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Intravenous immunoglobulin therapy for infants with Kawasaki diseaseyounger than 6 months

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Abstract :Infants with Kawasaki disease younger than 6 months have a high risk for developing coronary artery lesions (CAL). This retrospective study included 231 patients who received initial IVIG therapy at 2g/kg/dose from 1999–2016. Patients were divided into a younger group aged ≦ 6 months (n = 25), and an older group aged > 6 months (n = 206). The prevalence of incomplete type (defined as patients with fewer than five major symptoms) was higher in the younger group than the older group. However, this difference was not statistically significant (16.0% vs. 10.2%, *P* = 0.491). The start time of initial IVIG therapy was significantly earlier in the younger group than the older group, with median days of illness being 5 (range 4–6) vs. 5 (range 3–16), *P* = 0.017. The prevalence of CAL was similar in the two groups both before (4.0% vs. 4.4%, *P* = 1.000) and after 30 days of illness (4.0% vs. 1.5%, *P* = 0.370). Initial IVIG therapy at 2g/kg/dose before day 6 of the illness may suppress the prevalence of CAL development caused by Kawasaki disease in younger infants to a rate similar to that in older children.

Keywords -*Kawasaki disease, infants, intravenous immunoglobulin therapy, coronary artery lesions*

I. INTRODUCTION

Kawasaki disease is an acute systemic vasculitis of unknown cause that mainly affects infants and children [1]. Coronary artery lesions (CAL) are an important complication of this disease. Risk factors for CAL development caused by Kawasaki disease include infants younger than 6 months and children older than 5 years [2, 3]. A recent study showed that initial intravenous immunoglobulin (IVIG) therapy at 2 g/kg/dose before day 8 of the illness may improve CAL outcomes in older children with this disease [4]. However, the appropriate start time for initial IVIG therapy in infants younger than 6 months remains unclear. The hypothesis of this study was that initial IVIG therapy at 2g/kg/dose in the early stage of Kawasaki disease may suppress the prevalence of CAL development in infants younger than 6 months. Accordingly, this study aimed to investigate CAL outcomes among infants with Kawasaki disease who received initial IVIG therapy in the early stage of the disease.

II. METHODS

This retrospective study included 231 patients who received 2g/kg/dose IVIG therapy from January 1999 to September 2016 at the Department of Pediatrics, Aomori Prefectural Central Hospital, Japan. Diagnosis of Kawasaki disease was based on the Japanese criteria (fifth edition) [5]. Kawasaki disease of incomplete type was defined as patients with fewer than five major symptoms of the disease [6]. IVIG-resistance was defined as fever persistence or reappearance at 24 h after first-line treatment [6]. Recurrence and relapse were defined differently in this study. Recurrence was defined as Kawasaki disease that recurred after an initial disappearance of major symptoms and improvement of test results. An interval of at least 2 months from the onset of the first Kawasaki disease illness to the onset of a new episode was also defined as recurrence [7]. If a child became afebrile during the acute phase, any exacerbation or reappearance of major symptoms without other pyrogenic disease was defined as relapse.Six patients with a recurrence of the disease were included in the sample, with the first disease episodes in those patients included in the analysis. One patient who developed left ventricular dysfunction with a different protocol including plasma exchange in the early stage was excluded.Patients were divided into two groups: a younger group aged ≦ 6 months (n = 25), and an older group aged > 6 months (n = 206). Patients were also classified into an "S group" including patients who received an initial single IVIG therapy dose with the delayed use of anti-inflammatory (aspirin or flurbiprofen) drugs (n = 165), and a "T group" including patients who received anti-inflammatory drugs concomitantly with initial IVIG therapy (n = 66). In the S group, anti-inflammatory drugs were initiated within 24 h after completion of initial IVIG therapy [8].

2.1. Anti-inflammatory Drug Therapy and Initial IVIG Therapy

The choice between aspirin and flurbiprofen was made by each doctor after considering the patient's liver function and risk of Reye syndrome during the influenza pandemic. In Japan, flurbiprofen was used in

cases of severe aspirin hepatotoxicity, and Reye syndrome is not mentioned as an adverse effect or in flurbiprofen precautions [9]. A recent study using logistic regression analysis showed that the type of anti-inflammatory drug (aspirin or flurbiprofen) was not significant for CAL suppression [8]. In this study, aspirin was initiated at a dose of 30 mg/kg/day, and decreased to 5−10 mg/kg/day when the patient became afebrile. Flurbiprofen was initiated at a dose of 3–5 mg/kg/day, and decreased to 3 mg/kg/day when the patient became afebrile. 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. For some patients from 2004–2008, a regimen of initial IVIG therapy with delayed use of anti-inflammatory drugs was used. During this period, the choice between delayed and concomitant use of anti-inflammatory drugs was made by each doctor. After 2009, initial IVIG therapy with delayed use of anti-inflammatory drugs was used for all patients [8].

2.2. Rescue Therapy

The decision to use rescue therapies in resistant patients was made 48–72 h after completion of initial IVIG therapy. This decision was made comprehensively and based on clinical parameters, including body temperature, major symptoms of Kawasaki disease, general condition, and laboratory data. Second-line therapy was rescue IVIG therapy, and third-line therapy was ulinastatin infusion. Plasma exchange was adopted after 2014 as another third-line therapy option. This regimen was approved for use in the Aomori Prefectural Central Hospital. Written informed consent was obtained from the parents or guardians of all children before initial therapy.

2.3. Diagnosis of CAL

CAL was diagnosed by echocardiography as follows [10]. CAL was diagnosed when any of these examinations showed an internal lumen diameter ≧ 3 mm in a patient < 5 years of age or a diameter ≧ 4 mm in a patient ≧ 5 years of age; if the internal diameter of a segment was at least 1.5 times as large as that of an adjacent segment; or if the lumen appeared irregular. The transient CAL was defined as a disappearance of CAL within 30 days of illness.

2.4. Statistical Analysis

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

III. RESULTS

The younger group showed fewer major symptoms than the older group (Table 1). The prevalence of incomplete type was higher in the younger group than in older group, but the difference was not statistically significant (Table 1). The prevalence of major symptoms such as persistent fever (duration ≧ 5 days), conjunctival congestion, changes of lips and oral cavity, skin rash, and changes of extremities in the younger group was 88.0%–100.0% (Table 2). Neutrophil counts, C-reactive protein values, serum sodium values, and serum albumin levels of the two groups were similar (Table 1). In the younger group, hematocrit values were significantly lower and platelet counts were significantly higher than the older group (Table 1).

Table 1. Comparison between the younger and older groups before treatment

	Younger group (n = 25)	Older group (n = 206)	*P*-value
Sex (male)	13 (52.0 %)	107 (51.9 %)	1.000
Age (months)[a]	4 (2-6)	25.5 (7-159)	< 0.001
Number of major symptoms[a]	5 (3-6)	6 (3-6)	0.002
Incomplete type	4 (16.0 %)	21 (10.2 %)	0.491
Labo data			
Sampdi[a]	5 (3-6)	5 (3-16)	0.001
Leu	12800	13000	0.7

kocyte count (/mm3)[a]		(6500-23800)	(3500-30900)	54
Neutrophil count (/mm3)[a]		6864 (3296-15232)	8468 (600-22176)	0.272
		(n = 20)	(n = 163)	
Hematocrit (%)[a]		31.8 (27.9-40.1)	33.7 (22.4-45.1)	0.016
			(n = 205)	
Platelet count (/mm3)[a]		417000 (227000-739000)	310000 (52000-3940000)	< 0.001
			(n = 205)	
CRP (mg/dL)[a]		5.46 (2.96-18.38)	7.28 (0.16-26.47)	0.315
			(n = 205)	
AST (IU/L)[a]		33.5 (18.0-264.0)	34.0 (13.0-648.0)	0.926
		(n = 24)	(n = 205)	
ALT (IU/L)[a]		28.0 (12.0-498.0)	30.0 (6.0-485.0)	0.939
		(n = 24)	(n = 205)	
Na (mEq/L)[a]		136.0 (128.0-143.0)	135.0 (127.0-141.0)	0.397
		(n = 24)	(n = 204)	
Alb (g/dL)[a]		3.4 (2.7-4.2)	3.5 (2.3-4.4)	0.964
		(n = 23)	(n = 203)	

[a] median (minimum–maximum); Labo data: Laboratory data; Samp di: Sampling day of illness;
CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Na: Serum sodium; Alb: Serum albumin.Incomplete type: patients with fewer than five major symptoms.

Table 2. Clinical symptoms of patients in the younger group before treatment
BCG: bacilleCalmett-Guérin

Symptoms	Prevalence	(%)
Persistent fever ≧ 5 days duration	22/25	88.0%
Conjunctival	24/	9

congestion	25	6.0%
Changes of lips and oral cavity	23/25	92.0%
Cervical lymphadenopathy	6/25	24.0%
Skin rash	25/25	100.0%
Erythema and/or edema of the extremities	23/25	92.0%
Erythema at BCG inoculation site	4/25	16.0%

Initial IVIG therapy was started significantly earlier (days of illness) in the younger group than in the older group, with all patients in the younger group receiving initial IVIG therapy before day 6 (Table 3). The prevalence of patients in the S group and the type of anti-inflammatory drugs (aspirin or flurbiprofen) in the two groups were similar (Table 3). The prevalence of resistance to initial IVIG therapy, rescue therapies, and CAL development were also similar for the two groups (Table 3). One patient in the younger group received ulinastatin infusion as third-line therapy. In the older group, one patient received plasma exchange and three patients received ulinastatin infusion as third-line therapy.

Table 3. Comparison between the younger and older groups after treatment

	Younger group (n = 25)	Older group (n = 206)	*P*-value
IVIG			
Start di[a]	5 (4-6)	5 (3-16)	0.017
S group	16 (64.0 %)	149 (72.3 %)	0.384
Aspirin	12	97	
Flurbiprofen	13	109	0.931
Resistance	4 (16.0 %)	50 (24.3 %)	0.356
Rescue IVIG	3 (12.0 %)	19 (9.2 %)	0.715
for resistance	2 (8.0 %)	15 (7.3 %)	1.000
for relapse	1 (4.0 %)	4 (1.9 %)	1.000
3rd line therapy	1 (4.0 %)	4 (1.9 %)	1.000
CAL before	1 (4.0 %)	9 (4.4 %)	1.000
CAL after	1 (4.0 %)	3 (1.5 %)	0.370

[a] median (minimum–maximum); IVIG: intravenous immunoglobulin therapy; Start di: Start day of illness; CAL before: coronary artery lesions before 30 days of illness; CAL after: coronary artery lesions after 30 days of illness.S group: patients who received initial single IVIG therapy with delayed use of anti-inflammatory drugs.

The prevalence of CAL before and after 30 days of illness between the S vs. T groups was 2/165 vs. 8/66 (P = 0.001) and 1/165 vs. 3/66 (P = 0.072), respectively. The infant in the younger group with CAL after 30 days of illness received the T group regimen, and his maximal internal CAL diameter was 3.5 mm. The

maximal internal CAL diameter among entire study population was 4.8 mm. This patient (a 2-year-old girl) received S group regimen. She received plasma exchange on day 9 at the Hirosaki University School of Medicine hospital as third-line therapy. Four children who 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 showed all CAL had regressed without leaving stenotic lesions.

IV. DISCUSSION

This study showed that in infants younger than 6 months who received initial IVIG therapy before day 6 of Kawasaki disease had a similar prevalence of CAL to that of children in the older group. This finding suggests that initial IVIG therapy before day 6 may be appropriate for suppression of CAL development in infants with Kawasaki diseaseyounger than 6 months. Establishing appropriate initial IVIG therapy for infants younger than 6 months is important, as these infants have a high-risk for CAL development caused by the disease. A previous study demonstrated that patients younger than 6 months had a particularly increased risk for CAL and giant CAL, and IVIG therapy before day 10 of illness was associated with substantial reduction in the frequency of CAL and giant CAL in that high-risk population [2]. Recently, another study showed that five of 26 (19.2%) infants younger than 6 months who received initial IVIG therapy after 5.8 ± 2.0 (mean ± standard deviation) days of fever duration had CAL after 6 to 8 weeks from the initial IVIG administration [11]. In this study, 25 infants younger than 6 months received initial IVIG therapy before day 6, and one of the 25 patients (4.0%) had CAL after 30 days of illness. These findings suggest that initial IVIG therapy before day 6 may be preferable for suppression of CAL caused by Kawasaki disease in infants younger than 6 months. The previous study also showed that the infants who are treated appropriately may not have a chance to higher risk of CAL [3].

Another factor relating to the favorable CAL outcomes in this study might be the initial IVIG therapy with delayed use of anti-inflammatory drugs. A recent study found that aspirin and flurbiprofen had a negative impact on the suppressive effects of initial IVIG therapy for CAL development during the acute phase of Kawasaki disease, and initial single IVIG therapy with the delayed use of anti-inflammatory drugs might be effective for CAL suppression [8]. The results of the present study showed that the prevalence of CAL in the S group was significantly lower than in T group. Based on the CAL outcomes in the younger group, removal of the negative impact of anti-inflammatory drugs during initial IVIG therapy by their delayed use may be also effective for CAL suppression in infants younger than 6 months.

The parameters for high-risk Kawasaki disease (e.g., neutrophil counts, C-reactive protein values, serum sodium values, and serum albumin levels) were similar in the younger and older groups. Therefore, delay in the diagnosis of Kawasaki disease may be an important factor for infants younger than 6 months for CAL development caused by this disease.

Incomplete presentation of Kawasaki disease is the potential risk factor for delay in diagnosis [12]. A recent Korean study with infants younger than 6 months showed that the prevalence of incomplete type was significantly higher in younger than older children [11]. In contrast to that study, the prevalence of incomplete type was similar in the younger and older groups in the present study. The prevalence of major symptoms in infants younger than 6 months in this study also was higher than in infants in the Korean study. This may be a factor related to the different prevalence of incomplete type. A recent study conducted in India with infants younger than 6 months also demonstrated a low prevalence of major symptoms of Kawasaki disease and high prevalence of incomplete type and delay in diagnosis of this disease [13]. Differences in ethnicity may influence the different clinical features in infants younger than 6 months among these studies. The prevalence of infants younger than 6 months in the entire population with Kawasaki disease also differed among studies from different countries [13]. However, the prevalence of infants younger than 6 months in the present study was similar to that in a previous Japanese study [14].

In the study period, we experienced two infants younger than 6 months who received initial IVIG therapy of 1g/kg/dose in addition to the 25 infants included in the analysis. One of those infants received initial IVIG on day 5. However, the other received IVIG on day 12 after administration of anti-platelet therapy drugs on day 11. This 5-month-old female had two major symptoms, an atypical presentation, and CAL before treatment, and was diagnosed as Kawasaki disease on day 11. Therefore, during the study period, 26 of 27 (96.3%) infants younger than 6 months received initial IVIG before day 6. Previous studies showed that some infants younger than 6 months had difficulties in early diagnosis of Kawasaki disease because of fewer major symptoms and atypical presentation [13]. Therefore, critical observation of major symptoms is important for early diagnosis among these infants. This study demonstrated the high prevalence of five major symptoms in the younger group, with the exception of cervical lymphadenopathy, based on Japanese criteria. Suspicion of Kawasaki disease in infants with these symptoms may lead to early diagnosis of Kawasaki disease.

The low value of hematocrit and thrombocytosis in infants with Kawasaki disease were described in recent Korean study [11]. As mentioned in this study, the low value of hematocrit may be due to physiologic

anemia. The recent Japanese study showed that platelet counts of infants with CAL were significantly higher than those without CAL [15]. The thrombocytosis may relate to the more severe inflammatory reaction and high level of cytokine such as interleukin 6, which leads to thrombocytosis in the acute phase of Kawasaki disease [15].

V. CONCLUSIONS

This study showed that in infants younger than 6 months who received initial IVIG therapy before day 6 of Kawasaki disease had a similar prevalence of CAL to that of children in the older group. This finding suggests that initial IVIG therapy before day 6 may be appropriate for suppression of CAL development in infants with Kawasaki diseaseyounger than 6 months. Establishing appropriate initial IVIG therapy for infants younger than 6 months is important, as these infants have a high-risk for CAL development caused by the disease.

The limitations of this study include the small number of patients in the younger group and the retrospective nature of the study.

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