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

Gi Beom Kim, MD[1], Jeong Jin Yu, MD[2], Kyung Lim Yoon, MD[3], Soo In Jeong, MD[4], Young Hwan Song, MD[1], Ji Whan Han, MD[5], Young Mi Hong, MD[6], and Chan Uhng Joo, MD[7]

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).*

See editorial, p 7 and related article, p 120

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

From the [1]Department of Pediatrics, College of Medicine, Seoul National University, Seoul, Republic of Korea; [2]Department of Pediatrics, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Department of Pediatrics, College of Medicine, Kyung Hee University, Seoul, Republic of Korea; [4]Department of Pediatrics, Ajou University School of Medicine, Suwon, Republic of Korea; [5]Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [6]Department of Pediatrics, Ewha Womans University School of Medicine, Seoul, Republic of Korea; and [7]Department of Pediatrics, Chonbuk National University Medical School, Jeonju, Republic of Korea

The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.12.019

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.
*$P < .05$.