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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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Background: 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.
Methods: 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.
Results: 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.

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Conclusion: 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-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.