Efficacy of the Delayed Use of Low-dose Aspirin in Intravenous Immunoglobulin Therapy for Acute-phase Kawasaki Disease

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ABSTRACT

The mainstay of current standard therapy for acute-phase Kawasaki disease (KD) is intravenous immunoglobulin (IVIG) therapy at 2 g/kg. However, the efficacy of combining medium- or high-dose aspirin with IVIG therapy at 2 g/kg has not been fully investigated. Some studies suggested that aspirin may inhibit coronary artery lesion (CAL) prevention in IVIG therapy and that the delayed use of aspirin in IVIG therapy may be beneficial for the suppression of CALs and prevention of coronary artery stenosis in patients with KD. The efficacy of the delayed use of low-dose aspirin in IVIG therapy for acute-phase KD remains unclear. Therefore, this retrospective study aimed to assess the efficacy of the delayed use of low-dose aspirin, when combined with IVIG therapy for acute-phase KD. Data were obtained from 193 KD patients who underwent acute-phase treatment from January 2009 to October 2020 and IVIG therapy at 2 g/kg with the delayed use of aspirin/flurbiprofen. The patients were divided into three groups: (1) low-dose group, in which 40 patients received low-dose aspirin (5 mg/kg/day); (2) medium-dose group, in which 90 patients received medium-dose aspirin (30 mg/kg/day); and (3) flurbiprofen group, in which 63 patients received flurbiprofen (3–5 mg/kg/day). KD patients with liver damage or those present during influenza season underwent flurbiprofen therapy between January 2009 and November 2017. All patients except one received low-dose aspirin after December 2017. The serum albumin level (median 3.40 vs. 3.30 g/dL, $P = 0.026$) and Egami score (median 1.0 vs. 2.0, $P < 0.001$) before the initial treatment were significantly different between the medium-dose group and the flurbiprofen group. The rates of initial IVIG therapy resistance (25.0% vs. 18.9% vs. 25.4%, $P = 0.790$), rescue therapy (17.5% vs. 8.9% vs. 17.5%, $P = 0.721$), and CALs (5.0% vs. 0.0% vs. 4.8%, $P = 0.713$) were similar among the low-dose, medium-dose, and flurbiprofen groups. Overall, the efficacy of the delayed use of low-dose aspirin was similar to that of the delayed use of medium-dose aspirin/flurbiprofen in IVIG therapy for acute-phase KD.

Keywords: aspirin, coronary artery lesions, flurbiprofen, intravenous immunoglobulin therapy, Kawasaki disease.

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I. INTRODUCTION

Kawasaki disease (KD) is a form of acute febrile systemic vasculitis that primarily affects children younger than 5 years [1]. Coronary artery lesions (CALs) are a severe complication of KD [2].

The mainstay of the current standard therapy for acute-phase KD is intravenous immunoglobulin (IVIG) therapy at 2 g/kg with the concomitant use of medium-/high-dose aspirin. Moreover, evidence has established its efficacy in CAL suppression [3]. However, the efficacy of combining medium- or high-dose aspirin with IVIG therapy at 2 g/kg has not been fully investigated [4]. A randomized controlled trial on the effectiveness of IVIG monotherapy versus IVIG therapy combined with high-dose aspirin in the acute KD stage is ongoing [5]. Some studies suggested that aspirin may inhibit CAL prevention in IVIG therapy and that the delayed use of aspirin (DUA) for IVIG therapy may be

beneficial for the suppression of CALs and prevention of coronary artery stenosis in patients with KD [6]–[9]. Furthermore, a recent study showed favorable medium-term outcomes of CALs in KD patients who underwent IVIG therapy at 2 g/kg with DUA [10].

Moreover, the optimal dose of aspirin for the acute-phase treatment of KD has not been determined yet [11], [12]. Some studies showed that the use of low-dose aspirin (3–5 mg/kg/day) may be as effective as the use of medium-/high-dose aspirin (≥ 30 mg/kg/day) in the initial treatment of KD [13], [14]. The efficacy of the delayed use of low-dose aspirin in IVIG therapy for acute-phase KD remains unclear. Therefore, this retrospective study aimed to assess the efficacy of the delayed use of low-dose aspirin when combined with IVIG therapy for acute-phase KD.

II. PARTICIPANTS AND METHODS

Our institutional ethics committee approved the study protocol and waived the requirement of patient consent because of the retrospective nature of the study.

Data were obtained from 193 KD patients who underwent acute-phase treatment from January 2009 to October 2020 and IVIG therapy at 2 g/kg with the delayed use of aspirin/flurbiprofen. The patients were divided into three groups: (1) low-dose group, in which 40 patients received low-dose aspirin (5 mg/kg/day); (2) medium-dose group, in which 90 patients received medium-dose aspirin (30 mg/kg/day); and (3) flurbiprofen group, in which 63 patients received flurbiprofen (3–5 mg/kg/day).

A total of six patients with complications including CAL before the initial therapy were excluded.

KD was diagnosed based on the criteria (Japanese, fifth edition) mentioned in the diagnostic guidelines for KD until August 2019 and on the revised criteria (Japanese, sixth edition) from September 2019 [2], [15]. IVIG resistance was defined as a fever that persisted or reappeared 24 h after the first-line treatment [3]. Presentations of KD were considered as relapses when a second episode appeared within 2 months of the first one. [16], [17]. The Egami score, a risk score for predicting IVIG resistance based on clinical findings such as age, days of illness, platelet count, alanine aminotransferase level, and C-reactive protein level, was evaluated before the initial IVIG therapy [18]. The outcomes included the rates of IVIG resistance, rescue therapy, and CALs.

A. Initial Therapy

During the study period, a single IVIG infusion at 2 g/kg/dose was given as initial therapy starting on Day 5 of the illness, whenever possible [10]. Patients without inflammation or complications upon presentation underwent acute-phase therapy without IVIG [10]. Between January 2009 and November 2017, anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 h after the initial IVIG infusion ended [6]. Aspirin and flurbiprofen were started at 30 and 3–5 mg/kg/day, respectively, and decreased to 5–10 and 3 mg/kg/day, respectively, once the patient was afebrile [6]. Each treating physician chose aspirin or flurbiprofen after considering the patient's liver function and the risk of Reye syndrome during influenza season between January 2009 and November 2017. After December 2017, low-dose aspirin (5 mg/kg/day) was begun on Days 8–10 of the illness after the completion of IVIG infusion, including the second course of therapy [10].

B. Rescue Therapy

The decision to use rescue therapies in resistant patients was made 48 to 72 h after the completion of the initial IVIG infusion. Physicians made this decision using comprehensive clinical parameters, including body temperature, major KD symptoms, general condition, and laboratory data [10]. Course 2 of therapy comprised rescue IVIG infusion at 2 g/kg/dose, and course 3 was an ulinastatin infusion, third course of IVIG therapy, or plasma exchange [10].

C. Diagnosis of CAL

CALs were diagnosed using echocardiography based on the Japanese criteria reported by Kobayashi et al [19]. CAL

was diagnosed if any examination showed an internal lumen diameter of ≥ 3 mm in a patient younger than 5 years or a diameter of ≥ 4 mm in a patient older than 5 years if the internal diameter of a segment was at least 1.5 times larger than that of an adjacent segment or if the lumen appeared irregular. A transient CAL was defined as the disappearance of a CAL within 30 days of the illness.

D. Statistical Analysis

Statistical analyses were conducted using Stat Flex Version 6 for Windows (Artech Co., Ltd., Osaka, Japan). Chi-square test, Fisher exact test, Mann–Whitney U test, and Kruskal–Wallis test were used accordingly, with sample size considerations. $P < 0.05$ was considered statistically significant.

III. RESULTS

The rate of the era of onset after 2018 between the low-dose and medium-dose groups, and that between the low-dose group and the flurbiprofen group were significantly different (Tables I and II). The Egami score of the flurbiprofen group was significantly higher than that of the low-dose and medium-dose groups (Tables II and III). Furthermore, the Egami scores of the low-dose, medium-dose, and flurbiprofen groups were significantly different among the three groups (Table IV). The serum albumin level of the flurbiprofen group was significantly lower than that of the medium-dose group (Table III). The rates of the initial IVIG therapy resistance, rescue therapy, and CALs were similar among the low-dose, medium-dose, and flurbiprofen groups (Tables I, II, III, and IV).

IV. DISCUSSION

The main finding of this study was that the rates of initial IVIG therapy resistance, rescue therapy, and CALs were similar among the low-dose, medium-dose, and flurbiprofen groups (Tables I, II, III, and IV). This finding indicated that the efficacy of the delayed use of low-dose aspirin was similar to that of the delayed use of medium-dose aspirin/flurbiprofen in IVIG therapy for acute-phase KD.

Some studies showed that the use of low-dose aspirin (3–5 mg/kg/day) may be as effective as the use of medium-/high-dose aspirin (≥ 30 mg/kg/day) for the initial treatment of KD [13], [14], [20]–[24].

Current evidence based on a meta-analysis demonstrated that treatment combined with low-dose aspirin compared with high-dose aspirin (≥ 30 mg/kg/day) for the acute-phase treatment of KD showed no significant difference in the incidence of CAL, the risk of IVIG therapy resistance, or the length of fever or hospital stay [14]. According to this meta-analysis, the risk ratio of the low-dose aspirin group regarding CAL development was less than 1.0 in five of six studies compared with that of the high-dose aspirin group [13], [14], [20]–[24]. Moreover, one study showed that the adjusted risk difference was statistically significant, favoring the low-dose aspirin group (the low-dose vs. high-dose group: -4.0% vs. -1.9% , P value = 0.024) for medium or larger CAL caused by KD [13]. This was the result when combining the concomitant use of aspirin with IVIG therapy

[13].

Two studies from Korea reported the outcomes of CAL in patients who underwent IVIG therapy at 2 g/kg with delayed use of low-dose aspirin for the acute-phase treatment of KD [8], [25]. One study showed that no patients had CALs with an internal diameter of ≥ 6 mm, which indicates a risk of stenotic lesions [8]. Another study showed that the prevalence of CALs in the patients who underwent IVIG therapy at 2 g/kg with the delayed use of low-dose aspirin was similar to the prevalence in those who underwent IVIG therapy at 2 g/kg with the concomitant use of high-dose aspirin (3.9% vs. 7.8%, $P = 0.514$) [25]. Furthermore, a study using the data of the nationwide survey of KD conducted in Korea showed that the prevalence of CALs in 509 subjects who received low-dose aspirin was significantly lower than the prevalence in 7947 subjects who received medium-/high-dose aspirin during the acute febrile phase [21]. A recent meta-analysis showed that prescribing low-dose or no aspirin in the acute-phase KD might be associated with the decreased incidence of CAL [26].

Regarding the favorable outcomes of CAL in the low-dose group, those findings are consistent with those of the present study (Tables I, II, and IV). In our previous study, the findings suggested that the concomitant use of medium-dose aspirin/flurbiprofen may inhibit CAL prevention in IVIG therapy, whereas the delayed use of those anti-inflammatory drugs in initial IVIG therapy may be beneficial for the suppression of CALs in patients with KD [6]. Moreover, recent studies demonstrated the usefulness of IVIG therapy at 2 g/kg with DUA for the prevention of coronary artery stenosis and the favorable medium-term outcomes in patients with KD [9], [10].

A recent report regarding platelet activation characteristics and the effect of antiplatelet therapy for patients with acute KD using a newly automated flow chamber system to evaluate platelet aggregate formation under shear stress condition showed that the patients developed early and unstable platelet aggregates regardless of aspirin use at different dosages and the use of an alternative drug (flurbiprofen) [27], [28]. Furthermore, the characteristics of platelet thrombus formation under a high shear condition in children with KD were not specific compared with those in febrile child controls [27]. Those findings support the effectiveness of KD treatment without aspirin or with low-dose aspirin [27].

Although high-dose aspirin is generally well-tolerated in children, reports of adverse effects, including gastrointestinal bleeding and Reye syndrome, have been documented [29], [30]. Meanwhile, low-dose aspirin has not been associated with Reye syndrome [31], is administered once daily, and may be better tolerated. Given these potential advantages, an investigation into the outcomes of children treated with low-dose aspirin is important [32]. Some studies suggested that high-dose aspirin does not reduce CALs, with a surprising possibility that aspirin might be associated with a higher incidence of CALs [6], [7], [13], [20]–[26], [33]. A recent meta-analysis recommended a low-dose aspirin plus IVIG as the first-line therapy in the initial treatment of KD [12].

Previous studies found that treatment with IVIG alone without aspirin in the acute stage of KD did not affect the

response rate of IVIG treatment [34], [35]. Furthermore, the recent meta-analysis indicated that the rates of non-responders between the low-dose and high-dose aspirin groups were not statistically different [14]. This finding was consistent with the results of the present study: the rates of non-responders were similar among the three groups (Tables I, II, III, and IV). The decision for rescue therapy was comprehensively made according to clinical parameters, including body temperature, major KD symptoms, general condition, and laboratory data, after initial therapy in the present study [10], [36]. The similar rates of non-responders and rescue therapy among the three groups in this study may also be due to this strategy.

KD relapse is a risk factor for CAL development [17], [37]. A study showed that the rates of KD relapse and CAL development were similar between the patients who were treated with low-dose aspirin and those who were treated with high-dose aspirin [32]. Those findings were consistent with those of the present study: the rates of KD relapse and CAL development were similar among the three groups (Tables I, II, III, and IV).

The use of high-dose aspirin has a risk of salicylate-induced hepatitis and Reye syndrome in acute-phase of KD [11], [29], [38]. Flurbiprofen has been used in KD patients with elevated liver enzyme levels or during an influenza epidemic in Japan, and Reye syndrome was not considered as one of the adverse effects of flurbiprofen [27], [39]. A study on platelet aggregate formation under shear stress conditions supports the treatment for acute-phase KD using flurbiprofen instead of medium-dose aspirin as antiplatelet therapy as well as low-dose aspirin [27]. In fact, the efficacy of flurbiprofen was similar to those of low-/medium-dose aspirin, and no patients had salicylate-induced hepatitis or Reye syndrome in the present study.

An increase in liver enzyme levels is a risk factor for IVIG therapy resistance and CALs [18], [19]. In the present study, KD patients with liver damage or those present during influenza season received flurbiprofen therapy between January 2009 and November 2017. Low serum albumin level indicates severe arteritis in the acute-phase of KD, and is considered a risk factor for IVIG resistance and CAL development [40], [41]. The higher Egami score and lower serum albumin levels before initial therapy in the flurbiprofen group suggested more severe KD patients in this group (Tables II, III, and IV). The lower rate of initial IVIG therapy resistance, rescue therapy, and CALs in the medium-dose group may be due to the different severity of the disease before initial therapy because patients in the medium-dose group and those in the flurbiprofen group received IVIG therapy in the same period (between January 2009 and November 2017).

The limitations of this study include the small sample size and the retrospective study design.

In conclusion, the rates of initial IVIG therapy resistance, rescue therapy, and CALs were similar among the low-dose, medium-dose, and flurbiprofen groups. Furthermore, the efficacy of the delayed use of low-dose aspirin may be similar to that of the delayed use of medium-dose aspirin/flurbiprofen in IVIG therapy at 2 g/kg for acute-phase KD.

TABLE I: COMPARISON OF CLINICAL FINDINGS, TREATMENTS, AND OUTCOMES BETWEEN THE LOW-DOSE GROUP AND THE MEDIUM-DOSE GROUP

Variables	Low-dose group (n = 40)	Medium-dose group (n = 90)	P-value
Era of onset			
After 2018	36 (90.0%)	1 (1.1%)	< 0.001
Male gender	21 (52.5%)	43 (47.8%)	0.619
Age at KD onset (months)	28.0 (15.0–44.0)	26.0 (14.0–51.0)	0.776
Incomplete type	5 (12.5%)	12 (13.3%)	0.897
Egami score	1.0 (0.5–2.0)	1.0 (1.0–2.0)	0.394
CRP (mg/dL)	5.935 (4.095– 8.960)	6.585 (3.640– 11.550)	0.661
Albumin (g/dL)	3.40 (3.10–3.60)	3.40 (3.20–3.70) (n = 88)	0.328
NLR	2.91 (1.55–4.70)	2.46 (1.38–4.58) (n = 82)	0.571
Start day of illness of initial IVIG therapy	5.0 (5.0–6.0)	5.0 (5.0–6.0)	0.882
Non-responder	10 (25.0%)	17 (18.9%)	0.428
Rescue therapy	7 (17.5%)	8 (8.9%)	0.232
For non-responder	5 (12.5%)	7 (7.8%)	0.512
For relapse	1 (2.5%)	1 (1.1%)	1.000
For responder	1 (2.5%)	0 (0.0%)	0.308
CAL			
Less than one month after KD onset	2 (5.0%)	0 (0.0%)	0.093
One month after KD onset	1 (2.5%)	0 (0.0%)	0.308

Data are presented as n (%) or median (interquartile range).
KD: Kawasaki disease, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, IVIG: intravenous immunoglobulin, CAL: coronary artery lesion.

TABLE II: COMPARISON OF CLINICAL FINDINGS, TREATMENTS, AND OUTCOMES BETWEEN THE LOW-DOSE GROUP AND THE FLURBIPROFEN GROUP

Variables	Low-dose group (n = 40)	Flurbiprofen group (n = 63)	P-value
Era of onset			
After 2018	36 (90.0%)	0 (0.0%)	< 0.001
Male gender	21 (52.5%)	34 (54.0%)	0.884
Age at KD onset (months)	28.0 (15.0–44.0)	24.0 (14.0–43.3)	0.895
Incomplete type	5 (12.5%)	10 (15.9%)	0.636
Egami score	1.0 (0.5–2.0)	2.0 (1.0–3.0)	0.002
CRP (mg/dL)	5.935 (4.095– 8.960)	6.360 (3.820– 10.280)	0.797
Albumin (g/dL)	3.40 (3.10–3.60)	3.30 (3.10–3.50)	0.385
NLR	2.91 (1.55–4.70)	3.43 (1.70–6.90) (n = 57)	0.332
Start day of illness of initial IVIG therapy	5.0 (5.0–6.0)	5.0 (5.0–6.0)	0.804
Non-responder	10 (25.0%)	16 (25.4%)	0.964
Rescue therapy	7 (17.5%)	11 (17.5%)	0.996
For non-responder	5 (12.5%)	8 (12.7%)	0.976
For relapse	1 (2.5%)	3 (4.8%)	0.656
For responder	1 (2.5%)	0 (0.0%)	0.388
CAL			
Less than one month after KD onset	2 (5.0%)	3 (4.8%)	1.000
One month after KD onset	1 (2.5%)	1 (1.6%)	1.000

Data are presented as n (%) or median (interquartile range).
KD: Kawasaki disease, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, IVIG: intravenous immunoglobulin, CAL: coronary artery lesion.

TABLE III: COMPARISON OF CLINICAL FINDINGS, TREATMENTS, AND OUTCOMES BETWEEN THE MEDIUM-DOSE GROUP AND THE FLURBIPROFEN GROUP

Variables	Medium-dose group (n = 90)	Flurbiprofen group (n = 63)	P-value
Era of onset			
After 2018	1 (1.1%)	0 (0.0%)	1.000
Male gender	43 (47.8%)	34 (54.0%)	0.451
Age at KD onset (months)	26.0 (14.0–51.0)	24.0 (14.0–43.3)	0.671
Incomplete type	12 (13.3%)	10 (15.9%)	0.660
Egami score	1.0 (1.0–2.0)	2.0 (1.0–3.0)	< 0.001
CRP (mg/dL)	6.585 (3.640– 11.550)	6.360 (3.820– 10.280)	0.947
Albumin (g/dL)	3.40 (3.20–3.70) (n = 88)	3.30 (3.10–3.50)	0.026
NLR	2.46 (1.38–4.58) (n = 82)	3.43 (1.70–6.90) (n = 57)	0.066
Start day of illness of initial IVIG therapy	5.0 (5.0–6.0)	5.0 (5.0–6.0)	0.895
Non-responder	17 (18.9%)	16 (25.4%)	0.335
Rescue therapy	8 (8.9%)	11 (17.5%)	0.114
For non-responder	7 (7.8%)	8 (12.7%)	0.314
For relapse	1 (1.1%)	3 (4.8%)	0.306
For responder	0 (0.0%)	0 (0.0%)	1.000
CAL			
Less than one month after KD onset	0 (0.0%)	3 (4.8%)	0.068
One month after KD onset	0 (0.0%)	1 (1.6%)	0.412

Data are presented as n (%) or median (interquartile range).
KD: Kawasaki disease, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, IVIG: intravenous immunoglobulin, CAL: coronary artery lesion.

TABLE IV: COMPARISON OF CLINICAL FINDINGS, TREATMENTS, AND OUTCOMES AMONG THE THREE GROUPS

Variables	Low-dose group (n = 40)	Medium- dose group (n = 90)	Flurbiprofen group (n = 63)	P- value
Egami score	1.0 (0.5–2.0)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	< 0.001
Albumin (g/dL)	3.40 (3.10–3.60)	3.40 (3.20–3.70) (n = 88)	3.30 (3.10–3.50)	0.082
Non-responder	10 (25.0%)	17 (18.9%)	16 (25.4%)	0.790
Rescue therapy	7 (17.5%)	8 (8.9%)	11 (17.5%)	0.721
For non- responder	5 (12.5%)	7 (7.8%)	8 (12.7%)	0.794
For relapse	1 (2.5%)	1 (1.1%)	3 (4.8%)	0.348
For responder	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.138
CAL				
Less than one month after KD onset	2 (5.0%)	0 (0.0%)	3 (4.8%)	0.713
One month after KD onset	1 (2.5%)	0 (0.0%)	1 (1.6%)	0.868

Data are presented as n (%) or median (interquartile range).
KD: Kawasaki disease, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, IVIG: intravenous immunoglobulin, CAL: coronary artery lesion.

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Published articles

1. Nakada T. Acute phase treatment for infants younger than 1 year of age with Kawasaki disease: a single center retrospective study. Journal of Advanced Research in Medicine 2019; 6 (1): 1–6.

2. Nakada T. Risk stratification after initial therapy for intravenous immunoglobulin-resistant Kawasaki disease. Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences 2019; 5 (5): 1–13.