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ORIGINAL ARTICLE

Timing of Intravenous Immunoglobulin Treatment and Risk of Coronary Artery Abnormalities in Children with Kawasaki Disease

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Kawasaki disease (KD) is a type of febrile self-limiting systemic vasculitis, which affects the coronary arteries (CA) and may cause cardiac ischemia during childhood and adult life. Intravenous immunoglobulin (IVIG) has become the standard therapy for KD. However, it is still uncertain if CA outcome is associated with the timing of IVIG administration with reference to fever onset. The present study was designed to identify the risk for development and delay in resolution of CA abnormalities in association with IVIG administration within or after 10 days of KD onset. A retrospective analysis of clinical signs, laboratory data, and prospectively collected echocardiography (ECHO) results of 106 children hospitalized with KD was utilized. IVIG was administered to 86 (81.1%) patients within 10 days, and 20 (18.9%) patients received the first dose of IVIG after 10 days of illness. Among 23 (21.6%) patients who were diagnosed with CA lesions, 18 had a CA abnormality at initial ECHO, whereas they appeared after IVIG therapy in five patients. The risk for CA lesions on initial ECHO was higher among the patients who were admitted after 10 days of disease onset [odds ratio (OR) = 5.3, 95% confidence interval (CI) = 1.7–15.9] but comparable with the post-IVIG treatment group (OR = 3.1, 95% CI = 0.48–19.8). The age <1 year and erythrocyte sedimentation rate (ESR) > 40 mm/hour were associated with non-resolution of CA lesions within 9 weeks of KD onset. Overall, 95.6% of children had resolution of CA abnormalities within 6 months of onset of KD symptoms. The results of this study suggest that although IVIG treatment within 10 days is important to minimize development of cardiac pathology, neither occurrence of CA lesions in IVIG-

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treated children nor the time frame for resolution of established CA abnormalities was associated with the timing of IVIG administration. Age <1 year and high ESR (>40 mm/hour) predict a delay in resolution of CA lesions among children with KD.

1. Introduction

Kawasaki disease (KD) is an acute, febrile, self-limiting vasculitis of unknown etiology which leads to the formation of ectasia, dilatation, or aneurysm of the coronary arteries (CA) in approximately 25% of untreated children.[1–4] This disease has become the leading cause of acquired heart disease among children in the United States and other developed countries.[1] Consequential myocardial ischemia and/or infarction have been recorded not only shortly after KD, but also during later adult life in affected children.[5–7] The consensus statement of the American Heart Association (AHA), along with other organizations including the American Academy of Pediatrics, identified post-KD children as being at risk for atherosclerotic coronary arterial diseases depending on the status of the CA lesions.[8] Treatment with a high dose of intravenous immunoglobulin (IVIG) within 10 days from the onset of illness substantially reduced the risk for development of CA pathology as compared with untreated patients.[2–4,9] Administration of IVIG after the 10th day of illness due to delayed diagnosis in 25% of the KD cases increased the risk for the development of CA lesions.[10–12] The United States Multicenter Kawasaki Disease Study Group concluded that all patients who are diagnosed with KD should be treated with IVIG, because the scoring of clinical and laboratory data is imperfect in the prediction of CA lesions in children with KD.[13] The AHA recommends administration of IVIG to KD patients within 10 days and also after Day 10 of the illness, if the patients show unexplained persistent fever or develop CA lesions, although the potential effect of delayed IVIG treatment remains uncertain.[14] Therefore, the effect of delayed IVIG treatment (>10 days) on CA pathology is still a subject for discussion. Muta et al[15] reported no difference in the probability of occurrence of CA abnormalities after IVIG treatment for children receiving IVIG within 8 days or after 10 days of the onset of fever. No study has investigated the risk for the development of CA lesions in association with the timing of IVIG administration within and after Day 10 of disease onset. Moreover, no study has analyzed the association between appropriate or delayed IVIG treatment and resolution of established CA lesions. In one brief report, IVIG treatment of KD patients was associated with a decreased risk for incomplete resolution of CA lesions as compared with patients receiving only aspirin.[16]

The present study was designed to delineate the risk for the occurrence and resolution of CA pathology in association with the timing of IVIG treatment (≤10 days and >10 days of KD onset) independently from age and level of acute phase of inflammation. The results of this study will advance our understanding of the role of the timing of IVIG treatment, patient age, clinical signs, and laboratory inflammatory markers in the occurrence and resolution of CA lesions in children with KD.

2. Methods

The present study was approved by the Jersey Shore University Medical Center (JSUMC) Institutional Review Board. A cohort of children (0–18 years of age) with KD who were hospitalized at the JSUMC from January 1999 to December 2011 and followed in a single Pediatric Cardiology Clinic was identified as participants for this study. Their demographic, clinical, and laboratory data during the hospitalization were extracted from the medical records. The KD was classified in accordance with the existing guidelines.[14,17] Diagnosis of KD was established if the child had fever for at least 5 days along with: (1) four major symptoms, or (2) less than four major symptoms with CA abnormality based on echocardiography (ECHO) testing at the time of hospitalization. The identified laboratory data on admission were categorized as abnormal if the erythrocyte sedimentation rate (ESR) was >40 mm/hour, C-reactive protein (CRP) level was >3 mg/dL, platelet count was ≥500,000/mL, and white blood cell count (WBC) was >15,000/mL.[17,18] The results of the initial and consecutive echocardiograms at 3–4 weeks, 4–6 weeks, 6–9 weeks, and 6–12 months from onset of KD were collected from the medical records in the hospital and the Pediatric Cardiology Clinic. An ECHO was performed: (1) for all children at the time of hospitalization and at 3–4 weeks; (2) for 94.4% of patients at 4–6 weeks; (3) for 45.3% of patients at 6–9 weeks; and (4) for all children with established CA lesions at 9–12 months of KD onset. All initial echocardiograms were obtained by the Acuson Sequoia C512 (manufactured by Siemens Medical Solutions, Mountain View, CA 19043 USA) using the 10V4 probe. Follow-up echocardiograms were performed using the S8 probe of the HP Sonos 5500 machine (manufactured by HP, Philips, Bothel, WA 98041 USA). CA lesions including dilation, ectasia, or aneurysms were classified as CA pathology in accordance with the AHA guidelines.[14] We collected evidence of non-therapeutic responses characterized by persistence or recrudescence of fever lasting >36 hours after completion of the IVIG infusion.[14]

All children with confirmed KD received 2 g/kg of IVIG (Carimune, Flebogamma or Gamunex) over 12 hours. Aspirin (100 mg/kg) was given orally until the patients became afebrile for 96 hours followed by 4–6 mg per kg of body weight until 6 weeks after onset of illness. Children with abnormal ECHO continuously received aspirin (4–6 mg/kg) until resolution of coronary abnormality on echocardiogram.

2.1. Statistical analysis

The collected data were stratified with respect to the time of IVIG treatment, i.e., within 10 days or after 10 days of disease onset. The Chi-square test was used for the comparison of categorical and ANOVA for continuous

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data between the study groups. Data are presented as a percentage and mean ± standard deviation. Three sets of multivariate regression analysis were performed to identify the factors that may have an association with: (1) the development of CA lesions prior to IVIG treatment; (2) development of new cases with CA lesions after IVIG treatment; and (3) resolution of established CA lesions within 9 weeks of fever onset. We performed multicollinearity analysis that included correlation analysis (Pearson's $r > 0.70$) among the predictors in the models. In addition, the tolerance and variance inflation factor (VIF) was analyzed to identify the collinearity with cut-off for tolerance >0.1 and VIF <5 that indicated lack of multicollinearity among the predictor variables in the tested model. Statistical significance was identified with a p value < 0.05. Statistical analysis was performed using Statistica 10.0 (StatSoft, Tulsa, OK, USA).

3. Results

One hundred and six children with KD were included in this study. All hospitalized patients were initially treated with IVIG (2 g/kg) in a time frame ranging from 5 to 20 days of fever onset, and three patients who did not respond to the first injection of IVIG received a second dose. No other treatment except aspirin was provided for the hospitalized patients. Eighty-six patients (81.1%) received the first dose of IVIG within 10 days (7.2 ± 1.7 days) and 20 children (18.9%) after 10 days (13.7 ± 2.9 days) of the disease onset. Among three patients who received two doses of IVIG, two had been treated with the first dose after 10 days of disease onset. As shown in Table 1, the demographic and clinical characteristics of the patients stratified by the time of IVIG treatment (within 10 days vs. >10 days) were comparable, except for the higher prevalence of cervical lymphadenopathy and swelling of the extremities in children who were admitted within 10 days and peeling that was recorded at a higher frequency in children who were admitted after 10 days of disease onset. Overall, among the 106 patients included in the study, 23 (21.7%) were diagnosed with CA lesions. Aneurysm was diagnosed in 60.9% of 23 children with CA lesions. CA abnormalities were diagnosed at initial ECHO in 18 patients (78.3%). Following IVIG therapy, five children developed a CA abnormality on follow-up ECHO at 3–4 weeks from the onset of symptoms, which accounted for 5.7% out of 88 of unaffected patients. The distribution of the types of CA lesions with respect both to time of IVIG administration (within vs. after 10 days) and recording of CA pathology (at initial ECHO and at 3–4 weeks) is presented in Table 2. As shown in Table 2, aneurysms were recorded in 70% of 10 children diagnosed with CA lesions and treated after 10 days and in 53.9% of 13 children with CA lesions who received IVIG within 10 days ($p = 0.23$).

The frequency of CA lesions on initial ECHO was higher in children hospitalized after 10 days of disease onset as compared to those who were admitted prior to 10 days (Figure 1). As shown in Figure 1, the risk for development of CA pathologies at the post-IVIG treatment stage was slightly, but not significantly, higher in children treated after 10 days as compared with those who received IVIG after 10 days of KD onset.

Overall, resolution of CA lesions within 9 weeks was recorded in 65.2% of the 23 children with CA pathological findings. Among the children who received IVIG after 10 days and who were diagnosed with CA lesions, 50% showed

Table 1 Demographic and clinical characteristics of children with Kawasaki disease (KD) based on the time of intravenous immunoglobulin (IVIG) treatment.

Characteristics	Time of IVIG treatment		p
	≤10 d ($n = 86$)	>10 d ($n = 20$)	
Age (y)	3.5 ± 2.6	2.9 ± 1.7	0.361
Age <1 y	19.8	25.0	0.603
Gender (male)	65.1	55.0	0.398
Race/ethnicity			
White	91.8	85.0	0.079
Black	3.5	10.0	
Hispanic		5.0	
Asian	4.7	—	
Conjunctival injection	93.0	80.0	0.072
Oral mucosal changes	93.0	80.0	0.073
Cervical lymphadenopathy	79.1	55.0	0.026
Polymorphous exanthema	82.6	85.0	0.793
Swelling of the extremities	53.5	20.0	0.006
Peeling	19.8	45.0	0.018
Atypical KD	7.0	15	0.246
WBC > 15 × 106/mm^3	31.4	50.0	0.115
ESR > 40 mm/h	80.2	90.0	0.304
Platelets > 500,000/ml	23.5	35.0	0.290
CRP > 3 mg/dL	63.9	60.0	0.304

Data are presented as (%) or mean ± SD.

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Table 2 Distribution of coronary artery (CA) lesions by type with respect to time of diagnosis and intravenous immunoglobulin (IVIG) administration.

CA lesions	IVIG ≤ 10 d		IVIG > 10 d	
	Initial ECHO	ECHO at 3–4 wk	Initial ECHO	ECHO at 3–4 wk
Aneurysm	40% (4/10)	100% (3/3)	62.5% (5/8)	100% (2/2)
Ectasia	60% (6/10)	—	37.5% (3/8)	—

ECHO = echocardiography.

resolution as compared to 76.9% among children who received IVIG within 10 days of fever onset ($p = 0.178$). The follow-up ECHO showed resolution of CA lesions in 22/23 (95.65%) children within 6 months of the disease onset. Persistence of CA pathology during the 12 months of follow up was recorded in one child who received IVIG after 10 days of disease onset and who was diagnosed with a giant CA aneurysm at 3–4 weeks of disease onset.

Table 3 summarizes the multivariate regression analysis, which was designed to identify factors that may influence the development of CA lesions prior to treatment (Model 1), after treatment (Model 2), and resolution of CA lesions within 9 weeks of disease onset (Model 3). We found that children with established CA lesions were likely to have a prolonged duration (>10 days) of disease prior to IVIG treatment (Model 1). Patients with a normal initial ECHO who developed CA lesions after the IVIG treatment tended to be <1 year of age. Time prior to treatment and pathologic laboratory findings did not affect the occurrence of post-treatment CA lesions (Model 2). Model 3 included variables that may have an association with delayed resolution of CA lesions in affected children. The results showed that the time of IVIG treatment was not significantly associated with the resolution of CA lesions. Children <1 year of age and with an ESR >40 were associated with non-resolution of CA lesions within 9 weeks of KD onset. We also included in Model 3 the type of CA lesions, because we found that aneurysms were more likely to occur among infants than older children (81.8% vs. 41.7%, $p < 0.05$). The type of CA lesion was not significantly associated with a risk for delayed resolution of CA pathological findings ($\beta = -0.274 \pm 0.245$, $p > 0.05$).

We found no multicollinearity between the model variables. Among all pairs, a significant correlation was found only between ESR and age ($r = -0.267$, $p < 0.01$) suggesting a lack of multicollinearity. Moreover, the tolerance and VIF also indicated a lack of multicollinearity, because tolerance was > 0.1 (0.867, 0.898, 0.897, 0.924, and 0.962) and VIF was <5 (1.15, 1.11, 1.12, 1.08, and 1.03) for age, WBC, ESR, CRP, and treatment groups (<10 days vs. ≥10 days), respectively.

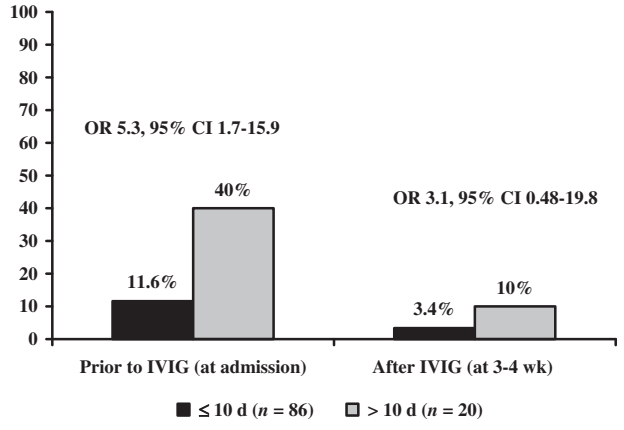

Figure 1 Frequency of diagnosed coronary artery (CA) lesions in children with Kawasaki disease (KD) with respect to the time of intravenous immunoglobulin (IVIG) administration. CI = confidence interval; OR = odds ratio.

4. Discussion

In this study we estimated the risk level for occurrence or incomplete resolution of CA abnormalities in children with KD with respect to the time of IVIG administration within and after 10 days of fever onset. As in previous reports,[10,12] we recorded a higher risk for development of CA lesions if IVIG was administrated after 10 days of disease onset. For instance, children with CA lesions diagnosed at initial ECHO had a 23.7% higher likelihood of being treated after Day 10 than those who received IVIG within 10 days of onset of fever, independently from the age and level of inflammatory markers. A significant beneficial effect of IVIG administration prior to 10 days of fever (as compared with patients not treated with IVIG within 10 days) was identified in randomized clinical trials.[19] Because IVIG is more likely to be able to interrupt vascular inflammation in the acute stage of illness, 10 days of fever was identified as an appropriate cut-off point for IVIG administration. Although IVIG treatment within 10 days was recognized as an evidence-based standard,[14] the best time for IVIG treatment with respect to the fever onset is still debatable. Observational studies have shown that patients treated by Day 7 of illness may develop aneurysms significantly less frequently as compared to those who are treated between Days 8 and 10 of illness.[20,21] Additionally, genotype polymorphisms may predict IVIG treatment response and susceptibility to KD.[22] None of the IVIG responder children required re-administration of IVIG to decrease the risk for development of CA pathology.[23,24] Children with KD are still at risk for coronary abnormalities after IVIG administration.[15,25] A risk of 8% has been reported for CA lesions irrespective of the administration of IVIG within 8 or after 10 days of fever onset.[15] In our study, the overall risk for development of CA lesions after IVIG treatment in the unaffected patients at the initial ECHO was around 6%, with no significant difference among patients who received IVIG within 10 days or after Day 10. Infants diagnosed with KD were significantly more likely (by 32.1%) to develop CA lesions after IVIG treatment as compared with older children. The younger

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Table 3 Factors that were associated with: (1) coronary artery (CA) lesions diagnosed at the initial echocardiography (ECHO) (Model 1); (2) CA lesions diagnosed after intravenous immunoglobulin (IVIG) treatment (Model 2), and (3) resolution of CA lesions within 9 weeks of Kawasaki disease (KD) onset (Model 3).

Variables	B ± standard error		
	Model 1	Model 2	Model 3
IVIG > 10 d (n = 20)	−0.237 ± 0.095*	−0.111 ± 0.068	0.129 ± 0.211
Age < 1 y old (n = 22)	0.166 ± 0.107	0.321 ± 0.072 **	−0.696 ± 0.230*
WBC > 15 × 10^6/mm^3 (n = 37)	0.121 ± 0.085	0.063 ± 0.056	0.454 ± 0.217
ESR > 40 mm/h (n = 87)	0.049 ± 0.108	−0.041 ± 0.066	−0.711 ± 0.261*
CRP > 3 mg/dL (n = 58)	0.021 ± 0.084	0.072 ± 0.053	−0.189 ± 0.263

Dummy variables of: (1) IVIG treatment: equals 1 if treatment conducted after 10 days and 0 if within 10 days; (2) CA lesions: equals 1 if CA lesions were diagnosed and 0 if not; (3) resolution of CA: equals 1 if CA lesions resolved within 9 weeks and 0 if not; (4) age: equals 1 if age less or equal 12 month and 0 if not; (5) WBC: equals 1 if WBC > 15 × 10^6/mm^3 and 0 if not; (6) ESR: equals 1 if ESR > 40 mm/h and 0 if not; (7) CRP; equals 1 if CRP > 3 mg/dL and 0 if not.
*$p < 0.02$. **$p < 0.0001$.
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; WBC = white blood cell count.

age-associated risk for KD susceptibility and development of CA abnormalities has been previously reported.[26–29] We also showed that the probability for incomplete resolution of CA lesions within 9 weeks was approximately 70% higher among infants and in children with KD who had an ESR > 40 mm/hour at the time of admission.

We have to acknowledge several limitations of the present report. First, the study results could have been limited by its retrospective design. However, information bias was possibly covered by reliable measurements of well-documented exposure (time of IVIG administration) and outcome (occurrence and resolution of CA lesions) variables. ECHO was performed on each individual in the assigned time frame during the follow up at a single Pediatric Cardiac Clinic. Moreover, ECHO data were blinded to the time of IVIG treatment. Additionally, the population-based design of the study reduced the impact of selection bias because all eligible cases diagnosed with KD who were hospitalized and followed in the Pediatric Cardiology Clinic during the 12-year period were included. We also used statistical adjustment for the 'measurable with high accuracy' known confounders (age and laboratory-reported inflammatory markers) to identify the independent effect of time of IVIG treatment within or after Day 10 of fever onset, although one of the important laboratory parameters, albumin, was not included because it was not consistently tested in all participants. Because of ethical considerations, no experimental design is available to identify the difference in CA outcomes between delayed (after 10 days) and timely IVIG treatment in children with KD. Secondly, due to the inconsistency in the frequency of laboratory testing, only initial laboratory measurements were analyzed in the present study. However, the study showed that for most of the KD cases, only the baseline laboratory measurements appeared to be good predictors of CA involvement during early follow-up.[30] Thirdly, the data were not analyzed in respect to the CA abnormalities because a larger study is needed to achieve the power to detect the effect of size of type of CA lesions on the time of resolution of CA pathologies.

We conclude that administration of IVIG within 10 days of onset of illness is important to minimize the risk for development of cardiac pathology, but that this does not significantly impact either the occurrence of CA lesions in IVIG-treated children or time of CA lesion resolution. Infant age group and high ESR should be considered for prediction of delayed resolution of CA lesions in children with KD.

Conflicts of interest

All authors declare no conflicts of interest.

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