RESEARCH ARTICLE

COMPARATIVE EFFECTS OF DIAZEPAM INFUSION AND DIVIDED DOSES OF DIAZEPAM ON THE TREATMENT OF ABSENCE STATUS EPILEPTICUS

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Abstract

Objective

Absence status epilepticus (ASE) is a common form of nonconvulsive status epilepcticus. It is characterized by loss of consciousness with spike and wave discharges in EEG simultaneously. The most effective treatment of ASE is diazepam, either infusion or in divided doses; the former is more expensive since patients must be admitted in an Intensive Care Unit. The aim of this study was to evaluate and compare the efficacy of diazepam infusion and parenteral diazepam in divided doses in the treatment of ASE.

Materials & Methods

This randomized controlled clinical trial, enrolled 20 patients with absence status epilepticus. Diagnosis was made based on the clinical manifestations and electroencephalogram (EEG). Prior to treatment, all patients underwent EEG and imaging. Patients were randomized to receive 0.2 mg/kg/h diazepam infusion or 0.2 mg/kg in six daily doses. Clinical and EEG improvements were considered to be optimal responses.

Results

Of the 20 patients studied, 13 (65%) were boys and the remaining 7(35%) were girls. There were no differences between the two groups regarding age and sex (non-significant). Following treatments after 48 hours, 1 week and 1 month respectively, clinical improvement in previous problems (loss of consciousness, ataxia, behavior and speech problems) and EEGs was similar in both groups (p=1). There were controlled seizures in 18 (90%), abnormal CT scans in 5 (25%), abnormal EEGs after treatments in 6 (30%) cases; however no significant differences were seen between the two groups.

Conclusion

This study demonstrates that there are no significant differences between treatments of ASE with diazepam infusion and parenteral diazepam in divided doses. Treatment of ASE, with divided doses of diazepam is easier, less expensive and patients do not require to be hospitalized in an Intensive Care unit.

Keywords: Status epilepticus, Diazepam, Absence

Introduction

Absence Status Epilepticus (ASE), a prolonged absence seizure, first described clinically and electrographically by Putaman and Lenox (1,2), is one subtype of nonconvulsive status epilepticus. The term was first proposed by the commission on classification and terminology of the International League Against Epilepsy (3, 4). Some synonyms are petit mal status, spike-and-wave stupor, and minor epileptic

status. The frequency of ASE ranges from 5% to 10% among patients with primary generalized epilepsy, being 3% in patients with absence seizures. In 75% of cases ASE occurs before the age of 20 years (5,6).

Absence status is divided to typical and atypical forms. In both forms, there is a paroxysmal loss of consciousness clinically associated with bursts of bilaterally synchronous spike-and-wave discharges on the EEG (5). The main distinction of atypical absence status is that it occurs mainly in children with symptomatic or cryptogenic generalized epilepsies. In addition, the interictal EEG is abnormal, with most of these patients also having moderate to severe learning and physical handicaps (6,7). Outcomes of ASE are related more to type and cause of the underlying epilepsy; it may occur only once in a life time or may be frequent and intractable in patients with symptomatic generalized epilepsies (6). Benzodiazepins, such as clonazepam, lorazepam or diazepam, that may be administrated orally or parenterally, are the drugs of choice for the treatment of absence status (6-9), and can be repeated every 3 to 4 hours (5). However ASE may recur (10,11). The aim of this study was to compare the efficacy of using diazepam either by its infusion or in divided parenteral doses in the treatment of ASE.

Materials & Methods

Between 2006 and 2007, twenty patients, aged between 1 and 14 years were enrolled in the Mofid children's hospital, Tehran, for this randomized controlled clinical trial. Diagnosis was based on clinical manifestations and electroencephalograms. We conducted this randomized study to compare using diazepam infusion and divided doses diazepam as first line treatment for ASE. Patients were selected randomly two groups-one treated with diazepam infusion and the other with divided doses diazepam-and sufficiently matched**.** All patients underwent EEGs prior to and 48 hours following treatments. Patients were randomized into two groups, the first receiving parenteral diazepam (0.2 mg/kg/hour), following hospitalization in ICU. The second group was hospitalized at the neurology ward and received diazepam parenterally 0.2 mg/kg in six daily doses. If, after 48 hours, there no clinical or EEG improvement were observed, therapy was discontinued. Basic work up included CBC (diff), BS (blood sugar), and UA (urine analysis), EEG, and imaging.

Results

Of the twenty patients studied, 13 (65%) were boys and 7 (35%) were girls. There were no differences between the two groups regarding sex and age. ($p>0.05$) (table1)

Before treatments, all patients had continuous spike and wave discharges in their tracings. Of twenty children, 18 (90%) had previous seizures, partial or generalized, which were controlled. Imaging (CT scan and MRI) was abnormal in 5 (25%) patients due to mild cortical atrophy (table 1). Major clinical manifestations at the time of admission, were lethargy in 14 (70%), ataxia in 10 (50%). Speech and behavior problems were found in 7 (35%) patients. There were no significant differences between the two groups ($P > 0.05$).

After the end of 48 hours of therapy, EEGs were done; of the twenty patients, 14 (70%) had normal EEG and 6 (30%) had mild abnormalities in their EEGs, without spike and wave discharges, indicating no significant differences between two groups ($P > 0.05$) (Table2).

Clinical manifestations for patients were assessed after 48 hours, 3-7 days and at One week and one month. In 5 (25%) patients, lethargy improved after 48 hours and in 9 (45%) after 3-7 days. Ataxia was found to have improved in 6 (30%) patients after 3-7 days, while in 4 (20%) patients the improvement was observed around 1 week to 1 month later. Speech and behavior problems in 4(20%) improved after 3-7 days, and between 1 week and 1 month in 3 (15%) cases. No side effects occurred during therapy.

Discussion

Treatment of absence status epilepticus (ASE) may be accomplished with either oral or parenteral antiepileptic drug therapy (5). Benzodiazepins are the drugs of choice, with the intravenous route being preferred usually if emergency facilities are available. Both typical absence status and late onset absence status respond to intravenous diazepam 0.2-0.3 mg/kg, clonazepam 1 mg/kg (0.5 mg in children) or lorazepam 0.1mg/kg (3, 5,6, 11), doses which can be repeated every 2 to 4 hours. If control is not easily achieved, i.v. valproate may be successful (3, 13) and sometimes rectal diazepam or buccal midazolam have also been effective (6,11). Some drugs such as

phenyton, carbamazipin, vigabatrin, and tiagabine may induce refractory ASE (6, 12). In a study four of five children in ASE responded rapidly after a single loading dose of 20-40 mg/kg i.v. valproate without significant side effects (13).

In our study, no significant differences were seen in response to treatments, between two groups. There were no side effects or recurrence in either group. we did not find any similar study as ours.

In conclusion, this study demonstrates that despite diazepam being effective in the treatment of ASE, diazepam, in divided doses, is recommended, since it is less expensive and the patients do not need to be hospitalized in the ICU.

Table 1: Comparison of sex, age, previous convulsion, imaging findings in two groups

		Two groups		**p. value**
		DI * (n=10)	**DD** (n=10)**	
Sex	boys	9 (9%)	4 (40%)	P = 0.057 (fisher test) non significant
	girls	1 (10%)	6 (60%)	
Age (year)	(mean ±SD)	8.35±3.44	8.35±4.60	P = 1 (T-test) non-significant
Previous convulsion	controlled	10 (100%)	8 (80%)	P = 0.474 (fisher test)
	uncontrolled	0	2 (20%)	
Imaging findings	normal	7 (70%)	8 (80%)	P = 1 (fisher test) non-significant
	abnormal	3 (30%)	2 (20%)	

* DI: Diazepam Infusion

** DD: Divided doses diazepam

Table 2: Treatment response after 48 hours, before and after 1 week in DI and DD groups

Time of treatment		Treatment Response			p-value
		Consciousness improv.***	Ataxia Improv.	Speech and behavior problems improv.	
48 hrs	DI *(n=10)	3 (30%)	—	—	P = 1 (Fisher test) non significant
	DD** (n=10)	2(20%)	—	—	
3-7 days	DI (n=10)	6 (60%)	4 (40%)	1 (10%)	P = 1 (Fisher test) non-significant
	DD (n=10)	3(30%)	2 (20%)	3 (30%)	
After 1 week	DI (n=10	—	3 (30%)	1 (10%)	P=1 (Fisher test) non-significant
	DD (n=10)	—	1 (10%)	2 (20%)	

* DI: Diazepam Infusion
** DD: Divided doses diazepam
*** improvement

Table 3: EEG status in the DI and DD groups after 48 h treatment

	EEG	
	Normal	Abnormal
DI* (n = 10)	7 (70%)	3 (30%)
DD** (n = 10)	7 (70%)	3 (30%)

* DI: Diazepam Infusion
** DD: Divided doses diazepam

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