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Comparing the Effects of Intravenous Methylpredonisolone Pulse Therapy with the Conventional dose of Corticosteroids for the Treatment of Acute Facial Nerve Palsy: A Propensity Score Analysis

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Abstract

Background

To evaluate and compare the effectiveness of intravenous methylpredonisolone pulse therapy with conventional dose of corticosteroids for the treatment of facial nerve palsy.

Methods

The recovery rate and treatment period were compared between the intravenous methylpredonisolone pulse therapy and conventional dose of corticosteroids in this retrospective observational study. Patients with acute facial nerve palsy were treated within 7 days after onset.

Results

A total of 74 patients with facial nerve palsy were included: 48 were treated with intravenous methylpredonisolone pulse therapy and 26 with conventional doses of corticosteroids. The recovery rates were 70.8% and 84.6% in the intravenous methylpredonisolone pulse therapy and conventional treatment, respectively. The median treatment periods were 61 days and 30 days in the intravenous methylpredonisolone pulse therapy and conventional treatment, respectively. A statistically significant difference was observed between the two groups (log-rank test $p=0.014$), with the conventional treatment group having a shorter treatment period.

Conclusions

In conclusion, no results showed that intravenous methylpredonisolone pulse therapies were more effective than the conventional steroid treatment.

Key Words: Facial nerve palsy; Bell's palsy; Ramsay Hunt syndrome; Zoster sine herpete; Intravenous methylpredonisolone pulse therapy

Introduction

Facial nerve palsy may occur due to various reasons; however, its primary causes are Bell's palsy

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and Ramsay Hunt syndrome (RHS). Bell's palsy, defined as an acute facial nerve paralysis of unknown origin, is recently presumed to be caused by reactivation of herpes simplex virus type 1 (HSV1)[1]. RHS occurs with vesicular eruption around the affected ear and with facial palsy caused by the reactivation of varicella-zoster virus (VZV)[2]. Zoster sine herpete (ZSH) is one of the atypical clinical manifestations of herpes zoster. ZSH is caused by the reactivation of VZV but without vesicular eruption. ZSH is one of the causes of facial nerve paralysis; however, distinguishing it from Bell's palsy is difficult. Therefore, it is commonly misdiagnosed as Bell's palsy[3-5]. ZSH is diagnosed with the detection of virus deoxyribonucleic acid (DNA) using polymerase chain reaction (PCR) or anti-VZV antibody in the serum[3,4]. It has also been reported in 8%-19% of patients clinically diagnosed with Bell's palsy[5]. Serological or PCR examinations should be performed to distinguish Bell's palsy from ZSH.

The prognosis of Bell's palsy is favorable, with approximately 70% of patients being completely resolved without treatment[6]. However, the prognosis of facial palsy caused by RHS and ZSH is worse than Bell's palsy[7]. Only 10% of complete facial palsy caused by RHS is resolved without treatment.

Reactivation of HSV1 or VZV in the geniculate ganglion causes facial nerve inflammation and edema, which resulted in facial nerve compression as it travels through the fallopian canal, the leading posited mechanism of Bell's palsy and facial paralysis of RHS. Corticosteroids target the inflammatory process and decrease nerve edema, thereby resulting in the return of facial nerve function.

Some randomized control trials (RCT) of the effectiveness of corticosteroid treatment for Bell's palsy, with higher recovery rate and shorter recovery time[8,9]. Some reports have described the effectiveness of corticosteroids for facial nerve palsy in RHS and ZSH[4,10].

Clinical practice guideline in the American Academy of Otolaryngology-Head, and Neck Surgery (AAO-HNS) recommends a 10-day course of oral steroids with at least 5 days at high dose [prednisolone {PSL} 50 mg/day for 10 days or 60 mg/day for 5 days then tapered for >5 days] to treat Bell's palsy[6]. The French Society of ENT (SFORL) recommends the PSL administration of 1 mg/kg/day for 7-10 days for the treatment of Bell's palsy and PSL 2 mg/kg/day for 10 days for the treatment of severe Bell's palsy[11]. The international guidelines for facial palsy in RHS are not yet established. The Japan Society of Facial Nerve Research proposed a dose of steroids according to the severity of facial palsy. PSL of 120-200 mg/day tapered within 10 days in complete facial palsy (<10 points in the Yanagihara score), PSL of 60 mg/day tapered in moderately facial palsy (18-10 points), PSL of 30 mg/day tapered in mild facial palsy (>20 points) are proposed in both Bell's palsy and RHS based on this guideline[12].

The efficacy of the intravenous methylprednisolone pulse therapy (methylprednisolone 1000 mg/day for 3-5 days) for central inflammatory diseases, such as multiple sclerosis, neuromyelitis optica, and acute transverse myelitis, has been already reported[13-15]. The intravenous methylpredonisolone pulse therapy is considered effective for acute facial nerve palsy but reports of their advisability have never been done before. The intravenous methylpredonisolone pulse therapy is a higher dose than the administration of the high dose steroids reported so far. There is no report comparing the effects of high-dose steroid administration and intravenous methylpredonisolone pulse therapy.

It is necessary to study whether ultra-high dose steroids have more effects to acute facial nerve palsy especially Bell's palsy and RHS than ever reporting.

In this study, we evaluated the effectiveness of intravenous methylprednisolone pulse compared

with the conventional dose of corticosteroids.

Methods

Study design and setting

A retrospective observational study was conducted at the Osaka City University Hospital and Tane General Hospital from April 2014 to March 2016. The ethical committee of Osaka City University Graduate School of Medicine approved this study (No. 2021-087). We included patients with acute facial palsy aged ≧16 years that occurred within 7 days of symptom onset. Precise history taking, thorough physical examination, stapedius reflex assessment, and serum test were performed on the first day. Electroneurography (ENoG) was measured 7-10 days after the symptom onset. Anti-HSV1 IgG and anti-VZV IgG in the serum were examined. A positive diagnosis was made when the HSV1 or VZV antibody was found to be 50 times higher. If both HSV1 and VZV antibodies were low, antibody testing was repeated 2 weeks after. If the increase doubled or higher, it was judged to be positive. HSV1-positive patients were diagnosed with Bell's palsy, VZV-positive with vesicular eruption as RHS, and VZV-positive without vesicular eruption as ZSH.

Patients were treated with (1) conventional dose of corticosteroid (PSL of -200 mg and 10 days tapering) or (2) intravenous methylpredonisolone pulse therapy (intravenous methylprednisolone 1000 mg for 3 days at 1-3 times). All the intravenous methylpredonisolone pulse therapy were performed at the Department of Neurology, Tane General Hospital.

Outcome measures

The facial movement was examined using the Yanagihara facial nerve grading system score at the first visit, one week after onset, the first month, and every month thereafter for up to 6 months. Recovery from the palsy was defined as a score ≧36 using the Yanagihara 40-point scoring system without facial contracture or synkinesis.

Statistical analysis

Continuous variables are represented by the median (interquartile range), and nominal variables are represented by the percentage (frequency). The chi-square test and Mann-Whitney test were used to describe the difference between the two groups. When ≧36 points indicated completely treated by the Yanagihara score, the duration for complete treatment between the normal treatment and steroid pulse groups was compared using the log-rank test with censoring. Patients who were not completely treated after 6 months or those who were lost to follow-up before 6 months were excluded. Next, we compared the time to complete treatment between the two groups using a Cox proportional hazards model with age, gender, and score at the start of treatment as regulators. In addition, a diagnosis was added to the model as interaction term and examined whether a difference in the therapeutic effect depends on the diagnosis. All statistical processing was performed using R (version 4.0.1), and the significance level was set to 5% on two sides.

Results

Among 80 patients diagnosed with acute facial nerve palsy, three were excluded because of diagnosis (facial nerve tumor, temporal bone fracture, and multiple sclerosis). Of 77 patients with facial nerve palsy, 52 were diagnosed as Bell's palsy and 25 as RHS and ZSH. Three of the patients with Bell's palsy not treated with steroid therapy were excluded from the analysis. Twenty-six patients in the conventional treatment group (17 with Bell's palsy, 9 with RHS and ZSH) and 48 in

the steroid pulse therapy group (32 with Bell's palsy, 16 with RHS and ZSH) were investigated. The baseline characteristics are shown in Table 1.

In the conventional treatment group, 17 patients (65.4%) were diagnosed with Bell's palsy and 9 (34.6%) as RHS and ZSH. In the steroid pulse therapy group, 32 patients (66.7%) were diagnosed with Bell's palsy and 16 (33.3%) as RHS&ZSH. No difference in the diagnosis was observed between the steroid pulse and conventional treatment groups. Stapedius reflex was negative in 14 patients (53.8%) in the conventional treatment group and 32 (66.7%) in intravenous methylpredonisolone pulse therapy group. No difference in the ratio of negative stapedius reflex between the steroid pulse therapy and conventional treatment groups. With regard to the ENoG value, the median value of ENoG in the conventional treatment and the intravenous methylpredonisolone pulse therapy was 37.4% and 33.3%, respectively, showing no significant difference. The proportion of patients with ENoG of <10% was 3.8% (1 patient) and 10.4% (5 patients) in the conventional treatment and the intravenous methylpredonisolone pulse therapy groups, respectively, showing no significant difference. The median values of the Yanagihara score observed at the start of treatment were 15.00

Table 1.

		Without steroid pulse	With steroid pulse	p	Overall
Number		26	48		74
Age (median [IQR])		49.00 [34.50-65.00]	61.00 [47.00-71.00]	0.006	58.00 [43.00-68.75]
Sex% (freq)	male	61.5 (16)	54.2 (26)	0.541	56.8 (42)
	female	38.5 (10)	45.8 (22)		43.2 (32)
Diagnosis% (freq)	Bell	65.4 (17)	66.7 (32)	0.911	66.2 (49)
	RHS &ZSH	34.6 (9)	33.3 (16)		33.8 (25)
SR%	negative	53.8 (14)	66.7 (32)	0.278	62.2 (46)
	positive	46.2 (12)	33.3 (16)		
ENoG%		37.40 [24.45-61.23]	33.30 [18.12-59.90]	0.365	33.75 [19.38-60.30]
ENoG 10%	more than 10%	96.2 (25)	89.6 (43)	0.323	91.9 (68)
	less than 10%	3.8 (1)	10.4 (5)		8.1 (6)
Baseline score		15.00 [7.50-18.00]	10.00 [6.00-14.00]	0.106	10.00 [6.00-17.50]

Baseline characteristics of all patients. Steroid pulse is intravenous methylpredonisolone pulse therapy. IQR, Interquartile Range; RHS, Ramsay Hunt syndrome; ZSH, Zoster sine herpete; SR, stapedius reflex; and ENoG, electroneurography.

Table 2.

	Percentage of cure	Treatment period
Treat with conventional treatment	22 (84.6%)	30 (95% CI 30-61)
Treat with steroid pulse	34 (70.8%)	61 (95% CI 30-122)

	Percentage of cure	Treatment period
RHS &ZSH	18 (72.0%)	61 (95% CI 30--)
Bell	33 (77.6%)	61 (95% CI 30-61)

The recovery rate and the treatment period. Steroid pulse is intravenous methylpredonisolone pulse therapy. RHS, Ramsay Hunt syndrome; and ZSH, Zoster sine herpete.

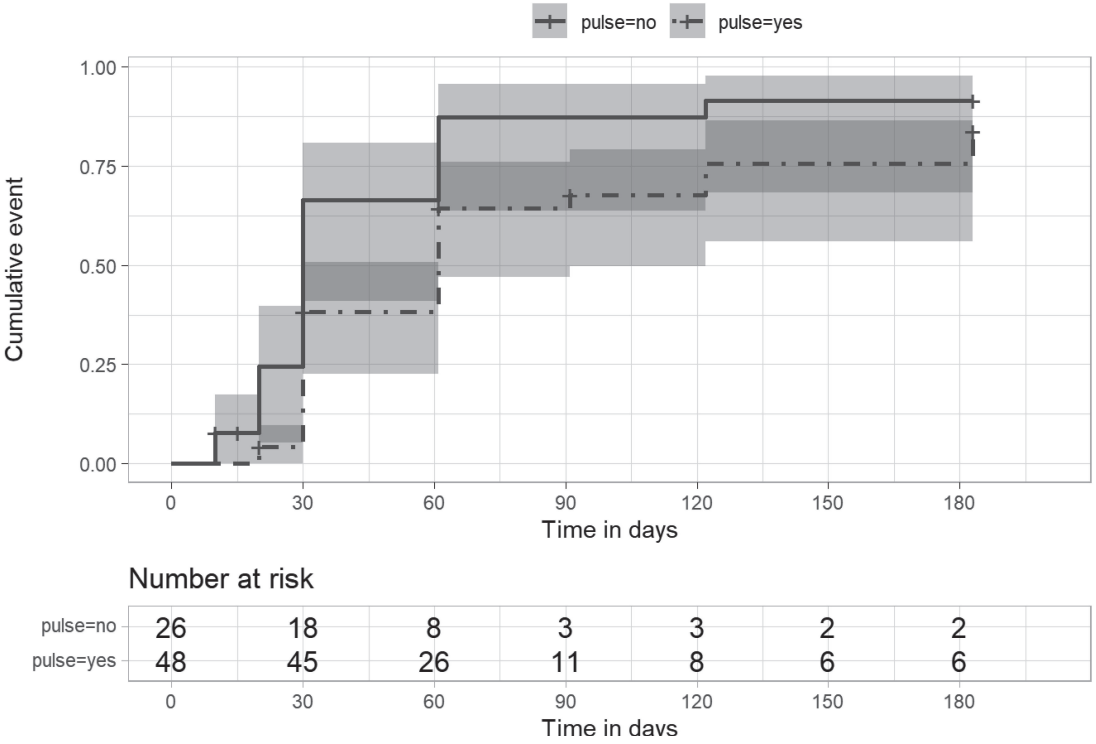


Figure 1. A Kaplan-Meier curve according to the treatment period of the steroid pulse therapy and the conventional treatment group. A statistically significant difference was observed between the two groups (log-rank test p=0.014), suggesting that the duration of for complete treatment the conventional treatment group is shorter than that in the s intravenous methylpredonisolone pulse therapy group. Pulse is intravenous methylpredonisolone pulse therapy. RHS, Ramsay Hunt syndrome; and ZSH, Zoster sine herpete.

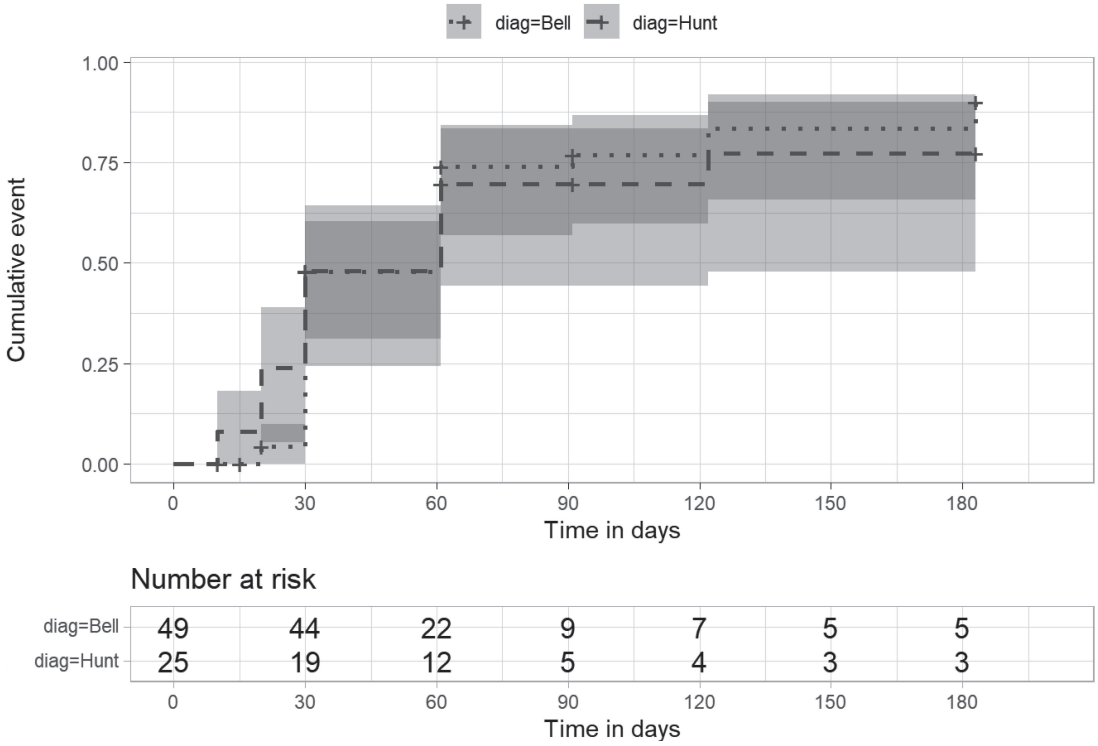


Figure 2. A Kaplan-Meier curve according to the treatment period of Bell's palsy and RHS and ZSH. Any difference between Bell's palsy and RHS and ZSH based on the treatment period were not detected.

and 10.00 points in the normal treatment and the intravenous methylpredonisolone pulse therapy groups, respectively, showing no significant difference.

The recovery rate of patients receiving the conventional treatment and the intravenous methylpredonisolone pulse therapy are shown in Table 2. Of 74 patients, 56 were completely treated with a Yanagihara score of ≧36 points. The rate of complete treatment was 70.8% (34 patients) and 84.6% (22 patients) in the intravenous methylpredonisolone pulse therapy and conventional treatment groups, respectively. The meaning values of the treatment period were 61 days and 30 days in the intravenous methylpredonisolone pulse therapy and conventional treatment groups, respectively. The rate of complete treatment was 77.6% (33 patients) and 72% (18 patients) in the Bell's palsy and RHS and ZSH, respectively. The median treatment period were 61 days in both Bell's palsy and RHS and ZSH groups (Table 2).

A Kaplan-Meier curve according to the treatment period of each group is shown in Figure 1. A statistically significant difference was observed between the two groups (log-rank test $p=0.014$), suggesting that the duration of for complete treatment in the conventional treatment group is shorter than that in the intravenous methylpredonisolone pulse therapy group.

Analysis of each disease is shown in Figure 2. We could not detect any difference between Bell's palsy and RHS and ZSH based on the treatment period.

Next, as a result of the Cox proportional hazard model adjusted for gender, age at the start of treatment, and Yanagihara score at the start of treatment, the hazard ratio for complete treatment in the intravenous methylpredonisolone pulse therapy to the conventional treatment group was 0.787 (95% confidence interval 0.359-1.722, $p=0.548$) (Fig. 3). Finally, when diagnostic were added as interaction, no difference was observed between the presence and absence of intravenous methylpredonisolone pulse therapy for complete treatment in patients with Bell's palsy (HR 1.051, 95% CI 0.504-2.194, $p=0.894$), but not in those with RHS and ZSH (HR 0.151, 95% CI 0.053-0.427, $p<0.001$) for complete treatment of the intravenous methylpredonisolone pulse therapy group, suggesting that the effectiveness of the intravenous methylpredonisolone pulse therapy differs depending on the cause of paralysis (p for interaction=0.003) (Fig. 4). In RHS and ZSH, treatment duration was longer when steroid pulse was administered.

Discussion

We evaluated the effectiveness of the intravenous methylpredonisolone pulse therapy for the treatment of Bell's palsy and RHS and ZSH. The results showed the steroid pulse therapy was not more effective than conventional therapy using 30-200 mg of prednisolone with several days of dose tapering.

Bell's palsy is one of the most common causes of acute facial nerve palsy with an annual incidence of 15-30/100000. Various diseases caused facial nerve paralysis (Table 3)[6]. Among them, Bell's palsy was considered as acute facial nerve palsy with unknown etiology but is currently considered as the reactivation of HSV1[1]. The prognosis of Bell's palsy is favorable, with approximately 70% of patients completely resolved without treatment[6].

RHS is acute facial nerve palsy with auricular vesicular eruptions and pain around the affected ear, with an annual incidence of 5/100000, and is caused by the reactivation of VZV. Its prognosis is worse than Bell's palsy, and spontaneous remission is available in only 30% of patients[10,16,17]. ZSH is an atypical clinical manifestation of herpes zoster, causing acute facial nerve palsy without vesicular

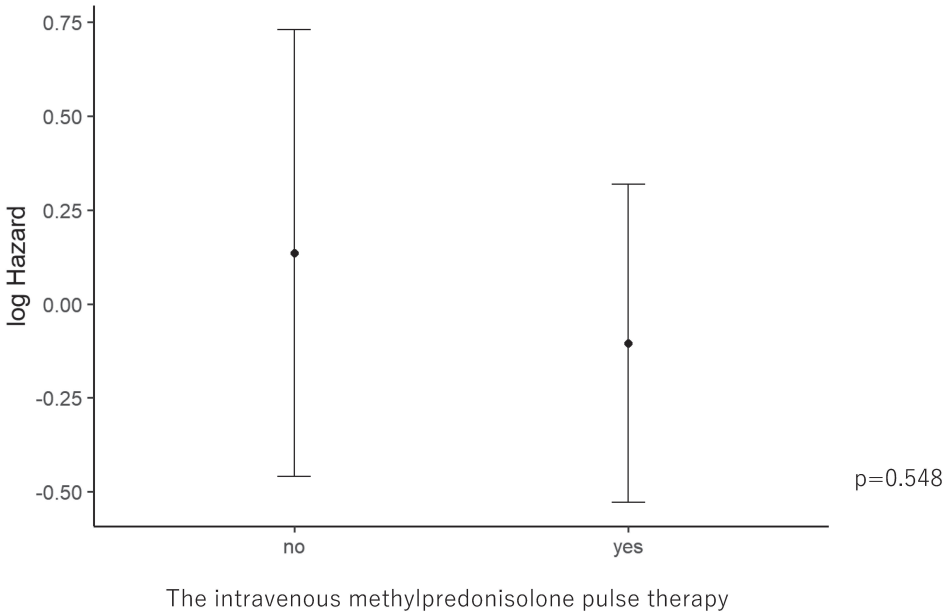
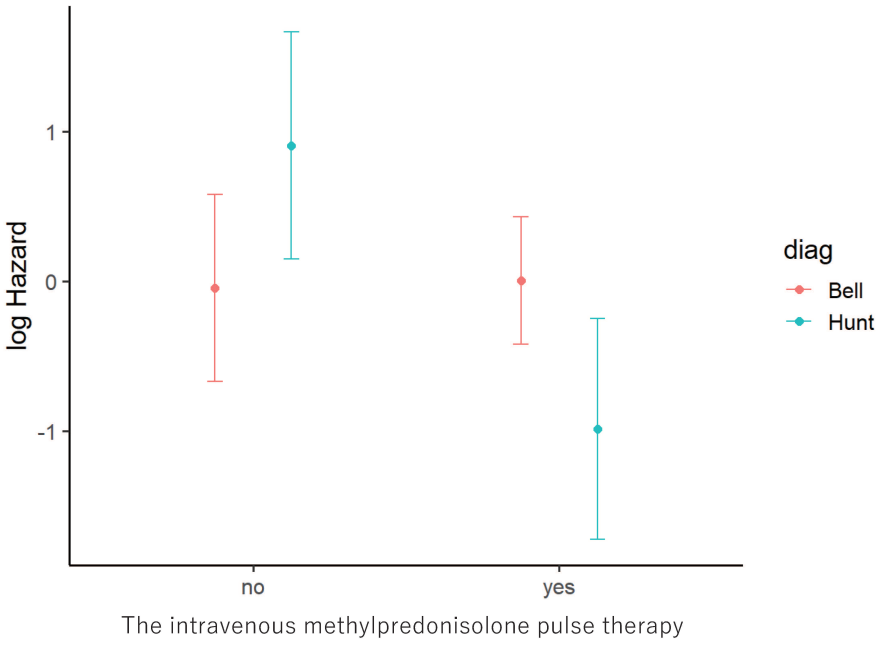


Figure 3. The hazard ratio for complete treatment in the intravenous methylpredonisolone pulse therapy and the conventional treatment group. The hazard ratio for complete treatment in the steroid pulse, intravenous methylpredonisolone pulse therapy to the conventional treatment group was 0.787 (95% CI 0.359-1.722, p=0.548). CI, confidence interval.



		Hazard ratio	95%CI	p value
RHS &ZSH	with/without steroid pulse	0.151	0.053-0.427	<0.001
Bell	with/without steroid pulse	1.051	0.504-2.194	0.894

Figure 4. The hazard ratio for complete treatment in the steroid pulse, intravenous methylpredonisolone pulse therapy and the conventional treatment group depending on the cause of paralysis. No difference was observed between the presence and absence of the steroid pulse therapy for complete treatment in patients with Bell's palsy (HR 1.051, 95% CI 0.504-2.194, p=0.894), but not in those with RHS and ZSH (HR 0.151, 95% CI 0.053-0.427, p< 0.001) for complete treatment of the steroid pulse, intravenous methylpredonisolone pulse therapy group. Steroid pulse is intravenous methylpredonisolone pulse therapy. HR, hazard ratio; RHS, Ramsay Hunt syndrome; ZSH, Zoster sine herpete; and CI, confidence interval.

eruptions and is also caused by the reactivation of VZV[18]. ZSH is diagnosed by increased anti-VZV antibody titer or virus DNA in the cerebrospinal fluid or serum[3]. ZSH is observed in 8%-19% of patients diagnosed with Bell's palsy[5] and involves pain around the affected ear; however, Bell's palsy is also sometimes accompanied by pain, and the degree of pain did not differ in both diseases[4]. Distinguishing Bell's palsy from ZSH is difficult based on physical findings alone. The prognosis of ZSH and RHS is poor. The poor prognosis of patients with Bell's palsy might be the presence of ZSH.

In this study, RHS and ZSH accounted for 31% of acute facial nerve palsy. The ratio of facial nerve palsy associated with VZV was higher than that of previous reports. Robillard et al reported that 185 (12.3%) of 1507 patients with facial nerve palsy were diagnosed as RHS[17] In our study, anti-VZV antibody titer and anti-HSV1 antibody titer were determined to diagnose acute facial nerve palsy; therefore, ZSH could be diagnosed as facial palsy associated with VZV. ZSH is likely to be diagnosed with Bell's palsy when testing for antibodies or PCR was not performed. Furuta et al reported that of 142 patients with acute facial nerve palsy, 56 were caused by reactivation of VZV and 86 by HSV1. They were diagnosed based on increased anti-VZV antibody titer in the serum or virus DNA in the saliva[19]. Our results of the RHS and ZSH ratio in acute facial nerve palsy were consistent with their findings.

Sullivav et al reported a double-blind, RCT about the effect of prednisolone (50 mg for 10 days) for the treatment of Bell's palsy. In their trial, 551 patients were divided into four groups (acyclovir plus prednisolone, acyclovir plus placebo, prednisolone plus placebo, and placebo). About 83% of patients randomized to prednisolone had recovered their facial nerve function, whereas 63.6% of those randomized to placebo had recovered 3 months after treatment ($p<0.01$). Moreover, 94.4% of patients randomized to prednisolone had recovered their facial nerve function, whereas 81.6% of those randomized to placebo had recovered 9 months after treatment[8]. Engström et al also had a substantially similar trial and reported a significant shortening of the treatment period by administering prednisolone (60 mg for 5 days with a 5-day taper)[9].

Based on these results, the AAO-HNS guideline recommends a 10-day course of oral steroid treatment (prednisolone of 50 mg for 10 days or prednisolone of 60 mg for 5 days with a 5-day taper) to treat Bell's palsy[6]. Conversely, Fujiwara et al reported that 50-60 mg prednisolone cannot adequately treat severe Bell's palsy. In their report, 120 mg of prednisolone (2 mg/kg) for 3 days with a 6-day taper can more effectively treat Bell's palsy than 60 mg of prednisolone[20,21].

No studies have reported the effectiveness of steroid pulse therapy for Bell's palsy to date. In our study, no significant effect was observed in administering conventional treatment and steroid pulse therapy, whereas short treatment periods were not observed. The steroid pulse therapy might not be necessary even for severe Bell's palsy.

Several studies have reported the effects of steroids in RHS; however, no RTC or meta-analysis has been conducted on steroid doses. In the review, Monsanto et al reported the difference in the effect of steroid type, each recovery rate was 69.2% in prednisone, 61.4% in prednisolone, 76.2% in hydrocortisone, and 81.3% in methylprednisolone[10]. Various reports have investigated steroid dosages for the treatment of RHS. Kinishi et al reported that 93.4% of patients had recovered facial nerve function using methylprednisolone of 500 mg for 1 day with a 6-day taper combined with acyclovir[16]. Only a few case reports have been published on intravenous methylpredonisolone pulse therapy for RHS. Donani et al reported that the patient who did not improve with initial therapy of oral prednisone (50 mg/day) recovered with the intravenous methylpredonisolone pulse therapy 37 days

after the onset[22]. The intravenous methylpredonisolone pulse therapy is possibly effective for RHS. However, in this study, intravenous methylpredonisolone pulse therapy did not effectively improve and reduce the treatment period compared to conventional treatment to treat RHS and ZSH.

The facial nerve grading system score identifies HSV-1 or VZV and ENoG as factors to predict the prognosis of facial movement. Antibody testing to confirm the cause takes approximately 1-2 weeks. The ENoG is considered as a valid prognosis from the 7th day to 14th days[23]. The administration of steroids to treat facial nerve palsy should be initiated within 72 h of symptom onset. Therefore, steroid doses are determined using the facial nerve grading system score only. In the guideline for facial paralysis of the Japan Society of Facial Nerve Research, the setting of the steroid doses is recommended by score, and if it is ≦8 points in the Yanagihara score, 120-200 mg of prednisolone is recommended[12]. Administration of steroids more than necessary should be avoided to prevent side effects, such as gastrointestinal disturbance, reactivation peptic ulcer disease, and loss of control of glucose level, elevated blood pressure, peripheral edema, and mood swings or episodes of acute psychosis.

In conclusion, the intravenous methylpredonisolone pulse therapy cannot be recommended for RHS and Bell's palsy. Bell's palsy does not require the intravenous methylpredonisolone pulse therapy because it has a good prognosis, but RHS & ZSH has a poor prognosis, so we considered the intravenous methylpredonisolone pulse therapy might be effective. However, the effectiveness of the steroid pulse therapy was not confirmed even in RHS & ZSH. Corticosteroids target the inflammatory process and decrease nerve edema, thereby resulting in the return of facial nerve function. For that purpose, even with severe paralysis, it is likely to be sufficient with 2 mg/kg/day prednisolone, and the steroid pulse therapy are not necessary.

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All authors have no COI to declare regarding the present study.

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