Brief Communication

Complications during the management of pediatric refractory status epilepticus with benzodiazepine and pentobarbital infusions

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Abstract

The objective of this retrospective study was to evaluate complications in the management of refractory status epilepticus (RSE) treated with benzodiazepine and pentobarbital infusions. Of 28 children with RSE, eleven (39%) were treated with a pentobarbital infusion after failure to control RSE with a benzodiazepine infusion; while 17 children (61%) required only a benzodiazepine infusion. The mean maximum pentobarbital infusion dosage was 5.2 ± 1.8 mg/kg/h. Twenty-five patients received a continuous midazolam infusion with an average dosage of 0.41 ± 0.43 mg/kg/h. The median length of stay was longer for the pentobarbital group. Children requiring pentobarbital therapy were more likely to develop hypotension, require inotropic support, need intubation, mechanical ventilation, peripheral nutrition, and blood products; furthermore, they were more likely to develop hypertension and movement disorder after or during weaning. In conclusion, children with RSE who required pentobarbital therapy had a longer hospital stay with more complications.

Keywords: Child, pediatric intensive care unit, status epilepticus, seizures

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Introduction

Refractory status epilepticus (RSE) is defined as seizures that are nonresponsive to adequate initial anti-epileptic therapy and require a continuous infusion of an antiepileptic medication or administration of inhalation anesthetic agent to stop the seizure activity.[1] RSE is associated with a high morbidity and mortality.[2] The care of children with RSE is largely based on extrapolations of limited evidence derived from adult literature and supplemented with case reports and case series in children. Midazolam and pentobarbital infusions are used in the treatment of RSE.[3] The use of a pentobarbital infusion in the management of RSE has shown to be associated with a high morbidity and mortality. The current study describes a single center experience of management of RSE with the use of midazolam and pentobarbital.

Methods

In this retrospective cohort study, children (age: 0-21 years) admitted to a tertiary-care pediatric intensive care unit with RSE, over a 3-year period, were identified and included. The study was approved by the institutional review board. Demographic and clinical data were collected from the hospital administrative database and electronic patient healthcare records. All children who continued to have either clinical or electrical seizure activity despite initial treatment with lorazepam, diazepam, phenytoin, and phenobarbital and required a continuous anti-epileptic medication infusion to control their seizure activity were included in the study. Children who had recurrent seizures and required a continuous infusion of anti-epileptic medication were included. Patients who were admitted with status epilepticus and did not require a continuous infusion to control their seizures were excluded from the study. Patients who were transferred from an outside

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institution, intubated and on a benzodiazepine infusion, and whose seizures had terminated were also excluded. All children who receive pentobarbital were monitored with a continuous electroencephalogram (EEG) recording.

Outcome of children who required continuous pentobarbital infusion to control RSE were compared with those who were controlled with continuous benzodiazepine infusion alone. Continuous data were analyzed with the Mann–Whitney U test, and binary data were analyzed using Fisher exact test. Differences were considered statistically significant at $P < 0.05$.

Results

Of 28 admissions, 4 (14%) were admitted with new onset of seizures and all others had a known seizure disorder and were taking multiple antiepileptic medications. The descriptive and analytic data are presented in Table 1. All children in this cohort received continuous infusion of a benzodiazepine (midazolam = 25; lorazepam = 4; both = 1) for seizure control. Eleven patients (39%) required pentobarbital infusion in addition to benzodiazepines to control seizures while others (61%) received only a benzodiazepine infusion. The mean maximum pentobarbital infusion dosage was 5.2 ± 1.8 mg/kg/h with a median duration of treatment of 14 (interquartile range [IQR]: 12–76) days. Twenty-five patients received a continuous midazolam infusion with a mean maximum dosage of 0.41 ± 0.43 mg/kg/h for a median duration of treatment of 4 (IQR: 1–16) days. Only one child died who did not receive pentobarbital and the death was not related to seizure management.

Discussion

All patients in our study received a benzodiazepine infusion as an initial anticonvulsant continuous therapy. Complications and resource utilization were less frequent in children whose seizures were controlled with only a benzodiazepine infusion. A meta-analysis of 111 children concluded that midazolam was as effective as other coma-inducing medications and involved a lower mortality (zero with midazolam),[4] however, Morrison noted that breakthrough seizure activity is common with midazolam.[5] A standardized protocol for escalation or weaning of anti-epileptic infusion therapy was not utilized in our cohort. Pentobarbital infusion was titrated to achieve a burst suppression pattern during continuous video-EEG monitoring; the required degree of burst suppression (number of burst patterns per unit time) was not standardized. An aggressive step-wise approach to maximize benzodiazepine prior to initiating a pentobarbital infusion may have prevented some patients from requiring pentobarbital, thus limiting their complications. Developing a protocolized treatment plan similar to Abend *et al*.[6] may have been beneficial in limiting the side effects that we noted in our patients.

Recent guidelines for the management of status epilepticus do not recommend preference to any one drug among midazolam, propofol, and pentobarbital for the management of RSE.[7] In a meta-analysis,

Table 1: Demographic, resource utilization, and complications of children with refractory status epilepticus were treated with and without pentobarbital

	Total (n=28)	Pentobarbital treated (n=11)	Pentobarbital not treated (n=17)	P
Female (%)	8 (29)	3 (27)	5 (29)	NS
Age (years)	7.41 (3.8-15)	7.41 (2-15)	7.41 (4.4-15)	NS
LOSH (days)	17 (8-55)	56 (36-121)	9 (5-17)	0.0001
LOSPICU (days)	10 (7-41)	56 (13-109)	8 (3-10)	0.0001
Midazolam duration (n=25; days)	4 (1-16)	15.5 (2.5-47)	3 (1-5)	0.039
Midazolam maximum dose (mg/kg/h)	0.3 (0.1-0.55)	0.55 (0.28-0.9)	0.2 (0.05-0.3)	0.0053
Pentobarbital duration (n=11; days)	-	14 (12-76)	-	NA
Pentobarbital maximum dose (mg/kg/h)	-	5 (4-6)	-	NA
Lorazepam maximum dose (n=4; mg/kg/h)	0.13 (0.05-0.3)	0.33 (0.33-0.33)	0.06 (0.05-0.2)	NA
Number of AEDs	3 (2-4)	4 (4-5)	2 (1.5-3)	0.0044
Hypotension during therapy (%)	61	91	41	0.016
Inotropic support (%)	50	91	24	0.0013
Intubation (%)	61	100	41	0.016
Total parenteral nutrition (%)	32	73	6	0.0004
Blood product use (%)	25	55	6	0.0069
Central venous line (%)	43	82	18	0.0015
Healthcare acquired infection (%)	79	100	65	0.03
Antibiotic use (%)	82	100	71	0.047
Hypertension after stopping continuous infusions (%)	21	55	0	0.0012
Movement disorder after stopping continuous infusion (%)	25	64	0	0.0003

Continuous variable presented as median (IQR). Categorical data presented as percentage. AEDs: Anti-epileptic drugs; LOSH: Hospital length of stay; LOSPICU: Pediatric Intensive Care Unit length of stay; NA: Not applicable; NS: Not significant; IQR: Interquartile range

pentobarbital treatment was associated with a lower incidence of short-term treatment failure, fewer breakthrough seizures, and decreased need for additional anti-epileptic medications, but was associated with a significantly higher frequency of hypotension as seen in our study.[3]

Studies of pentobarbital therapy for RSE in children have reported an efficacy of 74–100%.[8-10] The loading dose of pentobarbital is generally 5 mg/kg administered over an hour, followed by an infusion at a rate of 1 mg/kg/h, which can be increased as needed to 3 mg/kg/h. Continuous blood pressure monitoring is important because hypotension may occur with dose escalation. In our cohort, a loading pentobarbital bolus was used inconsistently, often requiring a higher continuous dose to achieve a therapeutic effect.

Our study noted two unexpected complications associated with prolonged pentobarbital treatment: Movement disorders that developed during weaning or after discontinuation of pentobarbital infusion therapy and hypertension, which required medical therapy. These two complications have not been previously described during pentobarbital treatment.

We report a lowest mortality in a cohort of children with RSE. Low mortality in our cohort may be due to lower percent of new onset RSE. Previously healthy children with encephalitis and presenting with RSE had a poor neurologic outcome. However, children with a known seizure disorder presenting with RSE had a low morality and their neurologic status did not worsen in spite of prolonged therapy with benzodiazepines with or without pentobarbital.

Conclusion

Patients who required pentobarbital to control RSE had a longer hospital stay with more complications. The mortality rate was low (3.5%) in children presenting with RSE. Whether aggressive escalation of midazolam therapy will reduce the use of pentobarbital and reduce complications warrants a prospective examination.

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