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High-dose prednisone therapy for infantile spasms and late-onset epileptic spasms in China: The addition of topiramate provides no benefit

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ABSTRACT

Purpose: To compare the clinical efficacy of high-dose prednisone monotherapy and the combination of hormone and moderate-dose topiramate (TPM) therapy in children with infantile spasms (IS) and late-onset epileptic spasms (ES), and to evaluate whether the addition of TPM would provide more benefits for patients.

Methods: All patients were assigned to receive either high-dose prednisone alone (the maximum doses was 60 mg a day) or high-dose prednisone with TPM (the moderate doses was 5 mg/kg/day). The primary outcome was the proportion of children who achieved cessation of spasms at day-49 or day-56 after initial treatment (the minimum duration of treatment were 49 days).

Results: 77 patients were randomly divided into two groups. The control rate of spasms on day-14 in hormone monotherapy was similar to combination therapy (71.8% *vs* 76.3%, $p = 0.796$). The cessation of spasms rate of patients on day-49 or day-56 was also similar between the two groups (71.8% *vs* 65.8%, $p = 0.569$). After 4 months, the cessation of spasms rate of patients in the group of hormone monotherapy was higher than the group of combination therapy, but there was no significant difference (61.5% *vs* 50.0%, $p = 0.308$).

Conclusion: The efficacy of the combination therapy was not better than that of the monotherapy in achieving spasm freedom at 14-days, 49-days or 56-days and day-120 in the patients. Adding-on moderate-dose TPM did not help more children achieve spasm freedom and provided no benefit for prevention of IS and late-onset ES in short term. Higher-dose regimens of TPM might be more effective.

1. Introduction

Infantile spasms (IS) has been described as a challenging epilepsy syndrome because its drug resistance and poor prognosis, which have given rise to a large burden on society and patients' families. IS typically have an onset between 3 and 12 months of age with a peak incidence around 6–7 months [1].However, the patients were divided into three groups by age at onset of spasms [2]: early onset (less than 3 months), classic onset (3 months and up to 12 months), and late onset (12 months and older), respectively. The West Delphi Group [2] proposed that ISs is the syndrome of ES with onset generally during the first 2 years of life. So the term *late-onset ES* will be more suitable for IS of age at onset > 2 years. Currently, the treatment of IS has a little class I data, but adrenocorticotropic hormone (ACTH), prednisolone and vigabatrin (VGB) have the best evidence as first-line medications [3,4]. However, the incidence of adverse effects of ACTH is high and VGB may induce visual-field defects with long-term use, and both agents are also difficult to obtain in our country. Our previous study had shown that high-dose prednisone alone was effective (the ratio of complete cessation of spasms was 65.0% after 7 weeks) and well-tolerated in children with IS [5]. However, it remains elusive whether the combination therapy (*e.g.*, add on TPM, valproate, levetiracetam or ketogenic diet) would be more effective than high-dose prednisone alone in the treatment of IS. In addition, there is scant evidence to guide the management of IS after successful response to short-term hormone therapy. There are no studies comparing high-dose prednisone alone with the combination therapy in the treatment of IS in China, so the answers to these clinical questions are unclear. Hence this study was planned to compare the efficacy and safety of high-dose prednisone alone with the high-dose prednisone and TPM in the treatment of IS, and to evaluate preliminarily whether TPM would be an agent for secondary prevention of IS.

2. Methods

2.1. Study design and participants

This study was conducted in the Department of Neurology of *Jiangxi*

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Children's Hospital from January 2015 to October 2016. Children with IS and late-onset ES (age at onset > 2 years) in clusters or a single attack with hypsarrhythmia or its variants on electroencephalogram (EEG) were enrolled. Inclusion criteria were: clinical diagnosis of IS and late-onset ES conformed the definition proposed by Lux et al. [2], newly diagnosed IS or late-onset ES, no previous hormone therapy. Exclusion criteria were: a contraindication to hormone treatment (eg., active tuberculosis), inability of parents or guardians to give informed consent or to implement doctor's advice. The ethical clearance was obtained from the institutional ethical committee. The written informed consent was obtained from each patient's parents or guardians.

2.2. Procedure

Prior to starting hormone therapy, detailed clinical history, neurological examinations and etiologies were evaluated and analyzed together with neuroimaging studies and routine laboratory examinations. Magnetic resonance imaging (MRI) was used in neuroimaging studies. And routine laboratory examinations contained chest X-ray, tuberculin test, blood cell count, liver and renal function, electrolyte analysis and blood glucose. All the cases underwent screening tests for inherited metabolic disorders, which included blood lactate, arterial blood gas, blood ammonia, urinary organic acids, and blood tandem mass spectrometry. In addition, all patients also underwent a 3–12 h video-electroencephalogram (VEEG) monitoring. VEEG monitored patients in both awake and asleep period, and it was performed before the treatment, 14 days after initial treatment and the end of the treatment of high-dose prednisone (49 or 56 days), respectively. The severity of developmental disabilities was assessed by the developmental quotient (DQ) test.

The eligible children were recruited one by one using random number tables by Zhen-qiu Sun et al. [6] into two groups. In our hospital we use prednisone (produced by Tianjin Tianyao pharmaceutical Co., LTD.) because both prednisone and prednisolone are bioequivalent. The monotherapy group received oral high-dose prednisone alone and the combination therapy group received oral high-dose prednisone and TPM. Prednisone was given orally 10 mg once, four times a day for 14 days [5,7]. If spasms sustained on day 7, the dose was increased to 15 mg once, four times a day for 7 days. In addition, TPM was used in the combination therapy group by initial dose of 1 mg/kg/day, two times a day, and then it was gradually titrated to 3 mg/kg/day in the 7th day and 5 mg/kg/day in the 14th day. After 14 days of treatment, whether the spasms completely ceased or not, prednisone was then reduced weekly to complete a 49-day or 56-day course (*e.g.*, 40 mg once daily for 1 week or 30 mg once daily for 1 week, 20 mg once daily for 1 week, 10 mg daily for 1 week, 5 mg daily for 1 week, then 5 mg alternate days for 1 week). For those children with the spasms-free in 14 days after initial treatment, no antiepileptic drugs (AEDs) (*e.g.*, TPM) were added unless the children appeared recurrence in the monotherapy group. However, other options (*e.g.*, TPM or ketogenic diet) were given in the non-responders of the monotherapy group. TPM was still given at 5 mg/kg/day on a bodyweight basis for the patients in the combination therapy group after 14 days of initial therapy for 35days or 42 days. The non-responders received other treatment (*e.g.*, ketogenic diet) in the combination therapy group after 56 days. Parents or guardians were trained to fill in a diary of spasm frequency for the first 14 days. All the children in both groups were followed-up for 4–24 months.

2.3. Outcome measures and follow up

All the children were hospitalized in the first 14 days during the study period. The spasm frequency of the seizure diaries combined with 3–12 h video EEG monitoring was noted. The primary outcome was the proportion of children who achieved cessation of spasms (no clinical spasms have been witnessed for a period of ≥ 28 consecutive days from the time of the last witnessed spasm) on day 49 or 56 in both the groups, and the secondary outcome were the proportion of children who achieved spasm freedom (for at least 48 h) as no reported spasms on day 14 and the rate of cessation of spasms on day 120, respectively. However, a primary responder should have both cessation of spasms and resolution of hypsarrhythmia [2,5]. Therefore, EEG outcome also should be evaluated and classified into three categories as follows [5]: complete remission (complete resolution of hypsarrhythmia, normalization of EEG or be replaced by local epileptiform discharge or slow wave), partial remission (complete resolution of hypsarrhythmia in awake period but hypsarrhythmia in asleep stages), no remission (no change or hypsarrhythmia in both awake and asleep stages). The proportion of children achieved spasm freedom and EEG resolution of hypsarrhythmia in the 14th day and 49th or 56th day in both groups was also noted.

The anticipated potential adverse reactions were listed as follows: weight gain, Cushing's symptoms, increased appetite, irritability, infections, drowsiness, hypertension and so on. Any other parental concerns regarding the side effects were also noted. The proportion of children with adverse effects in both groups was noted. After 49 days or 56 days, patient visits were arranged once every 3 months. Meanwhile, the clinical outcomes and VEEG recording were evaluated at each visit.

Among the responders, the DQ test would be evaluated again in the 6th month of follow-up. Up to now, the duration of follow-up of all patients ranged from 4 to 24 months. The relapse rate of the responders were noted in the different stages (*e.g.*, the end of 49 or 56 days, 3 months, 6 months, 12 months).

2.4. Statistical analysis

The statistical software SPSS version 20.0 was used for data analysis. Normal distribution data were expressed as the mean ± standard deviation. Skewed distribution data were expressed as the median and complete ranges. Fisher's exact test or chi-square test were used to investigate the proportions of responders with spasm-free and proportion of patients with adverse effects in the two groups. The measurement data in the two groups were compared using paired sample *t*-test. Statistical significance was defined as $P < 0.05$.

3. Results

A total of 77 children were enrolled, 38 children were in the combination therapy group and 39 were in the monotherapy group (Fig. 1). The study included 53 boys and 24 girls ranging in age between 3 and 52 months (mean age, 11.7 months). The age of onset was between 0.35 and 46 months (mean age, 8.3 months), including 8 early-onset and 9 late-onset IS.

The baseline demographic and clinical characteristics of the two groups were comparable (Table 1). The lead-time to diagnosis of spasms was between 0.1 and 31.0 months (mean time, 3.37 months). The majority of the children (71/77, 92.2%) had the developmental delay in our study. However, there were six children (6/77, 7.8%) whose developmental quotient (DQ) were normal. The severity of developmental disabilities was assessed by the DQ test. It was classified into four grades [5]: mild (29/77, 37.7%), moderate (8/77, 10.4%), severe (19/77, 24.7%) and profound (15/77, 19.5%). The most characteristic findings of EEG in patients was typical or variant hypsarrhythmia. There were 14 cases with typical hypsarrhythmia and 63 cases with modified hypsarrhythmia in our study.

The etiology was identified in 25 (25/39, 64.1%) cases in the monotherapy group and 23 (23/38, 60.5%)cases in the combination therapy group ($p = 0.746$).The underlying etiologies included HIE, cortical dysplasia and malformations, Post-Infectious brain injury, neonatal hypoglycemia, intracranial hemorrhage and so on, especially HIE was the most common cause (Table 1). No etiology could be found in 29 patients.

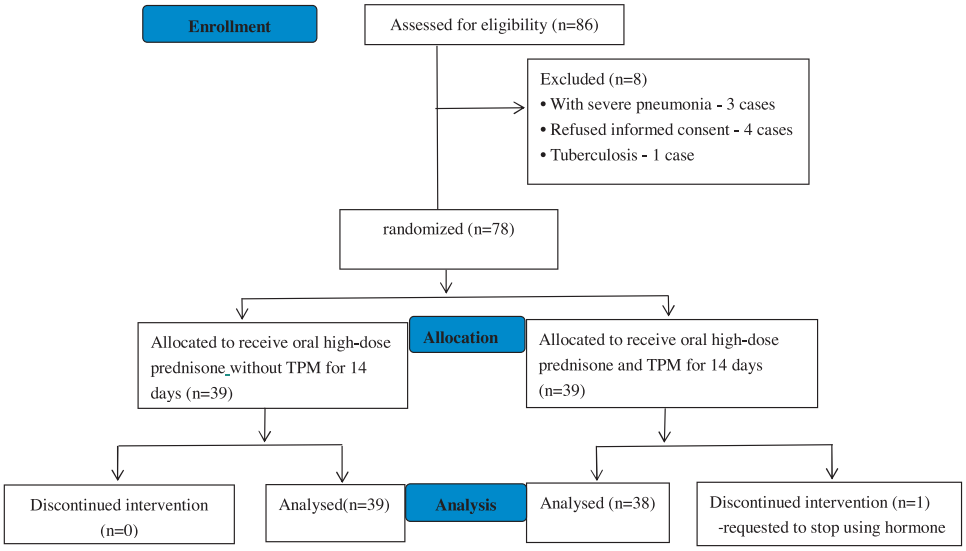

Fig. 1. Flow of the patients in the study.

Table 1
Baseline characteristics of the study participants.

	monotherapy group(n = 39)	combination therapy group(n = 38)	P Value
Gender			
Male (%)	26 (66.7%)	27 (71.1%)	0.678
Median age of onset in months(range)	6 (2-39)	5.7 (0.4-46)	0.443
Median age of treatment in months(range)	9.2 (3.5-40)	7.8 (3-52)	0.465
Median lead time in months(range)	1.5 (0.2-31)	1.75 (0.1-15)	0.934
EEG at presentation			
Hypsarrhythmia	8 (20.5%)	6 (15.8%)	0.591
Hypsarrhythmia variant	31 (79.5%)	32 (84.2%)	
Etiology (%)			
HIE[a]	14 (35.9%)	16 (42.1%)	0.577
Cortical dysplasia and malformations	6 (15.4%)	4 (10.5%)	0.737
Postinfection brain injury	2 (5.1%)	1 (2.6%)	1.000
Neonatal hypoglycemia	3 (7.7%)	0(0)	0.240
Intracranial hemorrhage	2 (5.1%)	0(0)	0.494
Tuberous sclerosis	1 (2.6%)	0(0)	1.000
Head trauma	0(0)	1 (2.6%)	1.000
Unknown causes	14 (35.9%)	15 (39.5%)	0.746
DQ[b] (%)			
normal	4 (10.3%)	2 (5.3%)	0.675
mild	14 (35.9%)	15 (39.5%)	0.746
moderate	4 (10.3%)	4 (10.5%)	1.000
severe	9 (23.1%)	10 (26.3%)	0.742
profound	8 (20.4%)	7 (18.4)	0.817

Abbreviations: [a] Hypoxic ischemic encephalopathy. [b] Profound: DQ < 20; Severe: DQ < 35; Moderate: DQ < 50; Mild: DQ < 70; Normal: DQ ≥ 70.

After 14 days of the therapy, the control rate of spasms were 71.8% (28/39) and 76.3% (29/38) in the monotherapy group and the combination therapy group, respectively, and there was no significant difference ($\chi^2 = 0.205$, $p = 0.796$) in Table 2. During the tapering period of subsequent 35 or 42 days, one patient achieved spasm freedom in the 17th day and one patient had relapsed in the monotherapy group, and there were four children who relapsed but no patient achieved spasm freedom in the combination therapy group. However, the rate of patients with cessation of spasms on day 49 or 56 was still similar between the group of hormone monotherapy and the combination therapy group (71.8% *vs* 65.8%, $p = 0.569$). After 120 days, the rate of children with spasm cessation in the group of hormone monotherapy was higher than the combination therapy group, but there was no significant difference (61.5% *vs* 50.0%, $p = 0.308$).

Among the 28 patients with seizure-free in the monotherapy group, there were 21 cases showed complete resolution of hypsarrhythmia and 7 cases with a partial remission of hypsarrhythmia. Meanwhile, among the 29 patients with seizure freedom in the combination therapy group, there were 20 cases showed complete resolution of hypsarrhythmia and 9 cases showed a partial remission of hypsarrhythmia. No one showed persistence of hypsarrhythmia in either group. The rate of children with spasms cessation and complete resolution of hypsarrhythmia on EEG was not significantly different between the monotherapy group and the combination therapy group on day 14(75.0% *vs* 69.0%, $p = 0.770$).

Adverse effects in both groups were listed in Table 3, which are similar to the previous study with IS in our center [5], and which included Cushing's symptoms, increased appetite, irritability, drowsiness, intercurrent infection, hypertension and sleep disturbance and so on. However, other adverse events of TPM were very rare in both groups, such as anorexia, loss of appetite and weight loss. There was no statistically significant difference in the rate of children with adverse events between two groups. The side effects were mild and well tolerated according to our observation and the parents' diaries. No death occurred in this study and no one patient discontinued the treatment because of the adverse events.

All the children were followed-up for 4–24 months. At final visit, the longest seizure freedom duration was 24 months and the shortest was 30 days in the 57 responders. All the responders whose follow-up data at 4 months was available in both groups. After 4 months, there were 4 children relapsed in the monotherapy group and 10 children relapsed in the combination therapy group (14.3% *vs* 34.5%, $p = 0.123$). The follow-up data at 12 months was available for 15/28 patients in the monotherapy group and 16/29 patients in the combination therapy group. At 12 months, there were 5 children relapsed in the monotherapy group and 10 children relapsed in the combination therapy group, respectively.

4. Discussion

IS is a refractory epilepsy syndrome which is internationally associated with poor neurodevelopmental outcome and subsequent seizures in many cases. Currently, the first-line agents for treatment of IS are adrenocorticotrophic hormone (ACTH), prednisolone and VGB. A Cochrane review [8] reported that hormone treatment is the best single

Table 2
Primary and secondary outcomes of patients in the two groups.

Outcome measure	Monotherapy group (n = 39)	Combination therapy group(n = 38)	*P* value
Number of children (%) with complete spasm freedom on day 14	28 (71.8%)	29 (76.3%)	0.796[#]
Median time to spasm resolution in days(range)	6 (2-14)	6 (2-14)	0.507
EEG at 2 weeks in children with spasm resolution			
Complete remission	21 /28 (75.0%)	20 /29 (69.0%)	0.770[#]
Number of children (%) with complete spasm freedom at the end of hormone therapy (day 49 or 56)	28/39 (71.8%) [a]	25/38 (65.8%) [b]	0.569*
Number of children (%) with complete spasm freedom at day-120 (4months)	24/39 (61.5%)	19 /38(50.0%)	0.308*
Number of the relapsed children in Follow-up			
7 or 8 weeks (on day 49 or 56)	1/28 (3.6%)	4/29 (13.8%)	0.352[#]
4 months	4/28 (14.3%)	10/29 (34.5%)	0.123[#]

[a] one patient became spasm freedom in the 17th day and one patient relapsed; [b] four patients had relapsed.
[#] Fisher's exact test was applied for the *P*-values; * Chi-square test was applied for the *P*-values.

Table 3
Adverse events reported in both groups.

Adverse effects	Monotherapy group (n = 39)	Combination therapy group (n = 38)	*P* value
Cushing's symptoms	34 (87.2%)	32 (84.2%)	0.780
Increased appetite	35 (89.7%)	29 (76.3%)	0.116
Irritability	18 (46.2%)	12 (31.6%)	0.190
Drowsiness	8 (20.5%)	7 (18.4%)	0.817
Intercurrent infection[a]	11 (28.2%)	12 (31.6%)	0.746
Hypertension	1(2.6%)	0 (0.0%)	1.000
Sleep disturbance	9 (23.1%)	7 (18.4%)	0.615

[a] included fever, upper respiratory tract infection, pneumonia and diarrhea.

treatment for cessation of spasms. Whereas, many investigators have found that the combinations of therapy might be the most effective way to treat severe epilepsy syndromes in childhood [9–11]. One published study [12] has also showed that hormone therapy with VGB (combination therapy) is significantly more effective in stopping infantile spasms than hormone monotherapy. However, the severe adverse events (*e.g.*, VGB-induced apoptosis in the brain, or visual-field defects) were extremely worrying and VGB is difficult to obtain in our country. So, its application is limited in our country. Since May in 2011, we have always used high-dose prednisone as the first-line agent for IS in our center. Our previous study [5] showed high-dose prednisone was effective and well-tolerated in children with IS. As we all known, doctors often aimed to avoid using multiple agents for pediatric epilepsy in order to minimise side-effects. Hence, we designed this trial to compare the efficacy and safety of high-dose prednisone alone with the high-dose prednisone and TPM in the treatment of IS in our center. In this way, we can evaluate whether the combination therapy would provide more benefits than monotherapy in the treatment of IS.

Two published studies [13,14] believed that using topiramate as primary or adjunctive therapy in children with IS was effective and safe. So we expected the combination of hormone therapy and TPM could have a synergistic effect in treatment of IS. This is the first study comparing the high-dose prednisone combined with TPM to the high-dose prednisone alone for the treatment of IS in China. We found a significantly higher rate of children with spasm cessation at day14 in both groups, but there was no significant statistical difference between the two groups (76.3% *vs* 71.8%, $p = 0.796$). In the UKISS study [7], the spasm-free rate was 70% in patients taking high dose oral prednisolone (40–60 mg/kg/d), which was similar to the monotherapy group in our study. However, another study [15] showed that using high oral dose of prednisolone (4 mg/kg/d) achieved the complete spasm freedom in 51.6% of children, which was lower than 71.8% response rate in our study. This is may due to the shortened lead-time to diagnosis of spasms (1.5 months *vs* 6.0 months) and predominance of cryptogenic etiology (35.9% *vs* 18%) in our patients. Because the prolonged lead-time to diagnosis of spasms may lead to lower rate of spasm cessation [16], and the cryptogenic children with IS had a better outcome of spasm cessation than the symptomatic children with IS [17]. The outcome definitions of these studies [7,15] are consistent with those of our study, so we believe the comparative results are reliable.

Our result demonstrated that the combination therapy was no more beneficial than the monotherapy in the children with IS. The addition of TPM did not show significant improvement in the response rate and shorten the duration of spasm resolution (6 days *vs* 6 days). At the end of hormone therapy, the cessation rate of spasms were 71.8% (28/39) and 65.8% (25/38) in the monotherapy group and the combination therapy group, respectively, and there was no significant difference ($\chi^2 = 0.324$, $p = 0.569$) (Table 2). With an intention-to-treat analysis, there was also no significant difference ($\chi^2 = 0.241$, $p = 0.624$). In addition, after 120 days, there were 4 children relapsed in the monotherapy group and 10 children relapsed in the combination therapy group (14.3% *vs* 34.5%, $p = 0.123$). Therefore, we speculated the addition of TPM would not help more children achieve spasm-free with the time and provide no benefit for prevention of IS and late-onset ES in the short term. This is likely due to inadequate dosage of TPM. One study reported by Korinthenberg and Schreiner [14] believed the median daily dose regarding seizure reduction was 10 mg/kg/day, which was considered to be the most effective dosage. In our study the dosage of TPM was only 5 mg/kg/day which could affect the drug efficacy. If we increase the dosage of TPM in children with IS and late-onset ES, it might could improve the outcome. Meanwhile, we are ready to design new trial to explore the appropriate dose of TPM in the children with IS.

The adverse effects like Cushing's symptoms, increased appetite and irritability were commonly seen in both groups, but there were not statistically significant (Table 3). As we all know, the side effects of TPM mainly include sedation, loss of appetite and weight loss. However, these adverse events were rarely found in our study. It is possible that the influence of hormone covered the expressions of those adverse effects. The adverse effects were consistent in some previous reports [5,15]. Although the occurrence rate of the adverse effects was high, no one stopped the treatment because of the adverse reactions.

As we all know, the aims of treatment of IS are improving not only the rates of spasms cessation but also the developmental outcomes. Unfortunately, in the 6th or 12th month of follow-up, the DQ test of more than half children would not be evaluated again. Most of parents or guardians believed that it was not necessary because their babies did not make a great progress after the treatment, especially the non-responders. So we didn't answer the question that whether the combination therapy or the monotherapy could improve the developmental outcomes. However, it's worth mentioning that the DQ scores of the responders were similar or higher than the base value before the treatment in our previous study [5]. Therefore, the neurodevelopment of those responders would not further deteriorate. Namely, the

neurodevelopment of those responders became better because their DQ scores may be decreased for the persistence of spasms and hypsarrhythmia.

In addition, the study was a randomized, open-label controlled trial and the patients' carers and the study researchers were not blinded to the treatment allocation. Despite these limitations, it would be prudent to conclude that the combination therapy (prednisone with TPM) may not be necessary in Chinese children with IS and late-onset ES. Our results revealed that the addition of TPM did not obviously improve the rate of spasm cessation and did not reduce the rate of relapse or prevent spasm relapse in short term. But it increased the economic burden of the families and potential side effects. Considering the limitations of study, multi-center, randomized, controlled and long-term studies are necessary to explore the long-term effects to neurodevelopmental and seizure outcomes, and whether the hormone combines with other AEDs would be more efficacious.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

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