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Use of Intravenous γ-Globulin for Kawasaki Disease: Effects on Cardiac Sequelae

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Abstract. The administration of intravenous γ-globulin (IVGG) for Kawasaki disease was investigated throughout Japan in 1993 by obtaining information from pediatric departments in 2652 hospitals that had more than 100 beds. Of 11,221 reported patients, 8958 patients (79.8%) received IVGG treatment.

Of all the patients to whom IVGG was administered, the most common total dose was 1000 mg/kg (36.3%) followed by 2000 mg/kg (16.9%) and 1200 mg/kg (16.8%). The treatment was started in 53.8% by day 5 of the illness and in 83.7% by day 7.

The proportion of those with cardiac sequelae was higher among patients administered >2000 mg/kg or in those started on IVGG on day 9 of their illness or later. The possible reasons are (1) those who were more severely affected were treated with high-dose IVGG earlier; or (2) IVGG does not effectively prevent cardiac sequelae. We concluded that there is a risk of unfavorable effects with IVGG regarding cardiac sequelae when the IVGG dose is >2000 mg/kg or if IVGG is started on day 9 or later. We believe that only a randomized controlled trial, undertaken prospectively, can adequately address the question of the optimal use of IVGG.

Key words: Gamma-globulin treatment — Kawasaki disease — Cardiac sequelae

Based on data from multicenter, clinically controlled studies in Japan and other countries, it is generally agreed that treatment with intravenous γ-globulin (IVGG) for Kawasaki disease is efficacious for avoiding cardiac sequelae [1, 2, 4–10]). IVGG treatment for the patients with this disease was adopted by Japanese pediatricians during the early 1980s mainly for the prevention of coronary aneurysms and other serious coronary lesions. The Japanese medical insurance agency agreed to bear the medical expense for treatment by the specified regimen (200 mg/kg for 5 days).

The purpose of our study was to analyze the effects of IVGG treatment on cardiac sequelae and determine the factors that interfere with the effectiveness of the IVGG treatment. We therefore evaluated the results of a nationwide epidemiologic survey of patients with Kawasaki disease during 1991 and 1992.

Methods

A survey form and diagnostic guidelines for Kawasaki disease with color-printed photographs of typical clinical symptoms were sent to all pediatric departments in hospitals with 100 or more beds throughout Japan. The subjects of this survey were all the patients with Kawasaki disease treated during the 2-year period of 1991–92.

The diagnostic criteria for typical cases of Kawasaki disease in this series were designed to include at least five of the following six main symptoms: (1) fever persisting for 5 days or more; (2) changes in the extremities; (3) polymorphous exanthema; (4) bilateral conjunctival congestion; (5) changes in the lips and oral cavity; and (6) acute nonpurulent cervical lymphadenopathy [3]. Atypical cases are those with at least four symptoms when a coronary aneurysm is detected by two-dimensional echocardiography or coronary angiography. In addition to the typical and atypical cases, incomplete cases are defined as patients who partially fulfill the criteria and are suspected of having the disease by the pediatrician.

We investigated the relation between IVGG treatment and the presence of cardiac sequelae. The factors observed are the total dose, the day of illness on which IVGG administration was started, the age and gender of the patient, the diagnosis (typical, atypical, incomplete), and cardiac sequelae (total cardiac sequelae and giant aneurysm). The cardiac sequelae in this series are defined as the presence of dilatation of a coronary artery (including aneurysm), stenosis (including occlusion), myocardial infarction, or valvular lesion 1 month after the onset of Kawasaki disease, ascertained by either coronary angiography or two-dimensional echocardiography.

Results

The questionnaire was sent to 2652 hospitals, of which 1826 hospitals (68.9%) responded. The number of patients diagnosed in the responding hospitals during the 2-year period from January 1991 to December 1992 was

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Table 1. Classification of patients according to sex, age, and IVGG treatment

Age (years)	All patients			Male patients			Female patients		
	Total	IVGG(+)	IVGG(−)	Total	IVGG(+)	IVGG(−)	Total	IVGG(+)	IVGG(−)
>1	3227	2639	588	1988	1631	357	1239	1008	231
1	2869	2286	583	1700	1367	333	1169	919	250
2	3058	2479	579	1777	1450	327	1281	1029	252
4	2028	1528	500	1110	828	282	918	700	218
Unknown	39	26	13	29	20	9	10	6	4
Total	11,221	8958	2263	6604	5296	1308	4617	3662	955

11,221 (6604 males, 4617 females). The numbers of typical cases, atypical cases, and incomplete cases were 9708 (86.5%), 415 (3.7%), and 1098 (9.8%), respectively. The average annual incidence was 89.4 per 100,000 children <5 years of age.

Of the patients reported, 8958 (79.8%) were treated with IVGG (80.2% of males, 79.3% of females). In a comparison of age groups, the proportions were 81.8% within <1 year, 79.7% within 1 year, 81.1% within 2–3 years, and 75.3% over 3 years (Table 1).

The distribution of total doses of IVGG per weight is shown in Table 2. Each class of the dose includes a fraction of 100 mg/kg. Of the total patients with IVGG treatment, 36.3% received 1000 mg; 16.9% received 2000 mg, 16.8% received 1200 mg, and so on (Table 2).

The distribution of the day of illness on which IVGG administration was started is shown in Table 3. The percentage was highest on day 5 of the illness (26.7%) followed by day 6 (20.2%) and day 4 (16.1%). Of all the patients receiving IVGG, 83.7% were given the drug on day 7 or before (Table 3).

Figure 1 shows the prevalence of cardiac sequelae according to the total dose of IVGG. The percentage was higher in the lowest dose group of 400 mg/kg or less (19.9%) and in the three highest dose groups: 25.7% with a dose of 2200 mg/kg, 35.7% with 2400 mg/kg, and 50.4% with 2600 mg/kg or more. The percentages in other groups from 600 mg/kg to 2000 mg/kg were between 8.6% and 15.2%.

Figure 2 illustrates the prevalence according to the day of illness on which IVGG administration was started. The percentage was higher in the late administration groups: days 10–14 (24.8%) and day 15 or later (54.9%).

To elucidate the combined effects of the dose and the day of IVGG administration, the prevalence by day of illness was compared between the two most popular dose groups (3248 patients with 1000 mg/kg and 1517 patients with 2000 mg/kg). The prevalence did not differ greatly between these two dose groups (Fig. 3).

The prevalence of giant aneurysms was higher in the patients treated on day 15 or later (6.1%) compared with days 10–14 or earlier (0.4–1.9%) (Fig. 4).

Table 2. Distribution of IVGG dose

Dose[a] (mg/kg)	No. of patients	%
≦400	196	2.2
600	403	4.5
800	384	4.3
1000	3248	36.3
1200	1506	16.8
1400	267	3.0
1600	756	8.4
1800	223	2.5
2000	1517	16.9
2200	74	0.8
2400	42	0.5
2600	137	1.5
Unknown	205	2.3
Total	8958	100

[a] Including fraction of 100 mg/kg.

Table 3. Distribution of day of illness on which IVGG administration was started

Day of illness	No. of patients	%
≦3	859	9.6
4	1438	16.1
5	2394	26.7
6	1816	20.2
7	993	11.1
8	529	5.9
9	270	3.0
10–14	310	3.5
15+	82	0.9
Unknown	267	3.0
Total	8958	100

Discussion

Many reports have described the efficacy of IVGG administration in controlled studies. The results of a number of multicenter controlled studies of IVGG for the prevention of coronary artery lesions, such as those conducted by the Japan Kawasaki Disease Research Committee [2], Matsushima et al. [4], the Osaka MCLS Study

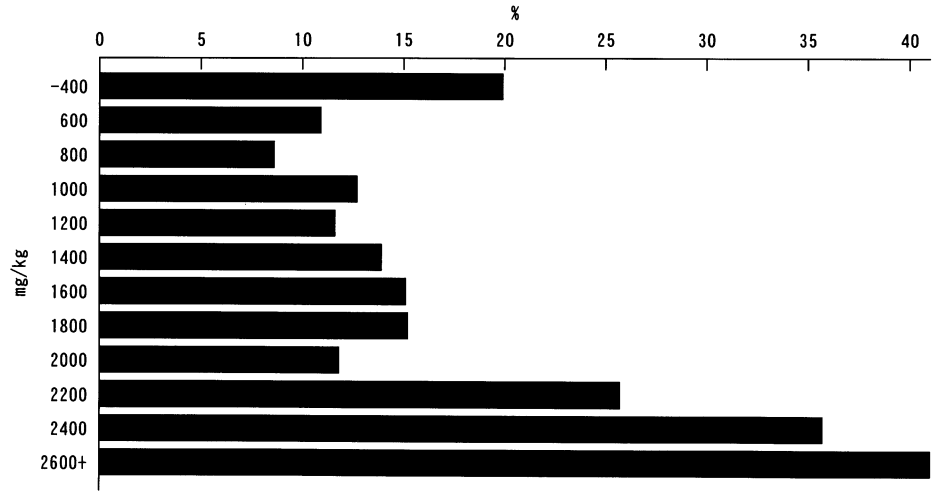

Fig. 1. Prevalence of cardiac sequelae according to the total dose of IVGG.

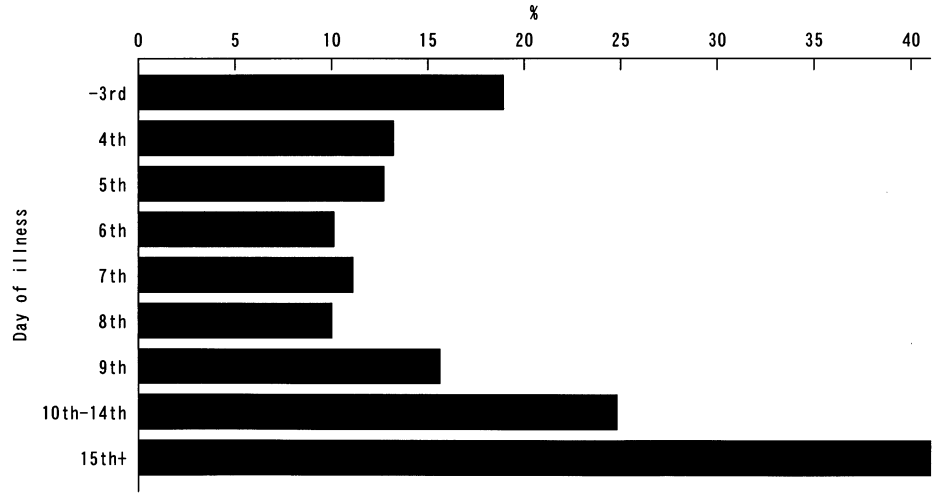

Fig. 2. Prevalence of cardiac sequelae by day of illness on which IVGG administration was started.

Group [8, 9], and Onouchi et al. [10], have consistently indicated that IVGG administration of 400 mg/kg for 4 or 5 days effectively prevented coronary artery lesions, and that a smaller dose of 100 or 200 mg/kg for 4 or 5 days was less effective. Newburger et al. later reported that a single infusion of 2000 mg/kg was more effective than a regimen of 400 mg/kg for 5 days [6, 7].

Japanese pediatricians generally agree that IVGG treatment is effective, although there is no agreement on the optimal regimen. In Japan, the percentage of patients treated with IVGG has rapidly increased over the past 10 years (from 8.2% in 1983 to 81.8% in 1992). According to nationwide surveys on Kawasaki disease, however, the percentage reduction of patients with cardiac sequelae is small (from 22.6% in 1983 to 16.6% in 1992), and one cannot help wondering if IVGG is as effective in practice as one might expect [12].

The present analysis is based on the results of a 1991–1992 nationwide survey of patients with Kawasaki disease [11]. Its purpose was to examine whether the IVGG therapy implemented in Japan has produced the expected effects and to discover what factors might have interfered with its effective use when the therapeutic outcome was unsatisfactory.

Let us first examine the relation between cardiac sequelae and the dosage of IVGG. It was found that the prevalence of cardiac sequelae increased rapidly and in proportion with the dosage in patients who received large quantities of IVGG (especially >2200 mg/kg). The following factors are possible causes to explain this finding: (1) higher dosages were given to patients with more serious conditions; (2) when IVGG does not produce a satisfactory effect on cardiac sequelae, the preparation is given for a longer period, thus increasing the total dosage; and (3) administration of 2200 mg/kg or more may augment the incidence of cardiac sequelae.

Among these explanations, reason 1 is only a statistical bias introduced when selecting the patients with a

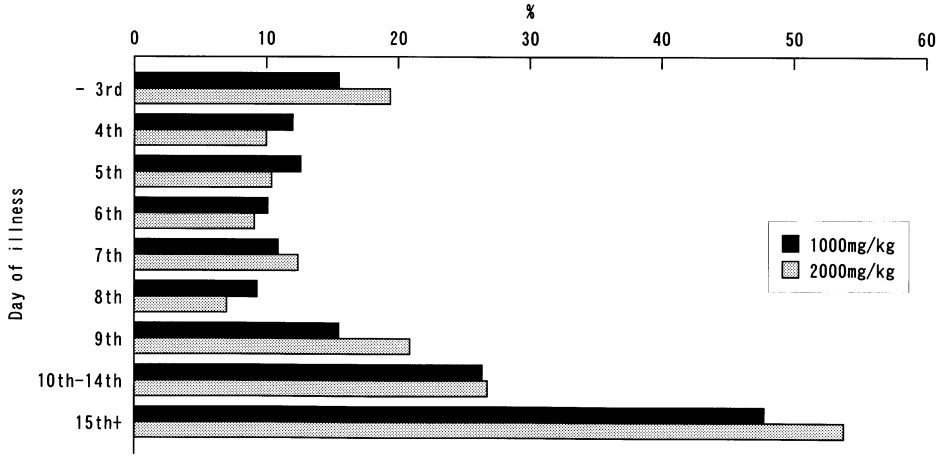

Fig. 3. Prevalence of cardiac sequelae by day of illness on which IVGG administration was started. Comparison between 1000 mg/kg and 2000 mg/kg.

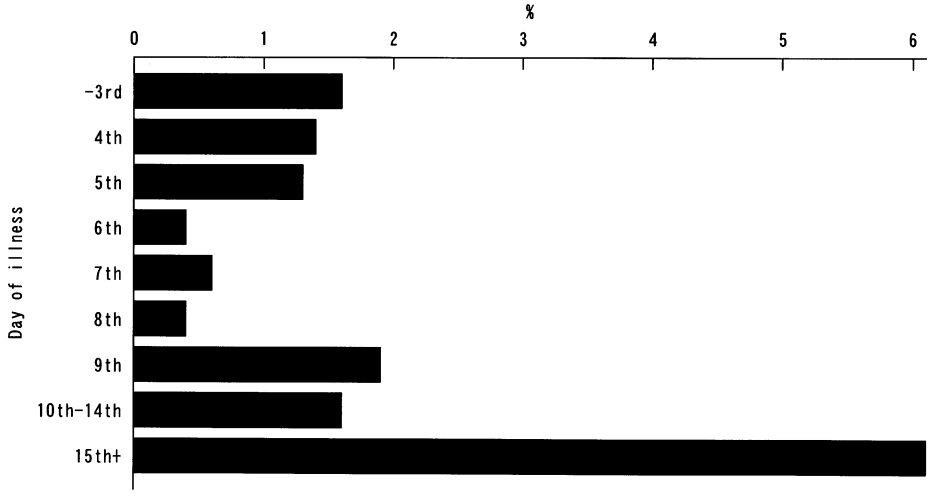

Fig. 4. Prevalence of giant aneurysms by day of illness on which IVGG administration was started.

high dosage of IVGG, so we do not devote any space to it here. For reason 2, however, we note that simple prolongation of IVGG therapy does not serve to improve the prognosis. When no improvement occurs after a certain quantity of IVGG has been given, the therapy should be immediately interrupted; and replacement with another pharmaceutical preparation (e.g., steroids) should be considered. For this reason, the ''high-dose one-shot'' approach should be applied for IVGG administration, and its efficacy should be confirmed as soon as possible after the onset. For patients who fail to respond to this therapeutic modality, a switch to another mode of treatment should be considered.

Reason 3 poses a serious problem to IVGG therapy. In view of the results from the nationwide survey, one cannot deny the possibility of the drug causing cardiac sequelae when IVGG is administered in excess of a certain dosage (2000 mg/kg). Continuation of IVGG therapy without clarifying this possibility may lead to a serious problem in the future. It is essential to investigate this possibility at the earliest date through such means as a randomized controlled trial.

Next we focus on the relation between cardiac sequelae and the timing of the start of IVGG therapy. Many reports suggested that IVGG treatment is effective if administration is started on day 7 or earlier [1, 5–7]. The incidence of cardiac sequelae increases regardless of the IVGG dosage in patients in whom IVGG administration was initiated on day 9 or later after onset, with the incidence being proportional to the lapse of time before the start of IVGG administration. The following factors may explain this phenomenon: (1) cardiac sequelae have already developed when the IVGG regimen is initiated, and the efficacy of the preparation cannot be expected; and (2) administration of IVGG following the development of cardiac sequelae may exacerbate the condition. At any rate, it appears that the initiation of IVGG therapy on day 9 after onset or later is meaningless.

The incidence of cardiac sequelae is increased slightly, even for patients in whom IVGG therapy was initiated on day 3 after onset or earlier. We suspect that it is due to a bias by including severe cases with full clinical symptoms as early as day 3 after onset.

It has already been agreed by the international medical community that IVGG is effective against cardiac sequelae caused by Kawasaki disease. However, no studies have been conducted to support the efficacy of its administration at a dosage of 2200 mg/kg or higher on day 9 after onset or later. It is also necessary to evaluate the difference in efficacy when the total dosage is given all at once or the same dosage is divided and given over a 5-day period. Few centers apply the former regimen in Japan, so it was not possible to evaluate it in this study.

When deciding whether to apply IVGG therapy and if so at what dosage, it is mandatory for the attending physician to consider the clinical picture and course of each patient. It may be difficult to evaluate the effects of IVGG by simply analyzing the results of a nationwide survey on Kawasaki disease. Even when we consider a possible bias, however, it may be that an efficacy such as that obtained in experimental studies cannot be expected for the prevention of cardiac sequelae in patients with Kawasaki disease, depending on the conditions of its administration. In fact, cardiac sequelae may be exacerbated at some dosages or by the timing of the administration of this preparation. The efficacy of IVGG should be urgently reevaluated, as we cannot deny the possibility of producing unfavorable effects on cardiac sequelae by inadequate administration of IVGG for these patients.

We have shown that the proportion of patients with Kawasaki disease who had cardiac sequelae was high among those treated with IVGG at a dosage >2000 mg/kg and among those who started IVGG treatment on day 9 of the illness or later.

Because the current study was based on retrospective observation of the patients who were reported in the nationwide incidence survey and the dose of IVGG administered and the days of illness at starting treatment depended on the severity of the clinical picture, considerable selection bias is likely to have occurred among the patients with the highest doses of IVGG. Therefore we cannot state definitively that IVGG treatment was not effective for some patients with Kawasaki disease in terms of preventing cardiac sequelae. We believe that only a randomized controlled trial, undertaken prospectively, can adequately address the question of the optimal dose of IVGG.

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