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Research Article

Acute Phase Treatment for Infants Younger Than 1 Year of Age with Kawasaki Disease: A Single Center Retrospective Study

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A B S T R A C T

Background: Infants younger than 1 year of age with Kawasaki disease (KD) have a high risk for coronary artery lesions (CAL). However, the appropriate acute phase treatment for the infants has not been established.

Objective: To ascertain the usefulness of an initial single intravenous immunoglobulin (IVIG) therapy (2g/ kg) with delayed use of aspirin (DUA) for the infants.

Materials and Methods: The outcomes in 205 patients who underwent initial single IVIG therapy at 2g/ kg/ dose with DUA for KD were investigated retrospectively. These subjects were divided into those aged <1 year (infant group, n = 43) and those aged 1 year or older (non-infant group, n=162). Statistical analyses were performed using Stat Flex Version 6 for Windows. Chi-square, Fisher's exact, and Mann-Whitney U tests were used as appropriate, with sample size considerations.

Results: Numbers of major signs in infant group were significantly fewer than those in non-infant group (median 5, interquartile range [IQ]: 5-5 vs. 6, IQ: 5-6, P <0.001). The prevalence of incomplete type (20.9% vs. 11.1%, P=0.091), timing of initial IVIG therapy in regards to day of illness onset (median 5, IQ: 5-6 vs. 5, IQ: 5-6, P=0.452), the prevalence of rescue therapies (9.3% vs. 13.6%, P=0.454), and CAL (0.0% vs. 3.1%, P=0.368) were similar between the 2 groups. No infants received steroids and had the CAL ≧3mm. The prevalence of initial IVIG therapy resistant patients in infant group was significantly lower than that in non-infant group (9.3% vs. 26.5%, P = 0.017). The defervescence days of illness in infant group were significantly earlier than those in non-infant group (median 6, IQ: 6-7 vs. 7, IQ: 6-8, P <0.001).

Conclusion: The infants who are treated appropriately may not have a chance to higher risk of large CAL. An initial single IVIG therapy (2 g/kg) with DUA was useful for prevention of CAL ≧3 mm in infants with KD.

Keywords: Coronary Artery Lesions, Infants, Intravenous Immunoglobulin Therapy, Kawasaki Disease, Treatment

Introduction

Kawasaki disease (KD) is acute systemic vasculitis of unknown cause that majorly affects the infants and child populations.[1] Coronary artery lesions (CAL) are a severe complication of KD. Infants younger than 1 year of age with KD have a high risk for CAL including giant aneurysmus.[2-4] However, the appropriate acute phase treatment for the infants has not been established.

At present, the standard therapy for the acute phase of this disease is intravenous immunoglobulin (IVIG) therapy at 2 g/ kg/ dose with the concomitant use of medium-or higher-dose aspirin.[5] However, the concomitant use of medium- or higher-dose aspirin is now controversial.[6] A randomized controlled trial regarding the effectiveness of intravenous immunoglobulin alone and intravenous immunoglobulin combined with high-dose aspirin in the acute stage of KD is ongoing.[7]

Recent studies have suggested that aspirin may inhibit CAL prevention.[8,9] The delayed use of aspirin (DUA) may be beneficial for the prevention of coronary artery stenosis in KD.[8, 10-12] This study aimed to ascertain the usefulness of an initial single IVIG therapy (2 g/ kg/ dose) with DUA for the infants younger than 1 year of age with KD.

Materials and Methods

The study protocol was approved by our institutional ethics committee and the requirement of patient consent was waived.

This retrospective study included 205 consecutive patients (105 boys, 100 girls; mean age, 2 years and 10 months; range, 2 months to 13 years 3 months) who received an initial 2 g/ kg/ dose of IVIG therapy with DUA for KD from January 2004 to May 2018 at our department. The data of these patients were collected retrospectively. Those subjects were divided into those aged <1 year (infant group, n=43) and those aged 1 year or older (non-infant group, n=162).

The diagnosis of KD was established based on the criteria (Japanese, fifth edition) mentioned in the diagnostic guidelines for KD.[13] Patients with a first episode of KD were included. Four patients with CAL before therapy, and one patient with status epilepticus at the first presentation who received the combined therapy with initial IVIG and steroid were excluded. Another patient who developed left ventricular dysfunction and underwent a different protocol using plasma exchange in the early stage was excluded.

IVIG resistance was defined as fever that persisted or reappeared at 24 hours after first line treatment. The Egami score, a risk score for predicting IVIG-resistance based on clinical findings such as age, illness days, platelet count, alanine aminotransferase level, and C-reactive protein level, was evaluated before the initial IVIG therapy.[14]

Initial Therapy

During the study period, an initial single IVIG regimen of 2 g/kg/dose, starting on day 5 of the illness, was used as first-line therapy, whenever possible.

Between January 2004 and November 2017, anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 hours after the end of initial IVIG infusion. 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.[8] 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 season.

A regimen of initial IVIG therapy with delayed use of anti-inflammatory drugs was used after 2004. Some patients received this therapy with delayed use of anti-inflammatory drugs between 2004 and 2008. The choice between delayed use of anti-inflammatory drugs and concomitant use of anti-inflammatory drugs was made by the individual doctors during this period. After 2009, initial IVIG therapy with delayed use of anti-inflammatory drugs was utilized for all patients until November 2017.[8,11] After December 2017, low-dose aspirin (5 mg/kg/day) was initiated at 8th to 10th day of illness after completion of IVIG infusion including 2nd therapy.[12]

Rescue Therapy

The decision to use rescue therapies in resistant patients was made between 48 and 72 hours after the initial IVIG therapy was completed. The decision was made comprehensively according to the clinical parameters, including body temperature, major symptoms of KD, general condition, and laboratory data. Second-line therapy was rescue IVIG therapy at 2 g/ kg/ dose, and third-line therapy was ulinastatin infusion, 3rd IVIG therapy, or plasma exchange.[12]

Diagnosis of CAL

CAL was diagnosed using echocardiography based on the Japanese criteria according to Kobayashi et al.[15] CAL was diagnosed when any of the examinations showed an internal lumen diameter ≧3 mm in a patient <5 years old or a diameter ≧4 mm in a patient ≧5 years old, if the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or if the lumen appeared irregular. Transient CAL was defined as the disappearance of CAL within 30 days of the illness.

Statistical Analysis

Statistical analyses were performed using Stat Flex Version

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6 for Windows (Artech Co., Ltd., Osaka, Japan). Chi-square, Fisher's exact, and Mann-Whitney U tests were used as appropriate, with sample size considerations. A value of P <0.05 was considered statistically significant.

Results

The infant group included 16 of 43 (37.2%) patients younger than 6 months (Figure 1).

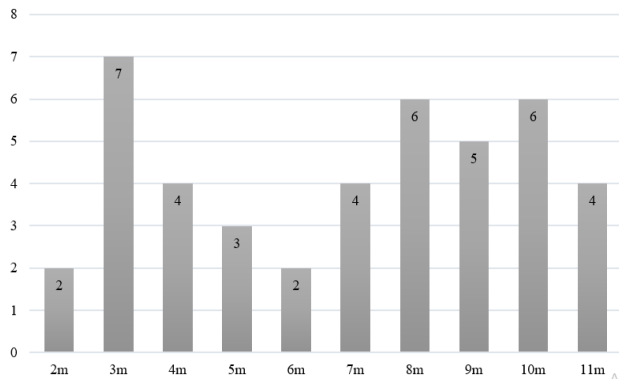

Figure 1.Histogram of the infant group patients regarding the age of onset (m: months)

Numbers of major signs in infant group were significantly fewer than those in non-infant group (Table 1). The prevalence of incomplete type and Egami scores were similar between the 2 groups (Table 1).

Regarding the laboratory findings before treatment, neutrophil % in the infant group were significantly lower than those in the non-infant group; platelet count and serum sodium in the infant group were significantly higher than those in non-infant group (Table 2).

The prevalence of low-dose aspirin/medium-dose aspirin/flurbiprofen administration, timing of initial IVIG therapy, the prevalence of rescue therapies and CAL were similar between the 2 groups (Table 3, Figure 2). The prevalence of initial IVIG therapy resistant patients in the infant group was significantly lower than that in the non-infant group (Table 3). The defervescence days of illness in the infant group were significantly earlier than those in the non-infant group (Table 3). No patient in the infant group received steroids. One patient in the non-infant group received the additional corticosteroid treatment as 4th line therapy for intractable arthritis.[16]

Table 1.Comparison of the clinical findings before therapy between the infant group and the non-infant group

Variables	Infant group (n=43)	Non-infant group (n=162)	P-value
Sex: male patients	26 (60.5%)	79 (48.8%)	0.172
Age (months)	7 (4-9)	31.5 (22-51)	<0.001
Numbers of major signs	5 (5-5)	6 (5-6)	<0.001
Incomplete type	9 (20.9%)	18 (11.1%)	0.091
Egami score	1 (1-2)	2 (1-3)	0.196

Data are presented as n (%) or as median (interquartile range).

Incomplete type, patients with fewer than five major symptoms of Kawasaki disease.

Table 2.Comparison of the laboratory findings before therapy between the infant group and the non-infant group

Variables	Infant group (n =43)	Non-infant group (n=162)	P-value
Sampling day of illness	5 (4-5)	5 (5-6)	0.020
Leukocyte count (/mm^3)	12700 (10400-15700)	12450 (10000-15600)	0.581
Neutrophil (%)	52.3 (46.5-58.2) (n=36)	70.5 (60.4-79.8) (n=141)	<0.001
Platelet count (/mm^3)	39.7 (29.6-44.4)	31.0 (25.8-35.2) (n=161)	<0.001
AST (IU/L)	30.5 (26.0-54.0) (n=42)	38.0 (27.0-70.5) (n=161)	0.218
ALT (IU/L)	27.0 (18.0-45.0) (n=42)	38.0 (15.0-123.3) (n=161)	0.260
Na (mEq/L)	136.0 (135.0-137.0) (n=42)	135.0 (133.0-137.0) (n=161)	0.017
CRP (mg/dL)	5.77 (3.61-12.37)	6.99 (4.57-11.15) (n=161)	0.572
Alb (g/dL)	3.40 (3.28-3.90) (n=41)	3.40 (3.20-3.70)	0.177

Data are presented as median (interquartile range); AST, aspartate aminotransferase; ALT, alanine aminotransferase; Na, serum sodium; CRP, C-reactive protein; Alb, serum albumin.

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Table 3.Comparison of the treatment and outcomes between the infant group and the non-infant group

Variables	Infant group (n=43)	Non-infant group (n=162)	P-value
Aspirin/ flurbiprofen			
Low-dose aspirin	3 (7.0%)	15 (9.3%)	0.920
Medium-dose aspirin	23 (53.5%)	79 (48.8%)	
Flurbiprofen	17 (39.5%)	68 (42.0%)	
Timing of initial IVIG (day of illness)	5 (5-6)	5 (5-6)	0.452
Resistant patients	4 (9.3%)	43 (26.5%)	0.017
Rescue therapy	4 (9.3%)	22 (13.6%)	0.454
For resistance	1 (2.3%)	19 (11.7%)	0.082
For relapse	3 (7.0%)	2 (1.2%)	0.063
For response	0 (0.0%)	1 (0.6%)	1.000
3rd line therapy	1 (2.3%)	3 (1.9%)	1.000
IVIG	1 (2.3%)	1 (0.6%)	0.376
Ulinastatin	0 (0.0%)	1 (0.6%)	1.000
PE	0 (0.0%)	1 (0.6%)	1.000
Defervescence			
Day of illness	6 (6-7)	7 (6-8)	<0.001
Days after IVIG	1 (0-1)	1 (1-2)	0.004
CAL			
Before 30 day of illness	0 (0.0%)	5 (3.1%)	0.368
After 30 day of illness	0 (0.0%)	2 (1.2%)	1.000

Data are presented as n (%) or as median (interquartile range); IVIG: intravenous immunoglobulin therapy, PE: plasma exchange.

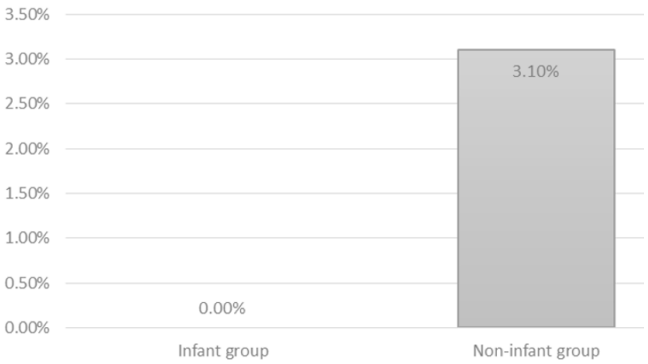

Figure 2.Comparison of the prevalence of coronary artery lesions between the infant group and the non-infant group

Discussion

This study showed that the appropriate treatment may lead the favorable outcomes in the infants with KD who have high risk for CAL. An initial single IVIG therapy (2 g/kg/dose) with DUA may be useful for CAL suppression in infants with KD.

A previous study suggested that infants aged <1 year are more likely to present with an incomplete clinical feature and that incomplete KD is associated with longer interval between symptom onset and treatment.[17] The delay in the diagnosis and timing of initial IVIG therapy is an important factor for CAL development caused by KD.[18-20] Although IVIG therapy within 10 days of illness minimize development of CAL, infants with KD younger than 6 months have a high risk of developing CAL, even if they are administered treatment within the first 10 days.[18,21,22] Previous study showed that initial IVIG therapy before day 6 of the illness may suppress the prevalence of CAL development in younger infants to a rate similar to that in older children.[23] Although the numbers of major signs in infant group were significantly fewer than those in non-infant group, timing of initial IVIG therapy were similar between the 2 groups in the present study (Table 3). This may be one of the factors which the outcome of the infant group was favorable. An appropriate timing of initial IVIG therapy may lead to favorable outcomes in infants with KD. The risk factors regarding IVIG-resistance and CAL development including Egami scores and inflammatory markers before initial therapy in the infant group were not severer than those in the non-infant group (Table 1, 2). An appropriate timing of diagnosis may be important for CAL suppression caused by KD. Recent study reported

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an identification of candidate diagnostic serum biomarkers for KD using proteomic analysis.[24] The early diagnosis of the disease may lead to the favorable outcomes of the infant with KD.

The use of IVIG therapy with DUA may be beneficial for the prevention of coronary artery stenosis in KD.[12] The delayed use of low-dose aspirin has been shown to reduce the incidence of large CAL caused in KD.[10] It has been suggested that the concomitant use of an anti-inflammatory drug may exert an inhibitory effect on the initial IVIG therapy at 2 g/kg/dose.[11] Thus, patients receiving an initial IVIG with delayed use of anti-inflammatory drugs may delay that inhibitory effect deemed adverse during the initial stages. Therefore, the combination order and timing of initial IVIG therapy with administration of anti-inflammatory drugs may be important to achieve the best outcome and inhibit the development of CAL.[12] The prevalence of CAL in the infant group was 0% and similar to that in the non-infant group (Table 3, Figure 2). This finding suggests that an initial single IVIG therapy at 2 g/kg with delayed use of anti-inflammatory drugs may be useful for suppressing CAL in the infants younger than 1 year of age.

Steroids are known to cause tissue fragility, and mainly affect small- to medium- sized arteries.[25] A study has shown that steroid therapy is an independent risk factor for significant CAL and that it should be used carefully for treating patients with high risks of CAL.[26] The infants younger than 1 year of age has high risk of CAL.[2,3] The small- to medium- sized arteries of infants may be more fragile compared to those of non-infant patients. Steroids may enhance the tissue fragility of the arteries in infants. The recent study showed that a higher incidence of medium and giant CAL was observed in infants who received steroids.[4] On the other hand, no infants in the present study received steroids and had the CAL ≧3 mm. The treatment without using steroids may be another factor of the favorable outcomes in the infants of the present study.

The major goal of acute phase KD treatment is the prevention of large and stenotic CAL that may lead to myocardial ischemia. The cut-off values for CAL, within the first 100 days after the onset of KD leading to a stenotic lesion in the late period, were a diameter ≧6.1 mm in patients with a body surface area <0.50 m.[2,27] In this study, CAL were evaluated in mm for the entire population because of the goal of preventing coronary artery stenosis in later stages. Currently, international criteria for CAL is based on z-score.[5] Japanese criteria do not account for patient size, which can substantially affect normal coronary artery dimensions, potentially leading to underdiagnosis and underestimation of the true prevalence of coronary artery dilation.[2,28] The prevalence of small CAL of the infants may be underestimated in the present study because Japanese criteria was utilized. However, no infants in the present study had the CAL ≧3mm. Therefore, the acute phase treatment in the present study may be useful for the prevention of large and stenotic CAL for the infants.

The limitations of this study included the inclusion of a small number of infant group patients and the retrospective study design.

Conclusion

The infants who are treated appropriately may not have a chance to higher risk of large CAL. An initial single IVIG therapy (2 g/kg) with DUA was useful for prevention of CAL ≧3 mm in infants with KD.

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Conflicts of Interest: None

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