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The effects of early intravenous immunoglobulin therapy for Kawasaki disease: The 22nd nationwide survey in Japan

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ABSTRACT

Background: Although intravenous immunoglobulin (IVIG) therapy is the standard therapy for Kawasaki disease (KD) to prevent coronary aneurysms including dilatations, it is unclear whether early IVIG therapy is more efficient in the acute stage of KD.
Methods: We conducted a cohort study using data from the 22nd nationwide survey of KD in Japan from January 2011 to December 2012. We excluded patients with recurrent KD and whose first admission day was later than seven days from the onset of symptoms. Finally, 20,933 patients with echocardiography assessment and IVIG therapy were divided into three groups according to the start of the IVIG therapy: 1) early: ≤4 days, 2) conventional: 5–7 days, and 3) late: 8–10 days. Then we investigated whether the early IVIG therapy prevented coronary dilatation or aneurysm after multiple adjustments for age, sex, total amount of IVIG, use of steroids, infliximab, other immunosuppressive agents, and plasma exchange.
Results: After multiple adjustments, conventional therapy had similar risks for coronary dilatation or aneurysm compared with early therapy (odds ratio [OR]:0.95; 95% confidence interval [CI], 0.78–1.16), whereas late therapy had a higher risk (OR:1.66; 95% CI, 1.03–2.68). Other risk factors for coronary dilatation or aneurysm were young male, older age, use of steroids, infliximab, other immunosuppressive agents, and a larger amount of total IVIG.
Conclusions: Early IVIG therapy for KD did not reduce the risk for coronary dilatation or aneurysm compared with conventional therapy. It is recommended to start IVIG therapy within 7 days from the onset of symptoms.

1. Introduction

The number of patients with Kawasaki disease (KD) is increasing worldwide [1–4]. The most important complication of KD is cardiac disease including coronary dilatation and aneurysm [5–8]. The mortality rate of KD is two-times higher than that of healthy subjects [9]. Intravenous immunoglobulin (IVIG) therapy is a standard therapy for the acute stage of KD to prevent coronary dilatation or aneurysm [8, 10]. The proportion of coronary lesions in untreated patients is 25% [11], but IVIG therapy reduces the proportion of coronary aneurysms to <5% [12,13]. A study from Japan showed that early IVIG therapy on day 4 from the onset of symptoms or earlier did not have greater efficacy in preventing cardiac sequelae compared with treatment on days 5 to 9 [14]. However, that study did not consider differences in additional treatments such as infliximab or steroids between institutions, which might be a significant confounding factor. In addition, the study included all cardiac lesions such as coronary stenosis, myocardial infarction, and valvular lesions for which it is uncertain whether treatment with IVIG is effective. Furthermore, Japanese guidelines for KD recommend starting IVIG for KD within 7 days from the onset of symptoms to prevent coronary dilatation or aneurysm because this is the timepoint at which vasculitis worsens; furthermore, histological studies have shown that arteritis typically develops by 8 or 9 days after the onset [15]. Therefore, this study investigated the hypothesis that risks for coronary dilatation or aneurysm are different among three categories (start of IVIG therapy up to 4 days, 5 to 7 days, and 8 to 10 days) with adjustment for additional treatments. This survey was conducted nearly every two years since 1970, and we used the 22nd nationwide surveys of KD in Japan to obtain data [9,16–18].

2. Methods

We conducted a retrospective cohort study using data of the 22nd nationwide survey of KD in Japan, targeting patients enrolled between January 2011 and December 2012 [9, 16–18]. This survey requested the participation of medical facilities and hospitals specializing in pediatrics, and hospitals with a bed capacity of 100 or more and a pediatric department. Of the 2006 hospitals asked to participate in the survey, 23 hospitals reported that the pediatric department had been discontinued or that the hospital was no longer used. Of the 1983 eligible hospitals, 1420 (71.6%) hospitals returned the questionnaire.

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A total of 26,691 patients (12,774 in 2011 and 13,917 in 2012) were reported (15,442 male and 11,249 female) [17].

This study was designed to investigate whether early IVIG therapy within 4 days can prevent coronary dilatation or aneurysm >1 month after the onset of symptoms compared with conventional therapy within 7 days, after multiple adjustments. We investigated the risk factors for coronary dilatation or aneurysm >1 month after the onset of symptoms among three categories based on the start date of the IVIG therapy: (1) early: 4 days or less, (2) conventional: 5 to 7 days, and (3) late: 8 to 10 days. The primary outcome of this study was coronary artery dilatation or aneurysm at more than one month after the onset of symptoms among the 3 categories. Therefore, this study used patient information including cardiac lesions on the basis of two-dimensional echocardiography at >1 month after the onset of symptoms. Echocardiography is the primary imaging modality for cardiac assessment because it has a high sensitivity and specificity for the detection of abnormalities of the proximal coronary artery segments [8,19]. Thomas et al. reported that the sensitivity of two-dimensional echocardiography to detect coronary artery dilatations was 100% and specificity was 97% in the proximal right coronary artery and the left main coronary artery [19]. Hirose et al., reported that the specificity was 96% for the entire coronary system, 99% for the right coronary artery, and 95% for the left coronary artery [20]. Coronary dilatation was defined as maximum absolute internal lumen diameter > 3 mm in children younger than five years or > 4 mm in children five years or older. [21] Coronary aneurysm was defined as a segmental internal diameter of any segment ≥1.5 times greater than that of an adjacent segment [21]. Typical KD was defined as having 5 or 6 symptoms of the 6 main symptoms of KD, or 4 symptoms of the 6 main symptoms and coronary dilation or aneurysm. Patients who did not satisfy the criteria for typical KD were defined as atypical KD. Exclusion criteria were (1) recurrent KD and (2) time of first admission later than seven days after the start of symptoms because these KD patients did not have a chance to receive IVIG therapy within 7 days from the onset of symptoms. We checked the cumulative incidence of coronary dilatation or aneurysm over 1 month in the very late IVIG therapy group (>10 days), but we did not include this group in the analyses because of the high cumulative incidence.

After checking for possible inconsistencies in the questionnaires, the forms were sent back to the respondents to correct any errors. The Ethical Board of Jichi Medical University approved this survey in advance (November 2012).

2.1. Statistical analysis

Statistical analyses were performed using SPSS Statistics software (IBM SPSS Statistics version 22 for Windows; IBM, NY). The statistically significant level was set at $p = 0.05$. These analyses were conducted with non-adjustment (crude) and multiple adjustment for age, sex, amount of IVIG, and steroid or infliximab therapies. Patient characteristics were compared among the three categories based on the start date of IVIG therapy by one-way analysis of variance (ANOVA).

3. Results

The 22nd nationwide survey of KD in Japan had data for 26,691 patients. Of these, we excluded patients with recurrent KD and those whose admission day was >7 days from the onset of symptoms. As a result, we investigated 23,155 cases, of which 22,688 had echocardiography assessments and of which 20,933 patients were treated with IVIG (Fig. 1). Moreover, of the 20,933 study patients, 6 patients had missing data regarding the start date of IVIG therapy. In patients with IVIG therapy, the cumulative incidence of coronary dilatation or aneurysm >1 month after the start of symptoms was 2.35% (491/20,933), of which 1.67% (349/20,933) had coronary dilatation and 0.68% (143/20,933) had coronary aneurysm (one patient had both). However, 1755 patients without IVIG therapy had a lower cumulative incidence of coronary dilatation or aneurysm >1 month after the start of symptoms (1.77%, 31 subjects) compared with patients with IVIG therapy, but there was no significant difference between groups ($p = 0.12$).

We also determined the cumulative incidence of coronary dilatation or aneurysm related to each start date of IVIG therapy (Fig. 2a). IVIG therapy at day 6 from the start of symptom onset had the lowest cumulative incidence of coronary dilatation or aneurysm (1.6%). The patient characteristics are shown in Table 1. Of the study subjects, 85% were typical KD. More than 90% patients with KD had IVIG therapy within 7 days from the start of their symptoms. One third of patients had early IVIG therapy within 4 days. The early therapy group characteristics were younger age, higher frequency of steroid use, higher rate of IVIG therapy non-response, higher frequency of additional IVIG therapy, larger total amount of IVIG, higher frequency of steroids, infliximab, and other immunosuppressive agents, and plasma exchange. The cumulative incidence of coronary dilatation or aneurysm in the early therapy, conventional therapy, late therapy, and very late therapy groups (>10 days) were 2.7%, 2.0%, 3.4%, and 19.5%, respectively (Fig. 2b).

By non-adjusted (crude) analysis, the conventional therapy group had a lower risk for coronary dilatation or aneurysm compared with

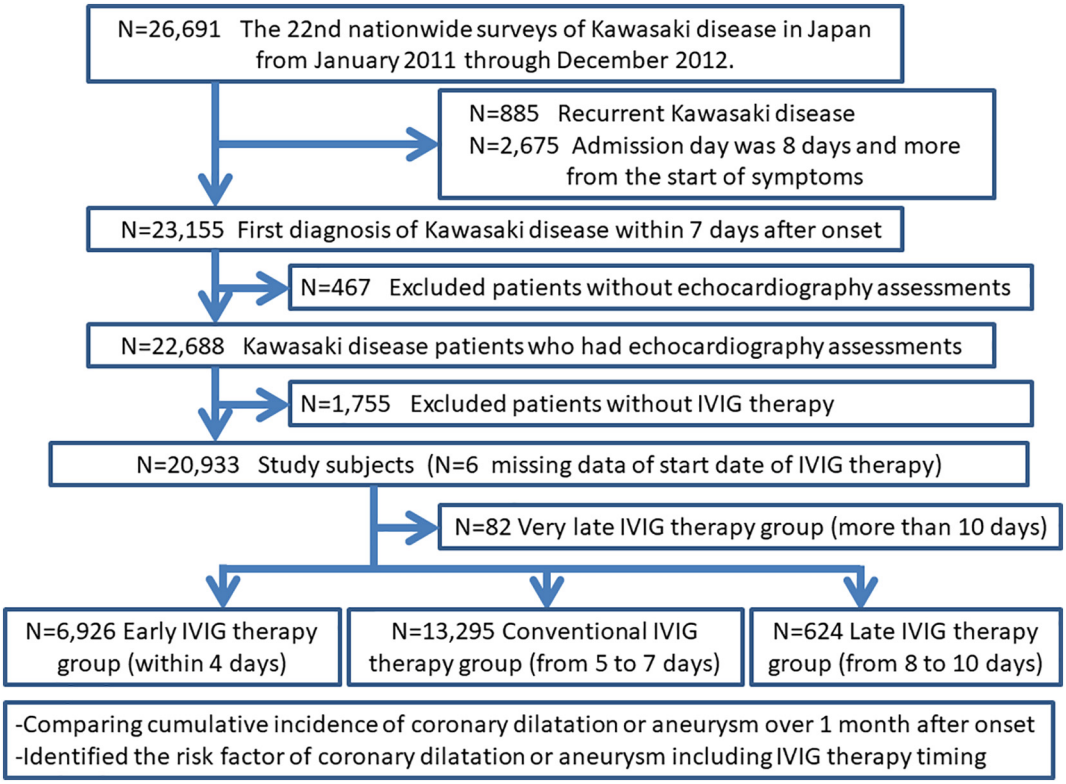

Fig. 1. Enrollment of study subjects. IVIG, intravenous immunoglobulin.

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