Reducing the Percent of Surviving Infants with Acute Symptomatic Seizures Discharged on Anti-Seizure Medication

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Article

Keywords:

Posted Date: May 10th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4356197/v1

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Additional Declarations: Yes there is potential conflict of interest.
Version of Record: A version of this preprint was published at Journal of Perinatology on July 23rd, 2024. See the published version at https://doi.org/10.1038/s41372-024-02044-9.
Abstract

Objective: To evaluate the impact of inclusion of an ASM weaning protocol in a neonatal seizure pathway on the percent of infants discharged on ASMs.

Study Design: This cohort study included surviving infants with acute symptomatic seizures treated with ASMs. We evaluated infants in 2 epochs, pre- and post-implementation of the ASM weaning protocol. The primary outcome was discharge on ASM.

Results: Of 116 included infants, the percent of infants discharged on ASMs was 69% in epoch 1 versus 34% in epoch 2 (p<0.001). There was no significant difference between epochs in recurrence of seizures after discharge by 1 year of age (p=0.125). There was an annual decrease in the percent of infants discharged on ASM for both delivery and referral NICUs.

Conclusion: Inclusion of a formal ASM weaning protocol as part of an institutional seizure pathway reduced percent of infants with acute symptomatic seizures discharged on ASM.

BACKGROUND

Gestational age and brain injury impacts neurodevelopmental outcome in neonates with seizures, but seizure burden has also been independently associated with worse neurodevelopmental outcomes.(1, 2) The standard of care is to treat seizures in neonates with anti-seizure medications (ASMs),(3) however commonly used ASMs, such as Phenobarbital, have also been associated with neurotoxicity in animal models and neurodevelopmental impairment in some infant studies.(4–9) Continuation of ASM at discharge may be associated with increased neurodevelopmental impairment.(10) While higher than the average population, epilepsy risk in neonates following acute symptomatic seizures remains relatively low and seizures often do not present until months to years after discharge.(11–13) Continuation of ASM after discharge does not decrease the risk of epilepsy.(14)

Despite the 2011 World Health Organization's recommendations to discontinue ASM after 72 hours of seizure freedom in neonates with a normal neurological exam and electroencephalogram, continuation of ASM at discharge remains common in many centers.(15) A recent review of this practice at various centers showed that ASMs were continued at discharge in 73% of those with acute symptomatic seizures.(16) In 2021, Glass et al. expanded on these guidelines and recommended discontinuation of ASM at discharge in most infants with acute symptomatic seizures.(14) Subsequently, the International League Against Epilepsy published a consensus recommendation to discontinue ASM before discharge following resolution of acute symptomatic seizures in infants, regardless of MRI or EEG findings.(3) Our primary aim was to evaluate the impact of an inpatient ASM weaning protocol on the percent of infants discharged on ASMs.

METHODS
This retrospective cohort study included infants from one referral hospital and two delivery hospitals covered by a single practice group born from January 1, 2018 to November 30, 2023. Infants were screened for study inclusion if they had seizures treated with ASM, but only infants with electroencephalogram (EEG) confirmed seizures and were discharged from our hospitals were included in the cohort. Infants were excluded if they died before discharge. Seizure etiology was determined by chart review and the population was further stratified to infants with acute symptomatic seizures. For the purposes of this study, acute symptomatic seizures were defined as seizures provoked by hypoxia ischemic encephalopathy, stroke, hemorrhage, meningitis, or transient metabolic disturbances such as sodium or glucose abnormalities. For subset analyses, infants were categorized by type of hospital of discharge, delivery versus referral; infants born at delivery hospital and transferred to referral center were included one time under referral hospital. The Emory University Institutional Review Board approved this study with waiver of consent.

An evidence-based ASM weaning protocol was added to the Neonatal Seizure Pathway in October 2020. This pathway was designed through a multidisciplinary collaboration including members from Neonatology and Pediatric Neurology. The pathway was formally presented to both divisions with subsequent feedback incorporated into the final pathway (Supplementary Fig. 1). We evaluated infants in two epochs, pre- and post-implementation of the ASM weaning protocol. The primary outcome was discharge on ASM. The primary outcome was also analyzed based on hospital type at discharge (delivery vs referral center). Additional secondary outcomes included whether or not ASM weaning was initiated prior to discharge, the number of ASMs at discharge per patient, and percent of infants with seizure post-discharge up to one year of age. Seizure post-discharge was included for infants with follow-up data available and determined by chart review of notes from neurology and developmental follow-up visits.

Demographic and clinical measurements were summarized using descriptive statistics. To compare between epoch 1 and epoch 2, Welch two-sample t-test was used for continuous data, and Pearson's Chi-squared test and Fisher's exact test was used for categorical data. P-values less or equal to 0.05 was considered as statistically significant. All statistical analyses were performed using R software v 4.3.2.

RESULTS

Study Population

One hundred ninety-three (193) infants had electrographic seizures and were discharged from our centers. Of these, 38 (19%) infants died prior to discharge and 39 (18%) infants did not have acute symptomatic seizures, leaving 116 infants in our final cohort (Fig. 1). Of these, 52 were in epoch 1 and 64 were in epoch 2. Demographic characteristics and underlying brain injury were similar between epoch groups (Table 1). Ninety-six infants (83%) of infants had a follow-up visit in our hospital system.
Table 1
Demographic and Neonatal Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 116)</th>
<th>Epoch 1 (N = 52)</th>
<th>Epoch 2 (N = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, mean (SD)</td>
<td>37.5 (3.9)</td>
<td>37.3 (4.0)</td>
<td>37.7 (3.9)</td>
</tr>
<tr>
<td>Birth weight in grams, mean (SD)</td>
<td>3 030 (883)</td>
<td>2 997 (853)</td>
<td>3 057 (912)</td>
</tr>
<tr>
<td>Male sex, N (%)</td>
<td>60 (52%)</td>
<td>30 (58%)</td>
<td>30 (47%)</td>
</tr>
<tr>
<td>Discharge hospital type, N(%)</td>
<td>49 (42%)</td>
<td>23 (44%)</td>
<td>26 (41%)</td>
</tr>
<tr>
<td>Delivery</td>
<td>67 (58%)</td>
<td>29 (56%)</td>
<td>38 (59%)</td>
</tr>
<tr>
<td>Referral</td>
<td>49 (42%)</td>
<td>23 (44%)</td>
<td>26 (41%)</td>
</tr>
<tr>
<td>Days of age at seizure diagnosis, median (IQR)¹</td>
<td>1 [0–2]</td>
<td>1 [0–2]</td>
<td>1 [0–3]</td>
</tr>
<tr>
<td>Etiology</td>
<td>82 (71%)</td>
<td>34 (65%)</td>
<td>48 (75%)</td>
</tr>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
<td>14 (12%)</td>
<td>8 (15%)</td>
<td>6 (9.4%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>10 (8.6%)</td>
<td>3 (5.8%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>5 (4.3%)</td>
<td>3 (5.8%)</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Meningitis or brain abscess</td>
<td>5 (4.3%)</td>
<td>4 (7.7%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Transient metabolic disturbances</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Fourteen missing variables (N = 102)

Outcomes

The percent of infants discharged on ASMs was 69% in epoch 1 versus 34% in epoch 2 (p < 0.001); The difference in infants discharged on ASMs between epoch 1 and epoch 2 was larger in infants discharged from delivery NICUs versus the referral NICU. There was an annual decrease in the percent of infants discharged on ASM for both delivery and referral NICUs (Fig. 2). There was no significant difference between epochs in seizures after discharge by 1 year of age (p = 0.125). The percent of infants with ASM wean initiated prior to discharge and the total number of ASM at discharge also decreased across epochs (Table 2).
Table 2
Short-term Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 116)</th>
<th>Epoch 1 (N = 52)</th>
<th>Epoch 2 (N = 64)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged on ASM – yes, N (%)</td>
<td>58 (50%)</td>
<td>36 (69%)</td>
<td>22 (34%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged on ASM – yes, N (%)</td>
<td>26 (53%)</td>
<td>18 (78%)</td>
<td>8 (31%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Delivery hospital</td>
<td>32 (48%)</td>
<td>18 (62%)</td>
<td>14 (37%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Referral hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure after discharge, N (%)</td>
<td>24/96 (25%)</td>
<td>15/47 (32%)</td>
<td>9/49 (18%)</td>
<td>0.125</td>
</tr>
<tr>
<td>Number of ASM at discharge per patient, N (%)</td>
<td>0.7 (0.9)</td>
<td>1.0 (0.9)</td>
<td>0.4 (0.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ASM wean initiated among infants discharged on ASM, N (%)</td>
<td>33/58 (57%)</td>
<td>16/36 (44%)</td>
<td>17/22 (77%)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

1 Twenty missing variables (N = 96)

2 One missing variable (N = 115)

**Supplementary Fig. 1 Summary:**

Neonatal seizure pathway with inclusion of anti-seizure medication weaning protocol. Reflects most current version following three revisions.

**DISCUSSION**

Among infants with acute symptomatic seizures in three local hospitals cared for by one provider group, we found that inclusion of an ASM wean protocol in the neonatal seizure pathway decreased the number of infants discharged on ASM, regardless of type of NICU. There was no difference in seizures after discharge between epochs. Among infants with acute symptomatic seizures who were maintained on ASM at discharge, we found more infants had a wean of ASM initiated prior to hospital discharge in epoch 2.

Previous studies have shown variation by center in the percent of infants with acute symptomatic seizures discharged on ASM.\(^{(10, 17, 18)}\) Historically our academic provider group working in three local hospitals, or has had a high proportion of infants with seizures discharged on ASM. This was compounded by challenges in obtaining neurology follow-up in a timely manner after discharge, resulting...
in infants being exposed to prolonged duration of ASM. There was initial hesitation about discontinuing ASM prior to discharge in infants with acute symptomatic seizures due to concerns for risk of seizure recurrence. Our original ASM weaning protocol consisted of a slow wean and repeat EEG, which was necessary to gain support from some of our pediatric neurologists. However, the subsequent publication in 2021 of the comparative effectiveness study from the Neonatal Seizure Registry demonstrating no difference in epilepsy at 24 months among children whose ASM was maintained or discontinued at discharge provided more support to our efforts.\(^ {14}\) Our current study also did not find an increase in seizure after discharge between epochs, although this was limited by loss to follow-up. We subsequently revised our ASM weaning protocol to be more efficient and not reliant upon repeat EEG in October of 2022. In parallel to the inclusion of the ASM weaning protocol in our seizure pathway, neurology also worked to increase clinic capacity to see NICU graduates within one month of discharge.

Previous work has shown that the development of a neurocritical care program can decrease the percent of infants discharged on ASM.\(^ {19}, 20\) Unfortunately these specialized programs are not available at the majority of hospitals caring for infants with seizures. Lack of consultation by pediatric neurologists and limited availability of technical resources further restrict wide-spread applicability of neurocritical care programs.\(^ {21}\) Our study demonstrates that decreasing ASM at discharge does not rely solely on a formal neurocritical care program. Inpatient neurology consults are not available at our delivery hospitals at the time of this publication, yet, through collaboration between divisions and buy-in from key stakeholders, we were still able to improve care for these high-risk infants.

The strength of this study is the impact of the implementation of an ASM weaning protocol on the evolution of ASM discontinuation at discharge in infants with acute symptomatic seizures across local hospitals managed by one academic group. Our work highlights opportunities for similar NICUs who may frequently discharge infants with acute symptomatic seizures on ASM. This study has some limitations. Generalizability may be limited as it was a retrospective cohort study across three hospitals covered by the same neonatology and neurology physicians. Additionally, we were not able to control for other factors that may have impacted whether an infant was continued on ASM at discharge. Our study was also limited by loss to follow-up in 17% of our cohort.

In conclusion, we found that inclusion of an ASM weaning protocol in a neonatal seizure pathway reduced the percent of infants with acute symptomatic seizures discharged on ASM. This difference was seen at delivery hospitals, in addition to a referral hospital, where inpatient neurology consults were not routinely available. This protocol highlights an opportunity for all NICUs to reduce the percentage of infants discharged on ASM.

Declarations

Conflicts of Interest:
Elizabeth Sewell has received consultant fees from Hospicom and Sun Pharmaceutical Industries, Inc. The remaining authors have no conflicts of interest to disclose directly related to this study.

Funding:

There were no external sources of funding for this study.

Author contributions:

AMN contributed to the data curation, investigation, and writing of the original manuscript. ZH contributed to the formal analysis and critical review of the final manuscript. ES contributed to the conceptualization, data curation, investigation, methodology, and drafting of the original manuscript. MD, SB, SH, AP, AC, AV, JB, and PJ contributed to the investigation and critical review of the final manuscript.

References


Figures
Figure 1: Flow Diagram.

Infants with electrographic seizures with final encounters in NICU system (N = 193)

Excluded 38 infants who died prior to discharge

Infants who survived to discharge (N = 155)

Excluded 39 infants with epilepsy

Infants with acute symptomatic seizures who survived to discharge (N = 116)

Figure 1

Flow diagram of cohort.
Figure 2

The percent of infants with acute symptomatic seizures discharged on ASM by birth year.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SuppFig1.pdf