

Original Article**Comparing the Effect of Intravenous Midazolam with Rectal Sodium Valproate in Controlling of Children with Refractory Status Epilepticus***T. Mahmoudian MD**, *M. Najafian MD*****ABSTRACT**

Background: Refractory status epilepticus usually defined as a seizure lasting at least 60 minutes which is uncontrollable by Diazepam, Phenytoin, or Phenobarbital. The aim of this study was to compare the effect of intravenous Midazolam and rectal Sodium valproate in controlling refractory status epilepticus.

Methods: In this case-control study; 76 children with (mean age of 37 ± 20 months) with refractory status epilepticus were randomly divided into two groups to receive IV Midazolam and rectal Sodium Valproate. The effect of the two drugs were compared in control of seizure during first 20 minutes of treatment.

Results: In 84.2 percent of children treated with IV Midazolam, the seizure was under control within 4.5 ± 0.5 minutes, while in 63 percent of those receiving Sodium Valproate, the seizure was completely controlled within 16.5 ± 0.8 minutes ($P < 0.00001$).

Conclusion: The IV Midazolam was more effective than Sodium valproate, but the latter can be used in hospitals or pediatric emergency wards without ICU for controlling of refractory status epilepticus.

Key words: refractory status epilepticus, midazolam, sodium valproate

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Seizures are the most common neurologic problem in children especially in their first year of life which usually have brief duration and resolve spontaneously. Status epilepticus is defined as a continuous seizure lasting for at least 30 minutes or recurrent seizures occurring with impairment of consciousness between seizure activity¹. This type of seizure has a fetal outcome in 3 to 20 percent of cases. On the other hand, status seizure might result in irreversible side effects in the brain. Prolonged seizure activity itself produces irreversible cerebral damage, independent of accompanying hypoxia, acidosis, and consequent biochemical derangements². Most of the children with status epilepticus have favorable response to treatment with intravenous Diazepam, Phenytoin, or Phenobarbital, but a small

percentage of them do not respond and the seizure leads to refractory status epilepticus in them (seizure duration of 60 to 90 minutes). The complications in this group of patients are manifested through motor disorders, mental retardation, learning problems, and speech disorders³. Febrile seizures, brain infections, head trauma, neurological based diseases (cerebral palsy), progressive encephalopathies, and idiopathic epilepticus are the etiologies of status epilepticus. 10 to 20 percent of epileptic children experience status epilepticus at least once in their lifetime. Among the children with a first unprovoked seizure, 9 percent had a history of status epilepticus⁴. In this study we compared the effects of treatment with IV Midazolam drip and rectal sodium valproate in children with refractory status epilepticus

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hospitalized in Alzahra hospital ,the only referral hospital for pediatric neurologic problems in Isfahan province, Iran.

Subjects and Methods

Within one year from April 1998, every child referred with seizure to pediatric emergency ward of Alzahra university hospital and his/her seizure continued despite intravenous Diazepam (0.3 mg/kg) followed by intravenous bolus Phenytoin (20 mg/kg) and then intravenous bolus Phenobarbital (20 mg/kg) was included in this study. The interval between each drug was 15-20 minutes. (Seizure lasting 60-90 minutes were considered as refractory status epilepticus). The patients must be admitted at intensive care unit (ICU) for controlling their refractory status epilepticus by general anesthesia, but when it was no available ICU bed, alternative treatments were chosen ethically.

The randomization was done by a pediatric assistant supervised by the author, according to the number of patients referred to emergency ward (even & odd). The odd group was treated with Sodium Valproate syrup (20 mg/kg) diluted with equal volume of water through rectal enema (IV Sodium valporate was not available). If seizure stopped within 20 minutes of enema, oral Sodium Valproate would be continued 20 mg/kg/24 hours divided into two equal doses after 12 hours from the first administration. The even group was treated with intravenous bolus Midazolam with a dose of 400 μ g/kg, followed by 200

μ g/kg/h through infusion up to 20 minutes. If the seizure stopped, Midazolam continued for extra 6 hour and it was discontinued gradually.

In both groups if there were no positive response after 20 minutes the treatment was discontinued and treatment with barbiturates coma (Sodium thiopental or Nesdonal) was started and the child was excluded from the study and was controlled by anesthesiologist.

A series of tests, such as CBC, sugar, calcium, electrolytes, BUN, liver function test, urinary analysis, CSF analysis and culture, and Brain CT and EEG were administered to the patients. A complete history of the patients and their families were also recorded for any seizure, drug use, trauma and developmental status.

The effectiveness of the drugs was tested with t-test method.

Results

After one year (April 1999) 38 children within the range of 2 months to 18 years old were studied ignoring their age, sex, and seizure etiology. They were divided into two groups (18 children in odd group and 18 in even group).

According to figure1, 16 of the 19 patients (84.2 percent) treated with Midazolam in the even group responded to the treatment after 4.5 ± 0.5 minutes, while 12 of the 19 patients (63 percent) in the odd group treated with Sodium Valproate responded to the treatment within 16.5 ± 0.8 minutes. There was significant difference between the two drugs ($P < 0.00001$).

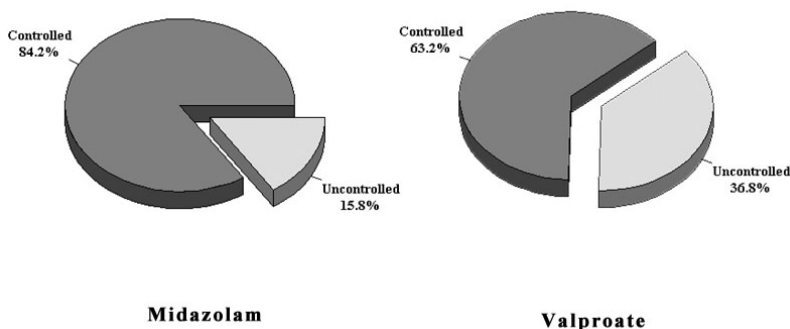


Figure 1. The percentage of studied patients according to their response to treatment with separate drug administration.

The age distribution of the patients in the two treatment groups is depicted in figure 2. The distribution shows that the status epilepticus in 2 to 12 months' age groups is more widespread than in other age groups.

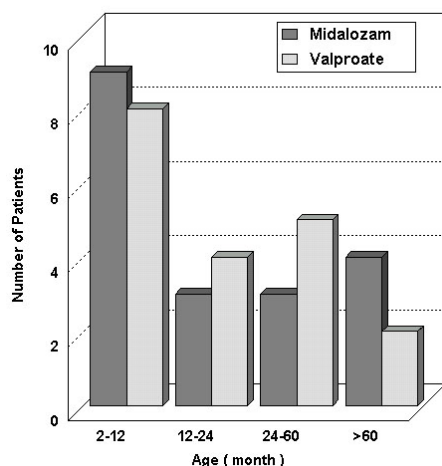


Figure 2. The distribution of the studied patients according to the age, with separate drug administration.

According to figure 3, status epilepticus was twice more prevalent in boys than in girls. The etiology of seizure, according to patient's age through the whole study is depicted in figure 4, indicating that the most prevalent cause of refractory status epilepticus is evident in those below the age of 1 year.

No side effect was noted during and/or after the end of treatment in neither groups of patients.

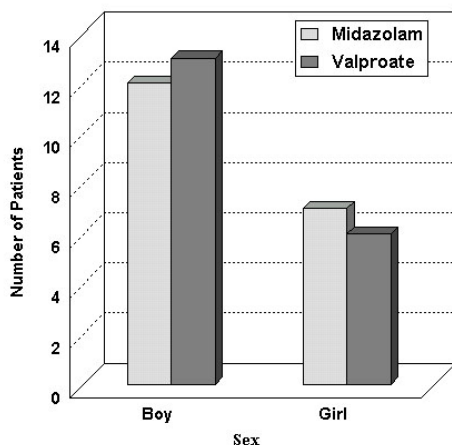


Figure 3. The distribution of the studied patients according to the sex, with separate drug administration.

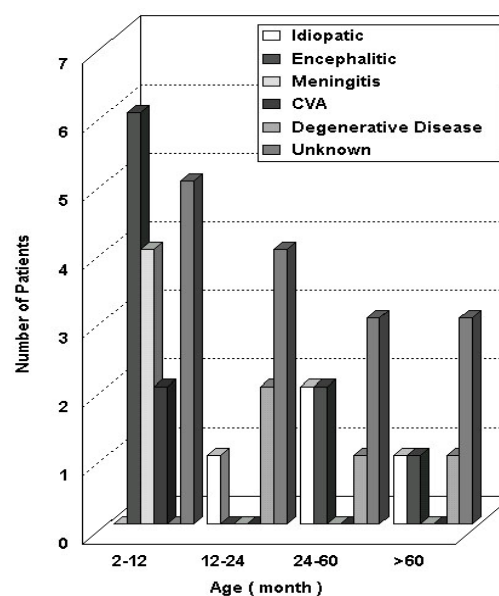


Figure 4. The distribution of the studied patients according to the age, groups with separate seizure causes.

Discussion

Children are considerably more prone to status epilepticus than adults. Although the mortality rate is lower in children and are also more resistant to permanent neurological damages than adults, but they show considerable complications after a refractory seizure. Rapid timely and intervention for disruption of seizure will result in a better prognosis and less mortality due to status epilepticus. The first step in the treatment of seizure is to administer Diazepam or Lorazepam and then Phenytoin or Phenobarbital, but 10 to 15 percent of seizures are resistant to the above-mentioned treatments⁵. The recommended treatment for this type of seizure is oral or rectal Sodium Valproate. In refractory status epilepticus gastric ileus is common and oral administration is of drug stopped. Rectal Sodium Valproate loading dose is 15-20 mg/kg of diluted syrup with water (1:1) for use as a retention enema. This route cannot be sustained for periods longer than about 48 hours because of the drug's strong cathartic effect⁶⁻⁹.

Lidocain infusion, barbiturates coma (Sodium thiopental or Nesdonal), and general anesthesia are used for controlling of intractable

status epilepticus but the two latter methods require severe cardiopulmonary and hemodynamic surveillance and are accompanied with considerable complications. Midazolam is a water soluble benzodiazepine metabolite. It can be used in seizure resistant to the above mentioned drugs ⁵.

In a study, Midazolam infusion was tried as treatment for 20 children with status epilepticus over a period of two years. Twelve children with refractory status epilepticus had received intravenous Diazepam, Phenyton /Phenobarbital before that. Midazolam was given to them with a dose of 150 µg/kg bolus, followed by 1-5 µg/kg/min infusion, and the seizure was controlled in 19 children (95%). The mean time required for complete cessation of seizure was 0.9 hour (15-240 minutes). The mean of required infusion rate was 2 µg/kg/min ².

In another study 24 patients (with ages of 2 months to 12 years old) were treated with a mean infusion rate of 138 µg/kg/h of Midazolam, following a 150 µg/kg bolus dose, when three repeated intravenous doses of Diazepam, Phenyton, and Phenobarbital failed (refractory status epilepticus). Seizures were completely terminated within 0.74 hour (with a range of 15 minutes to 4.5 hours) ⁵. It acts more rapidly but respiratory depression is often

potentiated by Midazolam when phenobarbital is administered. Sodium valproate is a more safe drug when ICU is not available.

We suggest that Midazolam is the drug of choice in refractory status epilepticus in referral hospitals with ICU, while Sodium valproate can be used in the pediatric emergency and hospitals without ICU, and will not have ethical concerns.

In the present study the effect of Midazolam infusion within 15 to 20 minutes after the first bolus dose was compared with the effect of Sodium valproate administered through rectal enema. After 20 minutes, 84.4 percent of the patients responded to Midazolam in 4.5±0.5 minutes while seizure was controlled in 16.5±0.8 minutes in 63 percent of the patients treated with Sodium Valproate. The percentage of the positive response to the Midazolam in the present study was lower, comparing with the above-mentioned studies, but the time taken for positive response (20 minutes) was greatly lower than the 0.9 hour in the former and 0.74 hour in the latter ones, respectively. On the other hand, the purpose of the 20 minutes devoted to this study, was to treat the patients with barbiturate coma immediately if there were a negative response to the drug so that no significant lapse would occur in the treatment of seizure.

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