Topiramate as an Adjunctive Treatment for Refractory Infantile Spasms

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Abstract

Background & Aim: Management of infantile spasms is difficult because current treatment regimens, including many anticonvulsants and hormones, are often ineffective in completely controlling of seizures. We conducted this study to determine the efficacy, safety and tolerance of Topiramate (TPM) as add-on therapy in children with intractable infantile spasms.

Subjects &Methods: A prospective clinical trial included 29 children with refractory infantile spasms, who were admitted to the neurological clinic at University Children's Hospital in Damascus between 1/12/2017-1/5/2020, and given Topiramate at a starting dose of 1-2 mg/kg/day in two doses. Daily dosage was increased by 1-2 mg/kg/day every 1-2 week until the spasms disappeared or to a maximum daily dosage of 10 mg/kg/day, during that we monitored the response.

Results: There were 18 males (62%) and 11 females (38%) registered in this study, and the age at onset of spasms was from 3 to 12 months (median 7.5). As to the etiology of infantile spasms, there were a cryptogenic group (n=7) (24%) and a symptomatic group (n=22) (76%). Overall, spasms in 4 patients (14%) were completely controlled. A ≥50% reduction in spasms was observed in 13 patients (45%), A ≤50% reduction in spasms was observed in 7 (24%), we found no difference in 4 patients (14%), while one patient (3%) quit the treatment because adverse effects. The mean dose of TPM during stabilization was 6.5 mg/kg/d.

Adverse events were mild to moderate and observed in 6 patients (20%). The most frequent symptom was body weight loss, which occurred in 17%.

Conclusions: We conclude that TPM as adjunctive therapy is a promising drug in children with intractable infantile spasms.

Key Words: Topiramate, adjunctive, refractory, infantile spasms.

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التوبيرامات كعلاج مساعد في علاج التشنج الطفلي المعنّد

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الملخص

خلفية البحث وهدفه: يُعتبر تدبير متلازمة التشنج الطفلي أمراً صعباً لأنّ المعالجات الحالية والتي تتضمن الأدوية المضادة للصرع والأدوية الهرمونية غالباً غير فعّالة في الضبط التام للنوب، لذلك تمّ إجراء هذه الدراسة لتحديد الفعالية والتحمّل والأمان ل التوبيرامات كعلاج مساعد واضافي في علاج حالات التشنج الطفلي غير المستجيب للمعالجة.

مواد البحث وطرائقه: أُجريت هذه الدراسة (تجربة سريرية مستقبلية) والتي تضمنت 29 طفلاً مصاباً بالتشنج الطفلي المقاوم من المراجعين للعيادة العصبية في مستشفى الأطفال الجامعي بدمشق في الفترة بين 2017/12/1 إلى 2020/5/1، حيث تمّ إعطاء التوبيرامات بجرعة بدئية 1-2 مغ/كغ/يوم مقسمة على جرعتين، مع زيادة تدريجية 1-2 مغ/كغ/يوم كل 1-2 اسبوع حتى توقف النوب أو الوصول للجرعة القصوى 10 مع/كغ/يوم، مع مراقبة الاستجابة.

النتائج: تضمنت حالات الدراسة 18 ذكر (62%) و 11 انثى (38%)، وكان عمر البدء للنوب من 3 إلى 12 شهراً (الوسطي 7.5)، تمّ تصنيف الحالات حسب الآلية الامراضية للتشنج الطفلي إلى مجهولة السبب في 7 حالات (24%) وعرضية في 22 حالة (76%). بالنسبة للاستجابة للدواء تمّ ملاحظة وجود 4 حالات مع ضبط تام للنوب (14%)، نقص ≤ 50% من النوب عند 13 حالة (45%)، نقص ≥ 50% من النوب عند 7 حالات (24%)، ولم نجد أي اختلاف عند 4 حالات (14%)، بينما تمّ ايقاف المعالجة عند مريض واحد بسبب التأثيرات الجانبية للدواء. وكانت الجرعة الوسطية المثالية ل التوبيرامات في ضبط النوب هي 6.5 مغ/كغ/يوم.

كانت التأثيرات الجانبية للدواء خفيفة أو معتدلة بشكل عام وتمّ ملاحظتها في 6 حالات (20%)، والعرض الأكثر شيوعاً هو نقص الوزن والذي لوحظ في (17%) من الحالات.

الاستنتاج والتوصيات: التوبيرامات دواء واعد ومفضّل كمعالجة اضافية في تدبير الأطفال مع حالات تشنج طفلي معنّد.

كلمات مفتاحية : التوبيرامات، اضافية، التشنج الطفلي، المعنّد.

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INTRODUCTION:

Approximately 2% of childhood epilepsy is comprised of a seizure type known as infantile spasms (IS).[1] Infantile spasms is a syndrome which includes an unique type of epileptic seizure, the spasms, which occur in approximately one child for every 2000–6000 live births. The initial seizure typically occurs within the infant's first year of life, the peak age at onset is between 4 and 7 months, and onset is always before 1 year of age.[2]

Patients with (IS) may be diagnosed as having West syndrome. This condition consists of a triad including infantile spasms, hypsarrhythmia, and developmental delay. The triad of West syndrome was originally described in 1841 by Dr.West who observed these findings in his own son.[3]

Infantile spasms is a rare seizure disorder commonly associated with severe learning difficulties, psychomotor retardation is frequently found at follow up, otherwise, still little is known about the pathophysiological basis for infantile spasms and treatment remains problematic.[4]

Classification

Patients with infantile spasms are classified into one of the three etiologic groups: **symptomatic**, **cryptogenic** and **idiopathic**.

The **symptomatic** group includes the patients in whom an underlying neurological disorder has been identified, An underlying cause can be determined in approximately 75% of patients; congenital malformations and perinatal asphyxia are common causes, and tuberous sclerosis accounts for 20% of cases in some series. Prognosis depends on the cause, but, as a rule, the symptomatic group does poorly.[5]

Classification as **cryptogenic** indicates that no specific cause has been identified but child was not developmentally normal prior to onset of seizures, thus, an underlying brain abnormality can be presumed.

Idiopathic spasms characteristically occur in children who had been developing normally at the onset of spasms and have no history of prenatal or perinatal disorders, and in whom no underlying cause can be identified.[6]

Prognosis is bimodal: Approximately one-fourth of children with IS those with favorable premorbid development, prompt diagnosis, and successful early treatment achieve enduring seizure freedom and normal (or near-normal) intellectual outcomes.[7]

In contrast, despite the therapies discussed below, the remaining children face substantial risk of intellectual disability, autism, and intractable seizures, often with transition to other epilepsy syndromes, like Lennox-Gastaut syndrome.[8]

Patients with idiopathic infantile spasms have the best response to pharmacological treatment; especially if the treatment is started before signs of developmental delay become evident.

Treatment of infantile spasms

The treatment of infantile spasms is still an unresolved problem because the disease is often resistant to multiple antiepileptic drugs and has a poor outcome.[9]

Many different treatments are currently used world-wide in the treatment of this disorder and many more have been tried in the past, often with little success. Not all treatments are licenced for use in all countries. The seizures are usually refractory to treatment with conventional antiepileptic drugs, furthermore, most treatments have significant side effects.[10]

Specific Management of Infantile Spasms

Goal: Cessation of spasms and normalization of the EEG. Aggressive treatment is usually associated with improved outcome with respect to development, cognition, and epilepsy.

(1)Hormonal therapy: The most popular hormonal therapies include natural adrenocorticotropic hormone, synthetic ACTH , prednisolone, and dexamethasone.[11]

The response to hormone therapy is never graded; control is either complete or not at all. Even when the response is favorable, one third of patients have relapses during or after the course of treatment, and the long term outlook in the patients is very poor, even if their spasm are controlled, and side effects of steroid therapy (electrolyte imbalance, reversible hypertrophic obstructive cardiomyopathy, hypertension, cushingoid features, glucosuria and bacteremia) may even be fatal at times.[12]

(2) Vigabatrin (VGB): is an irreversible inhibitor of c-aminobutyric acid (GABA) transaminase**,** has been shown to be especially

effective in the treatment of IS in patients with tuberous sclerosis complex (TSC) and perhaps cortical dysplasia.[11,13]

Despite this established efficacy, the use of VGB has been limited by reports of retinopathy manifesting with permanent bilateral concentric peripheral visual field defects, periodic ophthalmologic examinations and serial electroretinograms are required by the FDA. Other adverse effects include sedation, irritability, insomnia, hypotonia, and reversible nonspecific T2 signal changes on MRI in a particular pattern, MRI toxicity is moderately high and dose-dependent.[14]

(3) Sodium Valproate: valproate may reduce the frequency and severity of infantile spasms, and used in an increasing dosage up to 100 mg/kg/day reported control in half the patients. However, muscle hypotonia, lethargy and vomiting were commonly present and thrombocytopenia was found in one third of cases. Also, the concern for fatal hepatotoxicity at high doses has limited use in this age group.[15]

(4) Pyridoxine

Pyridoxine has been reported to be beneficial in treating a small number of patients with infantile spasms.[16]

(5) Other antiepileptic drugs: a plenty of other therapies including zonisamide, felbamate, and benzodiazepines (chiefly clonazepam and nitrazepam) are also used at times but lack strong evidence of efficacy.

(6) Ketogenic diet may be used in some refractory cases of infantile spasms, which is a high-fat, appropriate protein, and low-carbohydrate diet.[17]

(7) Epilepsy surgery: may be an option for patients with focal lesions and refractory spasms, the etiologies best suited to surgical resection include focal malformations of cortical development (chiefly cortical dysplasia), cortical tubers in association with TSC, and various acquired structural insults such as uni-focal stroke or hemorrhage.[18]

Although current therapy for infantile spasms includes anticonvulsants and hormone therapy, patients with this condition often remain resistant to both single- and multiple-drug therapies. Therefore, there is a significant need for new agents that are safe and effective in the control of refractory infantile spasms (refractory defined as seizures that cannot be managed with at least two first line antiepileptic drugs in adequate doses, at the maximal tolerated doses, as single or combined drug therapy including hormone therapy or anti-convulsion medicine), which not respond to precedent treatment.

Topiramate (TPM) is a potent new anticonvulsant, with proven efficacy against spasms in a broad range of seizure types. It seems to have multiple mechanisms of action such as (a) enhancement of γ- aminobutyric acid influences, (b) attenuation of voltage-gated sodium currents, and (c) blockade of the α-amino-3-hydroxyl-5-methyl-4- isoxazole-propionic acid (AMPA)/kainate receptor.[19]

It has been used for monotherapy and adjunctive treatment of partial and generalized onset seizures in children and adults. Thus, topiramate exerts beneficial effects on several seizure types, including those that are resistant to the old-generation antiepileptic drugs such as carbamazepine, nitrazepam, and valproate.[20]

Subjects and Methods:

Patients

From 1/12/2017 through 1/5/2020, 29 children with intractable infantile spasms were enrolled in this study, and throughout the whole study period of up to 28 months. The baseline seizure frequency was recorded for at least 2 weeks according to parental reports. The principal exclusion criterion was a response to previous treatment with any antiepileptic drug or hormone therapy.

Study Design

The study was designed as a prospective open-label study. All patients were treated with Topiramate (TPM) as an adjunctive therapy, It was begun at starting dose of 1-2 mg/kg/day, administered orally in two doses, daily dosage was increased by 1-2 mg/kg/day every 1-2 weeks until the spasms disappeared or to a maximum daily dosage of 10 mg/kg/day, concomitant antiepileptic drugs were not tapered off.

Seizure frequency was established before and after treatment with TPM, and the efficacy

measure was the comparison of the seizure rate before and after treatment.

The response to therapy was divided into the following categories: (1) completely controlled, (2) A ≥50% reduction in spasms, (3) A ≤50% reduction in spasms, (4) no difference.

Patients were followed-up at our outpatient clinic monthly for 6 months. Spasms were reported by parents. Beneficial effects can be seen, and improvement in behavior, development, verbal communication, concentration and alertness were reported.

Electroencephalograms and brain images were made for all subjects before beginning TPM therapy to determine the etiology. Electroencephalogram was recorded with 18 electrodes (in 10-20 system) during wakefulness and sleeping induced by chloral hydrate. The EEG was evaluated before and after treatment at the time caregivers reported clinical spasm cessation.

Ethics

This trial was conducted in accordance with the international rules of good clinical practice. Informed consent was obtained from each patient's parents before trial-related procedures were initiated.

Results

There were 18 males (62%) and 11 females (38%) registered in this study. The age at onset of spasms was from 3 to 12 months (median 7.5). A spasm was defined as a sudden symmetrical contraction of the muscles of the neck, trunk, and extremities. In 21 cases, mainly flexors were involved, in 5 cases, mainly extensors, and in 3 was mixed.

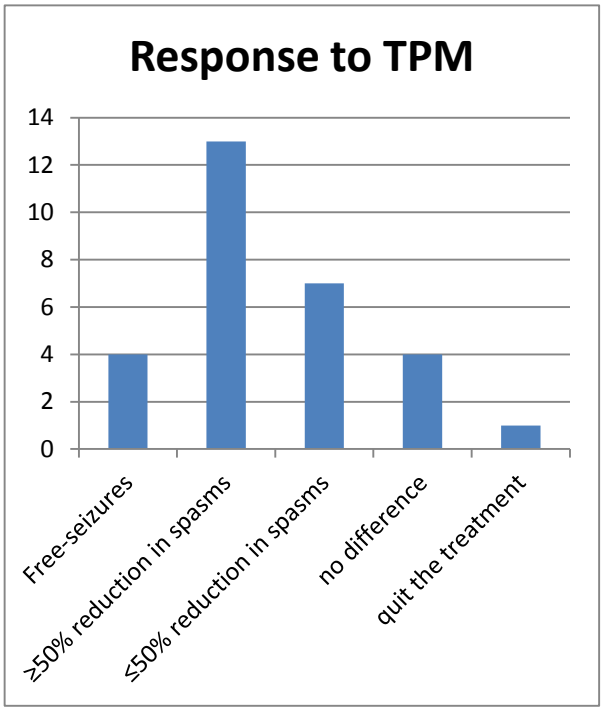
The duration of spasms before the study was from 3 to 8 months (median 5.5), and the age at study entry was from 5 to 14 (median 8.5) months. The baseline average spasm frequency was from 20 to 200 (median 50) spasms/day.

As to the etiology of infantile spasms, there were a cryptogenic group (n = 7) (24%) and a symptomatic group (n =22) (76%).

Accompanying medications averaged 1.6±1.4 (range, 0~4) kinds/patient. Previous therapies included steroid, valproate sodium, vigabatrin, vitamin B6, clonazepam, and lamotrigine.

Twenty one (72%) of the patients showed hypsarrhythmia at the beginning of the study.

Response to medication with TPM was found as in schedule 1



schedule 1 show response categories

Overall, spasms in 4 patients (14%) were completely controlled, and they were monitored for 6 months with no seizure relapse, normalization of the EEG was seen, we found a ≥50% reduction in spasms was observed in 13 patients (45%), a ≤50% reduction in spasms was observed in 7 (24%), we found no difference in 4 patients (14%), while one patient (3%) quit the treatment because unstable body temperature as an adverse effect. The mean dose of TPM during stabilization was 6.5 mg/kg/d.

Tolerability and safety of topiramate treatment

Adverse events occurred in 6 patients (20%) as shown in Table 1 ,but we found that the respective patients often had 2 or more adverse effects simultaneously.

Table 1 show adverse events

Adverse Event	No. Patients	Proportion(%)
Weight loss/ poor appetite	5	(17%)
Low fever (temperature37-38°C)	3	(10%)
Irritability	3	(10%)
lethargy	2	(7%)
anhydrosis	1	(3%)

The discomfort reported by the parents included poor appetite and body weight loss (n =5), an unstable body temperature (n=3), irritability (n=3), lethargy (n=2), anhydrosis (n=1), and the most common adverse events were mild to moderate except one patient (3%) quit the treatment because severe adverse effects. The most frequent symptom was body weight loss, which occurred in 17 %.

Discussion:

Although vigabatrin is an important new anticonvulsant for treating infantile spasms, its lack of availability in some countries (because high price, and it is not licenced for use in some countries), relapse rate, reported association with the development of other seizure types during therapy, and adverse effects of visual field defects imply that additional effective anticonvulsants for children with infantile spasms are needed. So this study investigated the clinical efficacy, safety, and tolerability of topiramate treatment in refractory infantile spasms.

Fifty nine percent (59%) of patients in this study presented had more than 50% reduction in seizure frequency or became seizure free on TPM. This indicates that TPM is an effective anticonvulsant therapy in children with drug resistant infantile spasms. Our findings are consistent with previous reports of Glauser et al.[21]

We do not know if there is a synergistic effect with combination therapy, because we did not discontinue the concomitant anticonvulsants. So further study is necessary to determine this.

The mean topiramate dosage of 6.5 mg/kg per day applied in our study is relatively low compared with an older study by Glauser et al.[21] However, it is similar to a study by Albsoul-Younes et al,[22] who recommended a dosage of 6 to 8 mg/kg per day.

Generally, topiramate was proved to be well-tolerated and safe; the adverse effects tend to occur early during treatment and to be not life threatening, These effects were usually dose related and decreased with dose reduction. In our study, 6 patients (20%) revealed adverse events. The most frequent symptom was body weight loss, which occurred in 17 %.

It is important to notice that 4 of the 6 patients who experienced side effects were bad responders to TPM, while none of the patients who became seizure free had adverse effects. No acute or long-term idiosyncratic organ toxicity was observed with topiramate, which is consistent with the safety profile in earlier studies.[22,23] While the frequency of adverse effects reported in our study was higher than reported in previous studies.[21]

We thought that a starting dose of 0,5-1 mg/kg/d, with increases of 0,5-1 mg/kg/d every 1-2 weeks can probably reduce the incidence of adverse effects.

Conclusions:

Control of refractory infantile spasms was achieved with good results using TPM as add-on therapy. Generally, patients tolerated the TPM therapy well with mild side effects, A body weight loss and decreased appetite were the main complaints by parents. Although the limitations of our study which include open-label design and the lack of a control group, but the results provide evidence that Topiramate is effective as adjunctive therapy in refractory infantile spasms.

References:

1. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522–530.
2. Hancock E, Osborne J, Milner P.Treatment of infantile spasms. Cochrane Database Syst Rev. 2003;3:CD001770.
3. Wong M, Trevathan E. Infantile spasms. Pediatr Neurol. 2001.24:89–98.
4. Gaily E, Lommi M, Lapatto R, et al. Incidence and outcome of epilepsy syndromes with onset in the first year of life: a retrospective population-based study. Epilepsia 2016;57:1594–1601.
5. Velišek L, Jehle K, Asche S, Veliškova J. Model of infantile spasms induced by NMDA in prenatally impaired brain. Ann Neurol 2007; 61:109–119.
6. Wong M, Trevathan E. Infantile spasms. Pediatr Neurol 2001;24:89-98.
7. Riikonen R. Long-term outcome of West syndrome: a study of adults with a history of infantile spasms. Epilepsia 1996;37:367–372.
8. Shields WD. Infantile spasms: little seizures, BIG consequences. Epilepsy Curr Am Epilepsy Soc 2006;6:63–69.
9. Buoni S, Zannolli R, Strambi M, et al. Combined treatment with vigabatrin and topiramate in infantile spasms. J Child Neurol 2004;19: 385-386.
10. Kobow K, Auvin S, Jensen F, LöscherW, Mody I, Potschka H, et al. Finding a better drug for epilepsy: antiepileptogenesis targets. Epilepsia. 2012;53:1868–76.
11. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia 2010;51:2175–2189.
12. Oguni H, Yanagaki S, Hayashi K, et al. Extremely low-dose ACTH step-up protocol for West syndrome: maximum therapeutic effect with minimal side effects. Brain Dev. 2006;28:8–13.
13. Elterman RD, Shields WD, Mansfield KA, et al. Randomized trial of vigabatrin in patients with infantile spasms. Neurology 2001;57:1416–1421.
14. Hussain SA, Tsao J, Li M, et al. Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent. Epilepsia 2017;58:674–682.
15. Dulac O, Schlumberger E. A simple effective and well tolerated treatment regime for West syndrome. Dev Med Child Neurol 1994, 36: 863-872.
16. Coker SB. Postneonatal vitamin B-6 dependent epilepsy. Pediatrics 1992, 90: 221- 223.
17. Hirano Y, Oguni H, Shiota M, et al. Ketogenic diet therapy can improve ACTH-resistant West syndrome in Japan. Brain Dev 2015;37:18–22.
18. Wirrell E, Livingston JH. Epilepsy beginning in middle childhood. In: Appleton R, Camfield P, eds. Childhood Epilepsy. Management from Diagnosis to Remission. Cambridge, UK: Cambridge University Press; 2011:29–72.
19. Lee SR, Kim SP, Kim JE. Protective effect of topiramate against hippocampal neuronal damage after global ischemia in the gerbils. Neurosci Lett 2000;281:183-6.
20. Wheless JW. Use of topiramate in childhood generalized seizure disorders. J Child Neurol 2000;15:S7-13.
21. Glauser TA, Clark PO, McGee K. Long-term response to topiramate in patients with infantile spasms. Epilepsia 2000;41:S91-S94.
22. Albsoul-Younes AM, Salem HA, Ajlouni SF, et al. Topiramate slow dose titration: improved efficacy and tolerability. Pediatr Neurol 2004;31: 349-352.
23. Mikaeloff Y, de Saint-Martin A, Mancini J, et al. Topiramate: efficacy and tolerability in children according to epilepsy syndromes. Epilepsy Res 2003;53:225-232.