Coronary artery status of patients with transient fever 24–36 h after first IVIG infusion did not differ from that seen in responsive patients

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Abstract

Background: Current management guidelines for patients with Kawasaki disease (KD) differ in their recommendations for fever observation times when determining resistance to initial intravenous immunoglobulin (IVIG). This retrospective study assessed coronary artery status in patients with transient fever 24–36 h after the completion of a first IVIG infusion.

Methods: Children with KD treated with IVIG between January 2006 and February 2017 were included. Subjects were divided into three groups according to response following the completion of initial IVIG treatment (Group 1, no fever after 24 h; Group 2, transient fever at 24–36 h; Group 3, others).

Results: A total of 879 children were evaluated (Group 1, n = 663; Group 2, n = 54; Group 3, n = 162). During the subacute phase, the left main coronary artery (LMCA) diameter z score in both groups was significantly lower than that in Group 3 (Group 1: 1.02, Group 2: 0.87, Group 3: 1.24; Group 1 vs 2, P = 0.298; Group 1 vs 3, P = 0.025; Group 2 vs 3, P = 0.042); similar results were seen with the left anterior descending coronary artery (LAD) diameter z score (Group 1: 0.64, Group 2: 0.38, Group 3: 0.98; Group 1 vs 2, P = 0.083; Group 1 vs 3, P = 0.001; Group 2 vs 3, P = 0.004). The coronary artery (CA) status also did not differ between Groups 1 and 2 during the convalescent phase (z score of LMCA was 0.70 in Group 1 and 0.74 in Group 2, P = 0.790; z score of LAD was 0.42 and 0.46 respectively, P = 0.630). A multivariate logistic regression analysis identified total bilirubin level (OR, 2.472; 95% CI, 1.284–4.762; P = 0.007) as the only significant predictor of persisting fever over 36 h in patients with fever 24 h after the completion of initial IVIG.

Conclusions: The CA status of patients with transient fever 24–36 h after the first IVIG infusion did not differ from that seen in responsive patients.

Keywords: Kawasaki disease, Intravenous immunoglobulin, Unresponsive, Fever, Prediction

Introduction

Kawasaki disease (KD) is an acute febrile illness of unknown cause that predominantly affects children under the age of 5 years [1]. In developed countries, KD is currently the most commonly acquired heart disease in children [1]. Although timely administration of intravenous immunoglobulin (IVIG) has reduced the incidence of coronary artery aneurysm (CAA) from 25 to 4% [1], approximately 10–20% of patients with KD are resistant to initial IVIG treatment [2, 3]. Resistant patients are, therefore, reported to be at increased risk of developing CAA [4–6]. However, the definition of resistance (based on resolution of fever) differs between two major management guidelines; the Japanese Society of Pediatric Cardiology and Cardiac Surgery (JCS) suggest an observation period of 24 h after completion of initial IVIG, whereas the American Heart Association (AHA) propose an observation period of 36 h [1, 7].
The purpose of this study was to investigate coronary artery parameters in patients with transient fever 24–36 h after the administration of initial IVIG by evaluating coronary artery status. A predictor of persisting fever over 36 h was additionally investigated.

**Materials and methods**

**Subjects**

The study included consecutive children admitted to the Asan Medical Center for the treatment of acute KD between January 2006 and February 2017. Many of subjects lived in the southeastern districts of Seoul, Korea. Patients were excluded if their fever spontaneously subsided before initial IVIG was administered, if they had been transferred to the Asan Medical Center from another center (therefore lacking a detailed record of early clinical features), and if the echocardiographic data of coronary artery status were incomplete.

This study was approved by the Institutional Review Board of the Asan Medical Center (2018–0004); the requirement for informed patient consent was waived due to the retrospective study design.

**Data acquisition**

The medical records of subjects were retrospectively reviewed to obtain demographic, clinical, and laboratory data, as well as coronary artery diameter measurements. A diagnosis of KD was made in accordance with the AHA guidelines [1].

Fever was defined as an axillary body temperature ≥37.5 °C. Subjects were grouped according to the presence and timing of fever: Group 1, patients without fever 24 h after IVIG treatment; Group 2, those with transient fever 24–36 h after treatment; Group 3, the others with persistent fever over 36 h or recrudescent fever 36 h after treatment.

The plasma level of brain natriuretic peptide (BNP) was log transformed (log-BNP) for statistical analysis. A diagnosis of pyuria was made by microscopic examination of urine samples (>10 white blood cells per high power field).

All echocardiographic examination was performed by one author (JJ Yu). Coronary artery diameter was measured during the subacute (between 2 weeks and 1 month after the onset of illness) and convalescent (at 2 months after the onset of illness) phases of KD; the highest value of measurement of diameter was recorded and converted to a z score as previously reported [8]. A z score ≥2.5 for any coronary artery was determined to indicate the presence of CAA [1, 9]. In addition, we have once again defined CAA according to the criteria of the Japanese Ministry of Health and Welfare as a coronary artery diameter ≥3 mm in children <5 years old and ≥4 mm in children ≥5 years old [10].

**Statistical analysis**

All data are presented as frequency (%) or mean ± standard deviation. The Chi-square or Student’s t test was used as appropriate. Univariate logistic regression analysis for the prediction of persistent fever was performed using data from patients in Group 2 and patients in Group 3 with fever starting between 24 and 36 h after completion of the first IVIG infusion. Multivariate analysis was performed using variables identified as statistically significant in the univariate analysis. In addition, receiver operating characteristic curve (ROC) analysis was performed for any identified predictors. SPSS version 21.0 (IBM Co., Armonk, NY, USA) was used for all statistical analysis. Statistical significance was defined as a P value < 0.05.

**Results**

**Subjects**

Patient enrollment and classification is summarized in Fig. 1. A total of 1056 patients were admitted during the study period; 177 were excluded from the analysis (102 due to spontaneous resolution of fever prior to IVIG administration, 11 due to incomplete records of early clinical features, and 61 due to incomplete data on coronary artery status). Therefore, 879 patients were included in the analysis, 663 (75.4%) in Group 1, 54 (6.1%) in Group 2, and 162 (18.4%) in Group 3. In Group 3, fever persisted from 24 h to beyond 36 h in 104 patients and started from 36 h in 58. All subjects received a 2 g/kg dose of IVIG as the initial treatment during the acute phase of illness.

**Comparison of clinical and coronary characteristics between groups**

The mean age of subjects in Group 1 was 2.43 years, which was lower than that seen in Group 3 (2.85 years, P = 0.014; Table 1). Body weight and height were also lower in Group 1 than Group 3 (P = 0.009 and P = 0.016, respectively). There were no significant differences between Groups 2 and 3 in age (P = 0.839), body weight (P = 0.663), or height (P = 0.784). Male gender was more frequent in Group 3 than in Group 1 (66.0% vs 57.0%, respectively; P = 0.041).

Although the proportion of male patients appeared to be lower in Group 2 (53.7%) than Group 3 (66.0%), this difference did not reach statistical significance (P = 0.108). No statistically significant differences were seen between the three groups in terms of clinical presentation, frequency of BCG site reactions, and treatment duration.

Comparison of laboratory data obtained prior to first IVIG infusion showed the neutrophil percentage and serum C-reactive protein levels to be higher in Group 3 than in Group 1 (P < 0.001 and P < 0.001, respectively). Serum albumin levels were lower in Group 3 (Group 1 vs 3, P < 0.001; Group 2 vs 3, P = 0.010), as were sodium concentrations (Group 1 vs 3, P = 0.001; Group 2 vs 3, P = 0.041).
Serum total bilirubin levels were higher in Group 3 than in Groups 1 and 2 (Group 1 vs 3, \( P < 0.001 \); Group 2 vs 3, \( P = 0.001 \)), as were log-BNP levels (Group 1 vs 3, \( P = 0.023 \); Group 2 vs 3, \( P = 0.027 \)). Liver enzyme levels were higher in Groups 2 and 3 than Group 1 (aspartate aminotransferase: Group 1 vs 2, \( P = 0.006 \); Group 2 vs 3, \( P < 0.001 \); alanine aminotransferase: Group 1 vs 2, \( P = 0.048 \); Group 2 vs 3, \( P < 0.001 \)).

A comparison of coronary artery diameter and CAA frequency z scores is shown in Table 1 and Figs. 2 and 3. No significant differences were seen between Groups 1 and 2. During the subacute phase, the mean left main coronary artery (LMCA) diameter was larger in Group 3 than in Groups 1 and 2 (Group 3 vs 1, \( P = 0.023 \); Group 3 vs 2, \( P = 0.042 \)). Similar results were seen with the left anterior descending (LAD) coronary artery diameter (Group 3 vs 1, \( P = 0.001 \); Group 3 vs 2, \( P = 0.004 \)). The mean diameter of the right coronary artery (RCA) was larger in Group 3 than Group 1 (\( P = 0.003 \)). There were, however, no significant differences in the frequency of CAA between the three groups.

During the convalescent phase, the diameter of the RCA and the frequency of CAA based on z scores were higher in Group 3 than in Group 1 (\( P = 0.014 \) and \( P = 0.006 \), respectively).

**Logistic regression analyses for the prediction of persisting fever**

Data from Group 2 plus the Group 3 patients with fever starting at 24–36 h and persisting beyond 36 h were included in the logistic regression analysis (\( n = 158 \)). As shown in Table 2, univariate analysis identified significant predictors of persistent fever beyond 36 h after completion of IVIG therapy to be neutrophil percentage (OR, 1.027; 95% CI, 1.003–1.052; \( P = 0.025 \)), serum albumin level (OR, 0.409; 95% CI, 0.195–0.858; \( P = 0.018 \)), total bilirubin level (OR, 2.621; 95% CI, 1.537–4.469; \( P < 0.001 \)), sodium concentration (OR, 0.848; 95% CI, 0.753–0.955; \( P = 0.007 \)), C-reactive protein level (OR, 1.063; 95% CI, 1.009–1.119; \( P = 0.022 \)), and log-BNP level (OR, 2.220; 95% CI, 1.132–4.354; \( P = 0.002 \)). However, multivariate analysis identified total bilirubin level (OR, 2.472; 95% CI, 1.284–4.762; \( P = 0.007 \)) as the only significant predictor. The ROC analysis for serum bilirubin level is shown in Fig. 4. The area under the curve was 0.668 (95% CI, 0.585–0.751); the sensitivity was 41.3% and the specificity was 92.6% at the cutoff level of total bilirubin level > 1.15 mg/dL.

**Discussion**

Key guidelines differ in their recommendations for the definition of resistance to initial IVIG therapy, with the JCS recommending a 24 h observation period and the
| Characteristics                  | Group 1 | Group 2 | Group 3 | P value               |
|----------------------------------|---------|---------|---------|-----------------------|
|                                 | n = 663 | n = 54  | n = 162 | 1 vs 2 | 1 vs 3 | 2 vs 3 |
| Age, years                       | 2.43 ± 1.88 | 2.91 ± 1.91 | 2.85 ± 2.07 | 0.072 | 0.014 | 0.839 |
| Male                             | 37 (57.0) | 29 (53.7) | 107 (66.0) | 0.670 | 0.041 | 0.108 |
| Body weight, kg                  | 12.9 ± 4.9 | 14.4 ± 5.1 | 14.1 ± 5.2 | 0.032 | 0.009 | 0.663 |
| Height, cm                       | 88.8 ± 16.7 | 93.0 ± 15.4 | 92.4 ± 16.2 | 0.075 | 0.016 | 0.784 |
| Diagnostic criteria              |         |         |         |          |          |       |
| Conjunctivitis                   | 640 (96.5) | 50 (92.6) | 154 (95.1) | 0.138 | 0.361 | 0.500 |
| Red lips/oral mucosa             | 606 (91.4) | 47 (87.0) | 145 (89.5) | 0.315 | 0.445 | 0.621 |
| Rash                             | 566 (85.4) | 50 (92.6) | 147 (90.7) | 0.159 | 0.075 | 0.788 |
| Cervical lymphadenopathy         | 406 (61.2) | 38 (70.4) | 111 (68.5) | 0.194 | 0.103 | 0.866 |
| Changes in extremities           | 563 (84.9) | 47 (87.0) | 144 (88.9) | 0.843 | 0.213 | 0.806 |
| Complete presentation            | 565 (85.2) | 48 (88.9) | 144 (88.9) | 0.551 | 0.258 | 1.000 |
| BCG site reaction                | 313 (47.2) | 21 (38.9) | 66 (40.7)  | 0.259 | 0.159 | 0.873 |
| Treatment duration, days         | 6.0 ± 1.2 | 5.8 ± 1.3 | 5.9 ± 1.2 | 0.174 | 0.441 | 0.424 |
| Laboratory findings              |         |         |         |          |          |       |
| WBC, x10^3/μL                    | 14.6 ± 4.9 | 14.4 ± 4.8 | 14.3 ± 5.4 | 0.855 | 0.600 | 0.901 |
| Neutrophil, %                    | 63.3 ± 13.9 | 66.6 ± 15.2 | 70.9 ± 14.0 | 0.094 | < 0.001 | 0.061 |
| Hemoglobin, g/dL                 | 11.3 ± 1.1 | 11.2 ± 1.0 | 11.2 ± 1.1 | 0.828 | 0.631 | 0.940 |
| Platelet, x10^9/μL               | 338.0 ± 99.9 | 316.6 ± 89.4 | 322.8 ± 107.1 | 0.112 | 0.088 | 0.702 |
| Protein, g/dL                    | 6.6 ± 0.7 | 6.7 ± 0.5 | 6.6 ± 0.8 | 0.835 | 0.795 | 0.732 |
| Albumin, g/dL                    | 3.4 ± 0.5 | 3.4 ± 0.3 | 3.2 ± 0.5 | 0.636 | < 0.001 | 0.010 |
| AST, IU/L                        | 81.5 ± 140.6 | 140.6 ± 249.3 | 144.9 ± 284.7 | 0.006 | < 0.001 | 0.922 |
| ALT, IU/L                        | 93.5 ± 139.0 | 134.3 ± 209.1 | 150.59 ± 200.6 | 0.048 | < 0.001 | 0.611 |
| Total bilirubin, mg/dL           | 0.72 ± 0.74 | 0.65 ± 0.50 | 1.21 ± 1.23 | 0.496 | < 0.001 | 0.001 |
| Na+, mmol/L                      | 136.1 ± 2.6 | 136.3 ± 2.6 | 135.3 ± 3.2 | 0.575 | 0.001 | 0.041 |
| C-reactive protein, mg/dL        | 8.63 ± 6.18 | 8.74 ± 7.16 | 10.91 ± 7.10 | 0.898 | < 0.001 | 0.054 |
| BNP, pg/mL                       | 108.0 ± 221.2 | 107.8 ± 286.3 | 143.9 ± 223.3 | 0.264 | 0.023 | 0.027 |
| Log-BNP                          | 1.65 ± 0.56 | 1.55 ± 0.59 | 1.77 ± 0.58 | 0.875 | 0.150 | 0.615 |
| Pyuria                           | 189 (28.5) | 16 (29.6) | 57 (35.2)  | 0.796 | 0.076 | 0.440 |

**Coronary artery diameter during subacute phase**

| LMCA, mm                         | 2.33 ± 0.44 | 2.36 ± 0.40 | 2.48 ± 0.52 | 0.298 | 0.025 | 0.042 |
| Z score                          | 1.02 ± 1.08  | 0.87 ± 1.02  | 1.24 ± 1.22  | 0.428 | 0.076 | 0.312 |
| LAD, mm                          | 1.85 ± 0.40  | 1.83 ± 0.31  | 2.05 ± 0.67  | 0.123 | 0.035 | 0.107 |
| Z score                          | 0.64 ± 1.07  | 0.38 ± 0.90  | 0.98 ± 1.40  | 0.487 | 0.090 | 0.051 |
| RCA, mm                          | 1.83 ± 0.48  | 1.92 ± 0.34  | 2.03 ± 0.68  | 0.875 | 0.150 | 0.615 |
| Z score                          | 0.37 ± 1.29  | 0.44 ± 0.85  | 0.73 ± 1.59  | 0.105 | 0.027 | 0.030 |
| CAA on z score (subacute)        | 81 (12.2)    | 5 (9.3)      | 27 (16.7)    | 0.665 | 0.152 | 0.268 |
| CAA on Japanese criteria (subacute) | 37 (5.6) | 1 (1.9)     | 11 (6.8)     | 0.350 | 0.574 | 0.302 |

**Coronary artery diameter during conv. Phase**

| LMCA, mm                         | 2.24 ± 0.40 | 2.33 ± 0.38 | 2.35 ± 0.40 | 0.790 | 0.139 | 0.552 |
| Z score                          | 0.70 ± 1.10  | 0.74 ± 1.10  | 0.84 ± 1.07  | 0.790 | 0.139 | 0.552 |
| LAD, mm                          | 1.79 ± 0.33  | 1.86 ± 0.24  | 1.92 ± 0.53  | 0.790 | 0.139 | 0.552 |
| Z score                          | 0.42 ± 1.02  | 0.46 ± 0.67  | 0.59 ± 1.14  | 0.790 | 0.139 | 0.552 |
| RCA, mm                          | 1.76 ± 0.36  | 1.80 ± 0.32  | 1.92 ± 0.65  | 0.790 | 0.139 | 0.552 |
Table 1 Patient characteristics (Continued)

| Characteristics                        | Group 1 (n = 663) | Group 2 (n = 54) | Group 3 (n = 162) | P value 1 vs 2 | P value 1 vs 3 | P value 2 vs 3 |
|----------------------------------------|-------------------|------------------|-------------------|---------------|---------------|---------------|
| Z score                                | 0.07 ± 1.07       | 0.00 ± 0.89      | 0.32 ± 1.50       | 0.630         | 0.014         | 0.135         |
| CAA on z score (conv.)                 | 38 (5.7)          | 5 (9.3)          | 20 (12.3)         | 0.363         | 0.006         | 0.681         |
| CAA on Japanese criteria (conv.)       | 16 (2.4)          | 1 (1.9)          | 7 (4.3)           | 1.000         | 0.187         | 0.683         |

Data are reported as mean ± standard deviation, or number (%)

WBC white blood cell, ESR erythrocyte sedimentation rate, AST aspartate aminotransferase, ALT alanine aminotransferase, BNP brain natriuretic peptide, LMCA left main coronary artery, LAD left anterior descending, RCA right coronary artery, CAA coronary artery aneurysm, conv convalescent

Fig. 2 Z score of coronary arteries in the three groups during the subacute (a–c) and convalescent phases (d–f). LMCA, left main coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery. *P value < 0.05
AHA suggesting a 36 h observation period from the end of treatment [1, 7]. In this study, patients with transient fever 24–36 h after the completion of first IVIG (Group 2) were compared with the other patient groups in terms of clinical characteristics and coronary artery status. The characteristics of subjects in Group 2 appeared to be more similar to those of subjects in Group 1 than Group 3, despite differences in body weight and liver transaminases between the two groups. Regarding other laboratory variables that reflect the degree of inflammation during the acute phase (white blood cell count, neutrophil percentage, C-reactive protein level, and hemoglobin level) [11], the values in Group 2 did not differ from those in Group 1. Subjects in Groups 1 and 2 showed higher levels of serum albumin and sodium and lower levels of total bilirubin and log-BNP than subjects in Group 3.

Univariate analysis showed that the neutrophil percentage, serum albumin level, total bilirubin level, sodium level, C-reactive protein level, and log-BNP were significant predictors of fever persisting beyond 36 h after completion of the first IVIG infusion. This is consistent with the results of previous studies of predictors of IVIG resistance [12–15]. However, multivariate analysis identified only a single predictor - total bilirubin level which has been reported to be a predictor of resistance to initial IVIG treatment [14, 16]. In this study, it was the only one predictor of persisting fever beyond 36 h in subjects with fever 24 h after initial treatment. However, its use in clinical practice will be limited due to the low sensitivity (41.3%). Analysis of coronary artery status showed no differences between Groups 1 and 2. During the subacute phase, the z scores of the diameter of LMCA and LAD in both Group 1 and Group 2 were significantly lower than those in Group 3. The coronary artery (CA) status also did not differ between Groups 1 and 2 during the convalescent phase. Based on these results, a 36 h period of observation after IVIG can be considered to be reasonable. With the JCS guidelines, the patients in group 2 would have received an unnecessary additional IVIG treatment. IVIG is a biological product made from pooled donor plasma, and several adverse effects including hemolytic anemia were reported [1, 17]. Therefore, efforts should be made to avoid unnecessary IVIG administration.

In the group 2, the frequency of CAA looks not to be reduced in the convalescent phase. We cannot clearly explain this result but assume that it may be a coincident result by the relatively small number of subjects in group 2.

**Table 2** Logistic regression analysis for the prediction of persistent fever in 158 patients with fever starting 24–36 h after the completion of initial IVIG therapy

| Characteristics       | Group 2 n = 54 | Group 3 n = 104 | Univariate P value | OR (95% CI) | Multivariate P value | OR (95% CI) |
|-----------------------|----------------|-----------------|-------------------|-------------|----------------------|-------------|
| Neutrophil, %         | 66.6 ± 15.2    | 72.1 ± 13.4     | 0.025             | 1.027       | 1.003–1.052          | 0.951       |
| Albumin, g/dL         | 3.4 ± 0.3      | 3.2 ± 0.5       | 0.018             | 0.409       | 0.195–0.858          | 0.109       |
| Total bilirubin, mg/dL| 0.65 ± 0.50    | 1.43 ± 1.33     | < 0.001           | 2.621       | 1.337–4.469          | 0.007       |
| Na⁺, mmol/L           | 136.3 ± 2.6    | 134.9 ± 3.1     | 0.007             | 0.848       | 0.753–0.955          | 0.803       |
| C-reactive protein, mg/dL | 8.74 ± 7.16 | 11.66 ± 7.40   | 0.022             | 1.063       | 1.009–1.119          | 0.884       |
| Log-BNP               | 1.55 ± 0.59    | 1.81 ± 0.59     | 0.020             | 2.220       | 1.132–4.354          | 0.493       |

Data are reported as mean ± standard deviation or number (%)

OR Odds ratio, CI confidence interval, BNP brain natriuretic peptide
This study has several limitations. The first one is the retrospective nature of this study. The outcome of patients cannot be compared between different observation times because we consistently observed patients for 36 h during the study period. A prospective study involving randomly selected patients managed according to two different guidelines (24 vs 36 h) is recommended to determine the appropriate observation time after the first IVIG treatment. Alternatively, a study involving multiple institutes using different guidelines could be conducted. Second, the number of patients with transient fever 24–36 h after completion of the first IVIG treatment was small and the follow-up period continued only until the convalescent phase. Third, the possible benefit of an earlier second treatment after 24 h of observation, rather than after 36 h, could not be investigated in this study. One hundred four (65.8%) of the 158 patients had fever persisting beyond 36 h after IVIG had fever persisting beyond 36 h. Finally, all subjects in this study were Korean, so the results need to be reproduced in other races.

Conclusion
The outcome of patients with transient fever between 24 and 36 h after the completion of first IVIG treatment did not differ from that of responsive patients. A future prospective or multicenter study to determine the appropriate observation time after initial IVIG therapy is recommended based on the outcome of this study.
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