Bradycardia Associated with Prednisolone in Children with Severe Kawasaki Disease

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Objective To identify the prevalence of bradycardia associated with use of prednisolone in patients with Kawasaki disease and analyze the association between bradycardia and responsiveness to intravenous immunoglobulin (IVIG).

Study design We performed a retrospective cohort study of 176 patients with severe Kawasaki disease admitted to the Tokyo Metropolitan Children's Medical Center between March 2010 and December 2015. The group treated with IVIG plus prednisolone therapy from February 2012 was compared with the control group who received IVIG monotherapy before this date. The primary outcome was the prevalence of bradycardia, defined as heart rate less than the first percentile for normal children. Next, we determined whether bradycardia was associated with the clinical course in the patient subgroup treated with IVIG plus prednisolone therapy.

Results The prevalence of bradycardia was significantly higher in the IVIG plus prednisolone subgroup than in the IVIG group (79.1% vs 7.1%; $P < .001$). The median time to bradycardia onset was 63.0 hours (2.6 days). Prednisolone decreased the heart rate by 15.1 beats/minute (95% CI 10.2-20.0; $P < .001$) on average from day 2 to 7 after the initial therapy. Logistic regression analysis revealed that bradycardia was associated with responsiveness to initial IVIG plus prednisolone therapy (OR 7.2; 95% CI 2.3-23.0; $P < .001$).

Conclusion Bradycardia frequently occurred during IVIG plus prednisolone therapy in patients with Kawasaki disease, and was associated with responsiveness to IVIG. *(J Pediatr 2017;185:106-11).*

Kawasaki disease (KD), an acute systemic childhood vasculitis primarily affecting the coronary arteries, is a major cause of acquired heart disease in developed countries. Its etiology is unclear, but marked activation of the immune system leading to increased cytokine production occurs during the acute phase. The efficacy of corticosteroid against KD had been controversial until Kobayashi et al reported that administering intravenous immunoglobulin (IVIG) and prednisolone concurrently decreased the duration of fever, reduced the need for additional therapy, and improved coronary artery outcomes.[1] In recent years, prednisolone has been widely used in combination with IVIG for treatment of severe KD in Japan. Severity of patients with KD has been assessed using the score established by Kobayashi et al[2] in which patients scoring 5 points or higher are expected to be at high risk for nonresponsiveness to initial treatment. However, little is known about the adverse reactions to prednisolone among patients with KD.

Many adverse events resulting from corticosteroid use, such as hypertension, gastric ulcers, adrenal suppression, and arrhythmia, have been reported. Among cardiovascular complications, major concerns in KD are supraventricular tachycardia, atrial fibrillation, premature atrial contraction, and ventricular fibrillation. Bradycardia is the most frequently observed cardiac abnormality in patients with rheumatic, immunologic, and malignant diseases who are treated with corticosteroids.[3-5] The incidence of bradycardia in patients with KD treated with prednisolone is not well-known, except in cases in which methylprednisolone pulse therapy was used as additional rescue therapy.[6] Some reports suggested that tachycardia was associated with the severity of the clinical course of KD and the development of coronary artery lesions (CAL).[7,8] We hypothesized that bradycardia is a frequent complication in patients with KD treated with prednisolone and that, in acute cases, it would be associated with suppression of inflammation and responsiveness to the initial treatment. The present study aimed to examine the frequency of corticosteroid-induced bradycardia in severe KD, and the correlation between bradycardia and the clinical course of the disease.

Methods

We performed a retrospective cohort study of patients with KD with high Kobayashi score (≥5 points), comparing the prevalence of bradycardia in those who

BT	Body temperature
CAL	Coronary artery lesions
HR	Heart rate
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease

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received IVIG monotherapy with those who received IVIG plus prednisolone therapy. Additionally, subgroup analyses were conducted to evaluate the effect of bradycardia on the clinical course. The ethical committee of Tokyo Metropolitan Children's Medical Center approved this study (approval number: H28b-58).

We reviewed the electronic medical records of all patients with KD admitted to Tokyo Metropolitan Children's Medical Center between March 2010 and December 2015. Patients who received initial treatment at another institution, were treated with aspirin without IVIG, required vasopressors for KD shock syndrome, or had a low Kobayashi score (≤4 points) were excluded. We administered IVIG monotherapy before January 2012, and IVIG plus prednisolone therapy thereafter to all patients with KD with a high Kobayashi score. The Kobayashi score criteria were as follows: 4 or fewer days of illness at initial treatment received 2 points; a serum sodium concentration of 133 mmol/L or less received 2 points; aspartate aminotransferase concentration of 100 U/L or greater received 2 points; white blood cells representing neutrophils 80% or greater received 2 points; a platelet count of $30 \times 10^4/\mu$ or less received 1 point; a C-reactive protein concentration of 10 mg/dL or greater received 1 point; and age 12 months or younger received 1 point.

We collected data on the patients' vital signs, demographics, laboratory findings, electrocardiogram, echocardiogram, clinical course requiring retreatment with IVIG, and additional rescue therapy from the electronic medical records. The distribution of the Kobayashi score criteria was also recorded. Twelve-lead electrocardiogram and echocardiogram were performed at admission, 1 week after admission, and 1 month after initial treatment and were assessed by pediatric cardiologists or trained echocardiogram technicians. Vital signs were measured at least 3 times daily during hospitalization, every 15 minutes after the start of IVIG for 2 hours, and thereafter every 4 hours during the remaining IVIG treatment by a trained nurse.

Additionally, we used data from another multicenter study—Prospective Observational Study on Stratified Treatment with Immunoglobulin plus Steroid Efficacy and Safety for Kawasaki Disease (Post RAISE)—that was conducted at our treatment center from February 2012 to January 2016 (Clinical Trial Registration: http://www.umin.ac.jp/ctr/ identifier: UMIN000007133). The demographics, laboratory findings, and echocardiograms of patients admitted between February 2012 and December 2015 were obtained from that study.

Bradycardia was defined as a decrease in heart rate (HR) to less than the first percentile for more than 2 successive days, as determined by reference to the normal HR percentiles for children.[9] The PR intervals of all the patients were assessed based on the pediatric electrocardiogram definition of the PR interval as 70-170 ms in newborns and 80-220 ms in young children.[10] CAL was defined by a *z* score of the coronary arterial internal diameter adjusted by body surface area of greater than or equal to 2.5 for the proximal right artery or the proximal left anterior descending artery according to the American Heart Association's 2004 statement on KD.[11] CAL was classified as saccular, fusiform, or ectatic according to visual findings by a pediatric cardiologist. Further, the saccular and fusiform types were defined as coronary aneurysms. Responsiveness to IVIG treatment was defined as the resolution of fever after initial IVIG treatment precluding further need for IVIG.

IVIG Group

Patients who were admitted before February 2012 received immunoglobulin 2 g/kg/day over 24 hours for 1 day and aspirin 30 mg/kg/day until fever resolution, followed by aspirin 5 mg/kg/day for at least 2 months after onset.

IVIG Plus Prednisolone Group

Patients admitted after February 2012 were treated with IVIG plus prednisolone. They received IVIG and aspirin according to the same schedule as the IVIG group, and further received prednisolone 2 mg/kg/day divided into 3 doses intravenously over 5 days. After 5 days, we changed the method of prednisolone administration from intravenous to oral except in cases unresponsive to initial treatment. After the C-reactive protein normalized (≤0.5 mg/dL), we tapered the prednisolone dose over 15 days at 5-day intervals from 2 to 1 to 0.5 mg/kg/day. Famotidine 0.5 mg/kg/day was administered concurrently with prednisolone to prevent gastric ulceration.

Retreatment with IVIG

When patients remained febrile (body temperature [BT] of more than 37.5°C) or experience recurrence of fever after initial treatment with IVIG only or IVIG plus prednisolone, they received IVIG retreatment.

Additional Rescue Treatment

If retreatment with IVIG was ineffective, steroid pulse or plasma exchange were administered by clinicians according to the 2012 Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery guidelines for the medical treatment of acute KD.[12]

Statistical Analyses

All statistical analyses were performed with the IBM SPSS Statistics for Macintosh Version 23.0 (IBM Corp, Armonk, New York). A 2-sided $P < .05$ was considered statistically significant.

We compared the IVIG only and the IVIG plus prednisolone groups in terms of the variables of patient demographics, laboratory findings, Kobayashi score criteria distribution, PR intervals measured by electrocardiogram, and the fraction of CAL. The Kolmogorov-Smirnov test was used to determine whether continuous variables had a normal distribution. The statistical difference was calculated using Student *t* test for continuous variables if the data had a normal distribution and Mann-Whitney *U* test if the variables had a non-normal distribution. Kaplan-Meier analysis was used to measure the time until the onset of bradycardia. Bradycardia was defined as a given event, and discharge was censored. The mean time to development of bradycardia was also calculated. We plotted the mean HR and BT changes in patients who responded to the initial IVIG treatment on 7 successive days