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Short Course and Early Switch of Vigabatrin for Infantile Spasms

영아연축의 치료에서 단기간 비가바트린 후
다른 항경련제로의 변경 치료

2016년 2월

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Short Course and Early Switch of Vigabatrin for Infantile Spasms

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이 논문을 의학석사학위논문으로 제출함

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Abstract

**Purpose** Vigabatrin has proven efficacy in the treatment of infantile spasms, but carries the risk of irreversible visual field constriction. Incidence of the vigabatrin-induced visual field constriction seems to depend on the extent of vigabatrin exposure. The aim of this study was to evaluate whether the therapeutic effect is maintained in patients with infantile spasms receiving a short vigabatrin course followed by switching to another antiepileptic drug (AED).

**Methods** Patients with infantile spasms responsive to initial vigabatrin treatment were divided into two groups: a vigabatrin switch group (n=25) and a vigabatrin maintenance group (n=41). Vigabatrin was switched to other drugs within 6 months of spasm remission. The rate of seizure recurrence at 6 and 12 months from spams remission was compared between the two groups.

**Results** There were no statistically significant differences between the vigabatrin switch and maintenance groups in the age of onset, presence of concomitant seizures, time from spasm onset to vigabatrin treatment, time from vigabatrin treatment initiation to spasm remission and vigabatrin dose at spasm remission. The number of patients with seizure recurrence at 12 months from spasm remission was 3 (3/25, 12%) in the vigabatrin switch group and 10 (10/41, 24.4%) in the vigabatrin maintenance group. The seizure recurrence rate at 12 months from spasm remission was not significantly different between groups. Ten of 13 patients with seizure recurrence had symptomatic etiology.

**Conclusion** A short course of vigabatrin could be considered in patients with infantile spasms who were responsive to initial vigabatrin treatment, since spasm remission was maintained after switching to other drugs. Whether this strategy could ultimately result in lower incidence of visual field defect should be further investigated.
Keywords: Vigabatrin, infantile spasms, visual field defect

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List of abbreviations

AED – antiepileptic drug

ACTH – adrenocorticotropic hormone

VFC – visual field constriction

EEG – electroencephalography

IS – infantile spasms

HIE – hypoxic ischemic encephalopathy

CNS – central nervous system
Introduction

Vigabatrin has proven efficacy in the treatment of infantile spasms resistant to conventional antiepileptic drugs (AED)\(^1\). No difference in long-term outcome was found between treatment with vigabatrin and that with adrenocorticotropic hormone (ACTH)\(^2\)\(^-\)\(^4\). Considering the serious side effects of ACTH, vigabatrin is a preferred treatment for infantile spasms and is currently considered as first-line therapy for infantile spasms\(^5\),\(^6\).

Despite its efficacy, vigabatrin treatment carries the risk of visual field constriction (VFC) as an adverse effect. Of the patients treated with vigabatrin, 44\% (738/1678) experience VFC\(^7\). Vigabatrin-induced visual field defect is irreversible, and its incidence increases with the duration of its exposure\(^8\),\(^9\). In a study examining the visual fields in school age children who received vigabatrin treatment in infancy, visual field defects were found in 9\% of children who received vigabatrin for 1 year or less, 30\% of children who received vigabatrin for 12 to 24 months, and 63\% of children who received vigabatrin for more than 2 years\(^10\). In an observational cohort study using electroretinogram to assess the vigabatrin-induced retinal toxicity, 5.3\% and 13.3\% of children were found to have developed retinal damage after 6 and 12 months of vigabatrin treatment\(^11\).

Patients receiving vigabatrin treatment require regular visual field examination; however, perimetry is impossible in young children or in children with cognitive impairment. Electroretinogram, which can monitor the retinal toxicity in young children, is difficult to perform because it requires general anesthesia\(^12\).

Since the incidence of VFC depends on the duration of vigabatrin treatment, use of a short-term vigabatrin treatment paradigm might reduce the risk of VFC. Controlled studies have not been performed to determine the optimal duration of vigabatrin treatment to maintain the therapeutic effect without adverse effects. In a long-term (mean 5.25 years) follow up of 21 patients with infantile spasms, three
patients experienced spasm relapse within the first 6 months\textsuperscript{13}. In another study, vigabatrin was stopped after 6 months without relapse in patients with infantile spasms with Down syndrome, cryptogenic etiology, or neonatal hypoxic-ischemic encephalopathy\textsuperscript{14,15}.

Although vigabatrin is effective for the treatment of infantile spasms, the risk of irreversible adverse events increases with increasing duration of treatment. Hence, if the recurrence rate does not increase in patients with a short treatment course of vigabatrin followed by switching to another AED when compared with that in patients receiving long-term vigabatrin treatment, it could provide a promising new strategy for treating infantile spasms. Therefore, the purpose of this study was to evaluate whether the recurrence rate increases when patients are switched to another AED after a short course of vigabatrin compared to long-term vigabatrin treatment in patients with infantile spasms.
Materials and Methods

1. Patients and baseline characteristics (Table 1)

This study was approved by the Institutional Review Board of the Seoul National University Hospital.

Medical records of patients newly diagnosed with infantile spasms and treated with vigabatrin at the Seoul National University Hospital between January 1997 and May 2014 were reviewed retrospectively. Infantile spasms was defined as follows: (1) epileptic spasm onset during infancy at less than 12 months of age; (2) spasms confirmed either by history or by video electroencephalography (EEG) monitoring; and (3) hypsarrhythmic pattern on interictal EEG. Other inclusion criteria included being a vigabatrin responder and having a follow-up period of at least 12 months from spasm remission. Vigabatrin responder was defined as (1) spasm free within 1 month of starting vigabatrin treatment; (2) remaining spasm free for more than 1 month; and (3) resolution of hypsarrhythmic pattern on EEG. For patients prescribed other AEDs before initiation of vigabatrin, patients without change of dose during the study period were included; patients for whom another AED was added after vigabatrin initiation were excluded.

Sex, date of birth, age at spasm onset, etiology, EEG record, time from spasm onset to vigabatrin treatment initiation, time from vigabatrin treatment initiation to becoming spasm free, vigabatrin dose when the patient was spasm free, and relapse at 6 and 12 months of spasm remission were reviewed.

2. Outcome

Patients were divided into two groups: a vigabatrin early switch group (switch group) and a vigabatrin maintenance group (maintenance group). Vigabatrin was
switched to other drugs within 6 months of spasms remission in the switch group. The recurrence rate of spasm and other seizures at 6 and 12 months from spasm remission was compared between the two groups.

3. Statistical analysis

Statistical analysis was performed using SPSS 22.0 for Windows. Statistical test used were \( t \) - test for comparison of means and \( \chi^2 \) test or Fisher’s exact test for comparison of proportion between groups. Statistical significance was defined as \( p < 0.05 \).
Result

1. Baseline patient characteristics (Table 1)

Two hundred and three children were newly diagnosed with infantile spasms and treated with vigabatrin between January 1997 and May 2014. Seventy patients were vigabatrin responders, and 66 patients satisfied the study inclusion criteria. Two patients who had less than 12 months of follow-up and 2 patients for whom vigabatrin was switched to other drugs between 6 and 12 months of spasms remission were excluded (Figure 1).

Of the 66 patients included in the analysis, 25 patients (12 boys, 13 girls) were in the switch group, and 41 patients (24 boys, 17 girls) were in the maintenance group. The mean age of infantile spasms onset was 6.1 months in the switch group, and 5.8 months in the maintenance group ($p = 0.562$). The mean time between onset of spasms and initiation of vigabatrin was 24.5 days in the switch group, and 35.2 days in the maintenance group ($p = 0.243$). The mean time between initiation of vigabatrin and spasm remission was 11.9 days in the switch group, and 13.5 days in the maintenance group ($p = 0.476$). The mean vigabatrin dose at spasm free was 70.5 mg/kg/day in the switch group, and 64.9 mg/kg/day in the maintenance group ($p = 0.451$). Six patients in each group had concomitant seizures when spasms occurred ($p = 0.348$).

The number of symptomatic cases was 12 [tuberous sclerosis complex 2, congenital malformation 1, brain injury 8, chromosome abnormality (Down syndrome) 1] in the switch group, and 27 (tuberous sclerosis complex 9, congenital malformation 7, brain injury 8, CNS infection 3) in the maintenance group.

The mean duration between spasm remission and vigabatrin tapering was 2.5 months (0.5 – 5.0 months), and vigabatrin was stopped after an average of 4.5 months (1.4 – 7.5 months) from spasm remission. Drugs used in the switch group
were zonisamide (n = 13), levetiracetam (n = 11), and topiramate (n = 1).

2. Outcome

Spasms recurrence at 6 months from spasm remission was as follows: 0 patients in the switch group and 2 in the maintenance group (p = 0.522). Other seizure recurrence at 6 months from spasm remission was as follows: 2 patients in the switch group and 2 in the maintenance group (p = 0.630) (Table 2). Spasm recurrence at 12 months from spasm remission was as follows: 0 patients in the switch group and 6 in the maintenance group (p = 0.075). Other seizure recurrence at 12 months from spasm remission was as follows: 3 patients in the switch group and 4 in the maintenance group (p = 1.000) (Table 3).

3. Risk factors for seizure recurrence

After 12 months from spasms remission, 13 of 66 patients developed subsequent seizures: 3 patients had spasms and 10 patients had other types of seizures. Clinical characteristics of patients by recurrence are shown in Table 4. There was no statistically significant difference between the recurrence group and the remission group. Six patients (46%) with recurrence and 30 patients (57%) without recurrence were male (p = 0.498). The number of patients in the switch group was 3 (23%) with recurrence and 22 (42%) without recurrence (p = 0.340). The number of symptomatic cases was 10 (77%) with recurrence and 29 (55%) without recurrence (p = 0.144). At spasms onset, 2 patients (15%) in the recurrence group and 10 patients (19%) in the remission group had concomitant seizures (p = 1.000). The mean age of onset of infantile spasms was 6.1 months for patients with recurrence and 5.8 months for patients without recurrence (p = 0.685). The mean time from infantile spasms to vigabatrin initiation was 36.5 days in patients with recurrence and 29.8 days in patients without recurrence (p = 0.551). The mean time
from vigabatrin initiation to spasm remission was 13.3 days in patients with recurrence and 12.8 days in patients without recurrence ($p = 0.856$). The mean vigabatrin dose at spasm remission was 59.2 mg/kg/day in patients with recurrence and 69.0 mg/kg/day in patients without recurrence ($p = 0.275$).
Table 1. Baseline patient characteristics

|                                | Switch (n = 25) | Maintenance (n = 41) | p-value |
|--------------------------------|----------------|----------------------|---------|
| Male (%)                       | 12 (48)        | 24 (59)              | 0.404   |
| Onset age, mean (months)       | 6.1            | 5.8                  | 0.562   |
| Time from IS onset to vigabatrin initiation, mean (days) | 24.5 | 35.2 | 0.243 |
| Time from vigabatrin initiation to spasm remission, mean (days) | 14.2 | 13.5 | 0.476 |
| Vigabatrin dose at spasm remission, mean (mg/kg/d) | 70.5 | 64.9 | 0.451 |
| Concomitant seizures (%)       | 6 (24)         | 6 (15)               | 0.348   |
| Symptomatic (%)                | 12 (48)        | 27 (66)              | 0.152   |
| Tuberous sclerosis complex     | 2              | 9                    |         |
| Congenital malformation        | 1              | 7                    |         |
| Brain injury (e.g. HIE)        | 8              | 8                    |         |
| CNS infection                  | 0              | 3                    |         |
| Others                         | 1              | 0                    |         |

IS, infantile spasms; HIE, hypoxic ischemic encephalopathy; CNS, central nervous system
|                                    | Switch (n = 25) | Maintenance (n = 41) | p-value |
|------------------------------------|----------------|----------------------|---------|
| **Spasms recurrence**              | 0              | 2 (5%)               | 0.522   |
| Cryptogenic                        | 0              | 0                    |         |
| Symptomatic                        | 0              | 2                    |         |
| **Other seizures recurrence**      | 2 (8%)         | 2 (5%)               | 0.630   |
| Cryptogenic                        | 0              | 0                    |         |
| Symptomatic                        | 1              | 2                    |         |
Table 3. Seizure recurrence at 12 month from spasms free

|                          | Switch (n = 25) | Maintenance (n = 41) | p-value |
|--------------------------|----------------|----------------------|---------|
| **Spasms recurrence**    | 0              | 6 (15%)              | 0.075   |
| Cryptogenic              | 0              | 1                    |         |
| Symptomatic              | 0              | 5                    |         |
| **Other seizures recurrence** | 3 (12%)       | 4 (10%)              | 1.000   |
| Cryptogenic              | 1              | 1                    |         |
| Symptomatic              | 2              | 3                    |         |
Table 4. Risk factors for seizure recurrence (at 12 months)

|                                | Recurrence (n = 13) | Remission (n = 53) | \( p \)-value |
|--------------------------------|---------------------|--------------------|---------------|
| Male (%)                       | 6 (46)              | 30 (57)            | 0.498         |
| Vigabatrin switch (%)          | 3 (23)              | 22 (42)            | 0.340         |
| Symptomatic (%)                | 10 (77)             | 29 (55)            | 0.139         |
| Concomitant seizures (%)       | 2 (15)              | 10 (19)            | 1.000         |
| Onset age, mean (months)       | 6.1                 | 5.8                | 0.685         |
| Time from IS onset to vigabatrin initiation, mean (days) | 36.5 | 29.8 | 0.551 |
| Time from vigabatrin initiation to spasm remission, mean (days) | 15.5 | 12.8 | 0.856 |
| Vigabatrin dose at spasm remission, mean (mg/kg/d) | 59.2 | 69.0 | 0.275 |

IS, infantile spasms
Figure 1. Flow diagram of patient enrollment

IS, infantile spasms
Discussion

Vigabatrin is effective in infantile spasms but can cause irreversible retinal toxicity that manifests as visual field constriction. Moreover, previous studies have reported that a longer duration of vigabatrin therapy increases the risk of retinal toxicity\textsuperscript{8-10}. Recent research has shown that there is a difference between the frequency of visual field defect at 6 months after vigabatrin initiation and that after 12 months\textsuperscript{11}. This indicates that vision loss can occur even if the treatment has not been prolonged for years. However, the duration of therapy to maintain therapeutic effects without increasing the risk of an adverse effect has not been investigated. In another study, vigabatrin was stopped after 3–6 months in 19 patients who were responding to vigabatrin. Follow up duration was short at 13–50 months, but there were no cases of spasm recurrence\textsuperscript{15}. However, in a study on long-term prognosis, a more than 50% recurrence rate was found of some form of epilepsy, including partial seizures\textsuperscript{4,16}. Therefore, treatment is often required for subsequent seizures after spasm remission. For patients with infantile spasms successfully treated with vigabatrin, short-term vigabatrin treatment followed by a switch to another AED may be considered.

If the recurrence rate after switching to another AED is not higher than that with long-term vigabatrin treatment, it could provide a new treatment strategy for reducing the risk of VFC treatment and maintaining its therapeutic effect.

We changed the medication to a different anticonvulsant drug in patients with infantile spasms who were successfully treated with vigabatrin within 6 months, and compared these patients to those who continued vigabatrin, to detect any differences in the recurrence rates of spasms and other seizures. Although there is no guideline for the optimal treatment duration of vigabatrin, result from a limited number of studies suggest that vigabatrin could be stopped after 6 months without
a relapse\textsuperscript{14, 15} and that the incidence of VFC seems to increase after 6 months of vigabatrin treatment\textsuperscript{11}. There was no statistically significant difference between the two groups with respect to baseline characteristics and recurrence rate at 6 and 12 months after spasm remission.

Although no medications have been proven to be effective for infantile spasms except for ACTH and vigabatrin, some cases of infantile spasms have been treated with medications that are effective for partial seizures, such as topiramate, zonisamide, and levetiracetam\textsuperscript{17-22}. Infantile spasms is an age-specific epilepsy. More than 50\% of the patients with a history of infantile spasms develop chronic epilepsy, and most of them have other types of seizures than spasms. AEDs that are effective for concomitant seizure and infantile spasms or for seizures that follow infantile spasms should be considered as potential switch drugs.

When patients who experienced recurrence at 12 months after spasm remission were compared to patients with no recurrence, no statistically significant difference was found, but recurrence tended to occur more frequently in cases where the cause of spasms was symptomatic.

This study has some limitations. It was a retrospective study in which the duration of vigabatrin treatment and the switch drug were not constant in the switch group, and the follow-up period was short. However, our data suggest that a short course of vigabatrin followed by switching to another AED can provide a new strategy for treating infantile spasms while limiting the adverse effects of vigabatrin. In future research, long-term prognosis and the difference in frequency of VFC between the two groups should be assessed.
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국문초록

비가바트린 (vigabatrin) 은 영아연축에 효과가 입증된 약이지만, 부작용으로 비가역적인 시야결손을 초래할 수 있다. 시야결손은 위험은 투약기간이 증가함수록 커진다. 비가역적인 시야결손의 위험을 줄이기 위해, 단기간 vigabatrin 투약 후 다른 항경련제로 변경하여 치료하여도 치료의 효과를 유지할 수 있는지 알아보고자 하였다.

Vigabatrin 투약시작 한달 이내에 연축이 치료된 영아연축 환자를 대상으로 하였다. 연축이 사라진 후 6개월 이내에 다른 항경련제로 변경한 투약 변경군 (n = 25)과 vigabatrin 투약을 유지한 유지군 (n = 41)으로 그룹을 나누어 연축이 사라지고 각각 6개월과 12개월에 연축 및 다른 형태의 발작의 재발 여부를 조사하였다.

연축의 발병연령, 동반된 다른 형태의 경련 유무, 발병부터 vigabatrin 투약 시작까지의 기간, vigabatrin 투약시작 후 연축이 사라지기까지의 기간 및 vigabatrin 용량에서 두 그룹간 통계적으로 유의한 차이는 없었다. 6개월에는 변경군 중에는 2명 (연축 0명), 유지군 중에는 4명 (연축 2명)에서 재발하였고, 12개월에는 변경군 중에는 3명 (연축 0명), 유지군 중에는 10명 (연축 6명)에서 재발하였고, 통계적으로 유의하지 않았다.

Vigabatrin 초기 치료에 반응이 있는 영아연축 환자에서 vigabatrin 단기 투약 후 다른 약물로 변경하여도 재발률이 증가하지 않기 때문에 시야결손의 부작용을 줄이기 위해 이 치료법을 고려해 볼 수 있다. 앞으로 장기간의 추적관찰과 실제로 이 치료법이 시야 결손을 줄여줄 수 있는지에 대한 추가 연구가 필요하다.
주요어: 비가바트린(vigabatrin), 영아연축, 시야결손

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