Received: 4 September 2024 | Revised: 7 November 2024 | Accepted: 11 November 2024

DOI: 10.1111/epi.18194

Epilepsia®

RESEARCH ARTICLE

Effectiveness of sodium channel blockers in treating neonatal seizures due to arterial ischemic stroke

Veronica Pegoraro[1] | Renaud Viellevoye[2] | Geneviève Malfilatre[3] | Robertino Dilena[4] | Jacopo Proietti[5,6] | Isabella Mauro[7] | Cecilia Zardini[8] | Mark Dzietko[9] | Laure Lacan[10] | Beatrice Desnous[11] | Duccio Maria Cordelli[12,13] | Francesca Campi[14] | Monica Reis Da Silva[15] | Monica Fumagalli[16,17] | Sylvie Nguyen The Tich[10] | Ursula Felderhoff-Müser[9] | Giulia Ventura[7] | Stefano Sartori[8] | Manon Benders[18] | Carla Pittini[7] | Maria Elena Cavicchiolo[19] | Mathieu Milh[11,20] | Gaetano Cantalupo[5,6] | Aline van Maanen[21] | Maria Luisa Tataranno[18] | Maria Roberta Cilio[1,22]

Correspondence
Maria Roberta Cilio, Department of Pediatrics, Division of Pediatric Neurology, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium.
Email: roberta.cilio@uclouvain.be

Present address
Veronica Pegoraro, Unit of Child and Adolescent Neuropsychiatry, Friuli Centrale Health University Authority, Udine, Italy

Mark Dzietko, Neonatology and Pediatric Intensive Care, University Hospital Düsseldorf, Düsseldorf, Germany

Funding information
European Paediatric Neurology Society; Fonds de Recherche Clinique, Cliniques Universitaires Saint-Luc

Abstract

Objective: Few studies have evaluated the efficacy of antiseizure medications (ASMs) according to the etiology of neonatal acute provoked seizures. We aimed to investigate the response to ASMs in term/near term neonates with acute arterial ischemic stroke (AIS), as well as the type of seizure at presentation and the monitoring approach.

Methods: We retrospectively evaluated neonates from 15 European level IV neonatal intensive care units who presented with seizures due to AIS and were monitored by continuous electroencephalography (cEEG) and/or amplitude-integrated EEG (aEEG) in whom actual recordings, timing, doses, and response to ASMs were available for review.

Results: One hundred seven neonates were referred, and 88 were included. Of those, 56 met the criteria for evaluating the treatment response. The mean time to treatment was 7.9 h (SD = 16.4), and the most frequently administered first-line ASM was phenobarbital (PB; 74/88, 84.1%). Seizures were controlled within 24 h from onset of symptoms in 64.3% (36/56) of neonates. Phenytoin (PHT) was effective in almost all neonates in whom it was trialed (24/25, 96.0%), whereas PB was effective in only 22.0% of patients (11/50). Infants treated with PB or PHT as first-line treatment (53/56, 94.6%) showed a higher response rate with PHT (6/6, 100.0%) than with PB (11/47, 23.4%). Monitoring approach and seizure types were evaluated in 88 infants. Forty-six of 88 (52.3%) were monitored with cEEG and 47.7% (42/88) with aEEG, with or without intermittent cEEG. The mean monitoring duration was

For affiliations refer to page 11.

65.8 h (SD = 39.21). In 83 of 88 (94.3%) infants, the type of seizure suspected clinically prior to monitoring was confirmed afterward. Unilateral focal clonic seizures were seen in 71 of 88 infants (80.7%), whereas 11 of 88 (12.5%) presented with ictal apneas. **Significance:** Our findings provide evidence in a large, homogenous cohort that PHT is more effective than PB in treating neonatal acute symptomatic seizures due to AIS.

KEYWORDS

aEEG, antiseizure medications, EEG, neonatal acute ischemic stroke, neonatal seizures

1 | INTRODUCTION

Arterial ischemic stroke (AIS) is the second most common cause of seizures in neonates[1,2] and an important cause of postneonatal epilepsy.[3] Differently than for older children and adults who typically present with acute hemiparesis, seizures are the most common presenting symptom in neonates. There is increasing evidence that successful response to treatment in neonates with acute symptomatic seizures might be time-critical, and persistent seizures might add to the initial brain injury.[4,5]

Most studies have addressed the treatment of neonatal seizures with all etiologies confounded.[6,7] Although many cases of neonatal AIS are reported in the literature, the cohorts are relatively small, and their description is often incomplete regarding antiseizure medications (ASMs).[8] We aimed to specifically evaluate the response to ASMs in a homogenous population of neonates with acute symptomatic seizures due to AIS.

Key points

- Many neonates with acute ischemic stroke present with focal clonic or apneic seizures.
- Focal clonic seizures are easy to recognize clinically, on aEEG and on EEG, and they should raise the index of suspicion for arterial ischemic stroke in neonates.
- Despite the current guidelines, access to full EEG monitoring is challenging, even in major neonatal intensive care units across Europe. In this context, aEEG represents a valuable diagnostic tool.
- Sodium channel blockers are more effective than PB and other ASMs in treating acute provoked seizures associated with arterial ischemic stroke in term neonates.
- Stratification of neonates with seizures may help in identifying the most effective ASM according to etiology.

2 | MATERIALS AND METHODS

Through a multinational European collaborative network, including the Italian Neonatal Seizure Collaborative Network, we queried level III–IV neonatal intensive care units (NICUs) for neonates with AIS presenting with seizures for whom detailed clinical, neurophysiological, and neuroimaging information and the actual electroencephalographic (EEG)/amplitude-integrated EEG (aEEG) recordings were available. The primary outcome was EEG-confirmed seizure freedom within 30 min after the administration of ASM without recurrence for at least 24 h. Secondary objectives were seizure type at presentation and monitoring type.

2.1 | Population

We retrospectively studied neonates with gestational age ≥36 weeks referred by 15 European NICUs with magnetic resonance imaging (MRI)–diffusion-weighted imaging (DWI) diagnosis of AIS, who presented with acute symptomatic EEG/aEEG-confirmed seizures, received at least one ASM, and were continuously brain monitored. Choice and doses of ASMs were based on internal protocols or at the discretion of the treating physician.

The diagnosis of neonatal AIS was confirmed by brain MRI-DWI showing an acute ischemic infarct in a location involving the middle cerebral artery (MCA), anterior cerebral artery (ACA), or posterior cerebral artery (PCA) territories. The infarct's characteristics and location were determined by review of neuroradiology reports.

2.2 | Brain monitoring (continuous EEG/aEEG)

Continuous EEG (cEEG) was performed according to the international 10–20 system, modified for neonates. When

cEEG was not available or recorded only intermittently, data regarding seizure frequency and treatment response were evaluated by two-channel aEEG with electrodes in the F3, P3, F4, and P4 positions along with unprocessed EEG trace.[9,10] The actual aEEG/cEEG recordings were reviewed by neurophysiologists and neonatologists experienced in neonatal EEG interpretation.

2.3 | Seizure definition

Seizure was defined as an abrupt onset of rhythmic EEG activity with a definite beginning and end, lasting at least 10 s, with a change in at least two of the following features: amplitude, frequency, or spatial distribution.[11] We defined status epilepticus (SE) as continuous seizure activity for at least 30 min or recurrent seizures for >50% of 1–3 h of recording time.[12]

On aEEG, seizures were defined as transient upward flections of the lower margin of the aEEG trend, confirmed by examining the corresponding raw EEG for simultaneous seizure activity.[13,14] Average seizure duration per patient was calculated on cEEG. Cumulative seizure burden was defined as the total number of seizures, including clinical events that occurred prior to the initiation of monitoring, and whose semiology was consistent with the recorded seizures. We defined the seizure window as the time between the first event later confirmed to be a seizure and the last recorded seizure.

Seizure semiology was determined according to the International League Against Epilepsy classification of seizures in neonates.[11]

Neonates with resolution of clinical events suspected to be seizures prior to monitoring were excluded.

2.4 | Treatment response

Patients were included for treatment response analysis if they received one or more adequate doses of ASMs and were continuously monitored for at least 24 h after the last seizure, and accurate documentation regarding timing, doses, and treatment response was available. For each ASM administration, we analyzed route, loading and maintenance dose, electrographic response, and presence of treatment at hospital discharge.

Successful response was defined as absence of seizures within 30 min from the ASM administration and for at least 24 h. Partial/incomplete response was considered as no response. Infants with brain monitoring initiated later than 12 h after symptom onset and/or not continued for at least 24 h of seizure freedom were excluded from treatment response analysis.

2.5 | Data collection and statistical analysis

Data were collected in case reporting forms in an electronic database using REDCap electronic data capture tools, hosted at Cliniques Universitaires Saint-Luc.[15,16]

Clinical characteristics, as well as treatment details (ASM type, order, loading dose and additional doses, time to administration, response), were reported using descriptive statistics (mean and SD or median and interquartile range [IQR] for continuous parameters with parametric or nonparametric distribution, respectively, and number and percentage for categorical parameters). Formal statistical tests were used to compare neonate characteristics between those excluded from and those included in the treatment response group using Fisher exact test, *t*-test, or Mann–Whitney *U*-test according to the parameter type and distribution . Fisher exact test was used for the analysis of treatment response for nonmissing data of patients who received phenobarbital (PB) or phenytoin (PHT) as first-line treatment (i.e., unpaired data) and McNemar test for those exposed to both treatments (i.e., paired data). Seizure window and doses (loading and total) were compared between responder groups using Mann–Whitney *U*-test where applicable, and repeated measures analysis of variance was used to assess the difference in time to treatment after symptom onset between outborn and inborn infants. Analysis was performed on SAS software (version 9.4, SAS Institute).

2.6 | Standard protocol approvals, registration, and patient consent

The study was approved by the ethics committee at Saint-Luc University Hospital, Catholic University of Louvain, and informed consent waiver was granted.

3 | RESULTS

Among 107 neonates referred for acute symptomatic seizures due to AIS, the primary analysis excluded 19 neonates (19/107, 17.75%), the majority of whom (13/19, 68.4%) were excluded because of insufficient treatment information. Three infants were initially treated with PB based on clinical observation but did not have EEG-confirmed seizures. In three patients, one with severe hypoglycemia and bilateral posterior MRI injury, and two with subarachnoid hemorrhage, the diagnosis of neonatal AIS was not confirmed during the primary analysis. Eighty-eight (88/107, 82.2%) patients were included in the analysis of monitoring type and seizure semeiology. Of those, 56 (56/88, 63.6%) met

the criteria for treatment response analysis. Infant characteristics are summarized in Table 1. Apart from the higher incidence of inborns among neonates included in the treatment response analysis, no significant difference was observed between the two groups.

3.1 | Clinical presentation

Most patients (74/88, 84.1%) presented within the first 3 days of life (mean = 25.2 h, SD = 15.86), with a median of 24 h (IQR = 12.0–35.7). Seventy-one of 88 (80.7%) presented with focal clonic seizures. Of these, 68 of 71 (95.7%) had unilateral clonic seizures (66.2% right, 33.8% left). Ictal apnea with cyanosis and desaturation was reported as the presenting symptom in 11 of 88 (12.5%). In all infants, brain monitoring confirmed the ictal nature of these events. Seven infants were initially diagnosed with hypoxic–ischemic encephalopathy (HIE); three of them underwent therapeutic hypothermia. In all of them, DWI-MRI confirmed the diagnosis of neonatal AIS.

TABLE 1 Demographics and clinical characteristics of neonates included in the monitoring approach and seizure type analysis ($n = 88$), neonates included in treatment response analysis ($n = 56$), and neonates excluded from treatment response analysis ($n = 32$).

Characteristics	All patients, $n = 88$	Included in treatment response, $n = 56$	Excluded from treatment response, $n = 32$	p
Female	44 (50.0%)	26 (46.4%)	18 (56.3%)	.50
Gestational age, weeks	40.0 (39.0–40.6)	40.0 (39.3–40.8)	39.6 (38.3–40.1)	.08
Birth weight, g	3355.0 ± 486.30	3408.7 ± 429.62	3263.1 ± 566.3	.21
Apgar score at 5 min	9 (8–10)	9 (8–10)	9 (8–10)	.99
Inborn infants	30 (34.1%)	24 (42.9%)	6 (18.8%)	.03
Delivery mode				.28
Spontaneous vaginal delivery	35 (39.8%)	26 (46.4%)	9 (28.1%)	
Urgent/emergency caesarean section	23 (26.1%)	13 (23.2%)	10 (31.3%)	
Planned caesarean section	19 (21.6%)	12 (21.4%)	7 (21.9%)	
Instrumental vaginal delivery	11 (12.5%)	5 (8.9%)	6 (18.8%)	
Age at seizure onset, hours of life	29 (13.0–46.0)	24 (11.8–39.9)	30 (24.0–48.0)	.05
Type of recorded seizure				
Focal clonic	78 (88.6%)	50 (89.3%)	28 (87.5%)	.28
Ictal apnea	24 (27.3%)	14 (25.0%)	10 (31.3%)	.62
Electrographic-only	48 (54.5%)	34 (60.7%)	14 (43.8%)	.18
AIS localization				
MCA	75 (85.2%)	47 (83.9%)	28 (87.5%)	
Left	47 (53.4%)	32 (57.1%)	15 (46.9%)	.38
Right	24 (27.3%)	13 (23.2%)	11 (34.4%)	.41
Bilateral	4 (4.5%)	2 (3.6%)	2 (6.2%)	.99
ACA	6 (6.8%)	1 (1.8%)	5 (15.6%)	
Left	4 (4.5%)	1 (1.8%)	3 (9.4%)	.54
Right	2 (2.3%)	0 (.0%)	2 (6.2%)	.27
PCA	6 (6.8%)	2 (3.6%)	4 (12.5%)	
Left	2 (2.3%)	1 (1.8%)	1 (3.1%)	.99
Right	4 (4.5%)	1 (1.8%)	3 (5.4%)	.54
Right PICA	1 (1.1%)	0 (.0%)	1 (3.1%)	.99

Note: Data are presented as n (%), mean ± SD, or median (interquartile range). Probability values between neonates included and excluded from treatment response analysis groups are from a Fisher exact test for categorical parameters and from a t-test or Mann–Whitney U-test as appropriate for continuous parameters.

Abbreviations: ACA, anterior cerebral artery; AIS, arterial ischemic stroke; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery.

3.2 | Neuroimaging

The initial assessment was performed by head ultrasound in 86.4% (76/88) of infants within the first 24 h after onset, which showed normal results or nonspecific alterations in 75.0% (66/88). All patients had an MRI-confirmed diagnosis of neonatal AIS with (9/88, 10.2%) or without (79/88, 89.8%) hemorrhagic transformation.

MRI was performed at a median of 2 days after symptom onset (IQR = 1.0–4.0). The MCA was involved in 75 of 88 (85.2%), twice as frequently on the left as on the right (53.4% vs. 27.3%); four infants (4.5%) had bilateral strokes. The ACA was involved in six of 88 (6.8%), the PCA in six of 88 (6.8%), and the inferior cerebellar artery in one of 88 (1.1%).

3.3 | Brain monitoring

Forty-six of 88 infants (52.3%) were monitored with cEEG and 42 of 88 (47.7%) with aEEG, with or without intermittent EEG (1–3 h). Among the cEEG-monitored neonates, eight of 46 (17.4%) were monitored using a sequential approach whereby aEEG was the initial monitoring tool followed by cEEG once seizures were confirmed. The median time to monitoring after symptom onset was 4.8 h (IQR = 2.0–9.0). No difference was found between inborn and outborn infants. The mean monitoring duration was 65.8 h (SD = 39.21): 85.3 h (SD = 42.89) for aEEG and 48.7 h (SD = 25.9) for cEEG. In 69.3% (61/88) of neonates, monitoring was continued for 24 h after the last seizure, with a mean of 54.6 h (SD = 30.13). The remaining 27 patients (27/88, 30.7%), monitored for <24 h after the last seizure, were excluded from treatment response analysis.

3.4 | Seizure semiology and cumulative seizure burden

All infants had electroclinical seizures. Thirty-six infants (36/88, 40.9%) had one seizure type, 35 (39.8%) two seizure types, and 17 (19.3%) more than two seizure types. Focal clonic seizures were observed in 78 of 88 infants (88.6%). Ictal apneas were reported in 24 of 88 patients (27.3%), and in six of them, ictal apnea was the only clinical manifestation. Interestingly, 18 of the 78 infants (23.1%) with focal clonic seizures also had ictal apneas. Electrographic-only seizures, in addition to electroclinical seizures, were recorded in 48 infants (48/88, 54.5%) at some point during monitoring, even prior (8/48, 16.7%) to any ASM administration. In most patients (83/88, 94.3%), there was a concordance between the semiology of recorded seizures and the events visually observed prior to recording. The mean seizure duration calculated on the 46 neonates monitored with cEEG was 3 min (SD = 2.6).

The cumulative seizure burden was calculated in 67 neonates (67/88, 76.1%). Of those, 42 infants (42/67, 47.7%) had a mean of 7.2 seizures (SD = 3.65), and 25 (25/67, 37.3%) had SE. In the remaining 21 infants (21/88, 23.9%), data regarding the number of seizures prior to or during monitoring were deemed inaccurate. The time between symptom onset and last recorded seizure (seizure window) was calculated in neonates monitored for at least 24 h of seizure freedom (56/88). In this group, the seizure window was 25.1 h (SD = 23.6). Seizures were completely controlled within 24 h from onset in 64.3% (36/56). Seizure window in ASM nonresponders was 41 h (SD = 29.2) versus 18 h (SD = 16.9) in responders ($p < .001$).

3.5 | Seizure treatment

The mean number of ASMs administered was 1.7 (SD = .85). Specifically, 48 neonates (48/88, 54.6%) received only one ASM, 26 (26/88, 29.5%) received two ASMs, nine (9/88, 10.2%) received three ASMs, and five (5/88, 5.7%) received four ASMs. PB was administered as first-line treatment in 74 of 88 (84.1%) infants. Median time to treatment was 3.3 h (IQR = 1.5–8.0) after symptom onset, with a .5-h mean time interval (IQR = .5–1.4) between EEG initiation and first ASM administration, with no difference between inborn and outborn infants.

Most neonates (52/88, 59.1%) were discharged without ASM, whereas 40.9% (36/88) had at least one ASM at hospital discharge (PB, 83.3%; sodium channel blockers [PHT or carbamazepine], 22.2%; levetiracetam [LEV], 2.8%; benzodiazepines, 2.8%; valproic acid, 2.8%), and four of them (4/36, 11.1%) had more than one ASM.

The median duration of treatment was 52.2 days (IQR = 11.0–97.2). There was no significant association between the duration of seizure window or the presence of SE, and the continuation of treatment after hospital discharge.

Thirty-two of 88 (36.3%) infants were excluded from the treatment response analysis, most of them (27/32, 84.3%) because of monitoring shorter than 24 h after the last seizure. Details are shown in Figure 1.

3.6 | Treatment response

The response to treatment was assessed in 56 of 88 neonates (63.6%).

Twenty-nine of 56 (51.8%) neonates were treated prior to monitoring for paroxysmal events presumed to be seizures based on clinical observation. In most of them

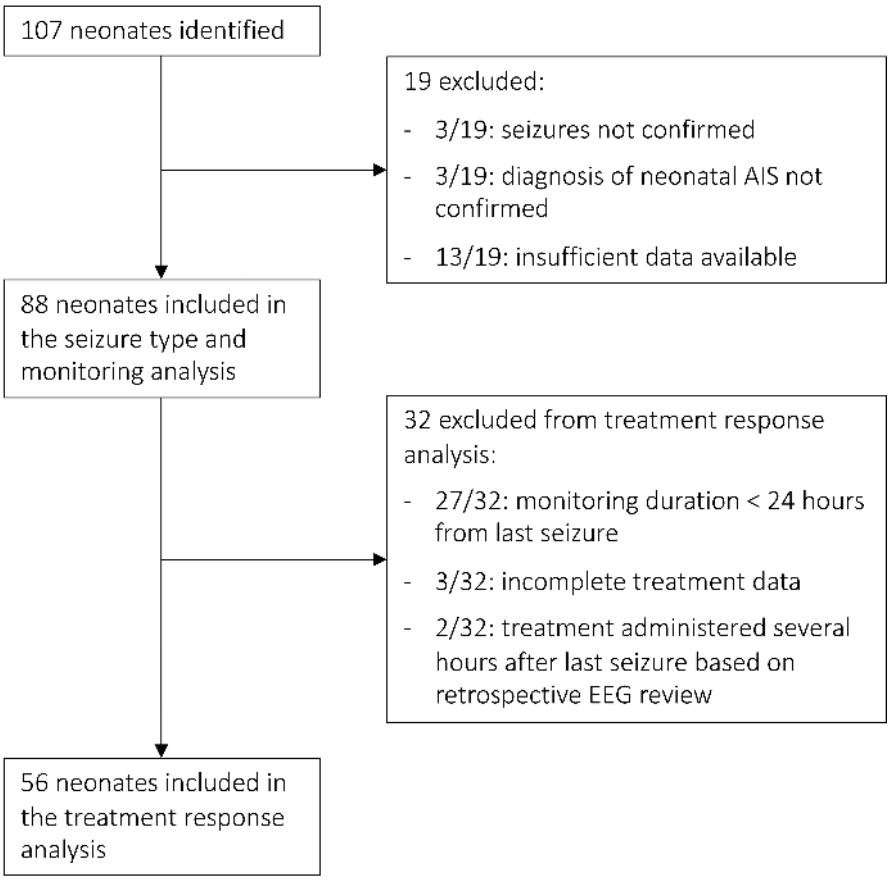

FIGURE 1 Flow diagram of included and excluded patients. AIS, arterial ischemic stroke; EEG, electroencephalographic.

(27/29, 93.1%), there was a concordance between semiology of visually observed and recorded seizures.

An intravenous PB 20-mg/kg loading dose was the first-line ASM in most infants (47/56, 83.9%), and only six of them (6/56) responded. Six neonates (6/56) received a 15–20-mg/kg loading dose of intravenous PHT as first-line treatment, and five of them responded (5/6). Two infants (2/56) were treated with benzodiazepines first-line, one with midazolam .6 mg/kg iv, and the other with diazepam .3 mg/kg iv, and none of them responded. One patient (1/56) received vitamin B6 100 mg iv and did not respond either. LEV was never used as first-line treatment. Twenty-nine of the 47 infants initially treated with PB (29/47, 61.7%) received at least one additional dose, which resulted in seizure control in an additional five patients (11/47, 23.4% total PB efficacy). Among the neonates who responded to PHT first-line, only one required an additional 10 mg/kg to reach seizure freedom (6/6, 100% efficacy). The one neonate initially treated with diazepam first-line received one additional dose of .5 mg/kg but did not respond.

Regarding the second-line treatment, three infants (3/27, 11.1%) received intravenous PB, and none of them responded. Fifteen infants (15/27, 55.5%) were treated with intravenous sodium channel blockers, including PHT and lidocaine, and 14 of them responded (14/15; 93.3%); the other one responded to a 20-mg/kg oral carbamazepine loading dose. Four patients received an LEV 20–40-mg/kg iv loading dose, and one responded. Five infants were treated with midazolam continuous infusion .06 mg/kg/h with no response.

Eighteen neonates (18/56, 32.1%) did not respond to any medications trialed and continued to seize for a mean of 39.2 h, until seizures spontaneously decayed. However, 12 of them (12/18, 66.6%) received only one ASM.

No adverse events were reported.

The cumulative response, regardless to the timing of administration, was 89.6% for sodium channel blockers, 22.0% for PB, and lower than 25% for LEV, benzodiazepines, or other ASMs.

Table 2 shows time to treatment, initial doses, additional doses, and treatment response rate for each ASM used.

The time sequence of the ASMs administered and their efficacy are illustrated in Figure 2.

Treatment efficacy comparison showed a significantly higher response rate in patients treated with PHT (24/25, 96.0%) than with PB (11/50, 22%), regardless of doses and order of administration. Formal comparison of treatment efficacy in infants treated with first-line PB (47/56, 83.9%) or PHT (6/56, 10.7%) showed a much higher response rate with PHT (6/6, 100.0%, $p < .001$%) than with PB (11/47,

TABLE 2 Time to treatment, loading doses, additional doses, and treatment response rate for each line of therapy.

Treatment	Patients	Time between onset of seizure and administration, h	Additional dose	Response
1st line	56 (100.0%)	7.3 ± 11.29	31 (55.3%)	17 (30.3%)
PB	47 (83.9%)	7.6 ± 12.25	29 (61.7%)	11 (23.4%)
PHT	6 (10.4%)	6.5 ± 2.24	1 (16.6%)	6 (100.0%)
BDZs	2 (3.6%)	2.2 ± 3.04	1 (50.0%)	0 (.0%)
Vit B6	1 (1.7%)	7.5 ± .00	0 (.0%)	0 (.0%)
2nd line	27 (48.2%)	17.2 ± 12.77	2 (7.4%)	15 (55.5%)
PB	3 (11.1%)	5.3 ± 3.16	1 (33.3%)	0 (.0%)
PHT	14 (51.8%)	17.7 ± 10.02	0 (.0%)	13 (92.8%)
MDZ	5 (25.0%)	24.6 ± 21.87	1 (20.0%)	0 (.0%)
LEV	4 (14.8%)	16.0 ± 9.53	0 (.0%)	1 (25.0%)
Lidocaine	1 (3.7%)	13.0 ± .00	0 (.0%)	1 (100.0%)
3rd line	8 (14.3%)	24.3 ± 14.27	3 (37.5%)	4 (50.0%)
PHT	3 (37.5%)	17.0 ± 6.24	1 (33.3%)	3 (100.0%)
CBZ	2 (25.0%)	29.0 ± 15.55	0 (.0%)	1 (50.0%)
MDZ	1 (12.5%)	13.5 ± .00	1 (100.0%)	0 (.0%)
LEV	1 (12.5%)	52.0 ± .00	1 (100.0%)	0 (.0%)
Vit B6	1 (12.5%)	20.2 ± .00	0 (.0%)	0 (.0%)
4th line	3 (5.3%)	23.3 ± 4.85	0 (.0%)	2 (66.6%)
PHT	2 (66.6%)	25.0 ± 5.53	0 (.0%)	2 (100.0%)
Lidocaine	1 (33.3%)	20.0 ± .00	0 (.0%)	0 (.0%)

Note: Data are presented as *n* (%) or mean ± SD.

Abbreviations: BDZ, benzodiazepine; CBZ, carbamazepine; LEV, levetiracetam; MDZ, midazolam; PB, phenobarbital; PHT, phenytoin; Vit, vitamin.

23.4%). No significant difference was found between first loading dose and additional doses.

Although the formal test (paired data) could not be run for the treatment response comparison in the 19 infants (19/56, 33.9%) exposed to both PB and PHT, because no response was obtained with PB, the higher efficacy of PHT was evident, with a response rate of 94.7% (18/19), regardless of dose or at what point in the clinical course they were administered.

Table 3 shows the response to PB versus PHT as first-line treatment, and the response to PB and PHT regardless of the order of administration.

A subanalysis of those excluded (27/88, 30.6%) because of duration of monitoring after last seizure being shorter than 24 h confirmed the higher cumulative response to PHT (6/8, 75.0%) versus PB (8/24, 33.3%).

4 | DISCUSSION

Despite significant advances in neonatal neurocritical care, the treatment of acute symptomatic seizures has not substantially changed for decades. Seizures in neonates have been traditionally treated with a "one-size-fits-all" approach, with PB as first-line treatment for neonatal seizures, all etiologies confounded.[17–20] The systematic review performed for the recent guidelines on seizure treatment in the neonate found that no studies evaluated the efficacy of ASM according to etiology of acute provoked seizures.[21]

The lack of stratification makes it difficult to interpret the results of many studies on neonatal seizures and challenges our effort to determine which drug represents the best therapeutic choice for specific etiologies and to advance toward precision medicine in neonates with seizures.[22]

After HIE, neonatal AIS is the second most common cause of acute symptomatic seizures in term neonates.[17,23] Seizures are reported in 75%–90% of infants diagnosed with AIS, and are associated with a nearly threefold increased risk of epilepsy later in life,[3] and higher seizure activity has been associated with worse developmental outcome.[24] To our knowledge, this is the first study that specifically addresses the treatment response in a homogenous population of neonates with acute symptomatic seizures due to AIS.

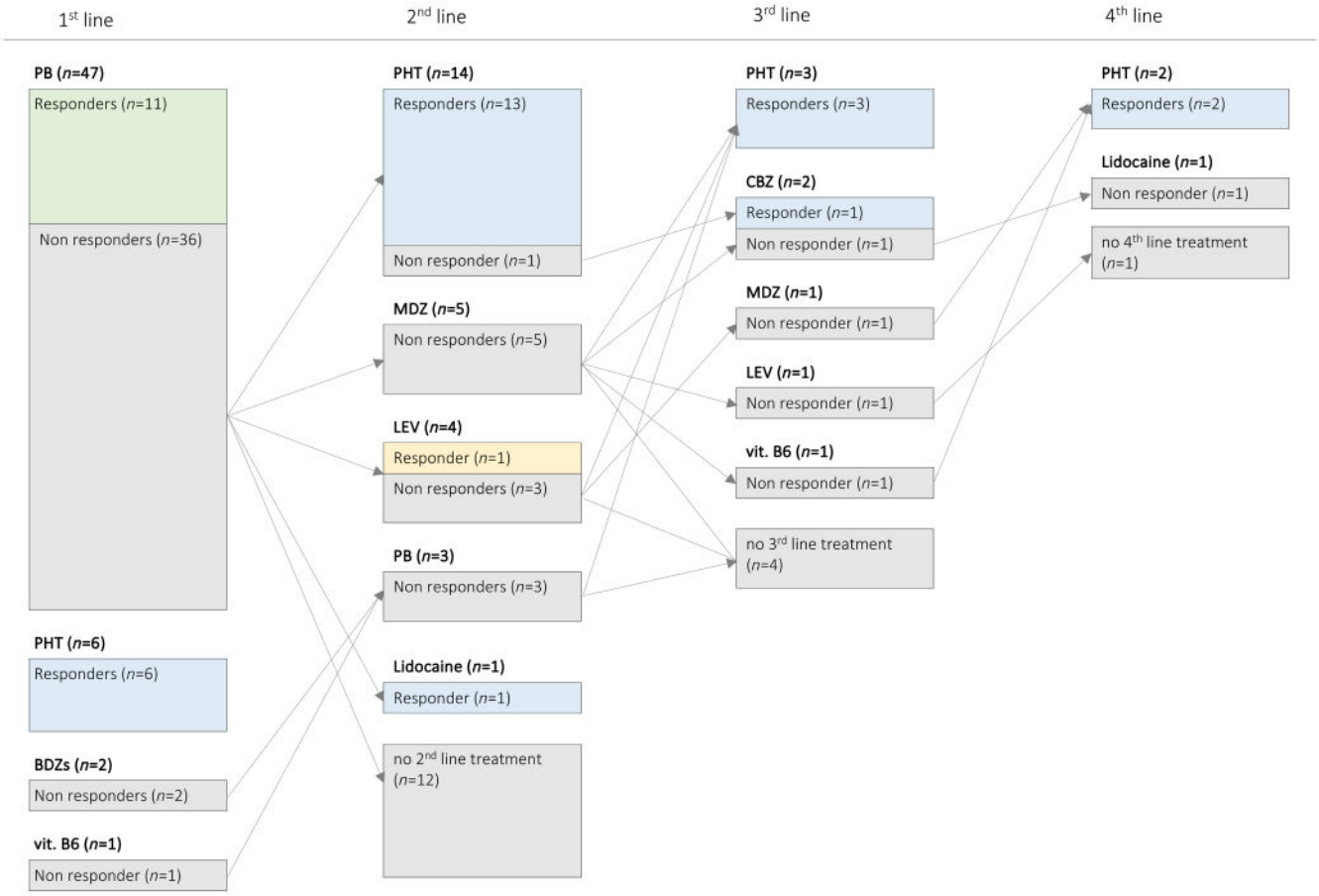

FIGURE 2 Treatment response according to line of treatment in the 56 neonates included in the treatment response analysis. BDZ, benzodiazepine; CBZ, carbamazepine; LEV, levetiracetam; MDZ, midazolam; PB, phenobarbital; PHT, phenytoin; vit., vitamin.

Although PB was used as first-line treatment in most infants (83.9%), our findings suggest that PHT is more effective than any other ASM in this population, because all infants who received it, including those with SE, responded regardless of the point at which it was initiated in the clinical course.

Among sodium channel blockers, PHT was the most frequently used, and it was more effective as a first-line treatment than PB, leading to seizure cessation in all patients who received it, compared with only 23.4% of patients who received PB. In addition, when used as a second-line treatment, PHT led to seizure control in 92.8% of infants. Compared with PHT, PB required a greater number of additional doses and higher cumulative dose per kilogram to be effective. Overall, PHT was effective in most patients. Other ASMs, including LEV, midazolam, diazepam, and vitamin B6, were ineffective in treating seizures in this population.

Interestingly, a previous study evaluating the response rate to lidocaine compared to midazolam in a large population of neonates with aEEG-confirmed seizures of different etiologies found that infants with a diagnosis of stroke, both ischemic and hemorrhagic, had the highest response rate (45.5%) to lidocaine as second-line ASM, and the response rate was up to 84.6% when lidocaine was given as third-line ASM.[25] Lidocaine belongs to the class of sodium channel blockers, as do PHT and carbamazepine. Its small therapeutic window associated with risk of cardiotoxicity has limited its use in many countries.[26] However, in our cohort, no adverse events were reported in neonates treated with lidocaine.

Incidence of seizures, including SE, in neonates with congenital heart disease following cardiac surgery has been reported to be between 5% and 26% of infants, with stroke, either of venous or arterial origin, being one the leading etiologies.[27] Seizures in neonates with cardiopulmonary diseases are often resistant to initial ASM. A retrospective comparison of PB and LEV for the treatment of seizures in this population showed that both ASMs were equally but incompletely effective, with response rates as first-line therapy of 58% and 45%, respectively.[28] Similarly to our findings, this study found that infants who did not respond to first-line PB received more loading doses and a higher total amount than responders, reflecting the common clinical practice in many NICUs whereby clinicians administer additional doses of PB

TABLE 3 Treatment response in infants treated with PB and PHT as first-line ASM, and in infants exposed to both ASMs.

	First-line ASM			
	PB, *n* = 47	**PHT, *n* = 6**	**Total, *n* = 53**	***p*[a]**
Response rate				**<.001**
No	36 (76.6%)	0 (.0%)	36 (67.9%)	
Yes	11 (23.4%)	6 (100.0%)	17 (32.1%)	
Mean loading dose, mg/kg				.42
n	47	6	53	
Mean	19.5	20.0	19.5	
SD	1.77	.00	1.68	
Median	20.0	20.0	20.0	
Min	10	20	10	
Max	20	20	20	
Any additional dose				.07
No	18 (38.2%)	5 (83.3%)	23 (43.3%)	
Yes	29 (61.7%)	1 (16.7%)	30 (56.6%)	
Total dose, mg/kg				.20
n	47	6	53	
Mean	28.1	21.7	27.4	
SD	8.63	4.08	8.48	
Median	30.0	20.0	27.5	
Min	25	20	20	
Max	60	30	60	
Infants treated with both PB and PHT	PB, *n* = 19	PHT, *n* = 19	*p*[b]	
Response rate			NA	
No	19 (100.0%)	1 (5.3%)		
Yes	0 (.0%)	18 (94.7%)		

Note: Data are presented as *n* (%) or mean. Statistically significant values are indicated in bold.

Abbreviations: ASM, antiseizure medication; NA, not applicable; PB, phenobarbital; PHT, phenytoin; SCB, sodium channel blocker.

[a]Fisher exact test or Mann–Whitney *U*-test as appropriate.

[b]McNemar test (paired) not computable.

when the first dose fails before starting another ASM. A recent study investigated seizure severity and treatment response in term and preterm neonates with seizures attributed to intracranial hemorrhage and showed that SE was more common in neonates with intracranial hemorrhage than in neonates with HIE, with 70% of patients remaining uncontrolled after the administration of the initial ASM.[29] Although the type and doses of ASMs were not specified, one could assume that PB was the first ASM used in these patients.

Our findings confirm that the main seizure type in neonates with AIS is focal clonic[30,31] Among the different types of neonatal seizures, focal clonic seizures are easy to recognize clinically, and particularly when unilateral, their presence in neonates should raise high suspicion for AIS.[32]

Interestingly, in our cohort, episodes of apnea and desaturation were the sole indication of seizures at presentation in a substantial minority of neonates. The recognition of ictal apnea may be particularly challenging in

the nursery. Previous case reports and small series showed that neonatal ischemic[33] and hemorrhagic stroke[34] is associated with apneic seizures, suggesting that brain monitoring should be performed in the setting of unexplained recurrent apneas, in term or late preterm neonates, especially in the absence of bradycardia, as this seizure type may be the only manifestation of AIS in the nursery.

Our work underlines the importance of seizure semiology in neonates, as it may indicate specific etiologies, helping to avoid misdiagnosis. For instance, in our cohort, seven infants were initially diagnosed with HIE, and three of them underwent therapeutic hypothermia.

Approximately half of the infants in our cohort had electrographic-only seizures in addition to clonic and apneic seizures, even prior to ASM administration, suggesting that the actual seizure frequency in this population may be higher than the one solely based on clinically observed seizures, and underlining the need for brain monitoring for accurate seizure detection and evaluation of treatment response.

Whereas half of the patients (52.3%) were monitored with cEEG, the others were primarily monitored with aEEG, which was complemented with spot/routine EEGs in approximately half of them. Our "real world" data provide a valuable insight into the existing gap in 24/7 access to cEEG monitoring for neonates. We strongly believe that modern neonatal neurocritical care should include cEEG monitoring, in accordance with the existing guidelines.[35] However, its implementation remains challenging even in level IV NICUs at major hospitals worldwide. In this context, aEEG, with all its limitations, can be an incredibly helpful tool for providing brain monitoring in many patients.[36]

Although the time interval between the initiation of monitoring and first ASM administered was short (mean = .8 h), we found a relatively large treatment gap in our cohort; both inborn and outborn infants received their first ASM at a mean of 7.9 h after the onset of symptoms. Yet, there is increasing evidence of an association between treatment timing and subsequent seizure burden,[5,37] and between seizure burden and worse long-term outcome.[3]

Recently, routine discontinuation of ASM prior to discharge in neonates with acute provoked seizures has been recommended.[21,38] In our cohort, 59.1% of patients were discharged without ASM, demonstrating that this change in practice is progressively taking place. However, the remaining 40.9% continued to be treated for a few months. Interestingly, PB was the most common ASM used after discharge, even in infants who did not respond in the acute phase.

Strengths of this study include the evaluation of the treatment response in a large, homogenous population of neonates with seizures associated with AIS who were continuously brain monitored, the review of actual recordings, and the analysis of type and doses of ASMs for each patient. However, there are limitations. As a retrospective study, the level of evidence is low compared with prospective studies and randomized–controlled trials. The choice and doses of ASM were either based on internal protocols or at the discretion of the treating clinician. It differed among centers and even within each center, reflecting a lack of evidence-based approach and shared protocols. The type and duration of monitoring was inconsistent among centers. The presence of adverse events was based on spontaneous reports, introducing a bias risk due to underreporting. However, it is unlikely that any major cardiac or blood pressure-related adverse events would have been omitted from the patient's medical records. A relatively large number of patients were excluded from the treatment response analysis because they were monitored for <24 h of seizure freedom. However, their characteristics and treatment response were similar to those included. Three infants were treated with PB based on clinical events and were excluded because they did not have subsequent EEG seizures. However, PB might have protected them from further seizures. Finally, we did not evaluate the impact of early termination of seizures on developmental outcome.

5 | CONCLUSIONS

Our findings from 15 NICUs in five European countries suggest that sodium channel blockers are effective and safe and should be used as first-line ASM in neonates with AIS. Considering that head ultrasound have low sensitivity to detect neonatal AIS, and that initiation of appropriate treatment cannot be delayed until MRI results are obtained, focal clonic seizures are a red flag that should raise suspicion for AIS in neonates and justify the administration of sodium channel blockers.

Neonates worldwide are treated with high doses of PB first-line for seizures, regardless of seizure type and etiology.[22] A game changer in this respect is represented by the treatment of neonates with KCNQ2/3-related epilepsies in whom sodium channel blockers provide rapid seizure control and may prevent the progression into an epileptic encephalopathy.[39–42]

Although we search for new compounds to treat neonatal seizures, we might not find the "magic bullet" that works for all infants. Stratifying neonates according to seizure type and etiology may build evidence for personalized medicine in this vulnerable population.[43] Prospective studies are warranted to confirm our findings.

AFFILIATIONS

[1]Department of Pediatrics, Division of Pediatric Neurology, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium
[2]Department of Pediatrics, Neonatal Intensive Care Unit, Centre Hospitalier Universitaire-Centre Hospitalier Régional (CHU-CHR) Liège, Liège, Belgium
[3]Neonatal Intensive Care Unit, CHU Tivoli, La Louvière, Belgium
[4]Department of Clinical Neurophysiology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy
[5]Department of Maternal and Child Health, Azienda Ospedaliera Universitaria Integrata (AOUI) Verona, Verona, Italy
[6]Department of Engineering for Innovation Medicine, University of Verona, Verona, Italy
[7]Department of Maternal and Child Health, Friuli Centrale Health University Authority, Udine, Italy
[8]Department of Women's and Children's Health, Division of Pediatric Neurology and Neurophysiology, University of Padua, Padua, Italy
[9]Department of Pediatrics I, Neonatal Intensive Care Unit, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[10]Department of Pediatric Neurology, Centre Hospitalier Régional Universitaire (CHRU) Lille University Hospital, Lille, France
[11]Department of Pediatric Neurology, Hôpital "La Timone" Enfants, University of Aix-Marseille, Marseille, France
[12]Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Delle Scienze Neurologiche di Bologna, Unità Operativa Complessa (UOC) Neuropsichiatria dell'età Pediatrica, Bologna, Italy
[13]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[14]Clinical and Academic Area Fetal–Neonatal and Cardiological Sciences, Neonatal Intensive Care Unit, Bambino Gesù Children's Hospital, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Rome, Italy
[15]Department of Pediatrics, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[16]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Neonatal Intensive Care Unit, Milan, Italy
[17]University of Milan, Department of Clinical Sciences and Community Health, Milan, Italy
[18]Department of Neonatology, University Medical Center, Utrecht Brain Center and Wilhelmina Children's Hospital, Utrecht University, Utrecht, the Netherlands
[19]Department of Women's and Children's Health, Neonatal Intensive Care Unit, University Hospital of Padua, Padua, Italy
[20]Institut National de la Santé et de la Recherche Médicale, Faculté Des Sciences Médicales et Paramédicales de la Timone, Aix-Marseille Université, Marseille, France
[21]Statistical Support Unit, Saint-Luc University Hospital, Brussels, Belgium
[22]Institute of Neuroscience, Catholic University of Louvain, Brussels, Belgium

ACKNOWLEDGMENTS

This study was supported by the Clinical Research Fund of Saint-Luc University Hospital and the EPNS research fellowship to V.P. We thank the INNESCO (Italian Neonatal Seizure Collaborative Network) group for fruitful collaboration. Cliniques Universitaires Saint-Luc is part of the Brussels Rare and Complex Epilepsies Consortium, a full member of the European Reference Network EpiCARE. Institute of Neurological Science of Bologna IRCCS, Bambino Gesú Children's Hospital IRCCS, Department of Maternal and Child Health, AOUI Verona, CHRU Lille University Hospital, University Medical Center and Brain Center Utrecht, and University Hospitals of Marseille are full members of EpiCARE.

CONFLICT OF INTEREST STATEMENT

V.P. has no conflict of interest to disclose in regard to this article. She has been awarded a research fellowship by the European Pediatric Neurology Society. M.R.C. has no conflict of interest to disclose in relationship to this article. She receives research funding from the Clinical Research Fund of Cliniques Universitaires Saint-Luc and the European Joint Program on Rare Diseases, EJP RD's Innovative Rare Diseases Challenge. She receives royalties from Elsevier as a coeditor of a book. She receives an honorarium from Springer Nature for her role as associate editor of *Pediatric Research*. She has served as a consultant for UCB, Sanofi Pharma, Eisai, and Jazz Pharmaceuticals. G.C. has no conflict of interest in relation to this article. He has received consultant fees from Ethos. on behalf of PTC Therapeutics, and from J. Medical Book Edizioni on behalf of Proveca Pharma Limited. S.N.T.T. has no conflict of interest to disclose in regard to this article. She receives honoraria for teaching sessions for UCB and Bioserenity. R.V. has received funding from Mithra Pharmaceutical for preclinical research on hypoxic-ischemic encephalopathy. D.M.C. has no conflict of interest to disclose in relationship to this article. He receives research funding from #NEXTGENERATIONEU by the Italian Ministry of University and Research, National Recovery and Resilience Plan, project MNESYS (PE0000006; A Multiscale Integrated Approach to the Study of the Nervous System in Health and Disease; DN. 1553 11.10.2022). He has served as a consultant for Jazz Pharmaceuticals, Sanofi Pharma, PTC Therapeutics, and Alexion. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared with appropriate data transfer upon request of qualified investigators from the corresponsing author.

ORCID

Veronica Pegoraro https://orcid.org/0000-0001-5616-7561
Jacopo Proietti https://orcid.org/0000-0002-5584-4724
Stefano Sartori https://orcid.org/0000-0002-0012-6848
Mathieu Milh https://orcid.org/0000-0002-2454-8543
Gaetano Cantalupo https://orcid.org/0000-0003-1343-8434
Maria Roberta Cilio https://orcid.org/0000-0003-2481-8053

REFERENCES

1. Ziobro J, Shellhaas RA. Neonatal seizures: diagnosis, etiologies, and management. Semin Neurol. 2020;40(2):246–56. https://doi.org/10.1055/s-0040-1702943
2. Pisani F, Spagnoli C, Falsaperla R, Nagarajan L, Ramantani G. Seizures in the neonate: a review of etiologies and outcomes. Seizure. 2021;85:48–56. https://doi.org/10.1016/j.seizure.2020.12.023
3. Fox CK, Glass HC, Sidney S, Smith SE, Fullerton HJ. Neonatal seizures triple the risk of a remote seizure after perinatal ischemic stroke. Neurology. 2016;86(23):2179–86. https://doi.org/10.1212/WNL.0000000000002739
4. Wusthoff CJ, Sundaram V, Abend NS, Massey SL, Lemmon ME, Thomas C, et al. Seizure control in neonates undergoing screening vs confirmatory EEG monitoring. Neurology. 2021;97(6):e587–e596. https://doi.org/10.1212/WNL.0000000000012293
5. Alharbi HM, Pinchefsky EF, Tran MA, Salazar Cerda CI, Parokaran Varghese J, Kamino D, et al. Seizure burden and neurologic outcomes after neonatal encephalopathy. Neurology. 2023;100(19):e1976–e1984. https://doi.org/10.1212/WNL.0000000000207202
6. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999;341(7):485–9. https://doi.org/10.1056/NEJM199908123410704
7. Sharpe C, Reiner GE, Davis SL, et al. Levetiracetam versus phenobarbital for neonatal seizures: a randomized controlled trial. Pediatrics. 2021;147(1):e2020036806. https://doi.org/10.1542/peds.2020-036806
8. Sortino V, Praticò A, Marino S, Criscione R, Ruggieri M, Pisani F, et al. Efficacy of the anti-seizure medications in acute symptomatic neonatal seizures caused by stroke. a systematic review. Acta Biomed. 2022;93(6):e2022328. https://doi.org/10.23750/abm.v93i6.13440
9. Bruns N, Sanchez-Albisua I, Weiß C, Tschiedel E, Dohna-Schwake C, Felderhoff-Müser U, et al. Amplitude-integrated EEG for neurological assessment and seizure detection in a german pediatric intensive care unit. Front Pediatr. 2019;7:358. https://doi.org/10.3389/fped.2019.00358
10. Glass HC, Wusthoff CJ, Shellhaas RA. Amplitude-integrated electro-encephalography: the child neurologist's perspective. J Child Neurol. 2013;28(10):1342–50. https://doi.org/10.1177/0883073813488663
11. Pressler RM, Cilio MR, Mizrahi EM, Moshé SL, Nunes ML, Plouin P, et al. The ILAE classification of seizures and the epilepsies: modification for seizures in the neonate. Position paper by the ILAE task force on neonatal seizures. Epilepsia. 2021;62(3):615–28. https://doi.org/10.1111/epi.16815
12. Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs recurrent neonatal seizures. Neurology. 2007;69(23):2177–85. https://doi.org/10.1212/01.wnl.0000295674.34193.9e
13. Boylan GB, Kharoshankaya L, Mathieson SR. Diagnosis of seizures and encephalopathy using conventional EEG and amplitude integrated EEG. Handb Clin Neurol. 2019;162:363–400. https://doi.org/10.1016/B978-0-444-64029-1.00018-7
14. Shah DK, Mackay MT, Lavery S, Watson S, Harvey AS, Zempel J, et al. Accuracy of bedside electroencephalographic monitoring in comparison with simultaneous continuous conventional electroencephalography for seizure detection in term infants. Pediatrics. 2008;121(6):1146–54. https://doi.org/10.1542/peds.2007-1839
15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81. https://doi.org/10.1016/j.jbi.2008.08.010
16. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208
17. Glass HC, Shellhaas RA, Wusthoff CJ, Chang T, Abend NS, Chu CJ, et al. Contemporary profile of seizures in neonates: a prospective cohort study. J Pediatr. 2016;174:98–103. https://doi.org/10.1016/j.jpeds.2016.03.035
18. Bartha AI, Shen J, Katz KH, Mischel RE, Yap KR, Ivacko JA, et al. Neonatal seizures: multicenter variability in current treatment practices. Pediatr Neurol. 2007;37(2):85–90. https://doi.org/10.1016/j.pediatrneurol.2007.04.003
19. Keene JC, Morgan LA, Abend NS, Bates SV, Bauer Huang SL, Chang T, et al. Treatment of neonatal seizures: comparison of treatment pathways from 11 neonatal intensive care units. Pediatr Neurol. 2022;128:67–74. https://doi.org/10.1016/j.pediatrneurol.2021.10.004
20. Vento M, de Vries LS, Alberola A, Blennow M, Steggerda S, Greisen G, et al. Approach to seizures in the neonatal period: a european perspective. Acta Paediatr. 2010;99(4):497–501. https://doi.org/10.1111/j.1651-2227.2009.01659.x
21. Pressler RM, Abend NS, Auvin S, Boylan G, Brigo F, Cilio MR, et al. Treatment of seizures in the neonate: guidelines and consensus-based recommendations—special report from the ILAE task force on neonatal seizures. Epilepsia. 2023;64(10):2550–70. https://doi.org/10.1111/epi.17745
22. Nickels K. Neonatal seizures: providing care with evidence, not just experience. Epilepsy Curr. 2021;21(6):427–9. https://doi.org/10.1177/15357597211040937
23. Weeke LC, Groenendaal F, Toet MC, Benders MJNL, Nievelstein RAJ, van Rooij LGM, et al. The aetiology of neonatal seizures and the diagnostic contribution of neonatal cerebral magnetic resonance imaging. Dev Med Child Neurol. 2015;57(3):248–56. https://doi.org/10.1111/dmcn.12629
24. Trowbridge SK, Condie LO, Landers JR, Bergin AM, Grant PE, Krishnamoorthy K, et al. Effect of neonatal seizure burden and etiology on the long-term outcome: data from a randomized, controlled trial. Ann Child Neurol Soc. 2023;1(1):53–65. https://doi.org/10.1002/cns3.8

25. Weeke LC, Toet MC, van Rooij LGM, Groenendaal F, Boylan GB, Pressler RM, et al. Lidocaine response rate in aEEG-confirmed neonatal seizures: retrospective study of 413 full-term and preterm infants. Epilepsia. 2016;57(2):233–42. https://doi.org/10.1111/epi.13286
26. Favié LMA, Huitema ADR, Broek MPH, et al. Lidocaine as treatment for neonatal seizures: evaluation of previously developed population pharmacokinetic models and dosing regimen. Br J Clin Pharmacol. 2020;86(1):75–84. https://doi.org/10.1111/bcp.14136
27. Naim MY, Gaynor JW, Chen J, Nicolson SC, Fuller S, Spray TL, et al. Subclinical seizures identified by postoperative electroencephalographic monitoring are common after neonatal cardiac surgery. J Thorac Cardiovasc Surg. 2015;150(1):169–80. https://doi.org/10.1016/j.jtcvs.2015.03.045
28. Thibault C, Naim MY, Abend NS, Licht DJ, Gaynor JW, Xiao R, et al. A retrospective comparison of phenobarbital and levetiracetam for the treatment of seizures following cardiac surgery in neonates. Epilepsia. 2020;61(4):627–35. https://doi.org/10.1111/epi.16469
29. Herzberg EM, Machie M, Glass HC, Shellhaas RA, Wusthoff CJ, Chang T, et al. Seizure severity and treatment response in newborn infants with seizures attributed to intracranial hemorrhage. J Pediatr. 2022;242:121–8. https://doi.org/10.1016/j.jpeds.2021.11.012
30. Santarone ME, Pietrafusa N, Fusco L. Neonatal seizures: when semiology points to etiology. Seizure. 2020;80:161–5. https://doi.org/10.1016/j.seizure.2020.06.025
31. Cornet M, Morabito V, Lederer D, et al. Neonatal presentation of genetic epilepsies: early differentiation from acute provoked seizures. Epilepsia. 2021;62(8):1907–20. https://doi.org/10.1111/epi.16957
32. Pellegrin S, Munoz FM, Padula M, Heath PT, Meller L, Top K, et al. Neonatal seizures: case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2019;37(52):7596–609. https://doi.org/10.1016/j.vaccine.2019.05.031
33. Castro Conde JR, González-Hernández T, González Barrios D, González CC. Neonatal apneic seizure of occipital lobe origin: continuous video-EEG recording. Pediatrics. 2012;129(6):e1616–e1620. https://doi.org/10.1542/peds.2011-2447
34. Sirsi D, Nadiminti L, Packard MA, Engel M, Solomon GE. Apneic seizures: a sign of temporal lobe hemorrhage in full-term neonates. Pediatr Neurol. 2007;37(5):366–70. https://doi.org/10.1016/j.pediatrneurol.2007.06.004
35. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American clinical neurophysiology Society's guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011;28(6):611–7. https://doi.org/10.1097/WNP.0b013e31823e96d7
36. Dilena R, Raviglione F, Cantalupo G, Cordelli DM, de Liso P, di Capua M, et al. Consensus protocol for EEG and amplitude-integrated EEG assessment and monitoring in neonates. Clin Neurophysiol. 2021;132(4):886–903. https://doi.org/10.1016/j.clinph.2021.01.012
37. Pavel AM, Rennie JM, de Vries LS, Blennow M, Foran A, Shah DK, et al. Neonatal seizure management: is the timing of treatment critical? J Pediatr. 2022;243:61–8. https://doi.org/10.1016/j.jpeds.2021.09.058
38. Glass HC, Soul JS, Chang T, Wusthoff CJ, Chu CJ, Massey SL, et al. Safety of early discontinuation of antiseizure medication after acute symptomatic neonatal seizures. JAMA Neurol. 2021;78(7):817–25. https://doi.org/10.1001/jamaneurol.2021.1437
39. Pisano T, Numis AL, Heavin SB, Weckhuysen S, Angriman M, Suls A, et al. Early and effective treatment of KCNQ2 encephalopathy. Epilepsia. 2015;56(5):685–91. https://doi.org/10.1111/epi.12984
40. Sands TT, Balestri M, Bellini G, Mulkey SB, Danhaive O, Bakken EH, et al. Rapid and safe response to low-dose carbamazepine in neonatal epilepsy. Epilepsia. 2016;57(12):2019–30. https://doi.org/10.1111/epi.13596
41. Kuersten M, Tacke M, Gerstl L, Hoelz H, Stülpnagel CV, Borggraefe I. Antiepileptic therapy approaches in KCNQ2 related epilepsy: a systematic review. Eur J Med Genet. 2020;63(1):103628. https://doi.org/10.1016/j.ejmg.2019.02.001
42. Pressler RM, Lagae L. Why we urgently need improved seizure and epilepsy therapies for children and neonates. Neuropharmacology. 2020;170:107854. https://doi.org/10.1016/j.neuropharm.2019.107854
43. Carapancea E, Cilio MC. A novel approach to seizures in neonates. J Paediatr Neurol. 2023;46:89–97. https://doi.org/10.1016/j.ejpn.2023.07.006

How to cite this article: Pegoraro V, Viellevoye R, Malfilatre G, Dilena R, Proietti J, Mauro I, et al. Effectiveness of sodium channel blockers in treating neonatal seizures due to arterial ischemic stroke. Epilepsia. 2024;00:1–13. https://doi.org/10.1111/epi.18194