Cardiac Complications, Earlier Treatment, and Initial Disease Severity in Kawasaki Disease

Joseph Y. Abrams, PhD[1], Ermias D. Belay, MD[1], Ritei Uehara, MD, PhD[2], Ryan A. Maddox, PhD[1], Lawrence B. Schonberger, MD[1], and Yosikazu Nakamura, MD[3]

Objectives To assess if observed higher observed risks of cardiac complications for patients with Kawasaki disease (KD) treated earlier may reflect bias due to confounding from initial disease severity, as opposed to any negative effect of earlier treatment.

Study design We used data from Japanese nationwide KD surveys from 1997 to 2004. Receipt of additional intravenous immunoglobulin (IVIG) (data available all years) or any additional treatment (available for 2003-2004) were assessed as proxies for initial disease severity. We determined associations between earlier or later IVIG treatment (defined as receipt of IVIG on days 1-4 vs days 5-10 of illness) and cardiac complications by stratifying by receipt of additional treatment or by using logistic modeling to control for the effect of receiving additional treatment.

Results A total of 48 310 patients with KD were included in the analysis. In unadjusted analysis, earlier IVIG treatment was associated with a higher risk for 4 categories of cardiac complications, including all major cardiac complications (risk ratio, 1.10; 95% CI, 1.06-1.15). Stratifying by receipt of additional treatment removed this association, and earlier IVIG treatment became protective against all major cardiac complications when controlling for any additional treatment in logistic regressions (OR, 0.90; 95% CI, 0.80-1.00).

Conclusions Observed higher risks of cardiac complications among patients with KD receiving IVIG treatment on days 1-4 of the illness are most likely due to underlying higher initial disease severity, and patients with KD should continue to be treated with IVIG as early as possible. *(J Pediatr 2017;188:64-9).*

Kawasaki disease (KD) can lead to several cardiac and noncardiac complications. In the US, risk factors for the development of coronary artery aneurysm and dilatation include male sex, Asian and Pacific Islander race, Hispanic ethnicity, recurrent KD, and age <1 year or >9 years.[1] The development of coronary artery abnormalities (CAAs) can occur in >20% of untreated patients.[2] Treatment within 10 days of illness onset with intravenous immunoglobulin (IVIG) and aspirin has proven effective in dramatically reducing the risk of cardiac complications; however, approximately 20% of patients with KD might not adequately respond to this treatment and may require a second dose of IVIG or alternative medications, such as steroids.[3]

Some studies have indicated an association between IVIG administration within 1-4 days of KD onset a higher risk of CAAs and nonresponse to initial IVIG treatment.[4-7] These data might lead some clinicians to withhold treatment until 5 or more days after illness onset. Although the underlying cause for the association between treatment within 1-4 days of KD onset and increased risk of CAA is unknown, several hypotheses have been suggested to explain this paradoxical finding. One of these includes the possibility that a disproportionate number of patients with KD receiving treatment within 5 days of illness onset may exhibit more severe clinical symptoms contributing to their early recognition and treatment.[8,9] This underlying severe KD may additionally be responsible for the higher risk of cardiac complications, so that disease severity could serve as a confounder of the association between time to IVIG treatment and CAA.

In the present study, we explored this hypothesis by evaluating risk factors associated with CAA or other cardiac complications among Japanese patients with KD treated within 10 days of illness onset. Specifically, we controlled for a potential proxy for initial disease severity to better estimate the true association between time to treatment and risk of cardiac complications.

Methods

The 15th, 16th, 17th, and 18th nationwide surveys on KD in Japan were accessed to obtain information about patients who visited hospitals between January 1, 1997, and December 31, 2004.[10-12] In those surveys, questionnaires and diagnostic

CAA	Coronary artery abnormality
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
RR	Risk ratio

From the [1]Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA; [2]Department of Health Science, Saitama Prefectural University, Koshigaya, Saitama, Japan; and [3]Department of Public Health, Jichi Medical University, Shimotsuke, Tochigi, Japan

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guidelines were sent to all Japanese general hospitals with a pediatric department and 100 or more beds (surveys 15-18) as well as smaller hospitals specializing in pediatrics (surveys 16-18). Physicians were requested to report all patients who had signs and symptoms consistent with a diagnosis of KD. Patients identified in the survey were categorized as having complete, incomplete, or suspected KD. Complete KD cases were defined based on the Japanese KD Committee's case definition, which mandates that patients have at least 5 of the following 6 signs: (1) fever lasting 5 days or more (or defervescence before the fifth day in response to treatment), (2) bilateral conjunctival injection, (3) oral mucosal changes (eg, reddening of lips, strawberry tongue), (4) polymorphous exanthema, (5) peripheral extremity changes (eg, reddening of palms and soles, edema, desquamation), and (6) cervical lymphadenopathy. Incomplete KD was defined as 4 of the above 6 signs in addition to CAAs. Suspected cases did not meet those strict guidelines, but were considered by the attending physician to be indicative of KD. Only complete and incomplete KD cases were included in the present analysis. Patients aged ≥18 years and patients who did not receive IVIG treatment on days 1-10 of illness were excluded from the analysis.

The surveys did not include information that directly described initial disease severity; however, previous studies have suggested that nonresponse to initial IVIG treatment is more common among patients with severe KD.[13-15] All 4 surveys included information on initially prescribed regimens of IVIG, as well as on any additional IVIG treatment administered subsequent to the initial regimen. Information on the use of other treatments (eg, steroids, ulinastatin, plasma exchange) was available only for survey 18 (January 1, 2003-December 31, 2004). We decided to assess the utility of information about administration of additional IVIG (all surveys) or administration of any additional treatment (survey 18) as a proxy for disease severity.

Surveys were sponsored by the Japanese Ministry of Health, Labour, and Welfare and approved by the Ethical Board of Jichi Medical University, Tochigi, Japan.

Part 1: Assessing Association of Additional Treatments with Cardiac Complications

The **Figure** depicts the proposed relationships among earlier IVIG treatment, initial disease severity, additional treatment, and cardiac complications. If this model is correct, then additional treatment (as a proxy for initial disease severity) should be associated with both earlier IVIG treatment and cardiac complications, and the control of additional treatment should result in a less-biased estimate of the causal effect of earlier IVIG treatment on the risk of cardiac complications.

First, we determined the association between use of additional treatments and cardiac complications. We used 4 progressively inclusive categories of cardiac complications which included the following survey variables: (1) giant aneurysms (aneurysms >8 mm in diameter); (2) all aneurysms (giant and non-giant aneurysms); (3) CAAs (all aneurysms, coronary artery ectasia, stenosis); and (4) major cardiac complications (CAAs, valvular lesions, myocardial infarction).

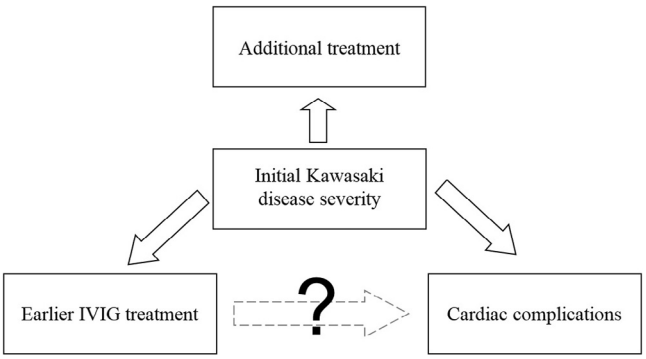

Figure. Diagram showing the hypothesized relationships between factors of interest for treating KD. High initial disease severity may increase the risk of earlier IVIG treatment, and also may increase the risk for CAAs, acting as a confounding variable. Disease severity also can lead to nonresponse to initial IVIG treatment and the subsequent need for additional treatment. If the receipt of additional treatment is considered a proxy for disease severity, then controlling for additional treatment may provide a more accurate estimate of the true causal association between earlier IVIG administration and CAAs.

For the years 1997-2004, we assessed the association between receipt of an additional dose of IVIG with the occurrence of each category of cardiac complications. In addition, for the years 2003-2004, we assessed the association between receipt of any additional treatment (additional IVIG, steroids, ulinastatin, or plasma exchange) with the occurrence of each category of cardiac complications.

Next, we determined the association of additional treatments with earlier initial IVIG treatment. Earlier IVIG treatment was defined as administration on days 1-4 of the illness, compared with days 5-10. We compared the relative odds of earlier IVIG treatment for patients receiving additional IVIG (1997-2004) or any additional treatment (2003-2004).

Part 2: Testing the Effect of Earlier Treatment While Stratifying by Additional Treatment

We first calculated the unadjusted relative risk of developing cardiac complications for patients receiving IVIG on days 1-4 of the illness. We then attempted to control for initial disease severity by stratifying by receipt/nonreceipt of additional treatment. Those recorded as receiving additional treatment were patients from 1997-2002 who received additional IVIG, and patients from 2003-2004 who received any additional treatment (additional IVIG, steroids, ulinastatin or plasma exchange). We then calculated Mantel-Haenszel stratified risk ratios (RRs) for the effect of earlier IVIG treatment on cardiac complications.

To ensure that we more fully controlled for potential confounding by initial severity, we also conducted an analysis limited to 2003-2004. We stratified all patients by the receipt of any additional treatment, then calculated the Mantel-Haenszel RRs for earlier IVIG treatment.