Preliminary Report

Treatment of Infantile Spasms with Sodium Valproate followed by Benzodiazepines

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Objective: To review the result of the infantile spasms’ treatment with sodium valproate followed by nitrazepam or clonazepam.

Study design: Descriptive retrospective study.

Setting: Srinagarind Hospital, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

Material and Method: Twenty-four infantile spasms admitted between January 1994 and December 2003 were analyzed. The inclusion criteria were the patients with infantile spasms clinically diagnosed by the pediatric neurologist, having hypsarrhythmic pattern EEG and receiving sodium valproate with or without nitrazepam or clonazepam. The patients who had an uncertain diagnosis, incomplete medical record, or that were incompletely followed up were excluded. Data were collected on sex, age at onset of seizure, type of infantile spasms, associated type of seizure, predisposing etiological factor, neuroimaging study, and the result of treatment including cessation of spasms, subsequent development of other seizure types, quantitative reduction of spasms, relapse rates of spasms, psychomotor development, and adverse effects of AEDs.

Results: The mean age at onset was 177 days. The male-to-female ratio was 1:1.2. There were 13 cryptogenic (54.2%) and 11 symptomatic (45.8%) infantile spasms. The most common predisposing etiological factors in symptomatic cases were hypoxic ischemic encephalopathy (45.5%) and microcephaly (36.4%), respectively. Ten patients received sodium valproate (41.7%), another 10 received sodium valproate with clonazepam (41.7%), and four received sodium valproate with nitrazepam (16.7%). Both, the complete cessation rate and the 50% reduction of spasms rate were 45.8%. The duration to complete cessation was 70 days. The relapse rate was 18.2%. The rate of delayed psychomotor development was 83.3%. The mean duration of follow-up was 49.6 months.

Conclusion: The authors propose to use sodium valproate concomitantly with benzodiazepines, especially clonazepam, in situations such as unavailability, intolerability, or adverse effects of ACTH or vigabatrin, or in a patient who does not respond to ACTH or vigabatrin.

Keywords: Infantile spasms, Sodium valproate, Benzodiazepines, Clonazepam, Nitrazepam, ACTH, Vigabatrin

J Med Assoc Thai 2007; 90 (9): 1809-14
Full text. e-Journal: http://www.medassocthai.org/journal

Infantile spasms are a unique form of seizure disorder that is characterized by a series of sudden, generally bilateral, and symmetric contraction of the neck, trunk, and extremities. The occurrence of infantile spasms is limited almost entirely to infants during the first year of life. Infantile spasms are usually associated with developmental retardation or deterioration and a characteristic electroencephalographic (EEG) pattern (hypsarrhythmia) that together configures a syndrome that is known as West syndrome(1). Treatment of infantile spasms is problematic and the long-term prognosis remains poor for both psychomotor development and subsequent development of other seizure types(2). Infantile spasms are resistant to most
conventional antiepileptic drugs (AEDs). Only ACTH, corticosteroids, and vigabatrin have conclusively 
demonstrated efficacy(1). However, both steroids and 
vigabatrin have potentially serious adverse effects. The 
problems with steroids are potentially life threatening 
and include depression of the immune system and 
modified response to infection leading to overwhelm-
ing sepsis. Less serious adverse effects, for example 
hypertension, are often transient but, have the poten-
tial to cause morbidity. There have been reports of both 
asymptomatic and symptomatic visual field defects 
with loss of peripheral vision to varying degrees in 
children treated with vigabatrin(2). ACTH is not avail-
able in Thailand and vigabatrin is not available in 
Srinagarind Hospital. Other AEDs reported to be bene-
"ficial in treatment of infantile spasms that available in 
our hospital are sodium valproate(3-5), nitrazepam(6,7) 
and clonazepam(8,9). The authors have used sodium 
valproate followed by nitrazepam or clonazepam since 
1994. To our knowledge, there was only one study that 
reported using this regimen(10). The purpose of the 
present study was to review the result of treatment of 
infantile spasms with sodium valproate followed by 
nitrazepam or clonazepam.

**Material and Method**

The authors retrospectively reviewed the 
medical records of pediatric patients with infantile 
spasms admitted to the Division of Pediatric Neuro-
logy, Department of Pediatrics, Srinagarind Hospital, 
which is the referral center in the northeast of Thailand, 
during the 10-year period between January 1994 and 
December 2003.

**Inclusion criteria**
1. Infantile spasms clinically diagnosed by 
the pediatric neurologist.
2. Hypsarrhythmic pattern EEG 
3. AEDs used were sodium valproate with or 
without nitrazepam or clonazepam

**Exclusion criteria**
1. Uncertain diagnosis
2. Incomplete medical record 
3. Incompletely followed up

The following data were collected: sex, age at 
onset of seizure, type of infantile spasms, associated 
type of seizure, predisposing etiological factor, neuro-
imaging study; and the result of treatment including 
cessation of spasms, subsequent development of 
other seizure types, quantitative reduction of spasms, 
relapse rates of spasms, psychomotor development, 
and adverse effects of AEDs.

**Types of infantile spasms**

1. Symptomatic type defined as those cases 
in which a definite predisposing etiologic factor can 
be identified or etiologic associations can be clearly 
specified.
2. Cryptogenic type defined as those for 
which no cause can be identified or those cases who 
were normal before the onset of spasms.

**Regimen of treatment**

The authors started with sodium valproate 30 
mg/kg/day and increasing by 5 mg/kg/day weekly 
until a maximum dosage of 60 mg/kg/day or blood level 
100 mcg/ml was reached. If the spasms did not cease, 
nitrazepam at the dose of 0.1-1 mg/kg/day or clonazepam 
at the dose of 0.04-0.2 mg/kg/day was added. The 
results of treatment were presented in the frequency 
tables with number of patients and percent. The con-
tinuous variables were described by median, mean, and 
standard deviation (SD).

**Results**

**General characteristics**

There were 24 patients recruited for the 
present study. Eleven patients were male (45.8%) and 
thirteen were female (54.2%). Male-to-female ratio was 
1:1.2. Their ages at onset ranged from 51 days to 425 
days (176.9 ± 110.6 days, median 143 days). There were 
13 cryptogenic (54.2%) and 11 symptomatic (45.8%) 
infantile spasms. The predisposing etiological factors 
in symptomatic cases were hypoxic ischemic encephal-
opathy [5(45.5%), microcephaly [4(36.4%), tuberous 
sclerosis [1(9.1%)], and cerebral palsy [1(9.1%]. The 
number of clusters per day was: 1-20 (5.4 ± 4.9, median 
4 clusters). The number of seizures per cluster was: 
4-20 (10.2 ± 5.7, median 9 seizures per cluster). Four 
patients had associated seizures (generalized tonic 
clonic, generalized tonic, generalized clonic, and focal 
seizures). Neuroimaging studies were done in four cases 
(16.7%). Two cases with computed tomography (CT) 
were normal. The other two cases with magnetic reso-
nance imaging (MRI) were tuberous sclerosis and 
hypoxic ischemic encephalopathy. The results of MRI 
had periventricular tubers and periventricular leuko-
malacia respectively.

**Results of treatment**

The patients received sodium valproate, so-
dium valproate with clonazepam and sodium valproate with nitrazepam in 10 (41.7%), 10 (41.7%) and four (16.7%) cases respectively. Dosages of sodium valproate used in each group were 20-60 (42.7 ± 11.83), 15-66 (49.70 ± 15.06), and 40-60 (52.2 ± 9.57) mg/kg/day respectively. Dosages of clonazepam were 0.07-0.17 (0.10 ± 0.03) mg/kg/day. Dosages of nitrazepam were 0.1-0.5 (0.35 ± 0.19) mg/kg/day. The rates of complete cessation of spasms in each group were 60, 40, and 25% respectively. The rates of at least 50% reduction of spasms in each group were 30, 50, and 75% respectively. The overall rate of complete cessation and at least 50% reduction of spasms were both 45.8%. The duration to complete cessation in each group was 23-105 (62.5 ± 26.6), 13-173 (56.0 ± 78.1), and 137 days respectively. There was one patient that received clonazepam concomitantly with sodium valproate and the duration to complete cessation was 13 days. There were two cases of relapse (18.2%), one case was treated with sodium valproate and the other was in the nitrazepam group. The rate of subsequent development to other seizure types in each group was 40%, 40%, and 25% respectively. The overall rate of subsequent development to other seizure types was 37.5%. The types of other seizures that developed later were generalized tonic, generalized tonic clonic, mixed gelastic and dacrystic, generalized clonic, and atypical absence seizures (4, 2, 1, 1 and 1 cases respectively). The rates of delayed psychomotor development in each group were 80%, 80%, and 100% respectively. The overall rate of delayed psychomotor development was 83.3%. The summary of overall treatment is shown in Table 1.

Complete cessation was achieved in seven patients (53.8%) of cryptogenic infantile spasms and four patients (36.4%) of symptomatic infantile spasms. In the cryptogenic group, the complete cessation rates in the patients received sodium valproate, sodium valproate with clonazepam, and sodium valproate with nitrazepam were 66.7, 50, and 0% respectively; the rates of at least 50% reduction of spasms in each group were 33.3, 50, and 100% respectively. In the symptomatic group, the complete cessation rates in each group were 50, 25, and 33.3% respectively; the rates of at least 50% reduction of spasms were 25, 50, and 66.7% respectively. The summary of treatment separated in the cryptogenic and symptomatic group is shown in Table 2.

**Adverse effects**

Six patients (25%) had adverse effects. Two patients in the benzodiazepine group had hypersalivation (one clonazepam and one nitrazepam). Another

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose range (mean ± SD mg/kg/day)</th>
<th>Cases (%)</th>
<th>Complete cessation</th>
<th>No. (%)</th>
<th>Delayed psychomotor development</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium valproate</td>
<td>10 (41.6) 20-60 (42.7 ± 11.83)</td>
<td>6 (60.0)</td>
<td>6 (60.0)</td>
<td>23-105</td>
<td>4 (40)</td>
<td>8 (80.0)</td>
</tr>
<tr>
<td>Sodium valproate with clonazepam</td>
<td>10 (41.6) 15-66 (49.70 ± 15.06)</td>
<td>3 (30.0)</td>
<td>3 (30.0)</td>
<td>13-173</td>
<td>1 (25)</td>
<td>8 (80.0)</td>
</tr>
<tr>
<td>Sodium valproate with nitrazepam</td>
<td>4 (16.7) 40-60 (52.2 ± 9.57)</td>
<td>1 (25.0)</td>
<td>1 (25.0)</td>
<td>137</td>
<td>1 (25)</td>
<td>7 (75.0)</td>
</tr>
<tr>
<td>Total</td>
<td>24 (100)</td>
<td>11 (45.8)</td>
<td></td>
<td></td>
<td>20 (83.3)</td>
<td></td>
</tr>
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</table>
four patients had excessive weight gain, thrombocytopenia, somnolence, and hypotonia. The mean duration of follow-up was 49.6 ± 37.3 months, median 40 months. There was no death in the present study.

**Discussion**

General characteristics of the presented patients were slightly different to other studies. In most large series, boys are more affected than girls(1), which differed from the present study that girls were slightly more affected than boys. This may be due to the small number of the presented patients. However, the age at onset and predisposing etiological factors are similar. The authors did neuroimaging studies in only four cases because of the poor economic status of the presented patients. In addition, the authors thought that it was unnecessary to do it because most infantile spasms have uncorrectable causes such as cerebral malformations, neurocutaneous syndrome, and perinatal ischemic damage(11).

Treatment of infantile spasms is the authors’ problem because of the limitation of medication and the nature of disease. The authors used the available AEDs that were reported to be beneficial in infantile spasms. Sodium valproate was reported to be beneficial but usually in very high doses 100 to 300 mg/kg/day leading to the risk of adverse effects(4,12). The efficacy of sodium valproate was 23-72%(12-16). Cessation of spasms was reported in 30-54% in the patients who received nitrazepam(6,7). Infantile spasms were completely controlled with clonazepam in 12-37% and at least 50% reduction in seizure frequency was obtained in 21-75% of patients(9). The efficacies of these conventional AEDs in controlling infantile spasms are lower than ACTH and vigabatrin. The efficacy of ACTH was 40-100%(13,17-19). The efficacy of vigabatrin was 35.5-61.8%(20-24). However, there were serious adverse effects and unavailability of the last two AEDs in the authors’ setting. Nitrazepam and clonazepam are known as the good add-on AEDs. Clonazepam is a broad-spectrum, effective AED with few side effects, is widely used as an add-on AED for polytherapy in pediatric patients. Clonazepam was found to affect fast wave activities in proportion to clonazepam concentrations in the epileptic children treated with sodium valproate(25). Therefore, the authors used sodium valproate in the usual dose in order to reduce adverse effects followed by these two benzodiazepines to increase the efficacy. The authors found that the rate of complete cessation and at least 50% reduction of spasms were 45.8% and 45.8% respectively which were as high as ACTH and vigabatrin. Time from initiation of ACTH to cessation of spasms was 7 to 12 days and of vigabatrin was 12 to 35 days(26). The mean duration to complete cessation in the presented regimen was 70 days, which was much longer than in ACTH and vigabatrin. The delayed controlling of spasms resulted in the high rate of delayed psychomotor development in the present study. The pre-existing brain lesion might be also the cause of delayed psychomotor development. A study reported the beneficial effect of sodium valproate in patients who have failed to respond to ACTH(5). The incidence and severity of adverse effects in the present study were less. In the authors’ opinion, this regimen should not be the first line of treatment but may have benefit in some conditions such as unavailability, intolerable adverse effects of ACTH or

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type of infantile spasms</th>
<th>Cases No.</th>
<th>Complete cessation No. (%)</th>
<th>≥ 50% Reduction No. (%)</th>
<th>&lt; 50% Reduction No. (%)</th>
<th>Delayed psychomotor development No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium valproate Cryptogenic</td>
<td>6</td>
<td>4 (66.7)</td>
<td>2 (33.3)</td>
<td>0 (0.0)</td>
<td>5 (83.3)</td>
<td></td>
</tr>
<tr>
<td>Sodium valproate with clonazepam Cryptogenic</td>
<td>6</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td>0 (0.0)</td>
<td>4 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Sodium valproate with nitrazepam Cryptogenic</td>
<td>1</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Sodium valproate symptomatic</td>
<td>1</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>0 (0.0)</td>
<td>3 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Sodium valproate symptomatic</td>
<td>3</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>0 (0.0)</td>
<td>3 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>11 (45.8)</td>
<td>11 (45.8)</td>
<td>2 (8.3)</td>
<td>20 (83.3)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. The results of treatment separated in cryptogenic and symptomatic group
vigabatrin, or in the patient that does not respond to ACTH or vigabatrin. The mean duration to cessation of spasms in sodium valproate with clonazepam group was 56 days, which was the least in the three groups. In the past, the authors tried monotherapy with sodium valproate first. There was one patient who received clonazepam concomitantly with sodium valproate and the duration to complete cessation was 13 days. This combination should be tried first and clonazepam should be given concomitantly with sodium valproate to shorten the duration to cessation of spasms.

Conclusion
The authors reviewed the results of treatment of infantile spasms with sodium valproate followed by benzodiazepines. The authors found that the rate of complete cessation and at least 50% reduction were 45.8, and 45.8% which is as high as the recommended AEDs, ACTH, and vigabatrin. The mean duration to cessation of spasms was 70 days, which was longer than ACTH and vigabatrin. The longer duration resulted in the high rate of delayed psychomotor development. The duration to cessation of spasms in sodium valproate with clonazepam group was 56 days. The patient that received clonazepam concomitantly with sodium valproate had a short duration to complete cessation. The authors propose to use clonazepam concomitantly with sodium valproate in some situations such as unavailability, intolerability, and adverse effects of ACTH or vigabatrin, or in a patient that does not respond to ACTH or vigabatrin.

References
การรักษาโรคลมชักชนิด infantile spasms ด้วย sodium valproate ตามด้วย benzodiazepines

ประสงค์: เพื่อทบทวนผลการรักษา infantile spasms ด้วย sodium valproate ตามด้วย clonazepam หรือ nitrazepam

ประเภทงานวิจัย: การศึกษาย้อนหลังเชิงพรรณนา

สถานที่ทำการวิจัย: โรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น

วัสดุและวิธีการ: ทบทวนเวชระเบียนของผู้ป่วย infantile spasms ที่เข้ารับการรักษา 24 ราย ผ่านการคัดอาการโดยกุมารแพทย์โรคระบบประสาท พบผู้ป่วยที่มีผลการตรวจสมอง elektroneurogram ชัดเจน ทำให้สามารถนิยามเป็นแบบ hypsarrhythma หรือ clonazepam หรือ nitrazepam ได้ ผู้ป่วยที่มีสมองอักเสบ หรือ ผู้ป่วยที่มีอาการล่าช้า โรคแยกหน้าท้อง หรือ ผู้ป่วยที่มีอาการล่าช้า อาจมีการหยุดชักได้

ผลการศึกษา: อายุเริ่มชักเฉลี่ย 177 วัน สัดส่วนเพศชายต่อหญิง 1:1.2 เมื่อ infantile spasms ชนิด cryptogenic 13 ราย  suger symptoms 11 ราย ส่งผลให้เกิดสมองป่วยสมองอักเสบ หรือ microcephaly ที่มีการรักษาด้วย sodium valproate 10 ราย หรือ sodium valproate 4 ราย พบการหยุดชัก ร้อยละ 50 ของผู้ป่วย หรือ 50 ราย ร้อยละ 45.8 ของการพักพิงระยะยาว หรือ 60 ราย ร้อยละ 50 ของการพักพิงระยะยาว ร้อยละ 70 ผู้ป่วยที่มีการกลับซ้ำ ร้อยละ 18.2 ผู้ป่วยที่มีการพักพิงระยะยาว ร้อยละ 83.3

สรุป: ผู้รายงานเสนอให้ใช้ sodium valproate ร่วมกับ clonazepam ในการรักษา infantile spasms ในกรณีที่ไม่มี ACTH หรือ vigabatrin ไม่สามารถทดแทนได้ หรือไม่ตอบสนองต่อ ACTH หรือ vigabatrin