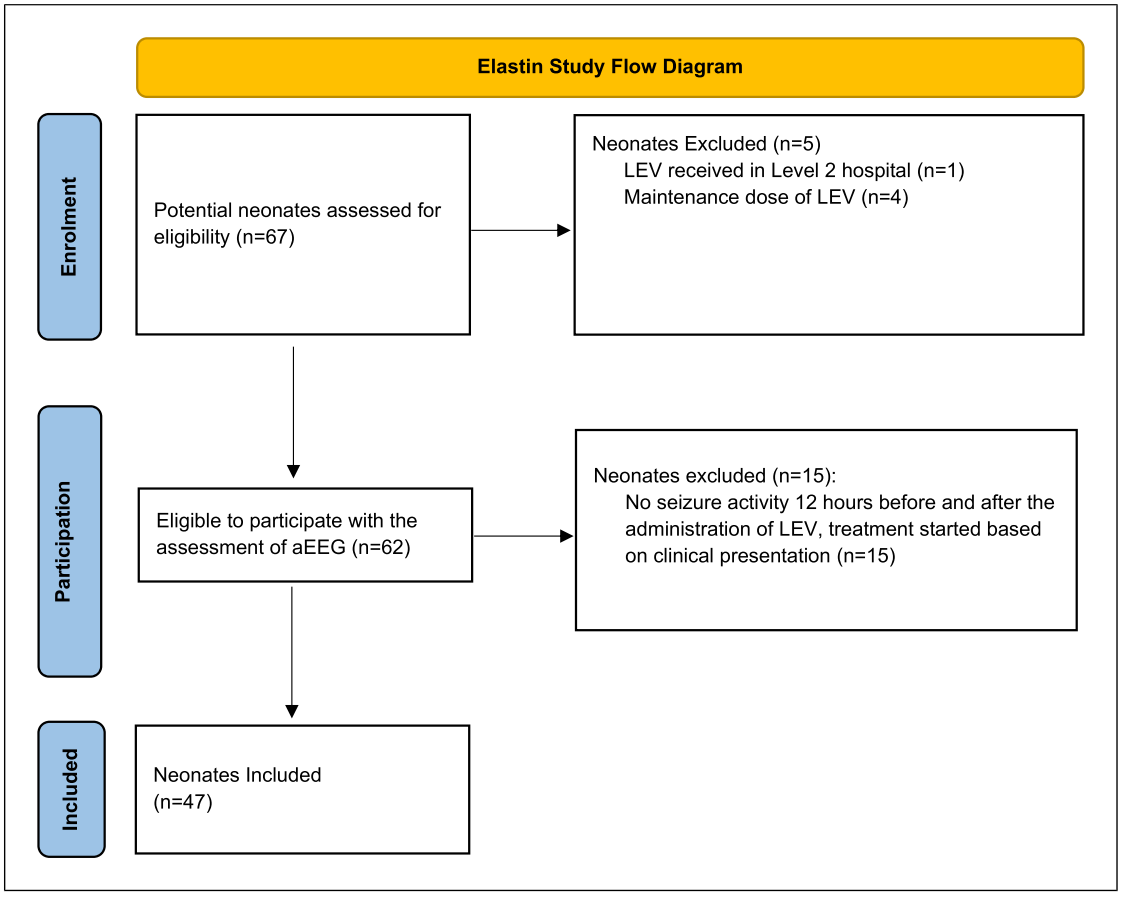


Fig. 1. Flow diagram of study population.

Statistical Analysis

Continuous data are presented as means with 95% confidence intervals (95% CI) and categorical data as numbers (*n*) and percentages (%). Primary and secondary outcome measures were calculated using Fisher's exact test. Data were analyzed using SPSS (version 28.0.1.0, IBM Corporation, Chicago, IL, USA).

Results

Clinical Characteristics

A total of 67 neonates were assessed for eligibility (shown in Fig. 1). Finally, 47 neonates were eligible for inclusion in the analysis. The mean GA was 39 weeks and 5 days (39 + 1–40 + 1). The seizure etiologies were HIE (*n* = 11; 23%), hemorrhagic stroke (*n* = 9; 19%), central nervous system infection (*n* = 8; 17%), genetic disorder (*n* = 8; 17%), arterial ischemic stroke (*n* = 7; 15%), metabolic disorders (*n* = 3; 7%), and unknown (*n* = 1; 2%). In total, 18 neonates died (38%) due to their underlying disease. Patient characteristics are also shown in Table 1.

Antiseizure Medication

LEV was administered as a second-line ASM in 12 (26%), third-line in 27 (58%), and fourth-line in 8 neonates (17%). First, second, and third loading doses were administered to 47 (100%), 38 (81%), and 11 (23%) neonates, respectively. The mean total loading dose was 40 mg/kg (36–44 mg/kg). The maximum loading dose varied between 20 and 60 mg/kg. After the total administered cumulative dose of LEV, 17% (8/47) of neonates achieved >80% seizure reduction (Table 2); achievement of >50% seizure reduction was seen in 43% of neonates (20/47). Only 4/47 (9%) neonates achieved 24-h seizure freedom after LEV. Administration of other ASM within 4 h after LEV was required in 45% (21/47).

Among the 47 neonates, 37 received MDZ. Six neonates were excluded from analysis because of no aEEG

Table 1. Characteristics of study population (n = 47)

Patient characteristics	Outcome
Sex female, *n* (%)	15 (32)
Gestational age, weeks	39.71 (39.14–40.14)
Birth weight, g	3,570 (3,384–3,756)
Delivery method	
Vaginal, *n* (%)	31 (66)
Caesarean section, *n* (%)	16 (34)
Apgar score	
5 min	7 (6–8)
10 min	8 (7–9)
Lactate[a], mmol/L	11.5 (4.2–18.7)
Cord pH[a]	7.1 (7.0–7.2)
Thompson score[a]	9 (6–13)
Neonatal death, *n* (%)	18 (38)
Seizure etiology	
HIE, *n* (%)	11 (23)
Arterial ischemic stroke, *n* (%)	7 (15)
Hemorrhagic stroke, *n* (%)	9 (19)
CNS infection, *n* (%)	8 (17)
Metabolic disorder, *n* (%)	3 (7)
Genetical syndrome, *n* (%)	8 (17)
Unknown, *n* (%)	1 (2)

Values are represented as exact number (*n*) or in percentages (%), and continuous variables are represented as mean with a 95% confidence interval. [a]In case of hypoxic-ischemic encephalopathy.

registration, and five received MDZ as sedation. Twenty neonates received MDZ as second-line and six as third-line ASM. In total, in 23% (6/26) and 27% (7/26) of the neonates, >80% and >50% seizure reduction, respectively, were achieved after administration of MDZ. The need for another ASM within 4 and 12 h after administration of MDZ was 50% (13/25) and 85% (22/25), respectively. Only one neonate (1/26) achieved 24-h, 48-h, and 72-h seizure freedom after the administration of MDZ.

A continuous infusion of LDC was administered as a third-line ASM in 7 and as fourth-line ASM in 18 neonates. The efficacy of LDC to achieve >80% and >50% seizure reduction was 92% (23/25) and 96% (24/25), respectively (Table 3). The need for ASM within 4 and 12 h after administration of LDC was 4% (1/25) and 20% (5/25), respectively. The 24-h, 48-h, and 72-h seizure freedom after administration of LDC were 56% (14/25), 48% (12/25), and 40% (10/25), respectively. Examples of aEEGs tracings in infants who received LEV, MDZ, and LDC are shown in Figure 2.

When comparing the three ASMs, LDC was more effective in achieving >80% seizure reduction than both LEV and MDZ ($p < 0.0001$). No statistical difference was observed between LEV and MDZ in achieving >80% seizure reduction ($p = 0.77$). An overview of the efficacy of LEV, MDZ, and LDC is shown in Figure 3.

When LEV was used as second-line therapy (n = 12), >80% seizure reduction was achieved in 33% (4/12) of cases. As third-line therapy (n = 27), >80% reduction was achieved in 7% (2/27) and fourth-line (n = 8) in 25% (2/8) of neonates. MDZ as second-line therapy (n = 20) resulted in >80% reduction in 15% (3/20). As third-line therapy, >80% reduction was achieved in 50% (3/6) of cases. With LDC as third-line add-on therapy, >80% reduction was achieved in 100% (7/7). For LDC as fourth-line add-on therapy, this was 89% (16/18 cases).

We performed a subgroup analysis of the efficacy of the different ASM regarding underlying etiology (HIE, arterial ischemic stroke, hemorrhagic stroke, metabolic disorders, and genetic disorders). Other etiologies were excluded from the analysis due to heterogeneity and small sample sizes. The results of the subgroup analysis are shown in online supplementary Table 2.

Discussion

In our single-center cohort of (near) term infants with EEG-confirmed seizures, add-on therapy with LEV had a limited effect, achieving >80% seizure reduction in only 17% (8/47) of neonates. In neonates with seizures caused by HIE or hemorrhagic stroke, LEV showed a somewhat higher efficacy of 27 and 33%, respectively. Both LEV and MDZ were not as effective as LDC where >80% seizure reduction was achieved in 92% of cases. In addition, 24 h of seizure freedom was higher, and the need for additional ASM within 4 h of administration was lower in newborns who received LDC. The results of this study have valuable implications as they reflect a comprehensive evaluation of the clinical efficacy of LEV, MDZ, and LDC as add-on therapies for seizures in neonates after PB treatment. The substantial cohort size compared to prior research, as well as the incorporation of commonly used outcome measures, further reinforces its relevance.

Few studies with a limited number of infants have reported the efficacy of LEV in the reduction of seizures by >80% and/or >50% [18, 19]. Abend et al. [18] described the efficacy of LEV in neonates (n = 23) who received an initial dose of 16 mg/kg and a mean maximum dose of 45 mg/kg. In agreement with our findings, they reported that LEV was associated with >50% seizure reduction within 24 h of treatment in 35% of neonates [18]. Rakshasbhuvankar et al. [19] described eight neonates (2 preterms) treated with LEV for refractory seizures with

Table 2. Efficacy of LEV

Characteristics/outcome measures	Outcome
Stage of administration (after PB as first-line treatment)	
Second line	12
Third line	27
Fourth line	8
Efficacy of LEV	
First dose, mg/kg (95% CI)	20 (19–21)
>50% seizure reduction, *n* (%)	21/46 (45.7)[a]
>80% seizure reduction, *n* (%)	10/46 (21.7)[a]
24-h seizure freedom, *n* (%)	2/47 (4.3)
48-h seizure freedom, *n* (%)	2/47 (4.3)
72-h seizure freedom, *n* (%)	2/47 (4.3)
Other ASM within 4 h of administration, *n* (%)	29/47 (61.7)
Other ASM within 12 h of administration, *n* (%)	41/47 (87.2)
Seizure burden 2 h before the administration, s	530 (188–1,215)
Seizure burden 4 h after the administration, s	766 (206–1,925)
Second dose, mg/kg (95% CI)	21 (19–22)
>50% seizure reduction, *n* (%)	11/38 (28.9)
>80% seizure reduction, *n* (%)	5/38 (13.2)
24-h seizure freedom, *n* (%)	2/38 (5.3)
48-h seizure freedom, *n* (%)	1/38 (2.6)
72-h seizure freedom, *n* (%)	1/38 (2.6)
Other ASM within 4 h of administration, *n* (%)	20/38 (52.6)
Other ASM within 12 h of administration, *n* (%)	31/38 (81.6)
Seizure burden 2 h before the administration, s	880 (216–1,814)
Seizure burden 4 h after the administration, s	1,169 (383–1,627)
Third dose, mg/kg (95% CI)	19 (16–21)
>50% seizure reduction, *n* (%)	4/11 (36.4)
>80% seizure reduction, *n* (%)	1/11 (9.1)
24-h seizure freedom, *n* (%)	0/11 (0)
48-h seizure freedom, *n* (%)	0/11 (0)
72-h seizure freedom, *n* (%)	0/11 (0)
Other ASM within 4 h of administration, *n* (%)	5/11 (45.5)
Other ASM within 12 h of administration, *n* (%)	7/11 (63.6)
Seizure burden 2 h before the administration, s	280 (85–634)
Seizure burden 4 h after the administration, s	612 (155–1,013)
Total administered dose, mg/kg (95% CI)	40 (36–44)
>50% seizure reduction, *n* (%)	20/47 (42.6)
>80% seizure reduction, *n* (%)	8/47 (17.0)
24-h seizure freedom, *n* (%)	4/47 (8.5)
48-h seizure freedom, *n* (%)	3/44 (6.4)
72-h seizure freedom, *n* (%)	3/44 (6.4)
Other ASM within 4 h of administration, *n* (%)	21/47 (44.7)
Other ASM within 12 h of administration, *n* (%)	31/47 (66)
Seizure burden 2 h before the administration, s	624 (145–1,699)
Seizure burden 4 h after the administration, s	931 (134–1,627)

All values are represented as exact number (*n*) or in percentages (%), continuous variables are represented as a mean with a 95% confidence interval. The seizure burden 2 h (within time period of 7,200 s) before and 4 h (within a time period of 14,400 s) after the administration are represented as median with the interquartile ranges. ASM, antiseizure medication; h, hours; PB, phenobarbital. [a]In one neonate the seizure reduction was not assessed for the first dose due to logistical reasons.

dosages between 10 and 35 mg/kg. This study reported that 75% (6/8) of the neonates accomplished >80% seizure reduction for the short term after the administration of LEV [19]. However, the number of infants studied was small, and they did not mention when the effect was accomplished, making comparison with our study impossible [19].

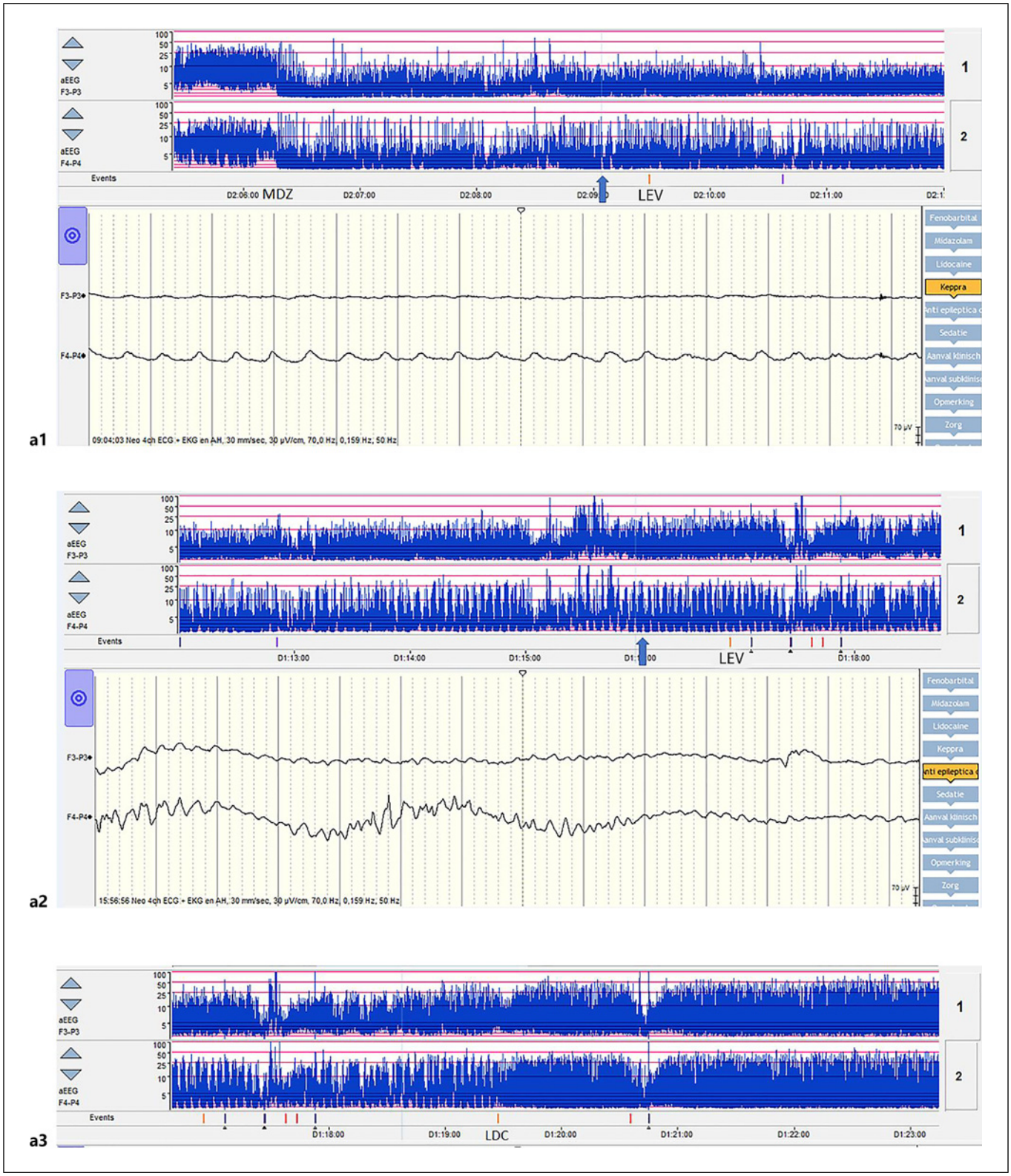
Table 3. Efficacy of midazolam (MDZ) and lidocaine (LDC)

Characteristics	Outcome, *n* (%)
MDZ	
Stage of administration (after PB as first line)	
Second line	20
Third line	6
Efficacy	
>50% seizure reduction, *n* (%)	7/26 (26.9)
>80% seizure reduction, *n* (%)	6/26 (23.1)
24-h seizure freedom, *n* (%)	1/26 (3.8)
48-h seizure freedom, *n* (%)	1/26 (3.8)
72-h seizure freedom, *n* (%)	1/26 (3.8)
Other ASM within 4 h of administration, *n* (%)	13/25 (50.0)
Other ASM within 12 h of administration, *n* (%)	22/25 (84.6)
Seizure burden 2 h before the administration, s	546 (290–763)
Seizure burden 4 h after the administration, s	1,001 (363–1,616)
LDC	
Stage of administration (after PB as first line)	
Third line	7
Fourth line	18
Efficacy	
>50% seizure reduction, *n* (%)	24/25 (96)
>80% seizure reduction, *n* (%)	23/25 (92)
24-h seizure freedom, *n* (%)	14/25 (56)
48-h seizure freedom, *n* (%)	12/25 (48)
72-h seizure freedom, *n* (%)	10/25 (40)
Other ASM within 4 h of administration, *n* (%)	1/25 (4)
Other ASM within 12 h of administration, *n* (%)	5/25 (20)
Seizure burden 2 h before the administration, s	2,198 (461–4,916)
Seizure burden 4 h after the administration, s	0 (0–76)

All values are represented as numbers (*n*) or in percentages (%). The seizure burden 2 h (within time period of 7,200 s) before and 4 h (within a time period of 14,400 s) after the administration are represented as median with the interquartile ranges. ASM, antiseizure medication; h, hours.

Sharpe et al. [1], Yau et al. [20], and Khan et al. [17] described the achievement of seizure freedom within 24–72 h after administration of add-on therapy of LEV after PB administration. Sharpe et al. [1, 16, 20] reported that 1/6 neonates (17%) accomplished seizure freedom within 24 h, with a mean dose of 20 mg/kg [1]. Yau et al. [20] described that, respectively, 58% (7/12) and 75% (9/12) of neonates were seizure-free after 24 and 72 h, with a loading dose of 7.5–20 mg/kg and maintenance of 5–60 mg/kg/day [20]. Khan et al. [17] reported that 14/22 neonates with seizures (64%), primarily with HIE as underlying cause (n = 12), were seizure-free 24 h after the administration of a loading dose of 50 mg/kg LEV [16]. and 100% (22/22) were seizure-free 72 h after the first administration and a maintenance dose of 25 mg/kg every 8 h [16]. In our study, seizure freedom for 24–72 h was 9% and 6.4%, respectively, after the total dose of LEV. A direct comparison of previous research with our study based on seizure freedom is not possible as we were interested in immediate seizure cessation that would hold for 24, 48, and 72 h after the administration of LEV instead of seizure cessation within 24, 48, and 72 h after the administration of LEV. This distinction holds significant relevance, particularly in light of the resolution of seizures in the newborn. A potential reason for the low efficacy of LEV could be the use of a lower cumulative dose and maintenance dose in our study compared to the previous studies mentioned. The optimal dosage of LEV in neonates remains uncertain, and previous studies have utilized a wide range of daily doses, from 10 mg/kg to 150 mg/kg [19].

The need for additional ASM within 4–12 h after administration of LEV was not reported in the literature. In our cohort, additional ASM within 4 h was often used to control seizures in neonates. This was in contrast to LDC where administration of additional ASM within 4 h was only necessary in a few cases. The need for administration of



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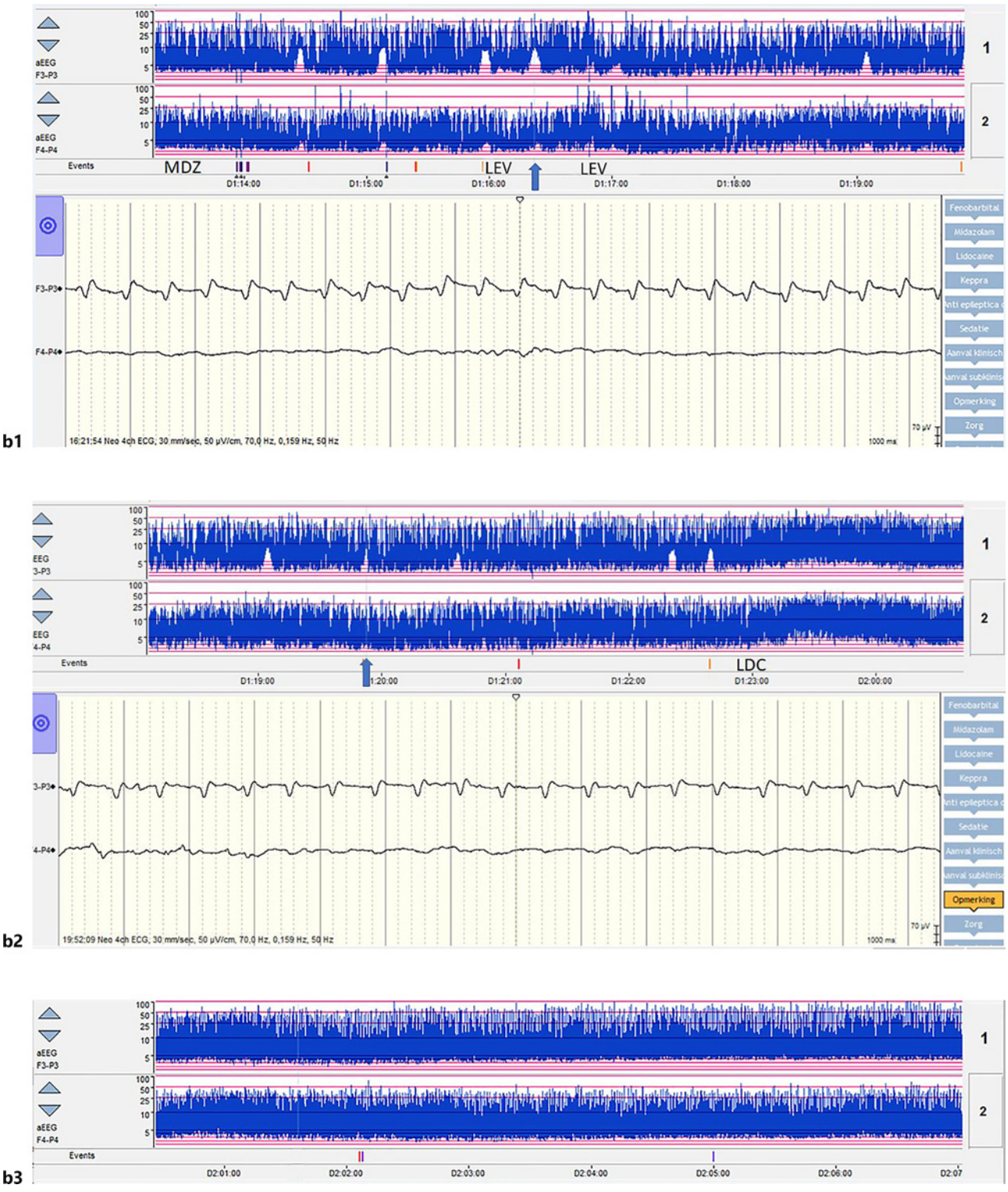

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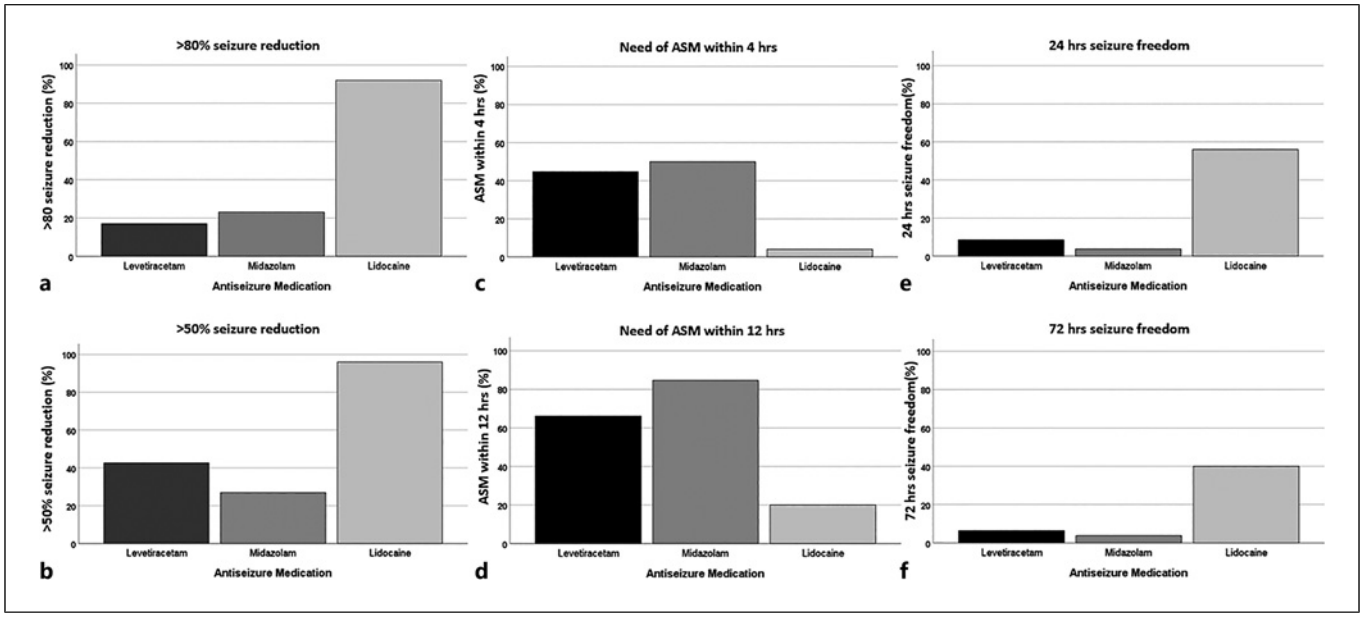

Fig. 3. Overview of the efficacy of levetiracetam (LEV), midazolam (MDZ), and lidocaine (LDC). The efficacy of LEV (n = 47), MDZ (n = 26), and LDC (n = 25) in achieving >80% seizure reduction (**a**) and >50% seizure reduction (**b**). The need for another ASM after initial administration of LEV (n = 47), MDZ (n = 25), and LDC (n = 25): within 4 h (**c**) and within 12 h (**d**). The figure presents the percentages of patients experiencing seizure freedom at 24 h (**e**) and 72 h (**f**) after the administration of LEV (24 h: n = 47; 72 h: n = 44), MDZ (n = 26), and LDC (n = 25) (online suppl. Fig. 1). Local protocol for seizures in neonates.

additional ASM within 4 h is an important measure of efficacy that is insufficiently described in the literature. The frequent need for additional ASM and low response rates of seizure reduction argue in favor of promptly administering an additional ASM if LEV fails.

Venkatesan et al. [24] determined the efficacy of LEV in the treatment of seizures in neonates due to HIE. In this study, 32 neonates received LEV of which in 84% (27/32) of the cases, the seizures stopped after administration. However, comparison with our study is challenging due to different seizure definition. Venkatesan et al. [24] identified seizures based on clinical observations rather than the electrographic confirmation recommended by ILAE guidelines [6, 24]. In our study, LEV was most effective when it was used as second-line add-on therapy, where it achieved >80% seizure reduction in 33%, compared to the use as third-line or fourth-line ASM. Data on efficacy in combination with timing of administration are limited in the literature [1, 18, 19].

This study has limitations. Due to the retrospective and uncontrolled design, which lacked randomization and double blinding, it was not possible to make unambiguous statements about the efficacy of LEV, MDZ, and LDC. It is also important to note that seizure reduction and seizure freedom (24-h, 48-h, and 72-h) may be influenced by other ASM. Furthermore, our subgroup analysis consisted of small numbers, with a limited contribution when assessing the impact of seizure etiology. It should be noted that the efficacy of LDC might be dependent on the preceding administration of MDZ

Fig. 2. Example of aEEG tracings in neonates after the administration of LEV, MDZ, and LDC. **a** Full-term neonate with perinatal asphyxia based on fetomaternal transfusion shows repetitive seizures at 5.30 u. After midazolam (MDZ), a temporary resolution of the seizures is visible, but repetitive seizures start from 07:00 h onward. An example of the seizure on the raw EEG is shown at the blue arrows (**a1**/**a2**). First administration of levetiracetam (LEV) did not result in seizure reduction. A second dose of LEV did not result in seizure reduction either (**a2**). Only after administration of lidocaine (LDC), a 100% seizure reduction with 72 h of complete seizure freedom was achieved (**a3**). **b** Full-term neonate with a meningitis had repetitive seizures, with a burst suppression pattern on the aEEG. LEV (up to 40 mg/kg) and MIDA (up to 0.3 mg/kg/h) were administered with no seizure control (**b1**). After LDC (**b2**), the seizures were successively controlled, the aEEG background pattern changed to discontinuous normal voltage pattern (**b3**). Afterward, no seizures were seen for at least 72 h.

and a potential pharmacologic synergy [23]. Therefore, the efficacy of LDC alone remains uncertain. Also, acute provoked seizures are known to resolve after some days, and LDC was given as the third or fourth ASM. Finally, this study used a 2-channel aEEG which has the disadvantage that it has a lower sensitivity and specificity compared to cEEG. Thence, despite our best efforts, some seizures may have been missed.

In conclusion, in our cohort of neonates admitted with encephalopathy and EEG-confirmed seizures, the effect of 1–3 loading doses of LEV as add-on therapy was limited based on low rates of seizure reduction and seizure freedom, as well as a high need for additional ASM. This study argues in favor of promptly administering an additional ASM if LEV fails as add-on therapy in the treatment of symptomatic seizures in the neonate. Further research is needed to assess what is the best strategy and order of ASM to treat seizures in neonates.

Acknowledgments

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Statement of Ethics

The need for informed consent was waived by the (non-WMO Committee Leiden University Medical Center, Division 3, reference 22–3078). This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. This study was conducted according to the guidelines for human studies and the principles of the World Medical Declaration of Helsinki.

Conflict of Interest Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

Mathies Rondagh conceptualized and designed the study, collected data, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dr. Linda de Vries and Dr. Sylke J. Steggerda conceptualized and designed the study, collected data, and critically reviewed and revised the manuscript. Dr. Cacha M. P. C. D. Peeters-Scholte and Dr. Selma C. critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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