Medium- or Higher-Dose Acetylsalicylic Acid for Acute Kawasaki Disease and Patient Outcomes

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Objective To investigate the effect of medium- or higher-dose acetylsalicylic acid (ASA) for treating acute-phase Kawasaki disease to prevent coronary artery aneurysm (CAA).

Study design Among the children with acute Kawasaki disease investigated in the eighth nationwide survey in the Republic of Korea, 8456 children with adequate data were included in this study. The subjects were divided into 2 groups according to the use of medium- or higher-dose ASA (≥30 mg/kg/day), or-low dose ASA (3-5 mg/kg/day) during the acute febrile phase. Both z- score–based criteria and Japanese criteria for CAA were used.

Results The prevalence of CAA based on *z*-score (24.8% vs 18.3%; $P = .001$) and on the Japanese criteria (19.0% vs 10.4%; $P < .001$) was higher in the 7947 patients who received medium- or higher-dose ASA compared with the 509 patients who received low-dose ASA. The use of medium- or higher-dose ASA was a significant predictor of CAA based on both sets of criteria by univariate analysis (based on *z*-score: OR, 1.472, 95% CI, 1.169-1.854, $P = .001$; based on Japanese criteria: OR, 2.013, 95% CI, 1.507-2.690, $P < .001$) and multivariate logistic regression analysis (OR, 1.527, 95% CI, 1.166-2.0, $P = .003$ and OR, 2.198, 95% CI, 1.563-3.092, $P < .001$, respectively).

Conclusions The use of medium- or higher-dose ASA in acute Kawasaki disease did not prevent CAA. A future randomized controlled trial is needed to determine the optimum dose of ASA. *(J Pediatr 2017;184:125-9).*

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Kawasaki disease is a common acquired cardiac disease that occurs in young children in industrialized countries. Because coronary artery aneurysm (CAA) develops in ~15%-25% of untreated cases,[1] preventing CAA is very important in the treatment of patients with Kawasaki disease during the acute febrile phase. High-dose (80-100 mg/kg) and medium-dose (30-50 mg/kg) acetylsalicylic acid (ASA; aspirin) have been recommended as standard treatment during the acute febrile phase by the American Heart Association and Japanese Society of Pediatric Cardiology and Cardiac Surgery, respectively.[1,2] The optimal dose of ASA remains controversial, however.[3-6] The administration of high- or medium-dose ASA has not been shown to have a protective effect for CAA.[7-13] Moreover, a possible negative effect of ASA on CAA suppression in the acute phase of illness has been suggested in recent studies.[13,14]

In the present study, we investigated the effect of medium- or higher-dose ASA in the treatment of acute phase Kawasaki disease for suppressing CAA.

Methods

In the eighth nationwide survey of Kawasaki disease conducted in the Republic of Korea, a questionnaire on the clinical characteristics of patients was sent to 116 hospitals by e-mail and regular mail, and the response rate was 94.8%. The survey was approved by the Institutional Review Board of Seoul National University Hospital (no. H-1412-094-634, approved December 29, 2014).

To investigate the effect of medium- or higher-dose ASA on the suppression of CAA, we sequentially excluded 1991 patients with only demographic information, 722 patients without information regarding the use of ASA, 460 patients with spontaneous alleviation of fever without first-line treatment, 96 patients in whom another anti-inflammatory drug (mainly ibuprofen) was used as a substitute for

ASA	Acetylsalicylic acid	IVIG	Intravenous immunoglobulin
CAA	Coronary artery aneurysm	TNF-α	Tumor necrosis factor α

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ASA, and 107 patients in whom an 1 g/kg infusion of intravenous immunoglobulin (IVIG) was administered as the first-line treatment. Among the remaining 11 540 patients, 8456 patients with data on the diameter of coronary arteries were enrolled in this study. The maximum diameter of coronary arteries on any echocardiographic examination performed within 3 months after the onset of Kawasaki disease was evaluated in the survey.

Among the data gathered in the nationwide survey, the demographic characteristics at the onset of disease, the presence/absence of 5 individual principal symptoms,[1] total duration of fever, laboratory test results before the initiation of first-line treatment, method of first-line treatment, whether or not second-line treatment was administered, and coronary artery diameter were the variables used in our analysis.

The subjects were divided into 2 groups based on the use of medium- or higher-dose ASA (≥30 mg/kg/day) or low-dose ASA (3-5 mg/kg/day) during the acute febrile phase. The presence of ≥4 principal symptoms was defined as complete disease presentation, and the absence of ≥2 principal symptoms was defined as incomplete presentation. The existence of second-line treatment was defined as unresponsiveness to first-line treatment.

The *z*-score of coronary artery diameter was calculated using previously reported formulas.[15] A *z*-score of ≥2.5 for any coronary artery was considered CAA, and a *z*-score of ≥10.0 or a diameter of >8 mm was considered a giant CAA, as suggested by Manlhiot et al.[16] CAA was also defined according to the criteria of the Japanese Ministry of Health and Welfare as coronary artery diameter ≥3 mm in children aged <5 years and ≥4 mm in children aged ≥5 years.[17] A giant CAA was defined as coronary artery diameter ≥8 mm.[2]

Statistical Analyses

SPSS version 21.0 (IBM, Armonk, New York) was used for data analysis. Continuous variables are reported as mean ± SD, and categorical variables are reported as frequency, expressed as a percentage. The unpaired *t* test and χ^2 test were used to compare variables between the 2 groups. Univariate logistic regression analysis was performed to identify predictors of CAA. Multivariate logistic regression analysis was performed using the predictors of CAA identified in univariate analysis. Statistical significance was defined as $P < .05$.

Results

Group 1 comprised 7947 subjects (94.0%) who received medium- or higher-dose ASA during the acute febrile phase, and group 2 comprised 509 subjects (6.0%) who received low-dose ASA. Clinical and laboratory variables of the 2 groups are compared in **Table I**. There was a trend toward a higher mean age in group 1, but the between-group difference was not significant ($P = .104$). Mean height was greater in group 1 than in group 2 ($P = .0132$). The complete presentation of illness was more common in group 2 (71.6% vs 80.4%;, $P < .001$). Group 1 had a higher mean hemoglobin level (11.5 g/dL vs 11.3 g/dL; $P = .004$) and mean serum albumin level (3.9 g/dL vs 3.8 g/dL; $P < .001$), and a lower mean total serum bilirubin level (0.65 mg/dL vs 0.75 mg/dL; $P = .013$).

Table I. Comparison of characteristics before first-line treatment with IVIG in the 2 groups

	Group 1 (n = 7947)		Group 2 (n = 509)	
Characteristics	**Number of patients**	**Value**	**Number of patients**	**Value**
Male sex, n (%)	7456	4350 (58.3)	495	284 (57.4)
Age, mo, mean ± SD	7945	32.6 ± 23.8	509	30.8 ± 23.5
Weight, kg, mean ± SD	7947	13.8 ± 5.5	509	13.4 ± 5.2
Height, cm, mean ± SD*	6303	91.8 ± 16.5	460	89.8 ± 17.1
Principal symptoms, n (%)				
Conjunctival injection	7816	6974 (89.2)	501	452 (89.3)
Changes in lips and oral cavity*	7726	6432 (83.3)	504	450 (89.3)
Changes in extremities*	7554	5406 (71.6)	501	400 (79.8)
Polymorphous exanthema*	7730	6432 (83.2)	497	448 (90.2)
Cervical lymphadenopathy*	7480	4394 (58.7)	489	322 (65.8)
Complete presentation of illness, n (%)*	7515	5363 (71.6)	491	395 (80.4)
Family history, n (%)	6133	59 (1.0)	419	4 (1.0)
Recurrent illness, n (%)	7587	412 (5.4)	470	21 (4.5)
Laboratory findings				
WBC count, /mm^3, mean ± SD	7885	13.87 ± 5.63	506	14.14 ± 4.78
Neutrophils, %, mean ± SD	7822	62.9 ± 16.8	507	63.7 ± 15.2
Hemoglobin, g/dL, mean ± SD*	7849	11.5 ± 1.0	507	11.3 ± 1.2
Platelet, ×10^3/mm^3, mean ± SD	7883	349.0 ± 115.5	507	347.2 ± 131.4
Albumin, g/dL, mean ± SD*	7794	3.9 ± 0.4	503	3.8 ± 0.5
AST, IU/L, mean ± SD	7843	86.2 ± 159.2	505	93.2 ± 158.0
ALT, IU/L, mean ± SD	7843	93.9 ± 148.6	506	106.4 ± 157.7
Total bilirubin, mg/dL, mean ± SD*	7526	0.65 ± 0.85	469	0.75 ± 0.89
Na^+, mEq/L, mean ± SD	7771	136.7 ± 2.7	505	136.7 ± 2.9
CRP, mg/dL, mean ± SD	7236	9.23 ± 8.45	505	8.99 ± 7.23
Pyuria, n (%)	7647	2844 (37.2)	491	177 (36.0)

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *CRP*, C-reactive protein; *WBC*, white blood cell.
*$P < .05$.

Table II. Comparison of outcomes after first-line treatments in the 2 groups

Outcomes	Group 1 (n = 7947)	Group 2 (n = 509)	*P* value
Unresponsive to IVIG, n (%)	838 (10.5)	86 (16.9)	<.001
Total duration of fever, d, mean ± SD	5.7 ± 2.2	6.1 ± 1.9	.001
CA diameter, mean ± SD			
Left main CA, mm	2.51 ± 0.65	2.47 ± 0.48	.134
z-score	1.26 ± 1.62	1.23 ± 1.19	.675
Left anterior descending CA, mm	2.0 ± 0.62	1.96 ± 0.53	.228
z-score	1.24 ± 1.72	1.20 ± 1.43	.660
Right CA, mm	2.14 ± 0.73	1.96 ± 0.56	<.001
z-score	0.92 ± 1.78	0.53 ± 1.37	<.001
Based on *z*-score, n (%)			
CAA	1968 (24.8)	93 (18.3)	.001
Giant aneurysm	54 (0.7)	3 (0.6)	.810
Based on Japanese criteria, n (%)			
CAA	1507 (19.0)	53 (10.4)	<.001
Giant aneurysm	17 (0.2)	0 (0.0)	.296

CA, coronary artery.

Treatments and Outcomes

The first-line treatment was the administration of 2 g/kg IVIG in all subjects. Outcome variables in the 2 groups are compared in **Table II**. The mean total duration of fever was shorter (5.7 days vs 6.1 days; $P = .001$), and the mean unresponsiveness to first-line treatment was lower (10.5% vs 16.9%; $P < .001$) in group 1 compared with group 2; however, the prevalence of CAA based on *z*-score (24.8% vs 18.3%; $P = .001$) and on the Japanese criteria (19.0% vs 10.4%; $P < .001$) was higher in group 1 (**Figure**). The prevalence of giant CAA based on either criteria did not differ between groups ($P = .810$ and $P = .296$, respectively).

Additional analyses of treatments and outcomes for the subgroup of patients with complete presentation of illness showed results similar to those in all subjects (**Table III**; available at www.jpeds.com). The rates of CAA based on *z*-score (21.9% vs 17.2%; $P = .028$) and on the Japanese criteria (16.6% vs 9.9%; $P < .001$) were higher in group 1.

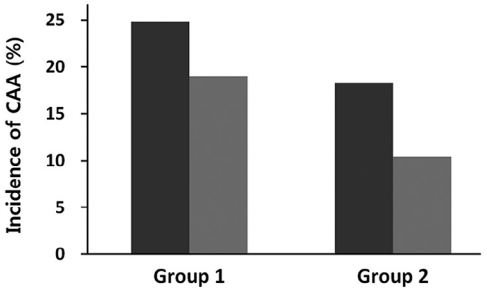

Figure. CAA incidence was significantly higher in patients who received medium- or higher-dose ASA (group 1) than in patients who received low-dose ASA (group 2) during the acute phase of Kawasaki disease, based on the z-score (24.8% vs 18.3%; $P = .001$; dark-gray column) and based on the Japanese criteria (19.0% vs 10.4%; $P < .001$; light-gray column).

Logistic Regression Analysis for Prediction of CAA

The results of logistic regression analysis for predicting CAA in all subjects are presented in **Table IV** (available at www.jpeds.com). The receipt of medium- or higher-dose ASA was predictive of CAA based on the *z*-score in univariate analysis (OR, 1.472; 95% CI, 1.169-1.854; $P = .001$) and in multivariate analysis (OR, 1.527; 95% CI. 1.166-2.0; $P = .003$). It was also predictive of CAA based on the Japanese criteria in univariate analysis (OR, 2.013; 95% CI, 1.507-2.690; $P < .001$) and in multivariate analysis (OR, 2.198; 95% CI, 1.563-3.092; $P < .001$). Among the other significant predictors for CAA, age had an inverse relationship with the 2 criteria for CAA (based on *z*-score: OR, 0.991; based on Japanese criteria: OR, 1.006).

Discussion

In this study, the prevalence of CAA was higher in patients treated with medium- or higher-dose ASA compared with those treated with low-dose ASA. In addition, the use of medium- or higher-dose ASA was a significant predictor of CAA according to logistic regression analyses. These results suggest that the use of medium- or higher-dose ASA is not protective against CAA, at the very least.

Although complications related to high-dose ASA, including anemia,[12] gastrointestinal hemorrhage,[18] and Reye syndrome,[19-21] have been reported previously, high- or medium-dose ASA has been used as standard therapy for preventing coronary artery lesions in patients with acute Kawasaki disease. The efficacy of high-dose ASA in reducing coronary involvement in Kawasaki disease was reported in 1 study.[22] That study had several apparent limitations, however; the number of subjects was small (36 with high-dose ASA and 18 without ASA), and it is possible that the diagnosis of Kawasaki disease was based on coronary involvement itself in the subjects without ASA. Other studies, including a randomized controlled trial,[8] did not identify a preventive effect of ASA on CAA.[7-13] Uncertainties regarding the method of treatment allocation in the randomized controlled trial involving 102 children were pointed out in the *Cochrane Review*.[23] Therefore, there have been no conclusive randomized controlled studies of the effect of ASA in patients with acute Kawasaki disease. Recently, a possible negative effect of ASA on initial IVIG therapy during the acute febrile phase was reported.[13] Another study found that pharmacologic doses of ASA enhanced the production of tumor necrosis factor α (TNF-α).[14] TNF-α has been reported to be elevated and associated with coronary involvement in children with acute Kawasaki disease,[24,25] and the suppression of TNF-α using a monoclonal antibody has been used as a treatment.[26]

There are some important aspects of our study to review. The number of subjects in the 2 groups was unbalanced (94.0% in group 1 vs 6.0% in group 2). Because the use of medium- or higher-dose ASA is the standard therapy for acute Kawasaki disease, this unbalance is inevitable given the uncontrolled retrospective cross-sectional design of the study. Nevertheless, the number of patients in group 2 was 509, which

is greater than the number of patients who did not receive medium- or higher-dose ASA in other, similar studies.[7-13,22] The higher proportion of patients with complete presentation of illness and of patients unresponsive to the first IVIG treatment in group 2 would be an accidental outcome resulting from the unbalanced number of subjects in the 2 groups. We also analyzed the subgroups with complete presentation of illness, but the results did not differ from those for all subjects.

A shorter duration of fever in patients receiving high-dose ASA was reported in several studies,[4,11] but not in others.[3,9,10,12] In the present study, the duration of fever was shorter in group 1; however, whether the shorter duration of fever in group 1 is the effect of medium- or higher-dose ASA is not clear. The higher proportion of patients unresponsive to IVIG is the cause of the longer duration of fever in group 2. The lower serum albumin and hemoglobin levels and higher serum total bilirubin level before treatment in group 2 are associated findings that are reportedly predictive of unresponsiveness to first-line IVIG therapy.[27-32]

The lower incidence of CAA with a higher prevalence of unresponsiveness to first-line therapy in group 2 is an interesting observation in this study, but the reason for it is unclear. Although patient age was not statistically different between the 2 groups, the shorter height in group 2 may mean that the patients in this group were relatively younger; however, the relationship of age with CAA showed an opposite direction between the 2 criteria for CAA. This opposite tendency might stem from the different methods of calculating body size in the 2 criteria.

Medium- or higher-dose ASA has an anti-inflammatory effect, but low-dose ASA does not. A possible negative impact of anti-inflammatory drugs on initial IVIG therapy was reported recently[13] and might be a reason for the lower incidence of CAA with a higher rate of unresponsiveness to first IVIG treatment in group 2.

The limitations of this study are related to the study design. The number of subjects was unbalanced, and the values of several variables before therapy differed between the 2 groups. Values of several demographic and laboratory variables were not available for some subjects. The uncertainty of the timing of CAA during the 3 months after the onset of Kawasaki disease is another significant limitation. Despite these limitations, however, the results of this study suggest that additional well-controlled randomized trials with sufficient numbers of patients are needed to investigate the role of medium- or higher-dose ASA for acute Kawasaki disease. ■

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Table III. Comparison of outcomes after first-line treatments in 2 subgroups in which all patients had complete presentation of illness

Outcomes	Subgroup 1 (n = 5363)	Subgroup 2 (n = 395)	*P* value
Unresponsive to IVIG, n (%)	607 (11.3)	65 (16.5)	.001
Total duration of fever, d, mean ± SD	5.7 ± 1.9	6.1 ± 1.8	.003
CA diameter, mean ± SD			
Left main CA, mm	2.51 ± 0.60	2.47 ± 0.46	.256
z-score	1.20 ± 1.49	1.21 ± 1.15	.943
Left anterior descending CA, mm	2.02 ± 0.63	1.96 ± 0.49	.064
z-score	1.27 ± 1.73	1.18 ± 1.32	.336
Right CA, mm	2.15 ± 0.71	1.95 ± 0.54	<.001
z-score	0.91 ± 1.70	0.49 ± 1.31	<.001
Based on *z*-score, n (%)			
CAA	1176 (21.9)	68 (17.2)	.028
Giant aneurysm	38 (0.7)	2 (0.5)	.640
Based on Japanese criteria, n (%)			
CAA	889 (16.6)	39 (9.9)	<.001
Giant aneurysm	14 (0.3)	0 (0.0)	.309

CA, coronary artery.
Subgroup 1: patients with complete presentation of illness in whom a medium or higher dose of ASA was administered during the acute phase of Kawasaki disease. Subgroup 2: patients with complete presentation of illness in whom low-dose ASA was administered.

Table IV. Predictors of CAA defined by *z*-score or by the Japanese criteria on logistic regression analyses

Variables	CAA on *z*-score						CAA on Japanese criteria					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Male sex	1.534	1.378-1.707	<.001	1.546	1.362-1.755	<.001	1.679	1.487-1.895	<.001	1.715	1.488-1.978	<.001
Age, mo	0.995	0.993-0.997	<.001	0.991	0.989-0.994	<.001	1.007	1.005-1.009	<.001	1.006	1.003-1.010	<.001
Fever duration, d	1.112	1.086-1.138	<.001	1.127	1.094-1.161	<.001	1.135	1.107-1.164	<.001	1.125	1.090-1.161	<.001
Incomplete presentation	1.567	1.404-1.749	<.001	1.537	1.345-1.755	<.001	1.666	1.478-1.877	<.001	1.715	1.482-1.985	<.001
Recurrent illness	1.587	1.291-1.950	<.001				2.050	1.659-2.533	<.001	1.511	1.155-1.976	.003
Use of high/medium-dose ASA	1.472	1.169-1.854	.001	1.527	1.166-2.0	.003	2.013	1.507-2.690	<.001	2.198	1.563-3.092	<.001
Nonresponse to first-line treatment	2.131	1.847-2.458	<.001	1.855	1.542-2.232	<.001	2.189	1.880-2.548	<.001	1.806	1.475-2.212	<.001
Hemoglobin, g/L	0.927	0.882-0.973	.002									
Platelets, $\times 10^3/mm^3$							1.0	0.999-1.0	.044			
Neutrophils, %							1.006	1.002-1.009	.001			
C-reactive protein, mg/dL	1.023	1.017-1.029	<.001	1.024	1.017-1.031	<.001	1.024	1.018-1.031	<.001	1.022	1.015-1.030	<.001
Albumin, mg/dL	0.862	0.771-0.965	.010				0.834	0.737-0.944	.004			
Total bilirubin, mg/dL	1.117	1.056-1.182	<.001				1.134	1.069-1.204	<.001	1.116	1.036-1.202	.004
Na^+, mEq/L	0.957	0.939-0.975	<.001	0.974	0.951-0.998	.032	0.962	0.943-0.982	<.001			