Neonatal Seizure Management – Is the Timing of Treatment Critical?

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Neonatal Seizure Management – Is the Timing of Treatment Critical?

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Data sharing statement: It is currently not possible to share the studies datasets. The clinical data were collected under a written proxy consent from the participants' guardians/parents which did not include permission for sharing or open data. To be allowed to share this data under Irish Health Research Regulations we will require to re-consent or to obtain approval by the Health Regulation Consent Declaration Committee.

Abbreviations: EEG – electroencephalography; cEEG – conventional electroencephalography; aEEG – amplitude integrated electroencephalography;; HIE – hypoxic ischaemic encephalopathy;

Key words: Anti-seizure medication; Newborn; Encephalopathy.

Objective: To assess the impact of the time to treatment of the first electrographic seizure on subsequent seizure burden; secondary aim was to describe overall seizure management in a large neonatal cohort.

Study design: Newborns (36-44 weeks' gestation) requiring electroencephalographic (EEG) monitoring recruited to two multicentre European studies were included. Infants who received anti-seizure medication exclusively after electrographic seizure onset, were grouped based on time to treatment of the first seizure: ASM within 1-hour, ASM between 1-2 hours and ASM after 2-hours. Outcomes measured were seizure burden, maximum seizure burden, status epilepticus, number of seizures and ASM dose over 24-hours following seizure onset.

Results: Out of 472 newborns recruited, 154(32.6%) infants had confirmed electrographic seizures. Sixty-nine infants were exclusively treated after onset of electrographic seizures: 21 infants received ASM within 1 hour, 15 infants between 1-2 hours and 33 infants after 2 hours of seizure onset. Significantly lower seizure burden and less seizures were noted in infants treated with ASM within 1 hour from seizure onset (p value=0.029 and 0.035, respectively). Overall, 258/472(54.7%) infants received ASM throughout the study period, of which 40 infants without electrographic seizures had treatment during EEG monitoring and 11 infants with electrographic seizures had no treatment.

Conclusion: Treatment of neonatal seizures may be time-critical, but more research is required to confirm this. We also need to improve neonatal seizure diagnosis and treatment.

Trial Registration: ClinicalTrials.gov: NCT02160171 and NCT02431780.

Due to the unique physiological properties of the immature brain [1], seizures are common in the newborn with an incidence of 1-3.5/1000 live births in term infants.[2-4] Although a large variety of causes are reported, the leading cause remains hypoxic-ischaemic encephalopathy (HIE), despite the introduction of therapeutic hypothermia.[3, 5] Seizure recognition is challenging in newborns because many seizures are subclinical or have subtle clinical manifestations, also treatment of seizures can cause an "uncoupling" of clinical and EEG features.[6] There has been an increase in the use of electroencephalography (EEG) in neonatal units for the diagnosis of seizures.[5, 7] Amplitude-integrated EEG (aEEG) is still preferred by some neonatologists, as it is easy to apply and not dependent on 24/7 neurophysiology support.[8, 9] International guidelines recommend the use of continuous conventional electroencephalography (cEEG) for a minimum of 24 hours as gold standard for seizure diagnosis in the newborn.[10-12] There is increasing evidence that neonatal seizures are associated with poor neurodevelopmental outcome and that untreated seizures might add to the initial brain injury.[13, 14] Responsiveness to anti-seizure medication may decrease with recurrent and prolonged seizures.[15-17] The hypothesis that earlier treatment leads to better response is supported by animal work in mice and rats and has shown progressive intracellular chloride increase with recurrent seizures, increasing the probability of more seizures and decreasing the responsiveness to treatment.[17] Current published guidelines for management of all neonatal seizures recommend ASM as soon as possible following seizure recognition, but there are no recommendations on specific target times for treatment.[18] There is still significant variability in the way seizures are diagnosed and managed, and consensus is required.[19-21]

Our group has previously shown that only 11% of "seizure episodes" were treated within the first hour after onset.[3] One study described the time from aEEG seizure onset to ASM, and found that 32.1% were treated within 1 hour, 19.8% within 1-2 hours and the majority

(48.1%) were treated after 2 hours.[22] The primary aim of this analysis was to assess if the time to treatment of the first electrographic seizure had an impact on subsequent seizure burden. To achieve this goal, we used a large multicentre European neonatal cohort. Our secondary aim was to describe the initial seizure management for all infants included in this cohort.

METHODS:

The current work is a secondary data analysis of two European multicentre cohort studies, which recruited newborns across eight European tertiary neonatal intensive care units, between January 2011 and February 2017 (ClinicalTrials.gov: NCT02160171 and NCT02431780). Both studies examined the feasibility and efficacy of continuous cEEG monitoring and a new automated neonatal seizure detection algorithm (ANSeR algorithm)[3, 23] and included infants (36 to 44 weeks corrected gestational age) requiring EEG monitoring for suspected seizures. Infants were excluded only if parental/guardian written consent was refused or corrected gestational age <36 weeks. Relevant information regarding delivery and neonatal course were recorded in study designed electronic databases. To assess the effect of treatment timing of the first electrographic seizure (main aim), we included all infants with ASM given exclusively after the electrographic seizure onset and with at least 24 hours of cEEG recording after electrographic seizure onset. The secondary aim was to describe the initiation of seizure management for all infants included in the two studies.

EEG monitoring

All infants had prolonged video cEEG monitoring performed as clinically indicated, using 10:20 EEG electrode modified neonatal system with disposable electrodes placed at F3, F4, C3, C4, Cz, T3, T4, O1/P3 and O2/P4. The following EEG machines were used for

monitoring: Nihon Kohden EEG (Neurofax EEG-1200, Japan), NicoletOne ICU Monitor (Natus, USA) or XLTek EEG (Natus, USA). Teams at each site were trained on EEG electrode application and maintenance of good quality recordings. The clinical teams at each site had displayed on the EEG monitors and available to review the aEEG signals from F3-C3 and F4-C4, eight raw EEG channels, electrocardiogram and respiratory traces. No standard EEG review protocol was imposed during the study period and the clinical teams were reviewing the monitoring as recommended by the local guidelines.

Seizure analysis

This analysis included the entire EEG monitoring performed for each infant, regardless of the time of study enrolment. Electrographic seizures were annotated by one of four neonatal neurophysiologists blinded to the infant's medical history and outcome. A standard EEG review protocol for seizure annotation was used. Electrographic seizures were defined as a minimum 10 seconds of sudden, repetitive and evolving stereotyped waveforms involving at least one EEG channel.[24] An infant was considered to have seizures if at least one electrographic seizure was annotated. The following summary measures of seizures were calculated: seizure period (period (hours) from the beginning of the first electrographic seizure to the end of the last electrographic seizure); total seizure burden (duration (minutes) of all seizures during the entire monitoring); maximum hourly seizure burden (maximum seizure burden within an hour, minutes/hour); status epilepticus defined as seizure burden of minimum 30 minutes within one hour; number of seizures (during the entire monitoring). Seizure characteristics were described for all infants with seizures throughout the EEG monitoring period.

ASM treatment

EEG recordings were reviewed by local teams from each site in real time and when seizures were detected, these were managed according to local protocols. ASM treatment of each infant was recorded in the study database (type of drug, dose and time of administration). Choice of anti-seizure medication used was according to local protocols and clinician discretion.

Treatment timing analysis

For the purpose of treatment timing analysis, we considered the first ASM dose administered after the first electrographic seizure. This analysis included only infants with ASM given exclusively after first electrographic onset and with minimum 24 hours of EEG recording after first electrographic seizure. Infants with ASMs given prior to the first electrographic seizure and infants with no ASM treatment throughout the study period were excluded from this analysis, as this could be a bias for seizure diagnosis and management by the clinical teams. The treatment timing cohort was divided in three groups: ASM within 1 hour from electrographic seizure onset; ASM between 1-2 hours from electrographic seizure onset; ASM after 2 hours from electrographic seizure onset. The primary outcome was seizure burden, and the secondary outcomes were maximum seizure burden, presence of status epilepticus, number of seizures and total number of ASM doses. The American Clinical Neurophysiology Society guidelines recommend at least 24 hours of cEEG monitoring for neonates at risk of seizures and when seizures confirmed at least 24 hours of seizure free cEEG[10] therefore, all outcomes were calculated over 24 hours from electrographic seizure onset. A post-hoc analysis was performed in the subgroup of infants diagnosed with HIE (infants with encephalopathy of other causes than hypoxic-ischaemic injury were excluded).

Statistical analyses

For continuous variables, data were reported as median and interquartile range (IQR). Categorical variables were described using frequencies and percentages. Differences in outcomes between the treatment groups were investigated based on type of data and normality. The Kruskal-Wallis test was used for continuous outcome variables and the chi-squared test was used for categorical outcome variables. Post-hoc pairwise comparisons, with a Bonferroni correction were performed if the omnibus test was significant. All tests were two-sided and a *P* value < .05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS Statistics (V.25.0; IBM Corp).

Ethical approval was granted for both studies by national and local ethics committees specific to each participating centre.

RESULTS:

The two studies included 472 infants: 318(67.4%) infants without seizures and 154(32.6%) infants with seizures (Figure 1). The neonatal characteristics for the whole cohort are described in Table 1 (available at www.jpeds.com). The percentage of infants with moderate and severe HIE, stroke and metabolic/genetic disorders was higher in the seizure group, compared with non-seizure group, but otherwise the two groups were similar.

Seizure characteristics and treatment (Table 2)

Out of 154 infants with evidence of electrographic seizures, 31(20.1%) infants had no ASM given after electrographic seizure onset (11 infants had no ASM given at all and 20 infants had ASM given only before electrographic seizure onset). Based on the timing of ASM treatment received after electrographic seizure onset: 26(16.9%) infants had ASM given within 1 hour, 23(14.9%) between 1-2 hours and 74(48.1%) after 2 hours.

The median (IQR) age of seizure onset for all infants was 22(14-54) hours after birth, with a median (IQR) TSB of 69(23-154) minutes. Infants in the group treated within 1 hour had an earlier seizure onset, a longer duration of first electrographic seizure and a higher seizure burden in the first hour after seizure onset, compared with infants in other groups (Table 2).

Primary aim - Treatment timing analysis (Table 3)

This analysis included infants with ASM given exclusively at any timepoint after the first electrographic seizure (n=69 infants). We excluded: infants without ASM during study period (n=11), infants with ASM given exclusively prior to electrographic seizure onset (n=20), infants with ASM both before and after electrographic seizure onset (n=52) and infants with less than 24 hours of EEG monitoring after first electrographic seizure (n=2).

Seizure burden and number of seizures were significantly different between the ASM treatment groups (p value=0.029 and 0.035, respectively). The pairwise analysis showed that, from the onset of first electrographic seizure, seizure burden calculated over the following 24 hours was significantly lower in ASM group treated <1 hour compared with the ASM>2 hours group (seizure burden median (IQR) ASM<1hour 36(15-70) minutes vs ASM>2hours 75(30-152) minutes, p value=0.025) (Figure 2; available at www.jpeds.com). The number of seizures was also significantly lower in the early treatment group (<1hour) compared with the ASM>2 hours group (number of seizures median (IQR) ASM<1hour 10(2-24) seizures vs ASM>2hours 28(11-50) seizures, p value=0.032).

Comparing the group of infants with ASM given exclusively after the first electrographic seizure (n=69 infants) with the group of infants with ASM given before and after first seizure (n=52 infants) there were no significant differences in terms of TSB (median(IQR) 74(32-167) vs 79(21-158) minutes, p value= 0.582), MSB (median(IQR) 24(13-34) vs 19(8-29)

minutes, p value=0.071), number of seizures (median(IQR) 25(10-50) vs 33(12-58), p value=0.449) and presence of status epilepticus (24(34.8%) vs 12(23.1%), p value=0.163)

We investigated etiology, therapeutic hypothermia status, age at start of EEG monitoring and age at first electrographic seizure as potential confounding variables and found they were not associated with ASM timing. The background etiologies were not statistically significantly different between the ASM treatment groups (ASM<1 hour group: moderate HIE = 7(33.3%), severe HIE = 5(23.8%), stroke = 3(14.3%), other = 6(28.6%); ASM within 1-2hours group: moderate HIE = 5(33.3%), severe HIE = 5(33.3%), stroke = 3(20%), other = 2(13.3%); ASM>2hours group: moderate HIE = 12(36.4%), severe HIE = 8(24.2%), stroke = 7(21.2%), other = 6(18.2%); p value=0.928). The infants receiving therapeutic hypothermia between the treatment groups were: ASM<1 hour group 12(57.1%) infants, ASM 1-2hours group 9(60%) infants, ASM>2hours group 18(54.5%) infants, p value=0.937. The age at start of EEG monitoring (median (IQR) was for ASM<1 hour group = 6.9 (3.4-38.6) hours of life, ASM 1-2 hours group = 9 (3.0-41.6) hours and ASM>2 hours group = 6.9 (3.6-33.1) hours (p value=0.976). The age at first electrographic seizure was (median(IQR)): ASM<1 hour group = 14.1 (8.6-39.6) hours of life, ASM 1-2 hours group = 16.2 (9-42.3) hours and ASM>2 hours group = 14.6 (9.9-48.2) hours (p value=0.851).

Post-hoc analysis was also performed in the subgroup of infants who had a diagnosis of HIE (n=42) and the seizure burden was significantly different between the ASM treatment groups (p value=0.009). The pairwise comparison showed a significantly lower seizure burden was recorded in the ASM <1 hour group compared with the ASM>2 hours group (seizure burden median(IQR) ASM<1hour 41(24-67) minutes vs ASM>2hours 86(68-168) minutes, p value=0.007) (Table 4). For the HIE cohort, therapeutic hypothermia status and age at start of EEG monitoring were investigated as potential confounders and were not associated with ASM timing (p value=0.834 and p value=0.984, respectively).

Secondary aim - Overall description of ASM treatment

From 472 infants, a total of 258(54.7%) infants received at least one dose of ASM before or during EEG monitoring. In the non-seizure group, 115(36.2%) infants received at least one dose of ASM: 58 infants before EEG monitoring commenced, 40 infants during EEG monitoring and 17 infants before and during EEG monitoring. Forty-seven infants with no electrographic seizures received multiple ASM doses throughout the study period. In the seizure group, 143(92.9%) infants received at least one ASM dose, however 20(14.0%) infants received ASM exclusively before the onset of electrographic seizures (including the period before start of EEG monitoring).

As first line treatment, Phenobarbital was the drug of choice (90.7% of infants), followed by Midazolam (6.9%), Lignocaine (0.7%), Levetiracetam (0.3%), Lorazepam (0.3%), Biotin (0.3%) and Paraldehyde (0.3%).

DISCUSSION:

The findings of this study demonstrate that the group of infants with electrographic seizures treated within 1 hour of seizure onset, had the lowest seizure burden and less seizures over the following 24 hours (despite a higher seizure burden in the first hour in this group) when compared with infants with ASM administered after 1 hour from seizure onset. Similarly, the post-hoc analysis investigating treatment timing in infants with a diagnosis of HIE showed a lower seizure burden in the early (within 1 hour) treatment group.

Current international guidelines recommend that treatment for neonatal seizures should be administered as soon as possible, but no optimal treatment target time is specified.[18] The ANSeR phase 1 study cohort published by Rennie et al was included in this analysis, together with a neonatal cohort (ANSeR phase 2 study) recruited for a randomised control

trial of a seizure detection algorithm[3,23]. Rennie et al showed that only 11% of "seizure episodes" (cluster of seizures with less than two hours between them) were treated within one hour. This current work analysed only the treatment of first electrographic seizure and showed that out of all infants with electrographic seizures, 26 infants (16.9%) had their first electrographic seizures treated within the following hour, however only 21 infants had ASM given exclusively after electrographic seizure onset (5 infants received ASM before EEG monitoring started due to clinical seizures). In one study 32.1% of infants had ASM treatment initiated within 1 hour from aEEG seizure onset.[22] The higher proportion of early treatment in this study compared with our findings, could be explained by the use of a seizure detection algorithm and a single expert site. Previous studies have shown that a high seizure burden is independently associated with worse brain injury on MRI and worse neurodevelopmental outcome, suggesting that early ASM treatment resulting in a reduction of seizure burden might lead to a decrease in MRI brain injury and better long-term outcomes.[13, 25-27] A randomised control trial demonstrated an increased efficacy of Phenobarbital for neonatal seizures which could relate to an earlier treatment facilitated by a frequent review of the EEG monitoring and a rapid diagnosis of electrographic seizures.[28] Although, we cannot make a direct comparison with the previous study, the current findings demonstrate a lower seizure burden in infants treated within 1 hour from the electrographic seizure onset, suggesting there might be an association between ASM timing and seizures. Furthermore, seizure burden was similar if ASM was received after the 1 hour cut-off (ASM within 1-2 hours and ASM after 2 hours groups), suggesting that the impact of ASM on seizure burden might be optimal within 1 hour of seizure onset. Different etiologies in our cohort, therapeutic hypothermia status, the age at EEG monitoring initiation and the age at first electrographic seizure were investigated as confounders for this analysis but we noted no significant differences between the treatment

groups. Our results are supported by previous animal and human work, demonstrating that the sooner the treatment, the better the response.[17, 29]

For treatment timing analysis we had available a large multicentre European neonatal cohort from eight tertiary neonatal intensive care units, therefore we have also described the overall seizure management of this cohort. Out of 472 newborns, 258(54.7%) infants received at least one dose of ASM throughout the study period. Seventy-eight infants received ASM before EEG monitoring was commenced for suspected clinical seizures, out of which 58 infants had no evidence of further electrographic seizures. We can only assume that in these infants the seizures responded to initial ASM treatment or that what was diagnosed as a clinical seizure was likely part of the neonatal movement disorder rather than a true seizure, as demonstrated previously by our group.[30] The majority of infants with ASM treatment given exclusively during EEG monitoring had demonstrated electrographic seizures. However, 40 infants received ASM during EEG monitoring and had no evidence of electrographic seizures. The majority of infants without ASM treatment had no electrographic seizure throughout the EEG monitoring (203 infants), however 11 infants with no treatment had electrographic seizures. Out of these 11 infants with electrographic seizures, six infants had a TSB >20 minutes and two infants had status epilepticus. These results demonstrate that recognition of seizures is still a major challenge for neonatologists and inappropriate ASM treatment (under and over treatment) remains an ongoing concern. Animal and human studies documented that exposure to ASM can lead to neuronal apoptosis, poor brain development and later cognitive impairments; therefore, it is important to administer ASM appropriately to infants who may already have some degree of brain injury.[31-35] These results illustrate the diagnostic difficulties that clinicians face, even when the gold standard diagnostic tool (cEEG) is used. Current guidelines recommend the use of cEEG monitoring for at least 24 hours to detect seizures in neonates, but there are no clear

protocols for EEG review and neurophysiology support is limited even in tertiary neonatal centres.[10] Implementation of EEG monitoring and seizure management protocols and specific EEG review and interpretation training have previously been shown to be beneficial.[29, 36]

Several limitations have to be considered when interpreting these results. This is a secondary analysis of infants recruited to two European studies of cEEG monitoring and it was not a prospective study investigating treatment of neonatal seizures. Given the sample sizes, only large differences between ASM groups could be detected across the outcomes investigated. When seizures were detected, treatment was initiated as per local clinical guidelines and because there is no consensus on optimal target time for treatment, the treatment cut offs used for this analysis were selected based on previous literature.[3, 22] This analysis included electrographic seizures with a minimum duration of 10 seconds, which might be considered by some as too short to intervene. However only 14 out of 154 infants had a first seizure duration less than 30 seconds and only one infant was included in the treatment timing analysis. Excluding this infant from the analysis did not change the significance of the results. On the other hand, the most recent ILAE definition for neonatal seizure does not include a minimum duration of 10 seconds as long as an evolution in frequency and morphology is demonstrated.[37] In the current cohort the mean (IQR) duration of the first electrographic seizure was 93 (46-273) seconds and only 9% of infants had a first electrographic seizure of <30 seconds. Although we cannot definitely rule out that this did not influence the overall results, we believe it is unlikely given that the majority of seizures in our cohort were over 10 seconds. However, we do believe that a more detailed analysis of shorter duration discharges using the ILAE definition could provide valuable insights into the impact of electrographic seizures on the developing brain and is a priority area for our future research. For treatment timing analysis, infants that received ASM prior to electrographic seizure onset (including prior EEG start) were excluded to minimise the cumulative ASM

effect on the electrographic seizure burden. When comparing the group of infants with ASM given exclusively after the first electrographic seizure (n=69 infants) versus the group of infants with ASM before and after the first electrographic seizure (n=52 infants), we noted no significant differences in terms of TSB, MSB, number of seizures and presence of status epilepticus. Also, infants with no ASM given after emergence of electrographic seizure were excluded, because electrographic seizures were not recognised and not treated by the cot side clinical teams. As a result, we could only include 45% (69 infants out of 154) of all infants with electrographic seizures in the treatment timing analysis. Comparing the group of infants included in the treatment timing analysis (n=69) with the group of infants excluded (n=85), we noted that more than half of excluded infants were born outside of the recruiting hospitals and thus the EEG monitoring was started significantly later in this group. All participating centres were tertiary, referral hospitals and almost half of the infants with electrographic seizures were outborn. This may explain the high proportion of infants that had ASM administered before EEG commencement. This analysis looked at short-term outcomes, derived from the seizure burden only as brain imaging and two-year developmental follow analysis is not yet complete. Our findings suggest there might be an association between treatment timing and subsequent seizure burden and that treatment of neonatal seizures might be time-critical. However this needs to be confirmed in a large prospective study. Inappropriate treatment remains an ongoing concern: many infants continue to be treated who do not require treatment and for those who do, delayed onset of treatment remains problematic. Recognition of electrographic seizures is still a major challenge for neonatologists. With the increasing use of prolonged neonatal cEEG monitoring and not enough neonatal neurophysiology expertise, additional support from automated seizure detection algorithms might be the solution.[23, 38, 39]

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Table 1. Neonatal characteristics (n=472)

	n	All infants	n	Seizure group	n	Non-seizure group	P value[&]
Gestational age at birth (weeks)	472	40 (39-41)	154	40 (39 - 41)	318	40 (38-41)	0.117
Birth weight (g)	472	3440 (3061-3800)	154	3400 (3088-3793)	318	3450 (3058-3818)	0.954
Gender (male)	472	292 (61.9%)	154	91 (59.1%)	318	201 (63.2%)	0.388
Mode of delivery	470		154		316		0.372
Spontaneous vaginal delivery		171 (36.4%)		57 (37.0%)		114 (36.1%)	
Instrumental vaginal delivery		126 (26.8%)		35 (22.7%)		91 (28.8%)	
Elective caesarean section		43 (9.1%)		18 (11.7%)		25 (8.0%)	
Emergency caesarean section		130 (27.7%)		44 (28.6%)		86 (27.1%)	
Place of birth	472		154		318		0.648
Inborn in recruiting hospital		255 (54.0%)		81 (52.6%)		174 (54.7%)	
Outborn home/prehospital		19 (4.0%)		8 (5.2%)		11 (3.5%)	
Outborn other hospital		198 (42.0%)		65 (42.2%)		133 (41.8%)	
Apgar at 1 minutes	447	3 (1-7)	148	2 (1 - 8)	299	3 (1-7)	0.094
Apgar at 5 minutes	451	6 (4-9)	148	6 (3 - 9)	303	6 (4-9)	0.185
Assisted ventilation at 10 minutes of life (yes)	461	216 (46.9%)	153	76 (49.7%)	308	140 (45.5%)	0.393
Lowest cord pH	339	7.11 (6.93-7.23)	104	7.10 (6.90-7.20)	235	7.12 (6.94-7.24)	0.182[£]
Therapeutic hypothermia (yes)	472	234 (49.6%)	154	84 (54.5%)	318	150 (47.2%)	0.133
Diagnosis before discharge	472		154		318		<0.001
Mild HIE		82 (17.4%)		0 (0%)		82 (26.0%)	
Moderate HIE		125 (26.5%)		50 (32.5%)		75 (23.6%)	
Severe HIE		56 (11.9%)		40 (26.0%)		16 (5.0%)	
Stroke		50 (10.5%)		26 (16.9%)		24 (7.5%)	
Metabolic/Genetic Disorder		43 (9.1%)		27 (17.5%)		16 (5.0%)	
Suspected seizures - unconfirmed		31 (6.6%)		0 (0%)		31 (9.7%)	
Perinatal asphyxia without encephalopathy		22 (4.7%)		0 (0%)		22 (7.0%)	
Sepsis/Meningitis		20 (4.2%)		3 (2.0%)		17 (5.3%)	
Intracranial haemorrhage		10 (2.1%)		1 (0.6%)		9 (2.8%)	
*Other**		33 (7.0%)		7 (4.5%)		26 (8.2%)	

Age at EEG monitoring start (hours)	472	14.5 (5.6-44.4)	154	14.5 (5.7–41.0)	318	14.5 (5.5-49.1)	0.576
EEG monitoring duration (hours)	472	65.7 (29.6-92.8)	154	86.4 (52.2-102.6)	318	47.6 (23.5-88.0)	<0.001

Data reported as median (IQR) unless otherwise stated. HIE, hypoxic-ischaemic encephalopathy; EEG, electroencephalography. P value <0.05 was considered statistically significant. [&] P value from Mann Whitney u test for continuous data and Chi-squared test for categorical data unless otherwise stated; [£] P value from Student's t-test; *n=8 seizures of unknown origin; n=7 transient metabolic deficit; n=5 congenital brain malformation; n=3 for each of: postnatal cardiorespiratory arrest; respiratory distress; n=2 for each of: neonatal drug withdrawal syndrome; congenital cardiac anomaly; n=1 for each of: congenital anaemia; meconium aspiration syndrome; tracheo-oesophageal atresia and cystic periventricular leukomalacia.

Table 2. Seizure characteristics* for all infants with electrographic seizures and for infants by treatment timing group after electrographic seizure onset – descriptive analysis (n=154)

	All n=154	ASM treatment <1 hour n=26	ASM treatment 1-2 hours n=23	ASM treatment > 2 hours n=74	No ASM treatment n=31
General characteristics					
Seizure period (hours)	16.5 (6.7–40.2)	18.1 (0.7-57.4)	16.6 (8.3-54.5)	26.6 (10.0-48.2)	8.1 (2.7–14.8)
Total seizure burden (minutes)	69 (23–154)	45 (21-127)	104 (34-167)	75 (27–162)	30 (4–106)
Number of seizures	21 (9–52)	23 (5-33)	28 (12-52)	32 (12–60)	10 (2–32)
Median seizure duration (seconds)	104 (65-189)	89 (56-495)	105 (75-191)	108 (64-160)	98 (45-164)
Maximum seizure burden (minutes/hour)	22 (10–32)	22 (12-36)	24 (16-35)	22 (10–31)	14 (2–28)
Age when maximum seizure burden was reached (hours)	35 (19–63)	21 (11-49)	32 (19-80)	36 (20–68)	38 (28–59)
Status epilepticus (yes)	43 (27.9%)	8 (30.8%)	8 (34.8%)	20 (27.0%)	7 (22.6%)
Characteristics related to first electrographic seizure					
Age (hours) at first electrographic seizure (hours)	22 (14-54)	14 (9-39)	20 (15-57)	21 (14-56)	36 (19-59)
First seizure duration (seconds)	93 (46-273)	268 (65-1385)	104 (37-681)	75 (43-161)	114 (45-287)
Seizure burden in the first hour of seizure period (minutes)	6.0 (2.3-15.1)	15.7 (10.0-30.8)	9.7 (2.6-22.1)	4.4 (1.8-10.2)	3.9 (1.9-11.7)
Number of seizures in the first hour of seizure period	2 (1-4)	2 (1-6)	3 (1-4)	2 (1-4)	2 (1-3)

*Seizure characteristics are calculated based on complete EEG monitoring throughout the study period; Data reported as median (IQR) unless otherwise stated. ASM, anti-seizure medication; EEG, electroencephalography.

Table 3. Antiseizure treatment group analysis (n=69*)

	Groups based on ASM timing for first electrographic seizure				
	ASM treatment < 1 hour n=21	ASM treatment 1-2 hours n=15	ASM treatment > 2 hours n= 33	P value[&]	Pairwise comparison
Seizure burden within 24 hrs (minutes)	36 (15-70)	71 (32-112)	75 (30-152)	0.029	<1h vs >2h
Maximum seizure burden within 24 hrs (minutes/hour)	16 (11-24)	20 (12-40)	27 (12-35)	0.224	
Number of seizures within 24 hrs	10 (2-24)	18 (6-32)	28 (11-50)	0.035	<1h vs >2h
Status epilepticus within 24 hrs (yes)	3 (14.3%)	4 (26.7%)	14 (42.4%)	0.089[£]	
Total doses of ASM within 24 hrs	2 (1-4)	2 (1-3)	2 (1-3)	0.712	

*infants included in this analysis: infants with no ASM given prior first electrographic seizure, with at least one ASM dose given after first electrographic seizure AND with at least 24 hours of EEG monitoring after first electrographic seizure. Data reported as median (IQR) or n (%) unless otherwise stated. ASM, anti-seizure medication. P value <0.05 was considered statistically significant; [&] P value from Kruskal-Wallis test unless otherwise stated; [£] P value from Chi-squared test.

Table 4. Antiseizure treatment group analysis for infants with Hypoxic-Ischaemic Encephalopathy (n=42*)

	Groups based on ASM timing for first electrographic seizure				
	ASM treatment < 1 hour n=12	ASM treatment 1-2 hours n=10	ASM treatment > 2 hours n=20	P value[&]	Pairwise comparison
Seizure burden within 24 hrs (minutes)	41 (24-67)	87 (34-113)	86 (68-168)	0.009	<1h vs >2h
Maximum seizure burden within 24 hrs (minutes/hour)	21 (13-35)	24 (11-41)	32 (23-40)	0.132	
Number of seizures within 24 hrs	10 (1-23)	15 (6-34)	24 (11-58)	0.056	
Status epilepticus within 24 hrs (yes)	3 (25.0%)	3 (30.0%)	12 (60.0%)	0.098[£]	
Total doses of ASM within 24 hrs	2 (1-4)	3 (2-3)	2 (1-4)	0.909	

*infants included in this analysis: infants with no ASM given prior first electrographic seizure, with at least one ASM dose given after first electrographic seizure AND with at least 24 hours of EEG monitoring after first electrographic seizure. Data reported as median (IQR) or n (%) unless otherwise stated. ASM, anti-seizure medication. P value <0.05 was considered statistically significance; [&] P value from Kruskal-Wallis test unless otherwise stated; [£] P value from Chi-squared test.