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Intravenous immunoglobulin therapy for older children with Kawasaki disease

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Abstract : The risk-benefit balance of the full dose intravenous immunoglobulin (IVIG) infusion of 2 g/kg body weight/dose in older children has not been established. In this study, I investigated the safety and efficacy of this therapy for older children. In total, I recruited 210 children who had received 2 g/kg/dose of IVIG therapy for Kawasaki disease between 1999 and 2015 at the Department of Pediatrics, Aomori Prefectural Central Hospital. The children were divided into two groups: an older group, comprising 18 children who were ≧ 72 months-old, and a younger group, comprising 192 children who were ≦ 71 months-old. The 18 children of the older group received a median IVIG dose of 50 g/dose (range, 36−105). None of the children had any major complications, including thrombosis. The prevalence of coronary artery lesions (CAL) before 30 days of illness was similar between the older and younger groups (1 / 18 vs. 9 / 192, $P = 1.000$). No older children had CAL after 30 days. An IVIG infusion of 2 g/kg/dose for older children with Kawasaki disease may be safe and effective for suppressing CAL caused by Kawasaki disease.

Keywords - *Kawasaki disease, Intravenous immunoglobulin therapy, Coronary artery lesions, Older children, Aspirin*

I. INTRODUCTION

Kawasaki disease is an acute systemic vasculitis of unknown cause that mainly affects infants and children [1]. Coronary artery lesions (CAL) are one of the most important complications of this disease. An onset at an older age is an independent risk factor for the development of cardiovascular sequelae in Kawasaki disease [2]. The prevalence of CAL is higher in older children compared with younger children [3]. Furthermore, a previous epidemiological study using a multivariate analysis showed that older age was also a risk factor for giant coronary artery aneurysms [4].

The current standard therapy during the acute phase of Kawasaki disease is 2 g/kg body weight/dose intravenous immunoglobulin (IVIG) therapy [5]. However, the safety and efficacy of an IVIG infusion of this dose have not been established for older children. In this study, I investigated the safety and efficacy of this IVIG infusion dose in older children.

Recent studies have disclosed that aspirin and flurbiprofen appeared to have a negative impact on the suppressive effects of initial IVIG therapy for CAL development during the acute phase of Kawasaki disease, and that an initial single IVIG therapy dose with the delayed administration of anti-inflammatory drugs might be effective for CAL suppression [6,7]. A previous study showed that high-dose intact IVIG therapy with and without delayed administration of aspirin had inhibitory effects on platelet adhesion and thrombus formation [8]. Therefore, I also investigated the safety of 2 g/kg/dose of IVIG therapy with and without delayed administration of aspirin or flurbiprofen for older children.

I excluded all children who received 1 g/kg/dose IVIG therapy and those who were associated with CAL before the start of therapy. Previous studies have showed that the prevalence of CAL was higher among children with recurrent Kawasaki disease and in those with left ventricular dysfunction during the acute phase of Kawasaki disease [9,10,11]. Therefore, I excluded such children from this study.

II. METHODS

This retrospective study included 210 consecutive patients who had received an initial 2 g/kg/dose of IVIG therapy for Kawasaki disease between January 1999 and September 2015 at the Department of Pediatrics, Aomori Prefectural Central Hospital. The diagnosis of Kawasaki disease was based on the Japanese Criteria (Fifth Edition) [12]. I excluded nine children with disease recurrence, four children who were associated with

CAL before the start of the therapy, six children who had received 1 g/kg/dose of IVIG therapy, and one children associated with left ventricular dysfunction during the study period.

The infusion speeds of IVIG were determined by each doctor according to the guidelines of each IVIG product. All children in this study received intact IVIG.

The 210 children were divided into two groups: an older group, comprising 18 children who were ≧ 72 months-old, and a younger group, comprising 192 children who were ≦ 71 months-old.

The 210 participants were also divided into S and T groups. The S group included 144 patients who had received an initial single IVIG therapy dose with the delayed administration of aspirin or flurbiprofen, whereas the T group included 66 patients who had received these anti-inflammatory drugs concomitantly with the initial IVIG therapy. In the S group, the anti-inflammatory drugs were initiated within 24 h after the end of the initial IVIG therapy. In this study, an initial single IVIG therapy was the regimen used to treat the children in both the S and T groups.

In this study, recurrence and relapse were defined differently. When Kawasaki disease recurred after an initial disappearance of the major symptoms and improvement in the test results, it was defined as a recurrence. If a child became afebrile during the acute phase, an exacerbation or reappearance of major symptoms without other pyrogenic disease was defined as a relapse.

2.1. Anti-inflammatory Drugs Therapy

The choice between aspirin and flurbiprofen was made by each doctor after considering the patient's liver function and the risk of Reye syndrome during the influenza pandemic. Flurbiprofen was more commonly used before 2009. Aspirin was initiated at a dose of 30 mg/kg/day and decreased to 5−10 mg/kg/day when the children became afebrile. Flurbiprofen was initiated at a dose of 3–5 mg/kg/day and decreased to 3 mg/kg/day when the children became afebrile. The regimen that was prescribed for the S group was not used until after 2004. Some children had received the S group therapy regimen between 2004 and 2008. After 2009, the S group regimen was used for all children.

2.2. IVIG Therapy

During the study period, an initial IVIG regimen of 2 g/kg/dose starting on Day 5 of the illness was used as first-line therapy when possible. The upper limit of the total IVIG/dose was restricted to 60 g/dose until 2006. This restriction was removed after 2007.

The indication for additional therapy in resistant patients was determined between 48 and 72 h after the end of the initial IVIG therapy. The diagnosis was made according to clinical parameters, including body temperature, major symptoms of Kawasaki disease, general condition, and laboratory data. Second-line therapy was additional IVIG therapy, and third-line therapy was ulinastatin infusion. Plasma exchange was adopted after 2014 as another third-line therapy option. Written informed consent was obtained from the parents or guardians of all children before the initial therapy.

Children with a response to IVIG therapy were defined as those children who became afebrile (temperature < 37.5 °C for 24 h) within 24 h after the completion of the initial IVIG infusion. IVIG-resistant children were defined as those who did not meet these criteria.

2.3. Diagnosis of CAL

CAL were diagnosed by echocardiography based on the Japan Ministry of Health and Welfare Criteria [13]. CAL was defined as an artery diameter ≧ 3 mm in a child < 5 years of age or a diameter ≧ 4 mm in a child ≧ 5 years of age. Transient CAL was defined as the disappearance of CAL within 30 days of the illness.

2.4. Statistical Analysis

Statistical analyses were performed with StatFlex Ver. 6 for Windows (Artech Co., Ltd. Osaka, Japan). Chi-square test, Fisher's exact test, and Mann–Whitney U test were used as appropriate. A value of $P < 0.05$ was considered statistically significant.

III. RESULTS

In this study, the 210 children included 109 boys and 101 girls. The median age was 2 years 0 month (range, 2 months–13 years 3 months). Aspirin and flurbiprofen were administered in 99 and 111 children, respectively. The S group included 144 children and the T group included 66 children.

The median start time of the initial IVIG therapy was Day 5 of illness (Day 3–16 of the illness). Initial IVIG therapy resistance occurred in 50 among 210 children (24%), and 19 children (9%) received additional IVIG. Four children received urinastatin and one patient received plasma exchange as a third-line therapy.

Before Day 30, the prevalence of CAL was 5% (10/210); after 30 days, it was 2% (4/210). The prevalence of CAL before and after 30 days of illness between the S and T groups was 2/144 and 8/66 ($P < 0.001$) and 1/144 and 3/66 ($P = 0.093$), respectively. The maximal internal CAL diameter was 4.8 mm (Z score = 6.3) among all children. The four children that developed CAL after 30 days of illness were evaluated using selective coronary arteriography at a median of 8 months (range, 6–16 months) after disease onset. The coronary arteriograms of all four children revealed that all CAL had regressed without leaving stenotic lesions.

Table 1 shows the clinical findings of the older children compared with the younger children. Sex, Egami score [14], and the prevalence of incomplete type were not significantly different between the two groups. The prevalence of the S group and of the anti-inflammatory drugs (aspirin or flurbiprofen) were also similar between the two groups. The median start time of the initial IVIG therapy of the older children was significantly more than that of the younger children [median 6 (range, 4–8) vs. 5 (range, 3–16) days of illness; $P = 0.038$]. The prevalence of resistant patients, need for additional IVIG, and need for third-line therapy were not significantly different between the two groups. The prevalence of CAL before and after Day 30 was similar between the two groups. No older children had CAL after Day 30.

Table 1. Clinical findings of the older children compared with those of the younger children

	older (≧ 72 m)	younger (≦ 71 m)	*P* value
	n = 18	*n* = 192	
Sex (male)	8(44%)	101(53%)	0.508
Age at onset (months)	97(72–159)a	22(2–71)a	<0.001
Egami score	2(0–4)a	1(0–5)a	0.193
		(*n* = 191)	
Incomplete type	2(11%)	19(10%)	1.000
S group	14(78%)	130(68%)	0.379
Aspirin	11	88	0.214
Flurbiprofen	7	104	0.214
IVIG therapy			
Start di	6(4–8)a	5(3–16)a	0.038
Resistant	7(39%)	43(22%)	0.116
Additional IVIG therapy	3(17%)	16(8%)	0.381
3rd line therapy	1(6%)	4(2%)	0.364
CAL before 30 di	1(6%)	9(5%)	1.000
CAL after 30 di	0(0%)	4(2%)	1.000

m: month, IVIG: intravenous immunoglobulin, di: day of illness, CAL: coronary artery lesions, a: median (minimum – maximum).

S group: patients who received initial single IVIG therapy with delayed administration of anti-inflammatory drugs (aspirin or flurbiprofen).

Incomplete type: children with fewer than 4 major symptoms.

Table 2 shows the clinical findings regarding the initial IVIG therapy of the older children. Eighteen children received median IVIG dose of 50 g/dose (range, 36–105) without any major complications including thrombosis, shock, or congestive heart failure. Only one children developed transient erythema during the IVIG infusion (Patient 9). Sixteen of 18 patients received at least 2.0 g/kg/dose of IVIG. The onset of disease in Patient 4 who received 1.6 g/kg/dose of IVIG was in 2006. The S group included 14 children (Patients 5–18) and the T group included 4 children (Patients 1–4).

Table 2. Clinical findings regarding the initial IVIG therapy for the older children

Patient No.	Sex	Age(m)	BW(kg)	Total IVIG(g)	IVIG(g/kg)	Time(h)
1	F	73	20	40	2.0	23
2	M	95	25	50	2.0	17
3	M	101	25	50	2.0	25
4	M	114	38	60	1.6	24
5	F	75	18	37.5	2.1	17
6	F	77	18	36	2.0	20
7	M	72	19	37.5	2.0	24
8	M	158	42	82.5	2.0	35
9	F	92	30	60	2.0	25
10	F	146	53	105	2.0	39
11	M	75	22	45	2.0	25
12	F	95	20	40	2.0	23
13	F	119	25	50	2.0	22
14	M	159	38	75	2.0	26
15	F	148	39	80	2.1	22
16	F	99	21	42.5	2.0	24
17	F	105	27	52.5	1.9	22
18	M	73	23	45	2.0	24

m: month, BW: body weight, IVIG: intravenous immunoglobulin, Time: time during total IVIG infusion, h: hour, F: female, M: male.

Fig 1 shows the histogram of the day of illness when the 18 older children manifested at least four major symptoms of Kawasaki disease. The median day of illness was 5 (range, 4–7), and 8 of 18 patients (44%) manifested at least four major symptoms after Day 6 of illness.

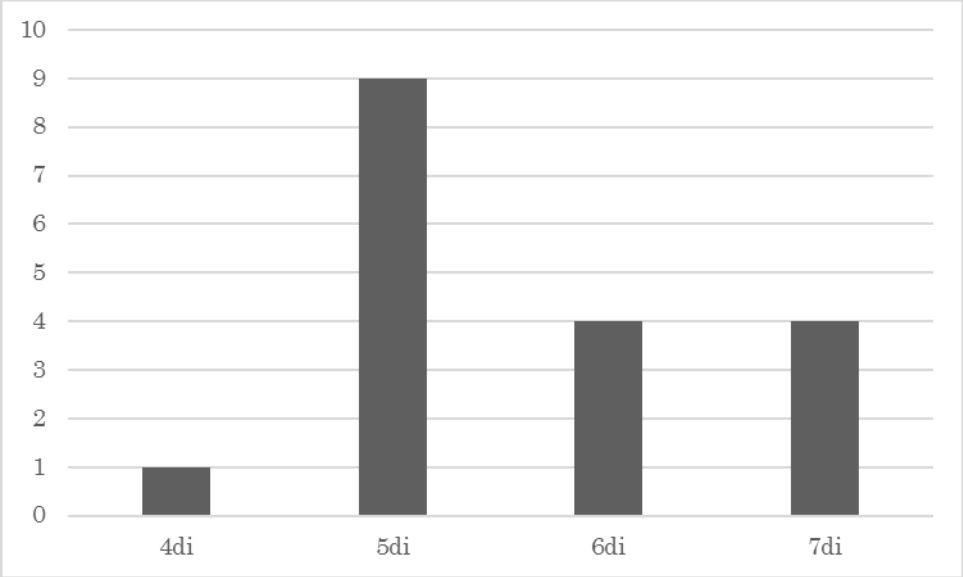

Fig 1. Histogram of the day of illness when the 18 older children manifested at least four major symptoms of Kawasaki disease

IV. DISCUSSION

This study evaluated the safety and efficacy of an IVIG infusion of 2 g/kg/dose in older children with Kawasaki disease. A previous study has shown that an older age was a risk factor for the development of cardiovascular sequelae in Kawasaki disease [2]. Therefore, the establishment of a safe and effective regimen for older children with Kawasaki disease to suppress CAL development during the acute phase is clinically important.

In this study, none of the children had any major complications, including thrombosis. This clinical finding was consistent with the results of a previous study; high-dose therapy with intact IVIG had inhibitory effects on platelet adhesion and thrombus formation [8]. A single infusion of high-dose IVIG during the acute phase of Kawasaki disease increased blood viscosity [15]. However, the prevalence of thrombosis after IVIG therapy in the acute phase of Kawasaki disease has been rare in children [16]. One factor for this finding may be due to an inhibitory effect on platelet adhesion and thrombus formation of intact IVIG [8].

Several potential mechanisms have been considered as explanations for the occurrence of strokes in Kawasaki disease, which are as follows: cardiogenic embolism (from a thrombus occurring on hypokinetic myocardia), artery occlusion (resulting from inflammation of the arterial wall), and acquired thrombophilia (related to inflammatory syndrome with major hyperthrombocytosis, disseminated intravascular coagulation, and hyperviscosity due to IVIG therapy) [16]. A literature review of cerebral infarctions associated with Kawasaki disease showed that older age was not a risk factor for this complication during the acute phase of this disease [16]. This clinical finding was also consistent with the results of this study.

Previous studies have shown that delays in the clinical manifestation of major symptoms, diagnosis at the acute phase, and start time of IVIG therapy were characteristics of the older children with Kawasaki disease [17,18]. These characteristics led to the high prevalence of CAL including giant coronary aneurysms after 30 days from the onset of this disease [3,4]. Clinical findings of older children regarding delays in clinical manifestation of major symptoms and the start time of IVIG therapy were consistent with the results of this study. However, the prevalence of CAL in the older children was similar to that in the younger children in this study, and no older children had CAL after Day 30. These findings suggested that an initial 2 g/kg/dose of IVIG therapy before Day 8 may improve the outcome of CAL in older children with Kawasaki disease. The initiation of IVIG therapy when the older patients manifested at least four major symptoms may be beneficial for the suppression of CAL caused by Kawasaki disease.

A recent study using logistic regression analysis, which included children who received IVIG therapy with and without delayed administration of anti-inflammatory drugs, showed that the significant variable for CAL development was the delayed administration of anti-inflammatory drugs and 2 g/kg/dose of IVIG therapy

and that the type of anti-inflammatory drugs was not significant [6]. These findings were consistent with a recent comparative study regarding the prevention of large CAL that assessed four studies in which four different types of anti-inflammatory drugs were administered [19]. Children who received an initial IVIG monotherapy with a delayed administration of anti-inflammatory drugs may not have a negative impact on the suppressive effects of anti-inflammatory drugs to IVIG therapy until the start of the anti-inflammatory drugs administration. However, children who received the initial IVIG therapy with concomitant use of anti-inflammatory drugs may have a negative impact from the anti-inflammatory drugs during the IVIG therapy. This suggested that the combination order of the initial IVIG therapy with the administration of anti-inflammatory drugs may lead to the suppression of CAL [19].

This study showed that the prevalence of CAL in the S group before 30 days of illness was significantly lower than that in the T group, and that regimen of the S group was safe and effective for the suppression of CAL even in older children. A previous study showed that intact IVIG therapy with delayed administration of aspirin had inhibitory effects on platelet adhesion and thrombus formation [8]. The results from the older children in this study were consistent with the findings of these previous studies [6,8,19].

V. CONCLUSIONS

An IVIG infusion of 2 g/kg/dose for older children with Kawasaki disease may be safe and effective for the suppression of CAL. An initial 2 g/kg/dose of IVIG therapy before Day 8 of the illness may improve the outcome of CAL in older children with Kawasaki disease. The initiation of IVIG therapy when the older children manifested at least four major symptoms during the acute phase of Kawasaki disease may be beneficial for suppression of CAL caused by this disease. One limitation of this study was the small number of children. The maximum IVIG/dose was 105 g/dose in this study; this is also a limitation of this study.

VI. ACKNOWLEDGMENTS

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There are no conflicts of interest to declare.

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