Risk Factors for Apnea in Pediatric Patients Transported by Paramedics for Out-of-Hospital Seizure

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Study objective: Apnea is a known complication of pediatric seizures, but patient factors that predispose children are unclear. We seek to quantify the risk of apnea attributable to midazolam and identify additional risk factors for apnea in children transported by paramedics for out-of-hospital seizure.

Methods: This is a 2-year retrospective study of pediatric patients transported by paramedics to 2 tertiary care centers. Patients were younger than 15 years and transported by paramedics to the pediatric emergency department (ED) for seizure. Patients with trauma and those with another pediatric ED diagnosis were excluded. Investigators abstracted charts for patient characteristics and predefined risk factors: developmental delay, treatment with antiepileptic medications, and seizure on pediatric ED arrival. Primary outcome was apnea defined as bag-mask ventilation or intubation for apnea by paramedics or by pediatric ED staff within 30 minutes of arrival.

Results: There were 1,584 patients who met inclusion criteria, with a median age of 2.3 years (Interquartile range 1.4 to 5.2 years). Paramedics treated 214 patients (13%) with midazolam. Seventy-one patients had apnea (4.5%): 44 patients were treated with midazolam and 27 patients were not treated with midazolam. After simultaneous evaluation of midazolam administration, age, fever, developmental delay, antiepileptic medication use, and seizure on pediatric ED arrival, 2 independent risk factors for apnea were identified: persistent seizure on arrival (odds ratio [OR] = 15; 95% confidence interval [CI] 8 to 27) and administration of field midazolam (OR = 4; 95% CI 2 to 7).


Please see page 303 for the Editor’s Capsule Summary of this article.

INTRODUCTION

Background
Seizure is the most common chief complaint for pediatric patients in the out-of-hospital setting, accounting for approximately 15% of all emergency medical services (EMS) transports of pediatric patients in the United States.1 Given the significant morbidity and mortality from prolonged seizures, including risk of permanent neurologic sequelae, treatment is recommended for any seizure lasting more than 10 minutes.1-3 The sooner the seizure is treated, the more likely it is to be controlled.1 For this reason, initiating treatment for persistent seizures in the out-of-hospital setting is common practice in EMS systems in the United States. Benzodiazepines are first-line therapy, and their out-of-hospital administration shortens overall seizure duration.4,5 Traditionally, diazepam was most often used to treat pediatric seizures. However, in the past decade, midazolam has emerged as a favored therapy because of its ease of administration by multiple routes and its rapid onset and clearance, making it less likely to result in adverse effects, including cardiovascular depression and apnea.2,6-8 Los Angeles County EMS Agency protocol was changed in July 2009, designating midazolam (through the intravenous, intramuscular, or intranasal route) as the treatment for pediatric seizure.

Importance
Respiratory depression is a potential complication of treatment with benzodiazepines, especially in children.5,6,9-13 The high risk of respiratory depression in several studies has caused some to question the use of benzodiazepines as first-line therapy for seizure.12 Others have argued that the risk of complications with benzodiazepines may be outweighed by the benefits of reduced seizure duration, which itself could lead to respiratory compromise.4 There is little knowledge of what other factors may contribute to respiratory depression in children with seizure. It has been suggested that children with developmental delay, those receiving previous seizure medications, and those with high fever may be more susceptible, but this is not well
studied. Furthermore, prolonged seizure is likely a risk factor for apnea. Children with persistent seizure activity are more likely to receive medication, so the true contribution of benzodiazepines in the onset of apnea remains unclear. It is important to account for these potential risk factors when evaluating the risk of apnea during paramedic treatment of out-of-hospital seizure. By identifying patients at higher risk of apnea, protocols may be tailored with consideration of these special populations for additional monitoring.

Goals of This Investigation

We sought to quantify the risk of apnea in children presenting with out-of-hospital seizure treated with midazolam by paramedics and to identify other risk factors associated with apnea in this population.

MATERIALS AND METHODS

Study Design and Setting

We conducted a multicenter retrospective chart review of pediatric patients with seizure who were transported by paramedics to the pediatric emergency department (ED) at Harbor-UCLA Medical Center and Los Angeles County/University of Southern California Medical Center during a 2-year period, from January 2010 to December 2011. The study was approved with waiver of informed consent by the institutional review board at both institutions. Harbor-UCLA Medical Center and Los Angeles County/University of Southern California Medical Center are public teaching facilities serving Los Angeles County, with an approximate population of 10 million. Both hospitals are designated pediatric referral centers, as well as pediatric trauma centers, with an annual pediatric ED patient volume of 21,000 and 25,000 at Harbor-UCLA Medical Center and Los Angeles County/University of Southern California Medical Center, respectively. In Los Angeles County, paramedic crews consist of 2 paramedic-level emergency medical technicians (paramedics) stationed at local fire departments. Protocols in Los Angeles County support administration of midazolam by paramedics for seizure termination in any patient actively seizing. The dose may be repeated as needed with online medical control guidance until the seizure terminates. Pediatric patients are defined as aged 14 years or younger, and Los Angeles County pediatric treatment protocols are specific to this age group. Pediatric airway management in the field consists of bag-mask ventilation for children younger than 12 years or less than 40 kg. Intubation is available by protocol for children aged 12 years and older or greater than 40 kg. The average time from dispatch to hospital arrival for pediatric patients transported by paramedics in Los Angeles County is approximately 20 minutes.

Selection of Participants

Inclusion criteria were patients younger than 15 years and transported by paramedics to the pediatric ED with the diagnosis of seizure. Patients with an initial chief complaint of seizure, but who were found to have another diagnosis on pediatric ED evaluation or whose primary complaint was traumatic injury, were excluded. At Harbor-UCLA Medical Center, patients were identified by chief complaint from the base-hospital log of all paramedic transports to the ED. Out-of-hospital care coordinators record all patient transports in a county-sponsored database. At Los Angeles County/University of Southern California Medical Center, an electronic medical record of pediatric ED patients is available. Patients with a chief complaint of seizure or a related discharge diagnosis were identified from an electronic record of all patients treated in the pediatric ED during the study period and screened for those patients transported by paramedics for out-of-hospital seizure. The following diagnoses were included in the search criteria: nonconvulsive epilepsy International Classification of Diseases, Ninth Revision (ICD-9) 345.00; epilepsy, convulsion, generalized ICD-9 345.1; epilepsy, petit mal status ICD-9 345.2; epilepsy, grand mal status ICD-9 345.3; seizure, grand mal ICD-9 345.3; epilepsy, without impairment of consciousness ICD-9 345.5; epilepsy (unspecified) ICD-9 345.9; epileptic convulsion (unspecified) ICD-9 345.9; epileptic seizure (unspecified) ICD-9 345.9; febrile convulsion ICD-9 780.31; febrile seizure ICD-9 780.31; seizure, febrile ICD-9 780.31; complex febrile convulsion ICD-9 780.32; and other convulsions (seizure not otherwise specified) ICD-9 780.39. An initial chief complaint of seizure identified by out-of-hospital personnel and a pediatric ED diagnosis of seizure were required to meet inclusion in the study; therefore, the final patient selection at each institution was similar.

Methods of Measurement

Charts were reviewed by 2 investigators at each institution; at Harbor-UCLA, a nurse practitioner in the division of pediatric emergency medicine and an EMS fellow board-certified in emergency medicine, and at Los Angeles County/University of Southern California Medical Center, a pediatric emergency physician and an pediatric emergency physician.
Southern California Medical Center an emergency medicine resident and an attending physician board-certified in pediatric emergency medicine. In addition, at Harbor-UCLA, a medical student initiated the data collection instrument with basic demographic information, which was reviewed and then completed by the investigators above. Abstractors were trained by the principal investigator to use a single data dictionary identical at both sites that contained definitions for each variable and coded response to be entered on the abstraction form.

The investigators were not blinded to the purpose of the study. The charts were abstracted for study variables: paramedic-administered midazolam, route of administration, number of doses of medication administered, and total dose of medication administered. During the entire study period, paramedics could administer midazolam intravenously, intranasally, or intramuscularly at a dose of 0.1 mg/kg.

Paramedics used the Broselow tape to estimate patient weight for medication dosing. In addition, investigators extracted information on sex, age, weight, fever, history of developmental delay, seizure on arrival to the pediatric ED, treatment with rectal diazepam by a caregiver, and current treatment with an antiepileptic drug. Weight was recorded as the measured value in the ED. If the measured value was not available but an estimated value was recorded, then this was used; otherwise, weight was recorded as missing. Fever was considered present if a temperature measured at any point during the patient’s stay in the pediatric ED was documented at or above 38°C (100.4°F) or if a parent or guardian reported a measured or tactile fever. It was considered absent if no temperature exceeded 38°C (100.4°F) and there was no documentation of fever reported at home. A patient was considered to be receiving an antiepileptic drug if there was documentation of currently prescribed medication. If noncompliance was reported, the variable was coded as positive if the last dose was within 1 week of presentation, considering negligible amounts of drug after 5 half-lives. Developmental delay was defined as neurologic delay; it was considered present if documented on any pediatric ED visit or inpatient stay and absent if not documented. Seizure on arrival to the pediatric ED was based on initial triage and physician documentation and was used as a proxy for prolonged seizure.

Age was coded as a continuous variable, whereas other variables were coded as binary predictors. With a designated, standardized collection instrument, data were tabulated and entered into a Microsoft Excel spreadsheet (Microsoft, Redmond, WA) and back-checked by the principal investigator for accuracy. This was accomplished by evaluating for any inconsistency, using the inherent redundancy of the data collection instrument, and revisiting any chart reviews in which inconsistencies were identified. The data were then imported into SAS for analysis (version 9.3; SAS Institute, Inc., Cary, NC).

Outcome Measures

Outcome variables for airway management for apnea were defined as bag-mask ventilation or intubation by paramedics or by pediatric ED staff within 30 minutes of arrival. For patients in whom airway intervention was required, the chart review included the respiratory status of the patient before airway management and the documented indications for intubation if performed to determine whether apnea was present. Outcomes were abstracted and then confirmed by agreement of the 2 investigators at the site, and any discrepancy was discussed and resolved with a third (for Los Angeles County/University of Southern California Medical Center patients, this was the principal investigator at Harbor-UCLA Medical Center; for Harbor-UCLA Medical Center patients, this was the senior investigator at Harbor-UCLA Medical Center). There were 2 patients at Harbor-UCLA Medical Center and 5 at Los Angeles County/University of Southern California Medical Center who required such review. After review, they were not included in the group with apnea. The discrepancies were due to the indication for intubation in 6 cases and the timing of airway management 1 case.

Primary Data Analysis

The study outcomes (intubation or bag-mask ventilation) for each group were calculated as proportions with exact binomial confidence intervals (CIs). Adjusted odds ratios (ORs) were determined with multiple logistic regression. All variables were selected a priori according to previous knowledge of potential risk factors for apnea and potential effect modifiers. They were introduced simultaneously into the model to determine the adjusted OR for apnea for each variable. Age was entered as a continuous variable and all other variables were binary. Model fit was determined by assessing the Hosmer-Lemeshow fit statistic, and model predictors were retained according to previous knowledge, as well as statistical significance. The interaction between seizing on arrival and receiving a field medication was considered, and effect measure modification of these 2 variables was assessed by comparing ORs for apnea, given one variable across categories of another. Finally, a propensity score–adjusted model was performed to confirm the results of the multivariate regression because of the large differences between the treatment groups. The propensity score–adjusted analysis also allowed adjustment by additional potential confounding factors (weight and treatment with rectal diazepam by a caregiver), given the limitations of the multivariate model because of the rarity of the outcome.

Risk Factors for Apnea in Pediatric Patients

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![Figure. Patient identification and inclusion.](image-url)
RESULTS

Characteristics of Study Subjects

As seen in the Figure, 2,403 patients were reviewed for study inclusion, of whom 815 were excluded. The remaining 1,584 pediatric patients transported by paramedics during the study period make up the study cohort, 770 patients transported to Harbor-UCLA Medical Center and 813 patients transported to Los Angeles County/University of Southern California Medical Center. Table 1 shows the characteristics of the study population as a whole and by treatment group. Of the 214 patients (14%) treated with midazolam, paramedics administered the drug intravenously to 87 (41%), intramuscularly to 53 (25%), intranasally to 57 (27%), and by multiple routes to 17 (8%). Paramedics dosed midazolam accurately; the median intravenous dose was 0.09 mg/kg (95% CI 0.08 to 0.1 mg/kg) and this did not differ across age groups. There was a 22% admission rate. Discharge diagnoses were simple febrile seizure (50%), complex febrile seizure (7%), epilepsy (27%), first-time seizure (8%), and seizure type undefined (8%).

Main Results

There were 71 patients with apnea (4.5%); 44 patients (62%) treated with midazolam and 27 (38%) not treated with midazolam. Table 2 shows patient outcomes. For the 53 patients (3.6%) who required intubation, the median time to intubation was 13 minutes (Interquartile range [IQR] 8 to 20) from pediatric ED arrival. The majority of patients (70%) who required airway intervention in the pediatric ED did not receive medications there before airway management for apnea. Paramedics did not intubate any patients in the field.

We evaluated the effect of the administration of midazolam in the field, age, fever, developmental delay, treatment with an antiepileptic drug, seizure on pediatric ED arrival, and the interaction between midazolam administration and seizure on pediatric ED arrival on the risk of apnea. The final model, simultaneously evaluating the above covariates, demonstrated 2 independent risk factors for apnea: persistent seizure on arrival (OR=15; 95% CI 8 to 27) and administration of field midazolam (OR=4; 95% CI 2 to 7) (Table 3). The interaction term was not a statistically significant predictor for apnea (OR=1.5; 95% CI 0.6 to 4.1), so it was not included in the final model. The results of the model including the interaction term have been provided in Table E1 (available online at http://www.annemergmed.com). A propensity score–adjusted model confirmed the association of field midazolam administration with apnea (OR=4.6; 95% CI 2.6 to 8.3). The Hosmer-Lemeshow goodness-of-fit statistics for the propensity score–adjusted and unadjusted models demonstrated a P value of .2 and .1, respectively, indicating adequate fit for both models.

A stratified analysis demonstrated that among those who were not seizing on arrival (n=1,431), the OR for apnea if patients were given midazolam was 16 (95% CI 7 to 39). Among patients who were seizing on arrival (n=153), the OR for apnea if patients were given midazolam was 1.5 (95% CI 0.8 to 3.1). Thus, there appears to be effect measure modification of

Table 1. Characteristics of the study population (n=1,584).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population</th>
<th>Midazolam (n = 214)</th>
<th>No Midazolam (n = 1,370)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (Median) %, IQR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>2.3 1.4-5.2</td>
<td>3.2 1.8-6.2</td>
<td>2.2 1.3-4.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>14 11-20</td>
<td>15 12-20</td>
<td>13 11-20</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>875 55</td>
<td>98 46</td>
<td>777 57</td>
</tr>
<tr>
<td>Female</td>
<td>709 45</td>
<td>116 54</td>
<td>593 43</td>
</tr>
<tr>
<td>Fever</td>
<td>1,074 68</td>
<td>125 58</td>
<td>949 69</td>
</tr>
<tr>
<td>Treatment with an antiepileptic drug</td>
<td>374 24</td>
<td>92 43</td>
<td>282 21</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>300 19</td>
<td>74 35</td>
<td>226 17</td>
</tr>
<tr>
<td>Seizure on pediatric ED arrival</td>
<td>153 10</td>
<td>86 40</td>
<td>67 5</td>
</tr>
<tr>
<td>Rectal diazepam administered</td>
<td>60 4</td>
<td>15 7</td>
<td>45 3</td>
</tr>
</tbody>
</table>

Table 2. Frequencies for patient outcomes and airway management (n=1,584).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No airway intervention</td>
<td>1,513</td>
<td>95.5</td>
</tr>
<tr>
<td>Any apneic event</td>
<td>71</td>
<td>4.5</td>
</tr>
<tr>
<td>Apnea in the field or at pediatric ED arrival</td>
<td>48</td>
<td>3.0</td>
</tr>
<tr>
<td>Field BMV</td>
<td>27</td>
<td>1.7</td>
</tr>
<tr>
<td>Pediatric ED BMV</td>
<td>49</td>
<td>3.1</td>
</tr>
<tr>
<td>Pediatric ED intubation</td>
<td>53</td>
<td>3.6</td>
</tr>
</tbody>
</table>

BMV, Bag-mask ventilation.

Table 3. Adjusted ORs for apnea.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR for Apnea (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure on pediatric ED arrival</td>
<td>15 8–27</td>
</tr>
<tr>
<td>Treatment with midazolam</td>
<td>4 2–7</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>1.9 0.8–4.3</td>
</tr>
<tr>
<td>Age (per year younger)</td>
<td>1.1 1.0–1.3</td>
</tr>
<tr>
<td>Treatment with antiepileptic drug</td>
<td>1.0 0.4–2.2</td>
</tr>
<tr>
<td>Fever</td>
<td>0.8 0.4–1.5</td>
</tr>
</tbody>
</table>

*Adjusted OR generated by the simultaneous entry of covariates in the logistic regression model. Hosmer-Lemeshow goodness-of-fit statistics P value 0.1, Akaike information criterion = 406.8.
persistent seizure on the association of midazolam with apnea. Midazolam administration was no longer associated with apnea among patients who were seizing on arrival, possibly because of small sample size.

Of the 60 patients (4%) treated with rectal diazepam by caregivers before EMS arrival, 8 had apnea, of whom half received additional treatment with midazolam by paramedics. We included treatment with rectal diazepam in the propensity score–adjusted analysis reported above. In addition, neither inclusion of all patients who received rectal diazepam by caregivers in the treated group nor their exclusion from the analysis affected the study results.

LIMITATIONS

This study has several limitations. Although it represents a large number of children treated for seizure by multiple EMS provider agencies and transported to 2 different hospitals, it is limited to a single urban area of Los Angeles County and may not be generalizable to all populations.

The retrospective nature of the study could lead to bias, given that the investigators were not blinded to the outcome when extracting the data and we did not calculate the interrater reliability between reviewers to confirm reliability of study variables. However, we attempted to mitigate this bias by choosing concrete outcomes (rather than hypoventilation). In addition, the definite outcome of ventilation by bag-mask or intubation for apnea in the field or within 30 minutes of pediatric ED arrival was selected to avoid misclassification of primary respiratory illnesses such as asthma and pneumonia, which would otherwise be a concerning source of bias. However, this could have introduced a different source of bias and affected our specificity if data for patients intubated for other reasons were included as positive outcomes. We believe that these misclassifications were unlikely to occur because of our rigorous chart review performed by trained investigators at each institution.

Misclassification of some exposure measurements may also have occurred. We considered seizure on arrival as a proxy for prolonged seizure because timing of seizure as estimated by witnesses is fraught with error. In addition, fever reported by parents has been shown to be present if measured in the pediatric ED or if reported by parents; witnesses is fraught with error. In addition, fever was considered prolonged seizure because timing of seizure as estimated by caregivers before EMS arrival, 8 had apnea, of whom half received additional treatment with midazolam by paramedics. We included treatment with rectal diazepam in the propensity score–adjusted analysis reported above. In addition, neither inclusion of all patients who received rectal diazepam by caregivers in the treated group nor their exclusion from the analysis affected the study results.

DISCUSSION

We determined that the occurrence of apnea in children with out-of-hospital seizure is multifactorial, and risk factors likely include treatment with midazolam and prolonged seizure. Other patient factors hypothesized to influence apnea risk, including age, fever, treatment with antiepileptic medication, and developmental delay, did not significantly contribute to outcomes in our patient population. To our knowledge, our study is the first to quantify the risk of apnea in children with out-of-hospital seizure that may be attributed to midazolam administration after accounting for other potential confounding risk factors.

The overall risk of apnea in our cohort was 4.5%. A high risk of apnea has previously been reported with benzodiazepine administration in the field for treatment of pediatric seizure, but the contribution of patient factors was not evaluated.\textsuperscript{6,13,15,20} The risk of apnea appears to be lower with midazolam than with other benzodiazepines traditionally used,\textsuperscript{6,7,21} but this is not consistent across studies.\textsuperscript{15,22–25} After adjusting for patient factors, Holsti et al\textsuperscript{22} found the proportion of respiratory complications to be similar between patients treated with midazolam and diazepam.

Although previous studies highlight the potential for apnea in pediatric patients with out-of-hospital seizure, simply describing the risk of apnea in patients treated with out-of-hospital benzodiazepines does not allow the assessment of the effect of other contributing factors. The risk of apnea caused by benzodiazepines in relation to the benefit of early seizure termination requires a large cohort of patients. Orr et al\textsuperscript{19} evaluated the association of diazepam with apnea in children treated in the ED, adjusting for patient age, weight, duration of seizure before medication, final diagnosis, and additional therapies and found a significant association between diazepam and apnea, with a reported OR of 49.4. Our study differs in its out-of-hospital setting, the benzodiazepine evaluated, and the inclusion of other potential confounders in our model.

The Prehospital Treatment of Status Epilepticus trial, a randomized study of adult patients treated by paramedics for out-of-hospital seizure, found equal proportions of respiratory complications in patients treated with benzodiazepines and patients who received placebo, suggesting that other factors contributed to overall apnea risk.\textsuperscript{20} They demonstrated that
benzodiazepines were safe and effective for treatment of out-of-hospital seizure in adults. In the Rapid Anticonvulsant Medication Prior to Arrival Trial study with adults and children (down to 13 kg body weight), the risk of intubation within 30 minutes in the ED in the lorazepam and midazolam groups treated out-of-hospital were similar, although for both medications the rate of apnea was much higher than reported here (14.3% and 14.6%, respectively). Other investigators report high proportions of apneic events in children with out-of-hospital seizure, and the possibility of increased risk in younger children has been suggested to explain this observation. Therefore, we thought it was important to evaluate the risk specific to pediatric patients.

Although treatment with benzodiazepines is a known risk factor for apnea, we found that the association of midazolam administration with the occurrence of apnea is greatly attenuated after accounting for other important patient factors. As has been suggested by previous studies, we determined prolonged seizure to be a significant risk factor for apnea, resulting in greater risk to the patient than administration of benzodiazepines. As one might anticipate, there was an association between prolonged seizure and field treatment with benzodiazepines. Sicker patients with complex seizures are less likely to spontaneously terminate seizure activity and more likely to require benzodiazepines by paramedics. We found this to be a predominant cause of the observed association between benzodiazepine administration and apnea. In addition, there appears to be interaction between benzodiazepines and prolonged seizure activity in regard to the outcome of apnea. Although seizing on pediatric ED arrival appeared to be the greatest risk factor for apnea, midazolam administration was an independent risk factor. This association was not statistically significant among patients who were seizing on pediatric ED arrival, likely because of the small number of patients in this group.

Age, fever, developmental delay, and current treatment with an antiepileptic drug do not appear to be associated with apnea in these children. Unlike in previous studies, intubation for other reasons, such as for airway protection, was not included in our predefined composite outcome for apnea. To specifically quantify the risk of apnea associated with benzodiazepines, we intended to focus our analysis on risk factors for apnea rather than risk factors for airway intervention.

In light of our findings, it would seem that the most important factor in reducing the risk of apnea in children with out-of-hospital seizure is termination of seizure activity. Because benzodiazepines help terminate seizure activity, their administration by paramedics in the field is justified and may reduce the overall incidence of apnea in children with seizure. Although there remains a risk of apnea associated with benzodiazepines, it is outweighed by the risk of apnea caused by persistent seizure activity.

In summary, we identified 2 risk factors for apnea in children transported for seizure: prolonged seizure as manifested by persistent seizure on pediatric ED arrival and out-of-hospital administration of midazolam. Although treatment with benzodiazepines is associated with occurrence of apnea, persistent seizure appears to be the strongest risk factor, and early termination of out-of-hospital seizure in children is warranted. Paramedics should be prepared to manage the airway of any child presenting with out-of-hospital seizure who is seizing at paramedic arrival or requires medication for seizure termination.

The authors acknowledge Paul Hsu, PhD for his contribution to the design of this study.


**DIAGNOSIS:**

*Peristaltic abdominal waves associated with infantile hypertrophic pyloric stenosis.*** Infantile hypertrophic pyloric stenosis is relatively common, occurring in 2 to 5 of every 1,000 births and is caused by the hypertrophy of the antropylocic portion of the stomach.*1,2* The cause is unknown but likely related to genetic and environmental factors.*1,3* Infantile hypertrophic pyloric stenosis usually presents at 4 to 6 weeks of age with nonbilious vomiting often described as “projectile.” If unrecognized, infantile hypertrophic pyloric stenosis can result in weight loss, dehydration, and hypokalemic hyperchloremic metabolic alkalosis.*** In severe cases such as this, peristaltic waves can be associated with significant weight loss and dehydration.*** Although challenging to detect and not observed in this patient, palpation of the hypertrophied pylorus or “olive” has a 99% positive predictive value.*** Sonographic thickness of the pyloric muscle wall greater than 3 mm or a length greater than 15 mm can confirm the diagnosis.***

The child underwent pyloromyotomy, did well, and was discharged several days later.

**REFERENCES**


Table E1. Adjusted ORs for apnea with interaction term.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR for Apnea (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with midazolam</td>
<td>17</td>
</tr>
<tr>
<td>Seizure on pediatric ED arrival</td>
<td>50</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>1.6</td>
</tr>
<tr>
<td>Age (per year younger)</td>
<td>1.1</td>
</tr>
<tr>
<td>Treatment with antiepileptic drug</td>
<td>1.0</td>
</tr>
<tr>
<td>Fever</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Interaction term</strong></td>
<td></td>
</tr>
<tr>
<td>Midazolam and seizure on pediatric ED arrival</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Adjusted OR generated by the simultaneous entry of covariates in the logistic regression model. Hosmer-Lemeshow goodness-of-fit statistics P value 0.2, Akaike information criterion = 392.6.