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Topiramate sprinkle is effective in the treatment of childhood epilepsy

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ABSTRACT

BACKGROUND
Epilepsy remains one of the most frequently occurring pediatric problems. Approximately 10-15% patients do not respond to conventional therapy. Topiramate as a novel antiepileptic drug has a broad spectrum activity, presumably indicative of multiple anti-seizure mechanisms. Previous studies of topiramate as adjunctive and monotherapy in adults have shown beneficial effects. The objective of this research was to evaluate the efficacy and tolerability of topiramate sprinkle monotherapy in pediatric epilepsy.

METHODS
This experimental research was conducted in the Pediatric Neurology outpatient clinic department, Soetomo hospital, Surabaya, involving 18 consecutive subjects. Subjects meeting the inclusion criteria were treated with topiramate sprinkle adjusted dose. Seizure frequency and side effects were observed in weeks 1, 4, 8, 12, 16, 20 and 24, respectively. Electro encephalogram (EEG) and laboratory examinations were performed prior to and after 6 months of treatment. The t-test for related samples and McNemar test were utilized for statistical analysis.

RESULTS
A total of 15 subjects completed the study. Topiramate-treated patients showed a statistically significant difference of seizure frequency reduction from 2.7 ± 1.16 to 0.13 ± 0.51 (p=0.000) with 93.7% patients being seizure free in 20 weeks. EEG recordings did not differ statistically in decrement of epileptiform activity in 20% subjects. About 7% subjects developed drowsiness and 33.3% subjects suffered from appetite suppression in the initial treatment. Laboratory results showed no abnormalities.

CONCLUSIONS
There was reduction of seizure frequency and no EEG recording alterations after topiramate sprinkle monotherapy. Topiramate as a monotherapy is highly effcicacious in childhood epilepsy.

Keywords: Topiramate sprinkle monotherapy, seizure frequency, side effect, childhood

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Topiramate sprinkle *efektif untuk pengobatan epilepsi pada anak-anak*

ABSTRAK

LATAR BELAKANG

Epilepsi merupakan masalah besar dalam bidang pediatri. Masih terdapat 10-15% penderita yang resisten terhadap pengobatan umum. Topiramate sebagai obat antiepilepsi baru mempunyai spektrum luas untuk anti kejang. Penelitian menunjukkan dan monoterapi topiramate mempunyai potensi yang baik pada orang dewasa. Data efektifitas dan efek samping topiramate sebagai monoterapi pada anak-anak masih terbatas. Tujuan penelitian ini adalah menilai efikasi dan tolerabilitas topiramate untuk monoterapi penderita anak-anak dengan epilepsi.

METODE

Penelitian eksperimental dilakukan di poliklinik neurologi anak RSUD Dr Soetomo Surabaya. Sebanyak 18 subjek anak-anak diikut sertakan pada penelitian. Subyek yang sesuai kriteria inklusi dan ekslusi diberikan terapi topiramate sprinkle dan dilakukan pengukuran frekuensi kejang serta efek samping pada minggu 1, 4, 8, 12, 16, 20 dan 24. Gambaran elektro ensefalogram (EEG) dan pemeriksaan laboratorium dilakukan sebelum dan sesudah 6 bulan terapi. Analisis statistik menggunakan T-test for related samples *dan McNemar.*

HASIL

Sebanyak 15 subjek berhasil diikuti sampai akhir penelitian. Frekuensi kejang awal sebanyak 2,7 ± 1,16 berkurang menjadi 0,13 ± 0,51 dengan 93,7% penderita bebas kejang pada minggu ke 20 (p=0,000). Gambaran EEG awal 100% menunjukkan aktifitas epileptiform menurun menjadi normal pada 20% subyek. Sebanyak 30% sampel mengalami penurunan nafsu makan pada saat awal terapi dan 7% subyek mengalami rasa kantuk. Setelah pemberian pengobatan topiramate sprinkle *hasil pemerikssan laboratorium tidak menunjukkan adanya kelainan.*

KESIMPULAN

Terdapat reduksi frekuensi kejang dan tidak terdapat perubahan EEG pasca pemberian pemberian topiramate sprinkle. Topiramate sebagai monoterapi sangat efektif untuk pengobatan epilepsi pada anak-anak.

Kata kunci*: Monoterapi, topiramate* sprinkle*, frekuensi kejang, efek samping, anak-anak*

INTRODUCTION

Epilepsy is a common chronic neurological disorder that is characterized by recurrent unprovoked seizures. These seizures are transient signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain. Most epilepsy cases begin in childhood. Therefore, epilepsy remains one of the biggest pediatric problems.[1,2]

Antiepileptic drugs (AEDs) can control seizures in 70-80% of epileptic children, and advanced studies in pediatric epilepsy have shown that 10-15% of patients are already resistant to conventional treatment.[1-3] The development of new AEDs for epilepsy over the last decade has been spurred by the fact that the available AEDs did not provide optimal care for patients with epilepsy. Many patients "failed" all available options, either because their seizures were not adequately controlled, or they were experiencing side effects. For ethical and medical reasons, new AEDs typically are evaluated first as adjunctive therapies in adults with AED-resistant seizures.[4]

Topiramate as a new AED appears to have multiple neurostabilizing activities, including

potentiation of ã-aminobutyric acid (GABA) neuroinhibition, state-dependent blockade of voltage-dependent Na^+ channels, modulation of high voltage-activated Ca^+ channels, and glutamate receptor antagonism at non kainate/ AMPA (N-methyl-D-aspartate/ NMDA) receptors. These activities may account for the broad spectrum of antiseizure effects seen experimentally and clinically.[3-5] Recent research has shown that topiramate as a new AED has a better efficacy than other AEDs. Previous studies of topiramate as adjunctive and monotherapy in adults has shown beneficial effects.[5-6] However, the data on the efficacy and tolerability of topiramate sprinkle monotherapy in children are still limited. The aim of the current study was to evaluate the efficacy and tolerability of topiramate sprinkle monotherapy in pediatric epilepsy.

METHODS

Study design

This was an experimental trial with 24-week treatment (titration and stabilization) phase conducted at the Pediatric Neurology outpatient clinic, Soetomo hospital, Surabaya, from August 2008 to January 2010.

Patients

Patients were included if they were above 6 months of age, had a first diagnosis of epilepsy with any type of seizures in accordance with the criteria of the International Classification of Epileptic Seizures, or had been treated with their first AED in monotherapy that failed in efficacy, tolerability, or both. Patients were excluded if they had pseudoseizures or the cause of the seizures was treatable, had any clinically relevant progressive or serious illness, which might interfere with the patient completing the trial, had a history or other indications of alcohol or drug abuse, were non-cooperative or were expected to be difficult to follow up, or had hypersensitivity to topiramate or any of its constituents.

Treatment

Topiramate sprinkle capsules were administered by the oral route, either by being swallowed whole or being opened and the contents mixed with a spoonful of soft food. Eligible patients selected by consecutive sampling received topiramate sprinkle monotherapy with adjusted dosages, starting from 0.5 mg/kg body weight once daily in the first week, and increasing to 1 mg/kg body weight twice daily in the second week. During the titration period, the dosage increments of topiramate were adjusted to the number of observed seizures. The patients were then followed for a 24-week maintenance period with a maximal tolerated dose of approximately 6 mg/kg body weight daily. If the patient did not tolerate the titration schedule, the rate of titration was either maintained or reduced at the discretion of the investigator. The background dose of AED, if any, was tapered during the titration period.

Evaluation

Throughout the trial, patients (or their parents or legal guardians) maintained diaries to record the type and frequency of seizures as well as adverse events. At each visit, the investigator reviewed the patient's seizure diary, classifying each seizure according to the International Classification of Epileptic Seizures, recorded any adverse experiences, and monitored vital signs. Patient visits were scheduled for weeks 1, 4, 8,12,16,20, and 24 (final visit), respectively. The primary efficacy analysis outcome was the seizure frequency distribution (i.e. the proportion of patients completing the trial seizure free or experiencing one or two seizures). The secondary efficacy analysis, including electroencephalogram (EEG) examinations, was obtained before and after topiramate treatment. The tolerability was monitored throughout the trial by physical examination, vital signs, clinical laboratory tests including hematology, blood chemistry, and adverse event reports. Blood samples for

confirmation of adverse events were collected at weeks 1 and 24.

Ethical clearance

The study protocol was reviewed and approved by the Medical Research Ethics Committee of Dr. Soetomo Hospital. The trial was conducted in accordance with international rules of good clinical practice. Written informed consent was obtained from the parent or legal guardian of each patient before study-related procedures were initiated.

Statistical analysis

Values are expressed as mean ± SD. The t-test for related samples was used for calculation of seizure frequency reduction and McNemar test for EEG demonstration analysis.

Table 1. Characteristics of the subjects (n=15)

Characteristic	n (%)
Age (years)*	3.81 ± 3.09
Sex	
Male	9
Female	6
Body weight (kg)*	15.22 ± 8.04
History of antiepileptic drug	
Yes (phenytoin)	3
No	12
History of familial seizure	0
Seizure frequency*	2.71 ± 1.16
Type of epilepsy	
General	7
Partial secondarily generalized	7
Absence	1
EEG	
Normal	0
Abnormal	15

* Mean ± SD

RESULTS

Patient characteristics

From 18 consecutive patients, 15 subjects completed the study. Three patients were excluded from analyses because no safety data were submitted. As shown in Figure 1, all subjects with newly or recently diagnosed localization-related epilepsy received topiramate monotherapy with adjusted doses starting from 0.5 mg/kg body weight. Most of the subjects were males with no history of familial seizure. Three types of epilepsy were recorded, i.e generalized, partial secondarily generalized, and absence. All subjects showed epileptiform activities on EEG before topiramate treatment (Table 1).

Topiramate efficacy

On weekly evaluation of the patients, no seizures were observed during the titration period. One patient was recorded as suffering from frequent seizures and hospitalized for a few days. The patient then received additional AED to control the seizure. The percentage of seizure frequency reduction showed 83.7% patients being seizure-free in the 8th week, increasing 93% in the 24th week. One patient did not show improvement up to 20 weeks (Table 2).

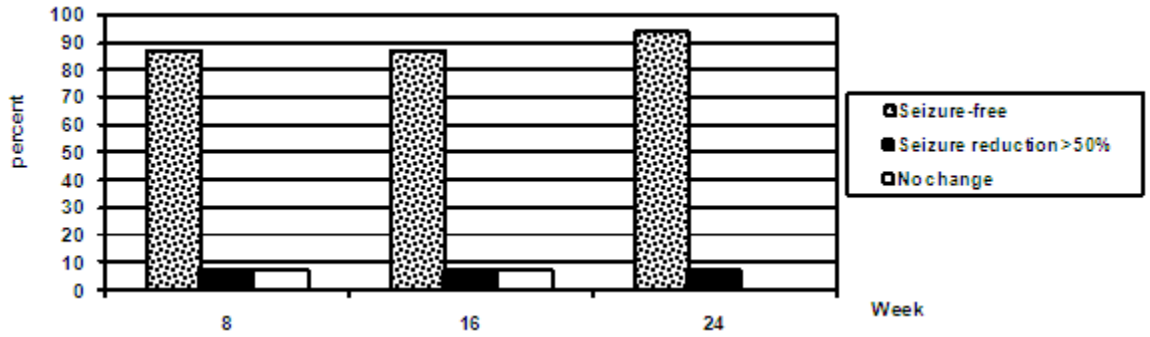

Figure 1. Percentage of seizure frequency reduction (weeks)

Table 2. Distribution of seizure frequency in each patient

Patients	Type	Seizure frequency [Dose mg/kg body weight/day]								EEG Evaluation
		W 0	1	4	8	12	16	20	24	
1	G	5	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
2	G	1	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
3	P	3	0	0	0	1	0	0	0	N
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
4	G	1	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
5	G	2	0	3	15	0	0	0	0	Ab
			[0.5]	[3]	[6]P*	[6]P*	[6]P*	[6]P*	[6]P*	
6	A	4	0	0	0	0	0	0	0	N
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
7	P	3	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
8	P	2	0	0	0	0	0	0	0	N
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
9	G	2	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
10	P	4	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
11	P	3	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
12	G	3	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
13	P	2	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
14	G	4	0	0	0	0	0	0	0	Ab
			[0.5]	[1]	[1]	[1]	[1]	[1]	[1]	
15	P	2	0	0	0	8	0	2	0	Ab
			[0.5]	[1]	[1]	[2]	[2]	[2.5]	[2.5]	

G=General, P=Partial secondarily generalized, A=Absence, Ab= Abnormal, N=Normal, W=week, *P= phenytoin added

The mean seizure frequency before treatment was 2.71 ± 1.16. In the first week of the study, 100% of subjects did not suffer from seizures. One patient suffered from frequent recurrent seizures in the 4th week of treatment, but the decrement in seizure frequency was statistically significant. The decrements in seizure frequency were not significant in the 8th week of the study, because one patient had intractable frequent seizures. Finally, the final observation indicated that the reduction in seizure frequency was statistically significant, despite the continued occurrence of seizures (Figure 2).

The topiramate dose started from 0.5 mg/kg body weight once daily at night. The titration dose was then increased to 1 mg/kg body weight daily, divided in two doses. The dose was incremented to 1.3 mg/kg body weight in the 8th week, and finally to 1.4 mg/kg body weight in the 12th week, this dose being sufficient to control frequent seizures. The incremental dose was statistically significant (Figure 3).

EEG recordings

All of subjects showed epileptiform activities on EEG before treatment. After 6 months of treatment, 3 patients showed normalized EEGs. However, the change in EEG recording was not statistically significant with McNemar test (Table 3).

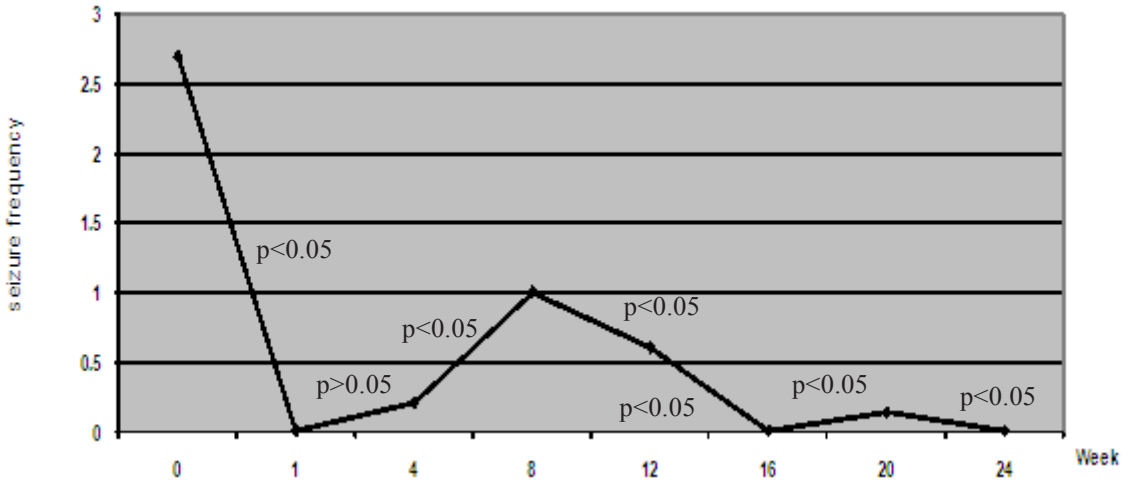

Figure 2. Seizure frequency reduction progress (weeks)

Adverse effects

Adverse effects were observed during the first weeks of the study. There were 33.3% of patients who suffered from poor appetite, while 7% of patients became drowsy. In the 8th week there were no more patient who were drowsy, while patients with poor appetite decreased to 7%. In the following weeks, there were no clinically apparent adverse effects. Laboratory examination of blood samples collected from the patients at baseline and after 6 months of treatment, revealed no abnormalities.

DISCUSSION

Monotherapy trials remain a complex and contentious issue with regard to new AEDs. Topiramate as a novel AED with broad-spectrum mechanism has been evaluated in previous studies for adjunctive therapy in partial-onset seizures and generalized tonic-clonic seizures. The efficacy results in adults have been very promising, suggesting that topiramate is one the most effective of the newer AEDs.[7-9] Trials of topiramate as monotherapy have been described in several studies with adults, but only in a few studies with children.[10]

Most of the studies presented seizure frequency reduction as a primary outcome measure. Seizure frequency reduction may be considered a surrogate marker for disease improvement.[4] Evaluation of seizure frequency reduction after topiramate monotherapy is shown in Figure 1. Significant seizure frequency

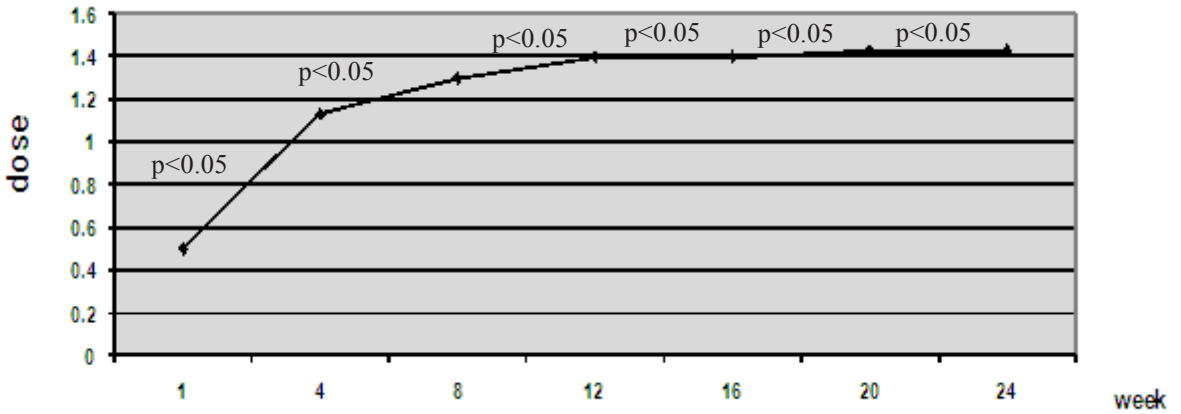

Figure 3. Topiramate adjusted dose progress (mg/kg body weight) (weeks)

Table 3. EEG results

	Before treatment	After treatment	p value
Normal	0	3	0,25*
Abnormal	15	12	

* Statistically not significant with McNemar

reduction was noted in the early titration period to week 4. However, there was one patient suffering from intractable seizures, who had to be titrated to the maximum dose, with the addition of other AEDs. This was the reason why the mean seizure frequency in week 8 was not significant, with 86.7% of patients being seizure free, 6.7% of patients with a reduction in seizure frequency of >50% from baseline, and 6.7% patients showing no improvement. The efficacy of topiramate in seizure frequency reduction was 93.7% in week 20.

In this study, the types of epilepsy found were generalized epilepsy, simple partial secondarily generalized epilepsy, and absences. The study by Valencia on various types of epilepsy found that among 7 patients receiving topiramate monotherapy, there was a seizure frequency reduction of more than 75% in 38.5% subjects.[11] Our study showed that topiramate could reduce seizure frequency in absence pediatric epilepsy. This trial is consistent with previous research by Cross on the efficacy of topiramate monotherapy in 5 subjects with absence seizures. Topiramate seemed to be effective in reducing absence seizures.[12]

According to Glauser, titration in monotherapy for children should be started from 0.5 mg to 1 mg/kg body weight once daily at night in the first week. The dose is then increased at intervals of 1-2 weeks, from 0.5 to 1 mg/kg body weight daily divided in two doses.[12] Glauser's study achieved a topiramate maintenance dose of 1.43 mg/kg body weight daily in week 20, which remained constant up to week 24. With this maintenance dose there was an increase in topiramate efficacy, with 93.7% of patients being seizure free. Kugler has described the topiramate efficacy in babies with partial epilepsy, with dose-related achieved to 7.7 mg/kg body weight, while Cross reported topiramate monotherapy efficacy in absence epilepsy to dose-related 5-12 mg/kg body weight.[13,14] A recommended target dose for topiramate monotherapy in children above 2 years is 3-6 mg/kg body weight daily. This research used maximal topiramate dose-related 6 mg/kg body weight daily. Patients tend to be highly individual in their responses to AED therapy; therefore the best dose and even the best AED for a specific patient is often a matter of trial and error. The best dose is the lowest possible dose delivering the optimal balance between maximum seizure control, preferably seizure freedom, and minimum adverse effects in early as well as long-term therapy. Gradual initiation of AEDs, including topiramate, can help clinicians achieve these goals.[14,15]

EEG is an essential component in the evaluation of epilepsy. The EEG provides important information about epileptiform discharges and is required for the diagnosis of specific electroclinical syndromes. Aidyn reported that 37.1% epileptic patients showed epileptiform activities in their EEG.[16] The present trial demonstrated mild post treatment EEG alterations, which however were not statistically significant. A report on infants 9 to 12 months of age, the EEG recordings had been described in 2 partial epilepsy babies who received topiramate. Interestingly, in one baby the EEG normalized in concert with the cessation of clinical seizure, while in the other the interictal EEG remained epileptiform despite the clinical efficacy.[13] The EEG alteration has been reported in 5 absence epilepsy children who received topiramate monotherapy for 6 weeks. It depicted 1 patient with normalized

EEG, 2 patients with confirmed reduction in epilepticform activity and 2 patients without any alterations.[14] The mild and nonspecific EEG abnormality has been found in 15% of the normal population, and approximately 10% epileptic patients have a normal EEG.[17]

Among the children in the present study there were generally mildly or moderately severe adverse events. Most adverse effects were CNS related, with appetite suppression and drowsiness being the most common side effects. The incidence of appetite suppresion was 70% on early treatment and tended to disappear without intervention. Gurreiro reported that appetite suppresion was observed in 42% of patients with Lennox-Gastaut syndrome treated with topiramate,[12] and drowsiness in 7%. Previous studies had shown that 47% patients with Lennox Gastaut syndrome suffered from drowsiness after topiramate administration.[18]

Most adverse effects events occurred early in treatment and related to rapid dose escalation and tended to disappear once patients became acclimatized to topiramate.[19] No acute or long-term idiosyncratic organ toxicity was observed with topiramate monotherapy, which is consistent with the laboratory results and the safety profile from earlier studies. There was no discontinuation of therapy due to adverse effects, and no deaths were reported during treatment.

As our findings illustrate, gradual initiation of topiramate sprinkle monotherapy can have a therapeutic effect during titration to effective maintenance dosages and enhance tolerability for pediatric epilepsy. Nevertheless, long-term safety and possible adverse sequelae have not been established.[19,20] Topiramate may represent a monotherapy option for children with epilepsy.

There were several limitations in this study. The experimental methods should have included comparison of subjects to increase the power of the study. This study used patients with several types of seizures. There were some difficulties in determining the type of epilepsy from the EEG results; it would be better to use a defined type of epilepsy that has the highest response to topiramate.

CONCLUSIONS

In this study there was a reduction of seizure frequency and no alterations in EEG recordings after topiramate sprinkle monotherapy. The most common adverse effects were drowsiness and appetite suppression. Topiramate as a monotherapy is highly effcicacious in childhood epilepsy.

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