Pediatric Neurology xxx (2014) 1–7

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Midazolam Fails to Prevent Neurological Damage in Children With Convulsive Refractory Febrile Status Epilepticus

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ABSTRACT

BACKGROUND: We conducted a retrospective study to compare the outcome of intravenous midazolam infusion without electroencephalography or targeted temperature management and barbiturate coma therapy with electroencephalography and targeted temperature management for treating convulsive refractory febrile status epilepticus. **PATIENTS:** Of 49 consecutive convulsive refractory febrile status epilepticus patients admitted to the pediatric intensive care unit of our hospital, 29 were excluded because they received other treatments or because of various underlying illnesses. Thus, eight patients were treated with midazolam and 10 with barbiturate coma therapy using thiamylal. Midazolam-treated patients were intubated only when necessary, whereas barbiturate coma therapy patients were routinely intubated. Continuous electroencephalography monitoring was utilized only for the barbiturate coma group. The titration goal for anesthesia was clinical termination of status epilepticus in the midazolam group and suppression or burst-suppression patterns on electroencephalography in the barbiturate coma group. Normothermia was maintained using blankets and neuromuscular blockade in the barbiturate coma group and using antipyretics in the midazolam group. Prognoses were measured at 1 month after onset; children were classified into poor and good outcome groups. **RESULTS:** Good outcome was achieved in all the barbiturate coma group patients and 50% of the midazolam group patients ($P = 0.02$, Fisher's exact test). **CONCLUSIONS:** Although the sample size was small and our study could not determine which protocol element is essential for the neurological outcome, the findings suggest that clinical seizure control using midazolam without continuous electroencephalography monitoring or targeted temperature management is insufficient in preventing neurological damage in children with convulsive refractory febrile status epilepticus.

Keywords: midazolam, refractory status epilepticus, barbiturate coma therapy, targeted temperature management, neurological damage, acute encephalopathy

Pediatr Neurol 2014; ■: 1-7

Introduction

Status epilepticus is often accompanied by fever; febrile status epilepticus is the most common type of status epilepticus and accounts for 20-50% of status epilepticus cases in children. Febrile status epilepticus is often separately analyzed because of its better outcome than nonfebrile status epilepticus because of differing etiologies. However, status epilepticus, other than febrile status epilepticus, is also often accompanied by fever. In some cases, status epilepticus with fever is categorized as central nervous system (CNS) infection even in the absence of pleocytosis or positive CNS culture.[1-8] Status epilepticus with fever is also known to result in subsequent neurological conditions, such as hemiconvulsion-hemiplegia-epilepsy syndrome,[9] acute encephalopathy with febrile convulsive status epilepticus,[10] or hippocampal abnormalities.[11-13] We recently reported that status epilepticus with fever lasting more than 60 minutes is likely to result in neurological sequelae in

Article History:
Received November 5, 2013; Accepted in final form February 26, 2014
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0887-8994/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.02.021

children without CNS infection.[14] Thus, it is still debated whether the management of status epilepticus with fever without evidence of CNS infection affects neurological outcome. For status epilepticus, seizure-control protocols vary widely in different countries depending on medication availability, licensing, and other factors.[15] The protocol for convulsive status epilepticus treatment in children in Japan is unique regarding midazolam infusion. US textbooks describe midazolam as a benzodiazepine that may be used as a third-line anesthetic agent for refractory status epilepticus with mechanical ventilation and continuous electroencephalography (cEEG) monitoring to attain a burst-suppression pattern in the intensive care unit (ICU) setting. Aggressive control of hyperthermia with cool blankets and neuromuscular-blocking agents is also recommended.[3,16] However, the Japanese guideline describes midazolam as a second-line agent for intravenous (IV) administration followed by continuous IV infusion without mechanical ventilation or cEEG monitoring before transfer to the ICU.[17] According to this guideline, IV midazolam is recommended when an initial dose of diazepam as a first-line therapy fails to terminate seizures. Regardless of the effectiveness of IV midazolam, continuous IV midazolam is recommended as the next step. Because continuous IV midazolam is not a coma-inducing therapy, mechanical ventilation is not routinely applied. When continuous IV midazolam is found clinically effective and seizures are controlled, it is continued for 24 hours. When it fails, IV phenytoin is recommended. Finally, barbiturate coma therapy is recommended if IV phenytoin fails. Because IV phenobarbital and fosphenytoin only became available in Japan in 2008 and 2012, respectively, phenytoin was the only second-line agent used in clinical practice for a long time. However, phenytoin was often avoided because of its risk of side effects such as infusion reaction. Thus, many patients actually received diazepam followed by midazolam. When IV midazolam effectively controls clinical seizures, it is followed by continuous IV midazolam. Barbiturate coma therapy is instituted only when clinical seizures cannot be controlled using continuous IV midazolam. Midazolam was reported to be effective for status epilepticus or even refractory status epilepticus. However, one study demonstrated that over half of the refractory status epilepticus patients who responded initially to continuous IV midazolam developed subsequent breakthrough seizures that were often detectable only with cEEG.[18] Another study reported that nonconvulsive status epilepticus was frequently observed after the control of convulsive status epilepticus.[19] Whether nonconvulsive status epilepticus damages the brain is still debated.[4,20-22] The optimal depth of electroencephalography (EEG) suppression and the effect of targeted temperature control for status epilepticus also remain under discussion.[23] In this study, we compared two therapy methods to control convulsive refractory febrile status epilepticus (FCRSE): barbiturate coma therapy with cEEG and induced normothermia and continuous IV midazolam without cEEG monitoring. We assessed neurological outcome to identify the safer treatment option of the two, which may help clinicians decide how deep seizures should be controlled and how strictly body temperature should be managed in children with status epilepticus.

TABLE 1.
Treatment Regimen

Clinical Parameter	Barbiturate Coma Group	Midazolam Group
Anticonvulsant	Thiamylal	Midazolam
Goal of status epilepticus control	EEG suppression or burst suppression pattern	Termination of clinical seizure
cEEG monitoring	Routine	None
Mechanical ventilation	Routine	Only when necessary
Temperature control	Normothermia (36°C) using cold blanket and neuromuscular blockade	Acetaminophen (10 mg/kg/dose, 6 hr apart)

Abbreviations:
cEEG = Continuous EEG
EEG = Electroencephalography

Methods

Patients

This study was approved by the local ethical committee of Hyogo Prefectural Kobe Children's Hospital. The medical records of consecutive FCRSE patients admitted to the pediatric ICU in Kobe Children's Hospital between October 2002 and November 2010 were retrospectively reviewed. FCRSE was defined as convulsive status epilepticus with fever lasting for >60 minutes that failed to respond to first-line therapy (i.e., IV diazepam administration).[14] In total, 49 FCRSE patients were identified. Treatment for status epilepticus was nonrandomly decided by the pediatrician in charge. Four patients with histories of neurological conditions, such as epilepsy, developmental delay, known metabolic disorders, or structural CNS anomalies, three patients with pleocytosis or positive CNS culture, and four patients with marked elevation of serum aspartate aminotransferase were excluded to clarify the effect of seizure with fever itself, i.e., without any potentially complicating effects of CNS infection or cytokine storms on the neurological outcome. Twenty children who underwent therapies other than barbiturate coma or continuous IV midazolam were also excluded. In total, 18 patients met our criteria. Patients were categorized based on which of the two treatments they received into either the barbiturate coma group or the continuous IV midazolam group. For the 10 patients in the barbiturate coma group, we administered thiamylal as an anticonvulsant agent. The goal of seizure control was EEG suppression or suppression-burst pattern using cEEG monitoring for 48-72 hours. For simplicity, cEEG was digitally monitored using four channels (A1-Fp1, A2-Fp2, A1-O1, and A2-O2) and viewed at bedside by the ICU nurse. Pediatric neurologists reviewed the cEEG record at least twice a day. Patients were routinely intubated, and targeted temperature management at 36°C was achieved using cool blankets and neuromuscular blockades. For the eight patients in the midazolam group, midazolam was continuously administered after IV bolus. The goal of seizure control was to terminate clinical seizures. Tracheal intubation was applied only when the patients could not breathe appropriately. Body temperature was controlled using acetaminophen (10 mg/kg/dose, 6 hours apart) (Table 1). Refractory status epilepticus was defined as convulsive status epilepticus lasting for >60 minutes that failed to respond to first-line diazepam therapy. The main outcome of this study was patient prognosis, which was measured using the Pediatric Cerebral Performance Scale (PCPC).[24] According to the PCPC score obtained at 1 month from onset, children were classified into two groups: poor outcome (PCPC = 2-6) and good outcome (PCPC = 1). Demographic data, laboratory data, and prognoses were compared between the barbiturate coma and midazolam groups. We also reviewed late seizures around day 5 because several researchers reported that patients with prolonged febrile seizure sometimes reveal late seizures around day 5, followed by neurological sequelae.[10,25,26]