Original article

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Outcomes among patients with infantile spasms treated with hormonal therapy and adjuvant topiramate *versus* hormonal therapy alone

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ABSTRACT – *Aims*. Hormonal therapy is the first-line treatment for infantile spasms and is sometimes used in combination with topiramate for better seizure control and potentially improved developmental outcomes.
Methods. Retrospective review of pediatric patients with infantile spasms, with data compiled on patient sex, age at onset, etiology, electroencephalographic and imaging findings, topiramate use, spasm resolution (at one, six, and 12 months), and developmental outcome (at 12 months).
Results. Of 105 patients screened, 55 (28 female) met inclusion criteria (28 [51%] had spasms with known etiology and 27 [49%] had spasms with unknown etiology). Forty-six patients were followed for 12 months or longer to determine seizure outcome; a 12-month developmental assessment was documented for 49 patients. Thirty-seven patients (67%) received combination therapy; 18 (33%) received hormonal therapy alone. Resolution of spasms was comparable among treatment groups, with no difference relative to spasm etiology ($p>0.18$ for all). No difference was found in developmental outcomes with and without adjunct topiramate ($p=0.38$).
Conclusions. Combination therapy was the most common treatment at our institution. However, combination therapy was not found to be beneficial for the treatment of spasms or developmental outcomes when compared to hormonal therapy alone.

Key words: adrenocorticotropic hormone, epileptic spasms, infantile spasms, prednisolone, topiramate, West syndrome

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Infantile spasms are a form of early-onset seizure that connotes a high risk of a developmental disorder and long-term epilepsy. Although hormonal therapy (HT) with adrenocorticotropic hormone (ACTH) or prednisolone is the standard of care, infantile spasms are resolved in only 42% to 87% of patients treated with ACTH and in 67% to 80% of those treated with prednisolone (Nelson, 2015).

Topiramate has been used as both a monotherapy and an adjunct therapy for patients with infantile spasms, with mixed results in efficacy (Hosain *et al*., 2006; Zou *et al*., 2008; Mahmoud *et al*., 2013; Weber *et al*., 2015). In a large 2008 multicenter study of 544 pediatric patients with infantile spasms, Zou *et al*. (Zou *et al*., 2008) found that seizure outcomes improved more with the use of topiramate as a monotherapy (122 of 243 [50%] patients had seizure freedom) than as an adjunct therapy (117 of 301 [39%] patients had seizure freedom) after 20 weeks of therapy. An earlier 2006 prospective study of topiramate monotherapy *versus* topiramate adjunct therapy for 15 (12 known etiology, three unknown etiology) pediatric patients with infantile spasms reported resolution of spasms in three of 15 patients (20%) at two months after treatment initiation (Hosain *et al*., 2006). Other notable findings were a greater than 50% reduction in infantile spasms in 33% of patients (*n*=5), and a 25% reduction in infantile spasms in three patients (20%). In contrast, Weber *et al*. (Weber *et al*., 2015) reported little benefit for topiramate as a monotherapy in 31 pediatric patients with infantile spasms (*n*=3 [9.3%] had clinical remission).

In a later prospective study reported in 2011, Zhu *et al*. (Zhu *et al*., 2011) enrolled 40 children with newly diagnosed infantile spasms who then underwent initial monotherapy with topiramate, up to a maximum dose of 6-8 mg/kg/day. If spasms were not fully controlled by one month, low-dose ACTH was added to the treatment regimen. Only 25% (*n*=10) of the 40 patients were spasm-free on topiramate alone, whereas 42% (*n*=17) achieved remission with topiramate in combination with low-dose ACTH.

At our institution, HT is used as a first-line therapy for infantile spasms in pediatric patients, but it is often paired with topiramate. In the above referenced study, the addition of hormonal therapy showed improved spasm remission. Our center was interested in whether the combination therapy itself was beneficial, or whether the remission was a result of the introduction of hormonal therapy. We hypothesized that using topiramate in combination with HT would lead to higher rates of freedom from spasms compared with use of HT alone. We also hypothesized that patients who received combination therapy would experience greater improvement in developmental outcomes at one year than patients who received HT alone.

Materials and methods

A retrospective study was performed to identify pediatric patients with infantile spasms who were treated at Phoenix Children's Hospital between January 1, 2008, and December 31, 2014. After approval by the institutional review board of Phoenix Children's Hospital, we queried the patient database to identify patients with a diagnosis of infantile spasms using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes, 345.60 (infantile spasms, without mention of intractable epilepsy) and 345.61 (infantile spasms, with intractable epilepsy). The need for consent was waived by the institutional review board due to the retrospective study design. Diagnosis was later confirmed by a chart review completed by two authors (JRF and NGE). Inclusion criteria were defined as patient age between one and 12 months at onset of spasms and treatment with HT (ACTH or prednisolone) or with combination therapy (HT and topiramate). Hormonal therapy was dosed as follows: prednisolone 40 mg total (divided for tolerability) daily as an initial dose with an increase to 60 mg daily if the patient was not responsive after two weeks; ACTH at 75 U/m^2 as low-dose therapy and 150 U/m^2 as high-dose therapy. Patients were dosed with hormonal treatment for two weeks and then the dose was tapered off over the remaining two weeks. Combination therapy was defined as the addition of topiramate at the time of diagnosis or within the first month after initiation of HT (mean dosage: 8 mg/kg/day; range: 2-16 mg/kg/day). Patients remained on topiramate therapy at the discretion of their neurology provider if deemed to be clinically effective with minimal side effects. Exclusion criteria were treatment with other antiepileptic medications or the ketogenic diet, patient age outside the included age range of 1-12 months at onset of infantile spasms, and lack of clinical one-month follow-up.

Outcome measures were defined as persistence of spasms at one month, six months, and 12 months after initiation of therapy. We also evaluated whether developmental delay was documented as present or absent in the medical records at follow-up visits, one year after the initiation of treatment. No standardized developmental testing was used. Additional data extracted from the medical records and analyzed included age at onset of infantile spasms, sex, etiology, electroencephalographic findings, and imaging findings.

Statistical analyses

The characteristics of patients and their outcomes were analyzed for the HT and combination therapy groups using appropriate descriptive statistics (*i.e.* mean [SD] for continuous measures and number and

percentage for categorical variables). Outcome rates and corresponding 95% confidence intervals were determined for both groups. Differences between the two treatment groups were evaluated using the Fisher exact test to quantify the association between treatment and each primary and secondary outcome after adjustment for potential confounders and risk factors, depending on data availability. Statistical significance was set at the 0.05 alpha level.

Results

Of 105 patients identified as having infantile spasms during the study period, 55 (52%) met the inclusion criteria. Mean (SD) age for all patients was 7.1 (2.4) months (range: 2-11 months). Male patients (27 of 55 [49%]) and female patients (28 of 55 [51%]) were almost equally represented (*table 1*). Of these patients, 28 (51%) had spasms with a known structural or genetic etiology (*table 2*). Most patients (49 of 55 [89%]) had hypsarrhythmia. In the six patients without definite hypsarrhythmia, infantile spasms with electrographic correlates were captured on electroencephalograms. The mean (SD) age at onset of spasms was 7.1 (2.4) months in the HT group and 6.1 (2.6) months in the combined therapy group. There were no statistically significant differences in the population characteristics of the two treatment groups ($p \geq 0.07$).

Eighteen (33%) patients were treated with HT alone (HT group), and 37 (67%) were treated with a combination of HT and topiramate (combination group). In the HT group, 13 of 18 (72%) patients, nine of 12 (75%) patients, and eight of 11 (73%) patients had resolution of spasms at one-month, six-month, and 12-month follow-up visits, respectively (*table 3*). In the combination therapy group, 24 of 37 (65%) patients, 26 of 36 (72%) patients, and 17 of 35 (49%) patients had resolution at one-month, six-month, and 12-month follow-up visits, respectively (*table 3*). The rates of spasm resolution for all patients treated with HT or combination therapy were compared using the Fisher exact test. No statistically significant differences were found at one-month ($p=0.76$), six-month ($p>0.99$), or 12-month follow-up visits ($p=0.18$). No statistically significant difference was found between patients with spasms with known *versus* unknown etiologies within each arm ($p \geq 0.19$). In addition, no statistically significant difference was found in the presence of a developmental delay between patients with spasms with known or unknown etiology within either treatment arm ($p \geq 0.38$).

Discussion

To our knowledge, no published studies have specifically assessed the benefit of adjunct topiramate therapy for infantile spasms in combination with HT compared with HT alone. This dearth of research was confirmed by our review of the PubMed database to retrieve articles published from 1990 to 2015 using the search terms *topiramate, infantile spasms, epileptic spasms, adjunctive therapy,* and *hormonal therapy*. Although class I and class II evidence (defined as evidence from large randomized controlled trials with high-quality design and avoidance of bias and evidence from trials in which any deficiencies are not likely to invalidate the results or introduce significant bias, respectively [*Evid Based Spine Care J*, 2013]) is lacking, the use of topiramate for prevention of infantile spasms has been reported, usually for treatment of refractory infantile spasms. These studies used topiramate at much higher dosages than those used in our

Table 1. Distribution of baseline characteristics among treatment groups.

Characteristic	All patients (*n*=55)		*p value*	Unknown etiology (*n*=27)		Known etiology (*n*=28)	
	HT (*n*=18)	HT+TOP (*n*=37)		HT (*n*=11)	HT+TOP (*n*=16)	HT (*n*=7)	HT+TOP (*n*=21)
Age, mean (SD), months	7.1 (2.4)	6.1 (2.6)	0.07	6.1 (1.7)	6.1 (2.4)	8.7 (2.5)	6.2 (2.8)
Sex							
Male	7 (39)	20 (54)	0.29	5 (45)	11 (69)	2 (29)	9 (43)
Female	11 (61)	17 (46)		6 (55)	5 (31)	5 (71)	12 (57)
Hypsarrhythmia							
Yes	16 (89)	33 (89)	0.97	9 (82)	15 (94)	7 (100)	18 (86)
No	2 (11)	4 (11)		2 (18)	1 (6)	0 (0)	3 (14)

Values are presented as number (percentage) unless otherwise indicated.
HT: hormonal therapy; TOP: topiramate; SD: standard deviation.

Table 2. Seizure etiology for 28 pediatric patients by treatment group.

Etiology	No. (%) of patients (*n*=28)	
	HT	HT+TOP
Myelomeningocele	1 (3.6)	
Stroke	2 (7.1)	1 (3.6)
Trisomy 21	1 (3.6)	6 (21.4)
Vascular malformation status post-resection		1 (3.6)
Global cortical malformation		1 (3.6)
Tuberous sclerosis		1 (3.6)
Hypoxic ischemic encephalopathy	1 (3.6)	1 (3.6)
17q21.31 deletion		1 (3.6)
FOXG1 mutation		1 (3.6)
Aicardi's syndrome		2 (7.1)
Intraventricular hemorrhage	1 (3.6)	
Hydranencephaly		1 (3.6)
Hydrocephalus		1 (3.6)
Cortical migration abnormality	1 (3.6)	1 (3.6)
GABRA3 mutation		1 (3.6)
Ring chromosome 21		1 (3.6)
Partial agenesis of corpus callosum		1 (3.6)
All	7 (25.0)	21 (75.0)

Percentages do not total to 100 due to rounding. HT: hormonal therapy; TOP: topiramate.

population (Glauser *et al.*, 1998, Hosain *et al.*, 2006). Combination therapy has proven successful in earlier small studies, which have reported spasm remission in 25% of patients who received topiramate alone and 42% of patients who received topiramate and combination ACTH (Zhu *et al.*, 2011).

Our results demonstrated no significant differences in the remission of infantile spasms or in the development of patients treated with HT alone or HT in combination with topiramate. Our observation regarding the frequent use of the combination treatment paradigm at our institution was confirmed in this study, as 67% of the patients in our study (37 of 55 patients) were treated with both HT and topiramate. The use of topiramate is not without potentially serious adverse effects, such as anorexia, metabolic acidosis, hypohydrosis, and nephrolithiasis. On the basis of the results from this study, our center's practice has changed.

Our findings confirmed developmental delay in all patients with a known structural or genetic etiology for their infantile spasms. However, more notably, the group with spasms with an unknown etiology had more variability, with some patients having normal development prior to onset of spasms, and no statistically significant difference was found with respect to the presence of a developmental disorder between the two treatment groups.

Limitations

Our study had several limitations. Its retrospective nature precluded the use of objective measures to define the resolution of spasms at specific intervals (including electroencephalogram data) and objective measures of developmental delay before and after treatment, with unequal numbers in each treatment arm and variability in topiramate dosing (mean dosage: 8 mg/kg/day; range: 2-16 mg/kg/day). Small sample size and loss of patients to follow-up also limited this study.

Table 3. Distribution of outcomes by treatment group and known or unknown etiology.

Patient group, outcome	Proportion (% [95% CI])		*p* value
	HT	HT+TOP	
All patients (*n*=55)			
Spasm: resolution at 1 month (*n*=55)	13/18 (72 [49-88])	24/37 (65 [49-78])	0.76
Spasm: resolution at 6 months (*n*=48)	9/12 (75 [47-91])	26/36 (72 [56-84])	>0.99
Free of spasm or seizure at 1 year (*n*=46)	8/11 (73 [43-90])	17/35 (49 [33-64])	0.18
Developmental delay (*n*=49)	9/12 (75 [47-91])	32/37 (86 [72-94])	0.38
Unknown etiology (*n*=27)			
Spasm: resolution at 1 month (*n*=27)	9/11 (82)	11/16 (69)	0.66
Spasm: resolution at 6 months (*n*=25)	8/9 (89)	11/16 (69)	0.36
Free of spasm or seizure at 1 year (*n*=24)	7/8 (88)	9/16 (56)	0.19
Developmental delay (*n*=26)	7/10 (70)	11/16 (69)	>0.99
Known etiology (*n*=28)			
Spasm: resolution at 1 month (*n*=28)	4/7 (57)	13/21 (62)	>0.99
Spasm: resolution at 6 months (*n*=23)	1/3 (33)	15/20 (75)	0.20
Free of spasm or seizure at 1 year (*n*=22)	1/3 (33)	8/19 (42)	>0.99
Developmental delay (*n*=24)	4/4 (100)	20/20 (100)	>0.99

HT: hormonal therapy; TOP: topiramate; CI: confidence interval.

Conclusions

The use of topiramate in the treatment of pediatric patients with infantile spasms was found to be not beneficial. Our findings contribute to the growing data on treatment outcomes of patients with infantile spasms who were treated with topiramate in combination with HT. Although this study did not show statistically significant results, it does provide further evidence on the subject and substantiates the need for additional studies focused on improving outcomes in this difficult-to-manage seizure type. □

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What is the current recommended treatment for infantile spasms (those not associated with tuberous sclerosis)?

(2) What are common adverse effects associated with topiramate?

(3) Did administration of hormonal therapy combined with topiramate have an effect on spasm remission or developmental outcomes in this retrospective study?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".