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Midazolam in the Treatment of Neonatal Electroencephalography–Confirmed Seizures

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Abstract：Neonatal seizures are not a rare condition that require emergency measures or may otherwise result in a serous consequence. However, only continuous electroencephalography (EEG) recording allows for the reliable detection of neonatal seizures and make it possible to evaluate the burden neonates. Furthermore, conventional treatment with phenobarbital may fail and the neurological outcomes of the newborns may thus be accordingly threatened. Midazolam is a first–line drug in the treatment of status epileptics in children whereas a few studies have been conducted to evaluate the efficacy of midazolam for neonatal electroencephalography–confirmed seizures (ESz). To evaluate the efficacy of midazolam for ESz, we reviewed 11 cases of neonatal seizures and found two cases of ESz which had been treated with midazolam. These two cases had been treated phenobarbital before using midazolam whereas their seizures had not been controlled. The ESz in these cases stopped immediately after a single bolus injection of midazolam and the following continuous infusion of midazolam. The seizures never relapsed during their neonatal period. This study suggests that midazolam is effective and might thus be an alternative second–line drug in the treatment of neonatal status epileptics albeit further prospective studies with a larger number of ESz are called for to obtain further evidence regarding the efficacy and adverse effects.

Key words：**Midazolam, Neonatal seizures, Status epileptics, EEG–confirmed seizures**

Introduction

Neonatal seizures are not a rare condition and they require emergency measures in order to avoid the occurrence of serious consequences. The efficient treatment based on a correct diagnosis is crucial. However, only continuous electroencephalography (EEG) recording allows for the reliable detection of neonatal seizure and evaluate the burden to the neonates because there is a poor correlation between the clinical and electrographic manifestations of seizure in newborns. Furthermore, conventional treatment with phenobarbital may fail and the neurological outcome of such newborns may accordingly thus be threatened.

Midazolam is a first–line drug in the treatments of status epileptics in children. However, little information is available regarding its application for neonatal seizures. This study shows our experiences of in administering midazolam to neonates with EEG–confirmed seizures (ESz) among the neonates who were admitted to our neonatal intensive care unit for seizure phenotypes in the past 5 years.

Subjects and Methods

We reviewed the records and findings of EEG, if

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available, of all newborns who had been hospitalized in our neonatal intensive care unit because of seizure phenotypes between January 2002 and December 2006.

We defined ESz as any continuous electrical seizures persisting for 30 minutes or discontinuous epileptiform activity occupying>50% of the total tracing.[1] The efficacies of treatments with conventional phenobarbital and midazolam treatments were evaluated by the clinical as well as EEG findings.

Results

Eleven patients had neonatal seizures among the 1293 patients who were admitted to our intensive care nursery during this period (0.85%). All the patients with neonatal seizures received a single loading dose of phenobarbital (20 mg/kg intra rectal). In five cases (45.5%) the seizures had not been controlled and they were then given midazolam (0.2–0.5 mg/kg, i.v.). Thereafter the seizures successfully stopped in all cases. Among them, EEGs had not been recorded regarding the seizure occurrence in three while ESz were confirmed in 2 full－term newborns. Both babies had been given 20 mg/kg of phenobarbital intra–rectally before undergoing EEG.

Midazolam successfully stopped the seizures in the two with ESz. Two neonates became seizure–free after the treatment with midazolam and accordingly the ictal EEG of these patients disappeared during the treatment.

The clinical presentations of the two patients with ESz are summarized below.

Case 1. (*Female*)：The patient was born at 40 weeks of gestation. She was delivered by an emergency cesarean section at 40 weeks and 4 days of gestation for late deceleration of fetal heart rate. Her Apgar scores were one and four at the time of one and five minutes, respectively. Her body weight was 2,777 g. She was ventilated because of meconium aspiration syndrome. She was given 20 mg/kg of phenobarbital intra－rectaly for the treatment of birth asphyxia. At eighteen hours after birth, she had a subtle seizure of gazing and EEG was performed (Fig. 1). Midazolam was then administered as a bolus with a dose of 0.5

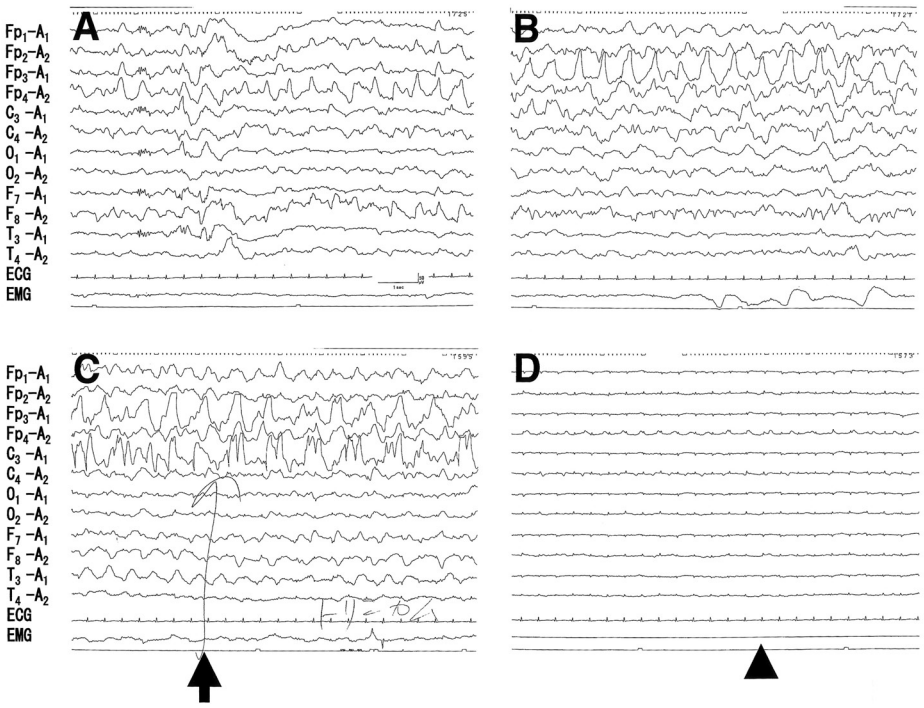

Fig. 1. EEG recordings of case 1
EEG confirmed seizures of Case 1. Subtle seizures of gazing were observed(A and B). Midazolam was administered as a bolus at a dose of 0.5 mg/kg (C：*arrow*). ESz were successfully stopped 200 seconds later (D：*arrow head*).

mg/kg and the seizures immediately ceased. The continuous infusion of midazolam at 0.2 mg/kg/hr was carried out for three days. After the treatment, phenobarbital (7.5 mg/kg/day) was given orally for eight months and then the medication was stopped. Her development was normal at one year of age.

Case 2. (*Male*) : The patient was born at 42 weeks of gestation by a normal vaginal delivery. His Apgar scores were six and ten at the time of one and five minutes, respectively. He was resuscitated with a mask and a bag with oxygen, and treated in an incubator because of poor milk feeding. At fifty-four hours after birth, he had a cyanosis attack and his blood sugar was less than 20 mg/dl at that time. He was therefore referred to our intensive care nursery. After the infusion of glucose, no hypoglycemia was seen whereas left or light hemi-convulsion emerged at 62 hours after birth. Phenobarbital (20 mg/kg) was administered intra rectally and EEG was recorded at 69 hours after birth (Fig. 2). Despite the administration of Phenobarbital, ESz still occurred. Midazolam was administered as a bolus with a dose of 0.3 mg/kg followed by continuous infusion at 0.25 mg/kg/hr for three days. Despite the termination of midazolam infusion, the seizures never occurred again during his neonatal period with oral phenobarbital administration. At six months of age, however, he started to demonstrate tonic spasms. His EEG showed hypsarrhythmia and a diagnosis of West syndrome was made. ACTH treatment was carried out and he became completely seizure free with the following oral zonisamide treatment. He demonstrated a developmental delay at one year.

No serious adverse effects associated with midazolam were seen in all five patients who received midazolam treatment in our intensive care nursery.

Discussion

In this study, we found 11 cases of neonatal seizures out of 1293 babies, who were admitted to our intensive care nursery in the past 5 years. Among them five required midazolam to stop seizures re-

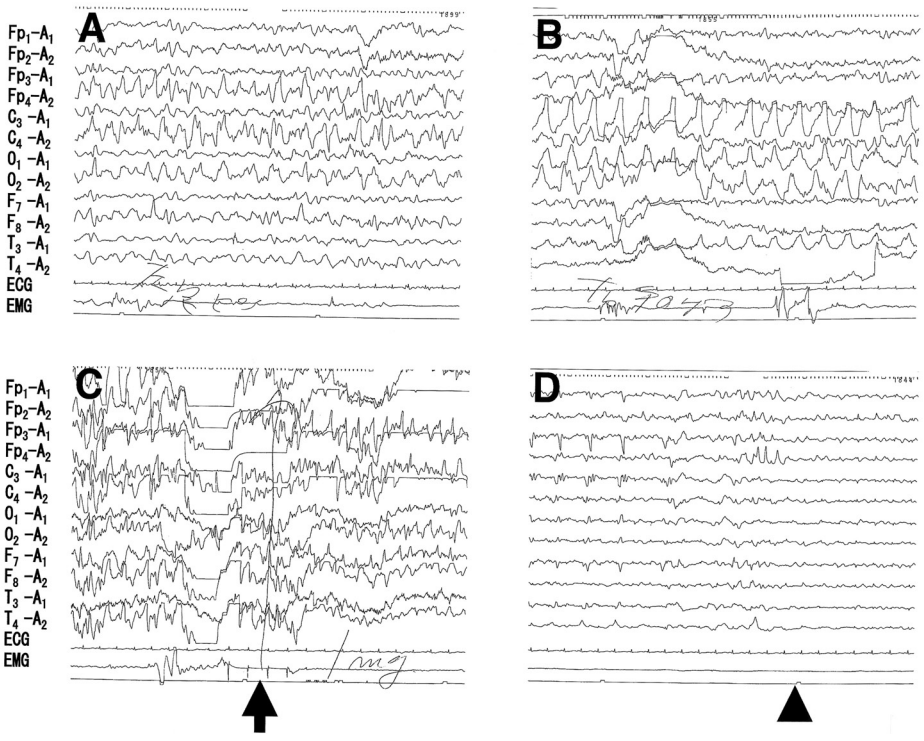

Fig. 2. EEG recordings of case 2
EEG confirmed seizures of Case 2. Left hemiconvulsions (A) and convulsions of the right hand (B) were observed. Midazolam was administered as a bolus at a dose of 0.3 mg/kg (C : *arrow*). ESz were successfully stopped 60 second later (D : *arrow head*).

fractory to the conventional treatment with phenobarbital while well responded to midazolam without any serious side effects. Two of the five confirmed to have ESz and their clinical and EEG findings were shown.

Seizures occur in 1 to 2% of the neonates admitted to an intensive care unit in accordance with our present findings which was 0.8%. Despite aggressive treatment with conventional anticonvulsant therapies, the clinical and electrical control of neonatal seizures still remains unsatisfactory.[2] The two most commonly used medications for neonatal seizures are phenobarbital and phenitoin. An earlier study[3] demonstrated that less than 50% of the infants who had been treated with either of those medications responded with an electrographic cessation of seizures.

Only continuous EEG can reliably detect and measure neonatal seizure and hence evaluate the burden because there is a poor correlation between the clinical and electrographic manifestations of seizure in the newborn.[4] In comparison to the responders to conventional treatments, non-responders presented more abnormal background EEGs and status epilepticus was observed in more than 50% of the cases as well. These non-responders are known to be most difficult to treat,[5] yet in this study, a successful clinical and EEG controls was achieved with midazolam. The end point of the antiepileptic treatment is the control of ESz rather than merely the suppression of abnormal behavior. Therefore, in that sense, midazolam seems to be an effective measure against neonatal seizures.

A similar study[8] demonstrated complete electrical control with midazolam in 13 nonresponders to phenobarbital and phenytoin while also correlating with significantly improved long-term neurodevelopment. In their study, midazolam was administered early (~1 hour) after a failure to control the seizures using the maximal doses of phenobarbital. They encountered no adverse effects either.

However, beyond simple side effects, in the treatment of neonatal seizures special attention should be paid to the development of the central nerve system of the newborns. Recent studies in immature rodents suggest that traditional anticonvulsants, in particular those that exert their anti convulsive effects via blocking voltage-dependent sodium channels (such as phenytoin) or those that enhance chloride flux through the $GABA_A$ receptor (such as the barbiturates), may produce the widespread apoptosis of neurons.[6] The use of midazoram, another $GABA_A$ receptor agonist, will continue to be associated with concerns about the potential neurotoxicity of such drugs on the immature brain.[7]

In summary, midazolam seems to be effective and relatively safe in the management of neonatal seizures. Further prospective studies with a larger number of ESz are necessary to obtain further evidence to support the use of midazolam treatment as a first-line antiepileptic treatment for neonatal seizures and to investigate the adverse effects especially regarding the developmental brain in the neonates.

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