RESEARCH ARTICLE

Efficacy and Safety of Topiramate as the First - Line Drug in the Treatment of Infantile Spasms

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Abstract

Objective

Infantile Spasms (IS) is one of the catastrophic epileptic syndromes of infancy. The purpose of this study was to evaluate clinical efficacy and safety of topiramate (TPM) as the first -line drug in the treatment of infantile spasms.

Materials and Methods

In a quasi- experimental study, efficacy and safety of TPM in treatment of forty children with IS who were referred to pediatric neurology clinic of Shahid Sadoughi University of Medical Sciences in Yazd, Iran, from September 2008 to 2010 was evaluated.

Results

Twenty two girls (55%) and 18 boys (45%) with a mean age of 9.2 ± 3.9 months (range= 3-20 months) were evaluated. Ninety percent of the patients had symptomatic IS. At the end of three months of TPM treatment, 40% of the patients became seizure free, 27.5% had more than 50% reduction in seizure frequency, 27.5% had no notable change in seizure frequency and 5% had an increased frequency of seizures.

Transient and mild side effects, which were seen in 32.5% of the patients, included drowsiness in 15%, hypotonia and hyperthermia (each one) in 7.5% and anorexia and weight loss in 2.5%. All side effects disappeared in two or three weeks of treatment.

Conclusion

Topiramate is an effective and safe drug in the treatment of IS and could be considered as the first line of treatment.

Keywords: Infantile spasms; Topiramate; Epilepsy.

Introduction

Infantile Spasms (IS) is the most common myoclonic epilepsy of infancy (1). The incidence of IS varies between 0.2 - 0.6 per 100 with a peak between 3 to 7 months of age. In 93% of the cases, it occurs before the age of two (2). The spasms are bilateral, symmetric sudden contractions of neck, trunk and extremities, and may be flexor, extensor or mixed type. The spasms may be single, but often occur in clusters with 20 to 100 spasms in a single cluster. Clusters frequently occur while patients are drowsy or immediately on wakening from sleep (1, 2).

A hypsarrhythmia pattern is noted on electroencephalography of these patients, which consists of chaotic, bilaterally asynchronous high-voltage polyspike and slow wave discharges interspersed with multifocal spikes and slow waves (3).

Etiologic classification of IS includes

1.Symptomatic: with identifiable prenatal, perinatal, and postnatal causes with developmental delay at the time of presentation

2.Cryptogenic: an unknown underlying cause, normal development at the onset of the spasms, normal neurological exams and neuroimaging and no abnormalities in metabolic evaluations

3.Idiopathic: pure functional cerebral dysfunction with complete recovery, no residual dysfunction, normal neurodevelopment, normal neuroimaging and normal etiologic evaluations. This class is based on final outcome, and cannot be confirmed with certainty based on the history and presenting symptoms. The terms idiopathic and cryptogenic have been used as synonyms in many studies (2, 4,5,6).

Treatment should be started without delay since early control of spasms may improve prognosis and is accompanied by a higher chance for normal develpomental outcome (5- 7).

There is no consensus on the first choice of drug treatment of IS and no single treatment regimen could be considered superior to others. ACTH or oral corticosteroids, vigabatrin and other drugs such as valproic acid, nitrazepam, pyridoxine, topiramate, zonisamide, lamotrigine, levetiracetam, felbamate, ganaxolone, liposteroid, thyrotropin-releasing hormone, intravenous immunoglobulin and also the ketogenic diet may be used for the treatment of spasms as the first or second line drugs (2,7,8).

ACTH is expensive and difficult to obtain in many countries and cities (including Yazd), and side effects of ACTH and oral corticosteroids include hypertension, infection, electrolyte abnormalities, weight changes, hyperglycemia, hypertrophic cardiomyopathy, adrenocortical dysfunction, sleep disturbance, brain shrinkage, sleep and behavior abnormalities, subdural hematoma / effusion, cushingoid appearance, development of new seizure types, decreased bone density sometimes with fractures, skin rashes with intravascular coagulation and even death (2,7,9).

Irreversible visual field defect is seen in 30 - 50 % of the children treated with vigabatrin (10).

It is difficult to provide recommendations for the treatment of IS in the absence of comparative trials. New antiepileptic drugs with better efficacy and fewer side effects are fiercely needed.

Topiramate (TPM) is one such agent and can also be used as a second-line agent for IS of tuberous sclerosis, and as a first-line agent for other symptomatic IS. Its anticonvulsant effect is based on the following mechanisms:

a) blockade of the voltage-dependent Na channels

b) enhancement of the inhibitory activity of GABA

c) inhibition of excitatory neurotransmission by blocking Kainate/AMP glutamate receptors

d) inhibition of erythrocyte carbonic anhydrase (2,7,11-20).

TPM may induce metabolic acidosis, especially in patients with renal disease or in those on a ketogenic diet or zonisamide (11).

There is no consensus on mean daily dose of TPM (12) and up to 35 mg/kg per day has been used in IS (7,12,13, 19), but a maximum dose of 12 mg/kg/day is effective and safe (16,17,21). Slow titration of drug dose has improved the efficacy and safety of TPM in the treatment of intractable epilepsy seizures (21).

The purpose of this study was to evaluate clinical efficacy and safety of TPM as the first -line drug in controlling infantile spasms in Yazd- Iran.

Materials and Methods

This quasi- experimental (before and after) study was conducted on children with infantile spasms who referred to the pediatric neurology clinic of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, from September 2008 to 2010.

The sample size, based on Z formula and a confidence interval of 95% with 80% power, S= 30 and d=15 to detect a significant difference between the two groups with a level of 0.05, was assessed to be 40 persons.

The diagnostic criteria for the IS in this study were based on International League Against Epilepsy (ILAE) classification and done with two groups: symptomatic or cryptogenic, and the main clinical criteria were spasms that usually occurred in clusters, almost always occurred during the first two years of life and frequently occurred in a drowsy state (4).

Care was taken to include IS patients aged 2 months to 2 years who did not use any antiepileptic drugs, ACTH or

oral corticosteroids, and did not have metabolic acidosis or kidney dysfunction.

Video –EEG monitoring facilities were not available in our city and successful management of IS was shown as the cessation of clinical seizures.

Variables such age, sex, age of seizure onset, type and frequency of spasms (flexor, extensor or mixed based on history), etiologic classification, EEG and neuroimaging results were reviewed.

Topiramate started as a minimum of two divided doses and to minimize side effects of the drug, the dose increased in a weekly fashion to reach the maximum dose or the dose which controlled seizures in a four-week period as follows: 3, 6, 9, 12 mg/kg/day.

Laboratory blood analysis consisted of calcium, urea, creatinine, alanine aminotransferase, aspartate aminotransferase and complete blood count. EEG was also done at the beginning of the study and after three months of treatment.

Patients were visited for three consecutive months and clinical information of their parents regarding the type and number of spasms, side effects of the drug and paraclinical investigations was recorded. At the end of the period, drug efficacy and safety was evaluated. Clusters frequency in a week was compared to that of before and three months after drug use and the following classification was done on this basis:

1. Seizure free: all the spasms stopped
2. Improved: more than 50 % reduction in spasms frequency
3. Unchanged: no notable change was noted in spasms frequency
4. Worsened: spasms frequency increased by more than 25%

Cessation of all spasms or more than 50% reduction in seizure frequency was considered as a good response.

Data was analyzed using SPSS 15 statistical software. Chi-square test or Fisher exact test were used for data analysis of qualitative variables and mean values were compared using paired -samples t-test. Differences were considered significant at P values of less than 0.05.

An informed consent was signed by patients' parents and the study protocol was approved by the ethics committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The researchers received no support from the drug company.

Results

Topiramate efficacy was evaluated in 40 infantile spasms patients. Clinical characteristics of patients are presented in Table I.

Etiology in symptomatic IS group was inborn error of metabolism in 10, structural CNS dysgenesia in 7, hypoxic ischemic encephalopathy in 6, congenital infection in 5, tuberous sclerosis in 2 and chromosomal abnormality and genetic syndromes in 6 children.

Abnormal neuroimaging results were brain atrophy in 15 patients (37.5%), intracranial calcification in 5 (12.5%), structural CNS dysgenesia in 5 (12.5%) and hydrocephaly in one (2.5%) patient.

EEG showed hypsarrhythmia in 33 (82.5 %) children.

Results of efficacy analysis of TPM therapy at the end of three months are shown in Table II and a good response (all seizures stopped or more than 50% reduction in seizure frequency) was seen in 67.5% of the patients.

Mean seizure frequency/week, before and after treatment, was 32.4 ±16.5 (range: 1-105) and 13.08 ±10.5 (range: 0- 55) respectively, demonstrating the efficacy of TPM (Confidence interval: 95%, t=4.34, P.value = 0.0001)

The mean dose of TPM for seizure control was 6.9 ± 3.4 mg/kg/day (range: 3-12).

Results of efficacy analysis based on etiologic class, type of infantile spasms, electroencephalography and neuroimaging results are illustrated in Table III indicating that topiramate efficacy was not statistically different in these clinical and paraclinical characteristics of patients.

No serious paraclinical adverse events such as hematologic abnormality, hepatotoxicity and nephrotoxicity were seen in two groups.

Transient and mild side effects which were seen in 32.5% (N=13) of the patients consisted of drowsiness in 15% (N=6), hypotonia and hyperthermia (each) in 7.5% (N=3) and anorexia and weight loss in 2.5% (N= 1). All side effects disappeared in one or two weeks and no patient stopped treatment.

Discussion

In this study, 90% of the participants had symptomatic IS among whom, inborn error of metabolism was the most common cause. In a study in Thailand, 45.8%

were symptomatic and the most common etiology in symptomatic cases was hypoxic ischemic encephalopathy (22). In karvelas's study, 63% were symptomatic IS and cortical dysgenesia was the most frequent cause. (23) In a study in Taiwan, 80% of the patients were symptomatic and tuberous sclerosis, asphyxia, and CNS malformation were the most common causes (24); in another study, 70% were symptomatic and brain malformations and tuberous sclerosis were seen in 35% of them. (25) In Zagreb, 81.2% had symptomatic IS and hypoxic-ischemic encephalopathy was the most common etiologic factor (26). In a study by Peltzer et al., 84% were symptomatic (13).

In the present study, 82.5% of the patients had a hypsarrhythmic pattern in EEG. Based on pediatric neurology textbooks, hypsarrhythmia may be seen in 66% of the patients and is most obvious in non-rapid eye movement (REM) sleep (3). This EEG pattern appears after 3-4 months of age and may only be present periodically. It may change or even resolve with time and during REM sleep and immediately after arousal from REM or non-REM sleep, electroencephalography can be normal for up to several minutes (2,3).

In this study, good response to drugs was not different in symptomatic and cryptogenic IS which dose not agree to other studies (6, 7,13,27).

In our study, control of all spasms was seen in 40 % of patients. However, in other studies this rate varied between 16.7 % and 57.4 % (12, 13, 15 - 19, 23,27, 28).

In the present study, more than 50% reduction in seizure frequency was seen in 27.5 % of the children. this rate was 33% (18), 36% (19), 47% (16) and 85% (29) in other studies. In a study in Valencia, 75% of IS patients (three of four) showed more than 75% reduction in spasms. (30) In Watemberg study, 87.5% of IS (seven of eight) cases improved with TPM treatment (31).

A possible explanation for these discrepancies is difference in sample size, duration of treatment, selection method of patients and dosage of drug.

Dose of TPM in this study was 3- 12 mg/kg/day while it was 25 mg/kg/day (19), 3.57-20 mg/kg/day (15) 1.56-26 mg/kg/day (28), 1-12 mg/kg/day (17), 3 -27 mg/kg/day (18) and 1-10 mg/kg/day (32) in other studies.

In our study, mean dose of TPM for seizure control was 6.9 ± 3.4 mg/kg/day which was almost similar to Taiwan study (7.35 ± 4.9 mg/kg/day on 13 children) (29).

In this study, TPM adverse effects were seen in 32% of the children and lethargy was the most common side effect.

In a study by Mikaeloff et al, the most common adverse effects were neurobehavioral problems (drowsiness, fatigue, hyperactivity) and gastrointestinal disorders (anorexia, loss of appetite) (12). About 10.5% of the patients (2 of 19) in a study by Pletzer et al showed side effects such as appetite loss, tremors, and lethargy (13).

Zou et al conducted two studies in china; in one study, 38.8% had adverse effect with anorexia and somnolence being the most common (15) and in the other one, 26% had side effects including poor appetite and anorexia, absence of sweating, and sleeplessness (28).

In a study by Korinthenberg et al in Germany, adverse effects were seen in 25% of the patients with sedation, loss of appetite, weight loss, and metabolic acidosis being the most common (16).

In Hosain's study, irritability was the most common side effect (18). Two studies were conducted by Grosso; in one study, adverse effects were seen in 58% of the children including weight loss, hyperthermia, sedation, and nervousness but the majority of them disappeared after slow titration or decreasing drug dose (33) and in the other one, the most common side effects were drowsiness, irritability, hyperthermia, and anorexia (27).

In a study by Al Ajlouni in Amman, Mild to moderate adverse effects, mainly somnolence, anorexia and nervousness were seen in 25 (53%) children. Only one child developed hypothyroidism.(32) Fifteen percent of the patients (2 of 13) in Valencia's study developed side effects, mainly lethargy, hyperthermia, and anorexia (30)

In conclusion, Education of parents and children's health care providers for early referral, diagnosis and treatment of infantile spasms is necessary. Topiramate is an effective and safe drug for the treatment of IS and should be considered as the first line of treatment.

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Table 1: Clinical characteristics of the patients

Sex	Female=22(55%) Male=18 (45%)
Age (in months)	Range = 3-20, Mean ± SD : 9.2 ± 3.9 months
Infantile Spasms Type	Mixed N=15 (37.5 %)
	Flexor N=14 (35 %)
	Extensor N=11 (27.5 %)
Etiologic classification	Symptomatic IS N=36 (90 %)
	Idiopathic IS N=4 (10 %)
Neuroimaging results	Abnormal N= 26 (65 %)
	Normal N=14 (35 %)

Table 2: Results of efficacy of topiramate in infantile spasms after 3 months

Result	
Seizure free: all the seizures stopped	40% (N=16)
Improved: > 50 % reduction in seizure frequency	27.5% (N=11)
Unchanged: no notable change frequency of seizures	27.5% (N=11)
Worsened: seizure frequency increased >25 %	5% (N=2)

Table 3: Frequency distribution of good response based on etiologic class and type of infantile spasms, electroencephalography and neuroimaging results

Data \ **Good response**		**Yes**		**No**		**P-value**
		Number	**Percent**	**Number**	**Percent**	
Etiologic class	Symptomatic	25	69.5	11	30.5	0.583
	Cryptogenic	2	50	2	50	
Type	Mixed	10	66.7	5	33.3	0.44
	Flexor	11	78.6	3	21.4	
	Extensor	6	54.5	5	45.5	
Hypsarrhythmia in EEG	Yes	20	60.6	13	39.4	0.074
	No	7	100	0	0	
Sex	Girl	15	68	7	32	1
	Boy	12	66.7	6	33.3	

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