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Original Article

Short-Term Outcome of Intravenous Methylprednisolone Pulse Therapy in Patients With Infantile Spasms

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ABSTRACT

BACKGROUND: Many studies advocate hormonal treatments including high-dose oral prednisolone as an effective treatment for epileptic spasms. However, little is known about the effects of intravenous methylprednisolone pulse therapy on infantile spasms. We investigated the short-term response to intravenous methylprednisolone pulse therapy for the treatment of infantile spasms. **METHODS:** Patients with newly diagnosed infantile spasms and hypsarrhythmia on electroencephalography (EEG) at two tertiary centers in Korea were included. Patients received intravenous infusions of 30 mg/kg/day methylprednisolone for three days with tapering doses of oral prednisolone for two to four weeks for the treatment of infantile spasms. Response to methylprednisolone pulse therapy was evaluated by seizure frequency and follow-up EEG within three weeks. **RESULTS:** Fourteen patients were sudied. The mean age at the onset of spasms was 7.0 months (range, 2.0 to 11.0 months). Etiological factors included structural abnormalities (N = 11), chromosomal anomaly (N = 1), and unknown (N = 2). Nine of 14 participants (64.3%) demonstrated complete freedom from spasm and resolution of hypsarrhythmia on EEG within 3 weeks; however, only five of nine responders (55.5%) remained free of spasms after the discontinuation of oral steroids. Adverse effects, including irritability or infection, were observed in four patients but were tolerable in all. **CONCLUSIONS:** Short-term methylprednisolone pulse therapy for the treatment of infantile spasms or hypsarrhythmia demonstrated rapid improvement in EEG and cessation of spasms without serious adverse effects. Further studies are needed to determine the long-term effects of spasm control.

Keywords: infantile spasms, West syndrome, hypsarrhythmia, steroid, methylprednisolone, short-term outcome

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Introduction

Infantile spasms represent an age-specific epileptic disorder of early infancy. They typically present with epileptic spasms occurring in clusters, a disorganized high-amplitude interictal electroencephalographic pattern known as hypsarrhythmia, and neurodevelopmental arrest or regression. One observational study noted that the duration of hypsarrhythmia affects mental developmental outcomes in infantile spasms.[1] Another study of infantile spasms due to tuberous sclerosis demonstrated that the total time with clinical spasms increases the risk of poor developmental outcomes.[2] The United Kingdom Infantile Spasms Study (UKISS) suggested that both early cessation of spasms and a short lead time to treatment reduce the total duration of the epileptic encephalopathy and improve developmental outcome.[3] Thus the treatment of infantile spasms is based on this consensus that rapid resolution of spasms improves the long-term outcome.

The optimal treatment of patients with infantile spasms has been debated for several decades. Publications from some developed countries suggest that adrenocorticotropic hormone (ACTH) is a first-line treatment. However, there

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are practical difficulties with ACTH treatment in terms of price and availability in many developing countries.[4] In addition, previous studies showed no difference in control of spasms between the ACTH and steroid groups, which means ACTH treatment is not alone a persuasive choice for infantile spasms.[5,6] Although several reports have described the efficacy of steroid therapy for children with in infantile spasms, questions remain regarding the type of corticosteroids, optimal dosage, and duration of steroid treatment.

A recent study revealed that intravenous methylprednisolone (MPD) pulse therapy to treat severe drug-resistant epilepsy is safe and effective, yet the role of MPD pulse therapy for infantile spasms remains unclear.[7] A previous small MPD trial for infantile spasms showed 50% (5/10) of the spasms remission among total patients and 83% remission among the infants treated within one month of onset,[8] which suggests the MPD treatment in new-onset patients can be effective. We present our experience of early high-dose intravenous corticosteroid pulse therapy with MPD for patients with newly developed infantile spasms. This is the first study to investigate the safety and short-term efficacy of pulse MPD therapy as the first-line treatment of newly diagnosed infantile spasms.

Methods

Study subject and outcome measures

This study was designed as a prospective, open-label, uncontrolled study to evaluate the efficacy and tolerability of intravenous MPD pulse therapy for newly diagnosed patients with infantile spasms. From February 2014 to January 2016, infants between the ages two and 11 months who presented with infantile spasms and hypsarrhythmia on confirmed by pediatric neurologists at two Seoul tertiary care hospitals, Asan Medical Center Children's Hospital and Sanggye Paik Hospital, were eligible.[9] The average number of referrals to these two centers for infantile spasms was about 30 patients per year. We excluded patients with a diagnosis of tuberous sclerosis, patients previously treated for infantile spasms, and patients with contraindications of hormonal therapy.[10] Ethical Committee and Institutional Review Board approval was obtained from all participating institutions, and the risks and benefits of MPD and alternative treatment regimens were discussed with each patient's caregivers.

All patients underwent magnetic resonance imaging, and metabolic and genetic investigations were performed when indicated. This study aimed to investigate the short-term response to intravenous MPD pulse therapy for the treatment of infantile spasms. Before treatment with MPD pulse therapy, we provided the patients' families with detailed information about the standard treatment options available for infantile spasms and the efficacy and potential adverse effects of MPD pulse therapy, and we obtained the informed consent from the parents.

Participants with newly diagnosed infantile spasms intravenously received 30 mg/kg MPD (Methysol, Albogenkorea, Korea) once daily for three days. Responders were then given a low dosage (1 mg/kg two doses) of oral prednisolone (Solondo, Youhan, Korea), which was rapidly reduced each week for two to four weeks. Nonresponders were immediately transitioned to other treatments including antiepileptic drugs or a ketogenic diet. Sleep EEG recordings were performed before and two to 22 days after the completion of MPD pulse therapy. All patients treated with MPD pulse therapy had laboratory monitoring of electrolytes and blood sugar, blood pressure, kidney function, and electrocardiography.

The outcome measurements were achievement of freedom from spasms and tolerability as per parental reports and improvement of hypsarrhythmia after the completion of therapy. Freedom from spasms was defined as the cessation of spasms for at least seven successive days after therapy initiation within 14 days after the MPD initiation. An electroclinical responder had clinical cessation of spasms and resolution of hypsarrhythmia on EEG within three weeks after completion of treatment. Time from therapy commencement to the cessation of spasms and time from cessation of spasms to recurrence were also measured. Spasm recurrence is referred to as reappearance of spasms during first three months after cessation of steroid. Clinical characteristics of patients were analyzed to identify the determining factors of the efficacy of pulse MPD.

Statistical analysis

Data were analyzed using SPSS version 23. Descriptive statistics, including mean and standard error of the mean for quantitative data and proportions for categorical data, were calculated. We used Fisher's Exact tests for comparisons of categorical baseline characteristics and independent *t* test in relation to quantitative baseline characteristics between complete responders and noncomplete responders. *P* value less than 0.05 was considered to be statistically significant.

Results

Baseline characteristics

During the inclusion period, 14 children with newly diagnosed infantile spasms were included in this study. The mean age at the onset of spasms was 7.0 months (range, 2.0 to 11.0 months). The group comprised ten males and four females. Etiologic factors were classified as structural (N = 11, 78.6%), genetic (N = 1, 7.1%), and unknown (N = 2, 14.3%). All but one patient exhibited delayed cognitive and motor developmental at the time of diagnosis, presenting with mild motor delay in one patient (7.1%), severe motor delay in one patient (7.1%), and severe global developmental delay in 11 patients (78.6%). All patients had hypsarrhythmia on baseline EEG. The median treatment delay from initial infantile spasm onset was 1.0 day (range, 1 to 14 days) (Table 1). This delay period was very short with a mean delay of 1.0 day suggesting a fast recognition of the spasms.

TABLE 1.
Baseline Characteristics of Enrolled Patients

Demographics	Number of Cases (Total N = 14)
Sex, male, N (%)	10 (71.4)
Age of onset of infantile spasms (months)	7.0 ± 2.5
Etiology, N (%)	
Structural	11 (78.6)
Periventricular leukomalacia	2 (14.3)
Hypoxic-ischemic encephalopathy	2 (14.3)
Hydrocephalus	4 (28.6)
Polymicrogyria	2 (14.3)
Lissencephaly	1 (7.1)
Genetic	1 (7.1)
Unknown	2 (14.3)
Median treatment delay from initial spasms (days)	1.0
Spasm load, clusters per day	3.6 ± 1.2
Gestational age at birth (weeks)	34.4 ± 5.6
Prematurity, N (%)	6 (42.6)
Birth weight (kg)	2.3 ± 1.2
Developmental delay before onset of infantile spasms, N (%)	13 (92.8)

Data presented as the mean ± standard error.