RESEARCH ARTICLE

MIDAZOLAM EFFICACY AND SIDE EFFECTS IN GENERALIZED AND PARTIAL REFRACTORY STATUS EPILEPTICUS IN CHILDREN

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Abstract

Objective

Midazolam is a significant and effective drug for control of a life–threatening condition, generalized and partial refractory convulsive status epilepticus. The goal of this study was evaluation of midazolam efficacy for management of this serious disease and its two side effects, hypotension and respiratory failure.

Materials & Methods

Our study was done using a quasi experimental method; 22 children with generalized refractory convulsive status epilepticus and 13 with partial refractory convulsive status epilepticus were enrolled for the study. All patients received 0.2mg/kg/dose as a bolus intravenous midazolam followed by 1-6 mcg/kg/min continuous intravenous midazolam. Following this, termination of seizures as well as hypotension and respiratory failure were evaluated.

Results

Midazolam ceased stop convulsions in 81.81% (18) patients with generalized seizures, and in 76.92% (10) patients with partial seizures, showing no significant difference between these two types of seizures (p=0.52)

Hypotension was induced in 18.18% (4) patients with generalized seizures and in 30.70% (4) patients with partial seizures, again difference not significant (p=0.14).

There was respiratory failure in 21.73% (5) patients with generalized seizure and in 7.69% (1) patients with partial seizure, difference not significant.(p=0.09)

Conclusion

There was no significant difference in efficacy and creation of hypotension and respiratory failure after continuous intravenous infusion of midazolam between generalized and partial refractory convulsive status epilepticus.

Key words: Midazolam, Refractory convulsive status epilepticus, Convulsive status epilepticus.

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Introduction

Refractory convulsive status epilepticus is a potentially life-threatening neurologic emergency that requires immediate medical intervention to prevent many neurologic sequelae (1, 2, 3, 4).

Convulsive status epilepticus is defined as a seizure or series of seizures that lasts 30 minutes or more without regaining consciousness between the seizures (5, 6)

In its most severe form, refractory convulsive status epilepticus, continuous or repetitive seizures do not respond to the first anticonvulsant drug therapy and

duration of seizure activity is at least 1 hour(7). It has an overall mortality of about 5-7% in children (5).

The first line anticonvulsant drugs for initial therapy are diazepam, phenobarbital, phenytoin, (8,9).

Midazolam is claimed to be an effective and safe drug for treatment of generalized and partial refractory convulsive status epilepticus, which is used in different methods especially continuous intravenous infusion. This drug adheres to the ABA-A receptor and leads to increasing activity of neuronal GABA- producing cells, controlling the seizures (10, 11).

However, it seems that the anticonvulsive potency of midazolam for termination of partial seizures is lower than for generalized ones (12), and time lasts quickly while; duration for which status epilepticus lasts has a significant effect on the outcome(6).

Our study was done on pediatric patients for evaluation of midazolam efficacy in generalized and partial status epilepticus. In addition, midazolam has two common and significant side effects, hypotension and respiratory insufficiency. In some studies, level of hypotension was not significant (9, 13). But mild to severe respiratory problems have also been reported (14, 15). These two side-effects were also investigated.

Materials & Methods

Our study, conducted using quasi experimental methods, investigated 40 children, 2 months to 16 years of age, with refractory convulsive status epilepticus, admitted to the pediatric intensive care unit (PICU) of Amirkola pediatric hospital in Babol city between 1/1/2004 and 1/6/2007. This institute is a 150-bed tertiary care and referral pediatric hospital. Exclusion criteria were the need for prompt neurosurgical intervention, electrolyte disturbances and diseases or conditions causing hypotension or respiratory insufficiency; ultimately 5 patients were excluded. Twenty-two patients had generalized convulsive status epilepticus, while 13 patients had partial convulsive status epilepticus.

Methods of patient selection

All patients with convulsive status epilepticus (15), received first line anticonvulsant drugs; thus twofold intravenous diazepam was given with 10 minute-interval in a dose of 0.2mg/kg at a rate of 0.2mcg/minute for a maximum 10mg(14); if this was unsuccessful, intravenous phenytoin was given immediately. The loading dose of phenytoin was 15-20mg/kg, infused at the rate of 1mg/kg/minute. If the status epilepticus was not controlled by the preceding strategy, intravenous Phenobarbital was initiated in a bolus dose of 10-15mg/kg over 20 minutes (16, 17); if seizure was yet uncontrolled, and 30 minutes had elapsed since beginning of attack, the patient was selected for intravenous midazolam infusion. Variables such as age weight, sex, history of seizure, underlying diseases, and the time required for control of seizures were recoded; and vital parameters including respiratory rate, heart rate and blood pressure were documented. Cleaning of airway oxygen administration by mask, and nasogastric tube insertion were done. Complete blood cells count blood chemistries (sodium, potassium, calcium, glucose) were measures and other necessary specimens were obtained on admission and again 24 hours later. If prompt measurement of blood glucose level was not possible, 5cc/kg bolus of 10% dextrose were infused (18) pulse oxymetry and cardiac monitoring were used, and the patients were transferred to PICU as soon as possible.

Electroencephalography was not used for the diagnosis, but was however, performed after the seizure had been controlled to diagnose electrical abnormalities. All children underwent computed tomography scanning or magnetic resonance imaging of the brain and other relevant investigations.

Evaluation of midazolam effects

All 35 children received intravenous midazolam at 0.15mg/kg as a bolus followed by a constant infusion starting by 1 mcg/kg/min up to 6mcg/kg/min, increasing by 1mg/kg/min, every 15 minutes until complete control of seizures was achieved (1). The optimum rate infusion at which seizure control was achieved was maintained for a period of 24 hours. Subsequently the midazolam infusion rate was gradually decreased (by 1mcg/kg/min every 2 hours) until tapering was completed (12). If seizures were not controlled with the maximum dose of the midazolam, other drugs were used.

Evaluation of midazolam side effects:

Systolic blood pressure preferably via radial artery, pulse and respiratory rates and oxygen saturation by pulse

oxymetry, were recorded before infusion of midazolam and every 30 minutes until 2 hours, then every 3 hours, until 24 hours after infusion.

If systolic blood pressure decreased below 15mmHg it was recorded as hypotension (5).

Regarding respiratory side effects, if FIO2 was at least 60% and oxygen saturation was under 90% or if Pco2 was over 50mmHg and PH under 7.3, patients were considered to have respiratory failure (19).

Statistical analysis:

Data were analyzed using SPSS software and were compared between two groups using Fisher's exact and Mann-Whitney and t-test.

Results

Of the 35 patients, 22 patients had generalized and 13 patients had partial refractory convulsive status epilepticus (table 1). Mean age, history of antiepileptic drug usage, previous seizure, fever, convulsion, and mean duration of convulsion after administration of midazolam are shown in table 1.

Midazolam effects

As shown in table 1, midazolam can stop seizures in both groups, with a higher rate of success for the generalized group (81.81%), but without any significant difference (p=0.52).

Mean time lapse since beginning of midazolam till cessation of seizures in the generalized group was 47.4 minutes, while for the partial group, it was 52.5 minutes; mean cumulative time for the two groups was 49.2 minutes.

Table 2 displays mean midazolam doses that caused cessation of convulsion, while mean midazolam dose was 3.28mcg/kg/min for the two groups without significant difference (p=0.5).

Midazolam side effects

Figure 1 displays hypotension and respiratory failure due to midazolam infusion.

Creation of these two side effects had no significant difference; P-value for hypotension (0.14) and for respiratory insufficiency (0.09).

Table 1. Comparison of patients with generalized and partial refractory convulsive status epilepticus.

Characteristics	Type of status	
	Generalized	Partial
Numbers of patients	22	13
Gender ratio: boys to girls	14:8	8:5
Mean age (years)	4.81	2.84
Prior seizure (%)	15(68.8)	10(78.92)
Prior anticonvulsant drug (%)	14(63.63)	9(69.23)
Fever (%)	10(45.45)	6(46.15)
Seizure control (%)	18(81.81)	10(76.92)
Mean time duration until control (min)	47.4	52.5

Table 2. Mean midazolam doses (mcg/kg/min) that caused cessation of convulsion.

Convulsive state	Mean dose (mcg/kg/min)	Standard deviation	P-value
Generalized	3.16	1.75	0.5
Partial	3.50	2.32	
Summation	3.28	1.94	

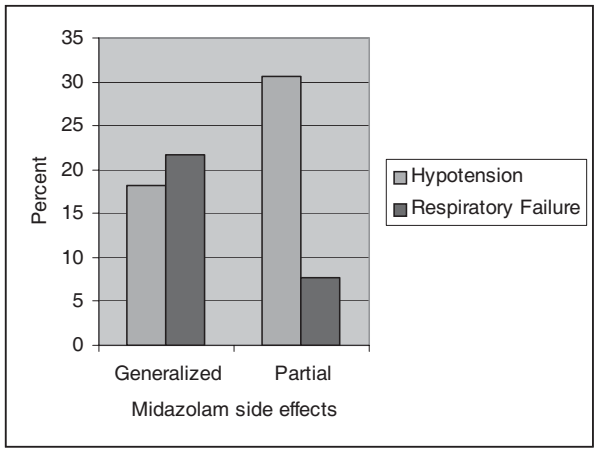

Figure 1. Frequency (%) of midazolam side effects.

Discussion

In our study, midazolam infusion controlled several cases of generalized and partial convulsive status epilepticus with no significant discrepancies between effects or side effects between these two seizures. Minagawa K. and coworkers found that midazolam is an appropriate drug for controlling these critical disorders (20); another research however claimed that midazolam was unsuccessful in the termination of partial refractory status epilepticus (12). In our study, although efficacy of midazolam had lower efficacy in partial seizures, there was no striking discrepancy between them, while mean doses for controlling generalized and partial seizures were 3.16 and 3.5 mcg/kg/min respectively.

Several studies have determined different means of midazolam doses for controlling seizures, (2 to 5.3 mcg/kg/min) (4, 20, 21). Thus if midazolam has no serious side effects, it can be initiated with continuous doses higher than 1mcg/kg/min. This approach can prevent neurological sequels with earlier control of seizure. We suggest further studies be designed with larger populations for evaluation of midazolam effects and side effects with starting doses above 1 mcg/kg/min.

Hypotension had a frequency of 15-40% in several surveys and improved easily (8,11,21). Our study revealed hypotension had frequencies of 18.18% and 30.70% in generalized and partial seizures respectively, and improved with intravascular fluid without need for vasopressin drugs.

Respiratory failure was mild and did not require mechanical ventilation in two previous studies (14, 22); however Ghofrani and co-workers and Roshan LK and colleagues showed it was so severe that 15% and 40% of patients needed mechanical ventilation (12, 14). According to our study, 21.73% and 7.69% of patients developed respiratory failure in generalized and partial seizures respectively. No children with partial seizures needed mechanical ventilation, while 11.43% of patients with generalized seizure did.

Both hypotension and respiratory failure occurred immediately after the midazolam bolus injection and we found no meaningful correlation between these side effects and increasing midazolam doses. Thus our study revealed that there was no significant difference in efficacy and creation of hypotension and respiratory failure after continuous intravenous infusion of midazolam between generalized and partial refractory convulsive status epilepticus.

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