Iranian Heart Journal; 2022; 23 (1)

Original Article

The Effects of Intravenous Immunoglobulin on Coronary Artery Abnormalities in Children With Kawasaki Disease

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ABSTRACT

Background: Kawasaki disease (KD) is an acute systemic vasculitis in childhood, with a strong effect on the heart. The present study aimed to evaluate the effects of intravenous immunoglobulin (IVIG) on coronary artery abnormalities in children with KD.

Methods: This study was performed on 101 children with KD between 2004 and 2019. Echocardiography was used to assess coronary artery abnormalities. A coronary artery was considered abnormal if the internal lumen diameter exceeded 2 mm in infants, 3 mm in children aged between 2 and 5 years, and 4 mm in children older than 5 years. Data analysis was done using the SPSS software, version 22. A *P* value less than 0.05 was considered statistically.

Results: Before IVIG administration, abnormal left coronary arteries were reported in 21 children. However, 2, 6, and 12 months following IVIG administration, the number of children with left coronary artery abnormalities dropped to 5, 2, and 1, respectively. Before IVIG administration, abnormal right coronary arteries were reported in 13 patients. Nonetheless, 2, 6, and 12 months after IVIG administration, the number of patients with right coronary artery abnormalities fell to 5, 1, and 1, respectively.

Conclusions: IVIG administration in our children with KD significantly affected left and right coronary artery abnormalities after 6 months, with the effect being stronger in the left coronary artery. ***(Iranian Heart Journal 2022; 23(1): 172-183)***

KEYWORDS: Kawasaki disease, Intravenous immunoglobulin, Coronary artery, Children

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Received: November 6, 2020 **Accepted:** February 5, 2021

Kawasaki disease (KD) is an acute systemic vasculitis in childhood. It is diagnosed with a fever of 5 days' duration, accompanied by at least 4 of the following symptoms: polymorphous rashes, mucosal ulcers, extremity changes, bilateral nonsuppurative conjunctivitis, and cervical lymphadenopathy. [1] KD is sometimes called "mucocutaneous lymph node syndrome", and its incidence rate varies from country to country such that in Northeast Asia, it is significantly higher than that in other parts

of the world. [2] Indeed, Japan, [3] South Korea, [4] and Taiwan [5] are the 3 Asian countries with the highest nationwide KD incidence. Limited patient series have been reported from countries in the Middle East, with the majority in Turkey and Iran. [6,7] KD is the second most common vasculitis in childhood, with a peak age of 2 to 3 years. (It is rarely seen above the age of 7 years.) Although KD affects various organs, the heart is most at risk, especially in children. [8] Coronary artery aneurysms occur significantly more often in patients with a delayed diagnosis of KD, not least when the total duration of fever is longer than 8 days. [9]

Intravenous immunoglobulin (IVIG) is an effective treatment in the majority of children with KD since it shows a rapid resolution of fever and symptoms. [10] IVIG treatment greatly reduces the risk of coronary artery aneurysms by about 5% to 20% in patients with KD. Children with KD require additional anti-inflammatory treatments such as acetylsalicylic acid (ASA), corticosteroids, and tumor necrosis factor inhibitors. [11] The American Heart Association recommends early IVIG plus ASA for KD treatment. [8] Risk factors for coronary artery aneurysm development in patients with KD include prolonged fevers; prolonged elevations of inflammatory markers such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelets (PLTs), and albumin (Alb); age younger than 1 year or older than 6 years at onset; and the male sex. [1] Recent studies have indicated that other anti-inflammatory agents such as cyclosporine A, anakinra, and plasma exchange therapy may be beneficial in reducing the incidence of coronary artery aneurysms and controlling the inflammatory process in patients with KD. [12,13] Between 6.7% and 26.8% of patients suffering from KD are IVIG resistant and at increased risk for coronary artery aneurysms. [14] Interestingly, the percentage of IVIG resistance is not proportional to the incidence of KD such that the incidence of KD in children aged below 5 years was 264.8/100 000 and 55.9/100 000 in Japan [11] and Taiwan, [5] and the percentage of IVIG resistance was 17.0% [11] and 12.5%, [5] respectively. Delayed initiation of treatment, genetics, immunological factors, younger age, and the brand of IVIG may all influence IVIG resistance.

In light of the aforementioned information, in the present study, we aimed to investigate changes in coronary artery abnormalities caused by IVIG plus ASA treatment in children with KD.

METHODS

Study Type

This retrospective study was carried out on 101 children admitted to Ali Ebne Abi Talib Hospital with a diagnosis of KD receiving IVIG plus ASA therapy between 2004 and 2019. From this total, 11 children were excluded because of their failure to return to the clinic after the initial treatment.

Study Design

The criteria for KD confirmation were a fever lasting more than 5 days and at least 4 of the following symptoms: polymorphous rashes, mucosal ulcers, extremity changes, bilateral nonsuppurative conjunctivitis, and cervical lymphadenopathy. After diagnosis confirmation, the patients underwent laboratory tests and transthoracic echocardiography. Data regarding age, sex, the duration of fever, conjunctivitis, cervical lymphadenopathy, mucocutaneous lesions, strawberry tongue, skin rashes, mucosal ulcers, scaling, fissure, ESR, CRP, the white blood cell (WBC) count, the PLT count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin (Hb), alkaline phosphatase (ALP), and Alb were

recorded. Echocardiography was employed to assess the left and right coronary arteries.

Ethical Approval

The study protocol was approved by the institutional ethics committee (code: 1348), which also granted permission for the use of medical files for data collection.

Definition of IVIG Resistance and Coronary Artery Abnormalities

Patients were considered IVIG resistant if they remained febrile or they had recurrent fevers 48 hours after the administration of the initial treatment. [15] Echocardiography was used to assess the patients' coronary arteries before the initial treatment and subsequently at 2 months, 6 months, and 12 months after the initial treatment. A coronary artery was considered abnormal if the internal lumen diameter exceeded 2 mm in infants, 3 mm in children between 2 and 5 years of age, and 4 mm in children aged above 5 years.

Statistical Analysis

Data were analyzed with the SPSS software, version 18 (SPSS Inc, Chicago, Ill, USA). The mean ± the standard deviation (SD) was considered for descriptive statistics and the paired *t* test and the Pearson χ^2 test for inferential statistics. The level of significance was considered 0.05.

RESULTS

The study population's age ranged from 7 to 108 months (average =44.1±28.33 mon). The majority of the patients (81.1%) were younger than 5 years. Among those aged below 5 years, 58.9% were boys. This trend was 52.9% for patients older than 5 years. Totally, boys comprised 57.8% of the study population.

Fever was reduced in 78.9% of the patients within the first 2 days of the initial treatment and 14.4% after the first 2 days. One patient reached the normal level after 3 days, 3 patients after 4 days, 1 patient after 5 days, and 1 patient after 7 days.

As can be seen in Table 1, 88.89% of the study population received IVIG plus ASA early (≤10 d), and about 81.11% had a fever for 10 days or less. Additionally, 53.3% had cervical lymphadenopathy, 46.7% conjunctivitis, 86.7% strawberry tongue, 72.2% desquamation, 80% skin rashes, 60% indurative edema, 43.3% pyuria, 4.4% diarrhea, and 2.2% had arthritis. Regarding laboratory tests, normal CRP levels were reported in 12.2% of the study population, normal ESR in 2.2%, normal AST in 35.6%, normal ALT in 63.3%, and normal ALP in 26.7%. ESR rose in tandem with a significant increase in the patients' age (χ^2=0.214, *P*=0.043), and a similar trend was observed in CRP (χ^2=0.267, *P*=0.011).

Before IVIG administration, abnormal left coronary arteries were reported in 21 children. Nonetheless, 2, 6, and 12 months following IVIG treatment, the number of children with left coronary artery abnormalities dropped to 5, 2, and 1, respectively. Before IVIG administration, abnormal right coronary arteries were reported in 13 patients. Nevertheless, 2, 6, and 12 months after IVIG administration, the number of patients with right coronary artery abnormalities fell to 5, 1, and 1, respectively (Table 2).

Table 3 shows the status of the detected abnormalities in the patients' right and left coronary arteries at different time points based on early or late diagnoses. Late diagnoses were reported in 19 patients, of whom 31.6% and 26.30% had abnormalities in the left and right coronary arteries, respectively. In patients with early diagnoses, 21.10% and 11.30% had abnormalities in the left and right coronary arteries, respectively. Two months after medication, in the patients with late diagnoses, the rate of abnormalities in the

left and right coronary arteries fell to 15.80% and 0%, respectively. Similar decreasing trends were observed in the number of patients with abnormalities in the left coronary artery at 6 and 12 months after receiving the medication. A patient with an early diagnosis of an abnormal left coronary artery was reported 12 months after receiving IVIG plus ASA.

Table 4 demonstrates the association between coronary artery abnormalities and the medication time and age. No association was observed between the time of receiving medication and age. However, abnormalities in the right coronary artery were associated with sex 2 months after the initial medication (Table 5).

Table 1. Characteristics of the patients with KD

Variables	Status	Frequency	Percentage
Medication	Early (received IVIG plus ASA before 10 days with fever)	80	88.89
	Late (received IVIG after 10 days with fever)	10	11.11
Fever duration	Early (≤10 d)	73	81.11
	Late (>10 d)	17	18.89
Lymphadenopathy	yes	48	53.3
	no	42	46.7
Conjunctivitis	yes	78	86.7
	no	12	13.3
Strawberry tongue	yes	78	86.7
	no	12	13.3
Desquamation	yes	65	72.2
	no	25	27.8
Skin rashes	yes	72	80.0
	no	18	20.0
Indurative edema	yes	54	60.0
	no	36	40.0
Pyuria	yes	39	43.3
	no	51	56.7
Diarrhea	yes	4	4.4
	no	86	95.6
Arthritis	yes	2	2.2
	no	88	97.8
CRP (15)	Normal	11	12.2
	Abnormal	79	87.8
ESR (20)	Normal	2	2.2
	Abnormal	88	97.8
AST (40)	Normal	32	35.6
	Abnormal	58	64.4
ALT (40)	Normal	57	63.3
	Abnormal	33	36.7
ALP (360)	Normal	24	26.7
	Abnormal	66	73.3

KD, Kawasaki disease; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; AST, Aspartate transaminase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase

Table 2. Changes in CAAs in association with the timing of medication

Measures	Status	Statistics	Normal	Abnormal	Total	χ^2	*P* value
Left CA 2 months receiving medication Left CA 2 months receiving medication	Normal	n	69	0	69	17.395	<0.001
		%	100.00%	0.00%	100.00%		
	Abnormal	n	16	5	21		
		%	76.20%	23.80%	100.00%		
Left CA 6 months after receiving medication	Normal	n	84	1	85	7.701	0.006
		%	98.80%	1.20%	100.00%		
	Abnormal	n	4	1	5		
		%	80.00%	20.00%	100.00%		
Left CA 12 months after receiving medication	Normal	n	87	1	88	0.023	0.88
		%	98.90%	1.10%	100.00%		
	Abnormal	n	2	0	2		
		%	100.00%	0.00%	100.00%		
Right CA 2 months after receiving medication	Normal	n	76	1	77	18.41	<0.001
		%	98.70%	1.30%	100.00%		
	Abnormal	n	9	4	13		
		%	69.20%	30.80%	100.00%		
Right CA 6 months after receiving medication	Normal	n	85	0	85	17.191	<0.001
		%	100.00%	0.00%	100.00%		
	Abnormal	n	4	1	5		
		%	80.00%	20.00%	100.00%		
Right CA 12 months after receiving medication	Normal	n	89	0	89	-	-
		%	100.00%	0.00%	100.00%		
	Abnormal	n	1	0	1		
		%	100.00%	0.00%	100.00%		

CA, Coronary artery; CAAs, Coronary artery abnormalities

Table 3. Association between CAAs and the time of diagnosis at different time points after medication

Left Coronary Artery	Status	Statistics	Diagnosis		χ^2	*P* value	Right Coronary Artery	Diagnosis		χ^2	*P* value
			Early (≤10 days with fever)	Late (>10 days with fever)				Early (≤10 days with fever)	Late (>10 days with fever)		
Before receiving medication	Normal	n	56	13	0.915	0.339	before receiving medication	63	14	2.747	0.097
		%	78.90%	68.40%				88.70%	73.70%		
	Abnormal	n	15	6				8	5		
		%	21.10%	31.60%				11.30%	26.30%		
2 months after receiving medication	Normal	n	69	16	4.807	0.028	2 months after receiving medication	66	19	1.147	0.234
		%	97.20%	84.20%				93.00%	100.00%		
	Abnormal	n	2	3				5	0		
		%	2.80%	15.80%				7.00%	0.00%		
6 months after receiving medication	Normal	n	70	18	1.025	0.311	6 months after receiving medication	70	19	0.271	0.603
		%	98.60%	94.70%				98.60%	100.00%		
	Abnormal	n	1	1				1	0		
		%	1.40%	5.30%				1.40%	0.00%		
12 months after receiving medication	Normal	n	70	19	0.271	0.603	12 months after receiving medication	71	19	-	-
		%	98.60%	100.00%				100.00%	100.00%		
	Abnormal	n	1	0				0	0		
		%	1.40%	0.00%				0.00%	0.00%		

CA, Coronary artery; CAA, Coronary artery abnormalities

Table 4. Association between CAAs and the timing of medication and age

CAA	Status	Statistics	Age			χ^2	*P* value
			≤24 mon	24–60 mon	≥60 mon		
LCA before receiving medication	Normal	n	23	30	16	3.644	0.162
		%	74.2%	71.4%	94.1%		
	Abnormal	n	8	12	1		
		%	25.8%	28.6%	5.9%		
RCA before receiving medication	Normal	n	25	35	17	3.643	0.162
		%	80.6%	83.3%	100.0%		
	Abnormal	n	6	7	0		
		%	19.4%	16.7%	0.0%		
LCA 2 months after receiving medication	Normal	n	29	39	17	1.249	0.535
		%	93.5%	92.9%	100.0%		
	Abnormal	n	2	3	0		
		%	6.5%	7.1%	0.0%		
RCA 2 months after receiving medication	Normal	n	28	40	17	2.054	0.358
		%	90.3%	95.2%	100.0%		
	Abnormal	n	3	2	0		
		%	9.7%	4.8%	0.0%		
LCA 6 months after receiving medication	Normal	n	30	41	17	0.535	0.765
		%	96.8%	97.6%	100.0%		
	Abnormal	n	1	1	0		
		%	3.2%	2.4%	0.0%		
RCA 6 months after receiving medication	Normal	n	30	42	17	1.925	0.382
		%	96.8%	100.0%	100.0%		
	Abnormal	n	1	0	0		
		%	3.2%	0.0%	0.0%		
LCA 12 months after receiving medication	Normal	n	30	42	17	1.925	0.382
		%	96.8%	100.0%	100.0%		
	Abnormal	n	1	0	0		
		%	3.2%	0.0%	0.0%		
RCA 12 months after receiving medication	Normal	n	31	42	17	------	------
		%	100.0%	100.0%	100.0%		
	Abnormal	n	0	0	0		
		%	0.0%	0.0%	0.0%		
Total		n	31	42	17		
		%	100.0%	100.0%	100.0%		

CAAs, Coronary artery abnormalities; RCA, Right coronary artery; LCA, Left coronary artery

Table 5. Association between CAAs and the timing of medication and sex

CAA	Status	Statistics	Sex		χ^2	*P* value
			Girls	Boys		
LCA before receiving medication	Normal	n	30	39	0.191	0.662
		%	78.90%	75.00%		
	Abnormal	n	8	13		
		%	21.10%	25.00%		
RCA before receiving medication	Normal	n	35	42	2.283	0.131
		%	92.10%	80.80%		
	Abnormal	n	3	10		
		%	7.90%	19.20%		
LCA 2 months after receiving medication	Normal	n	35	50	0.686	0.408
		%	92.10%	96.20%		
	Abnormal	n	3	2		

		%	7.90%	3.80%		
RCA 2 months after receiving medication	Normal	n	38	47	3.869	0.049
		%	100.00%	90.40%		
	Abnormal	n	0	5		
		%	0.00%	9.60%		
LCA 6 months after receiving medication	Normal	n	37	51	0.051	0.822
		%	97.40%	98.10%		
	Abnormal	n	1	1		
		%	2.60%	1.90%		
RCA 6months after receiving medication	Normal	n	38	51	0.739	0.390
		%	100.00%	98.10%		
	Abnormal	n	0	1		
		%	0.00%	1.90%		
LCA 12 months after receiving medication	Normal	n	38	51	0.739	0.390
		%	100.00%	98.10%		
	Abnormal	n	0	1		
		%	0.00%	1.90%		
RCA 12 months after receiving medication	Normal	n	38	52	------	-------
		%	100.00%	100.00%		
	Abnormal	n	0	0		
		%	0.00%	0.00%		
Total		n	38	52		
		%	100.00%	100.00%		

CAAs, Coronary artery abnormalities; RCA, Right coronary artery; LCA, Left coronary artery

DISCUSSION

The present study was conducted on children with KD to assess the effects of IVIG on coronary artery abnormalities. Many studies have reported the effects of IVIG plus ASA on the resolution of coronary artery abnormalities, with variations in the timing of diagnosis and fever duration. [1,6,9-15] Boys accounted for the majority of our study population with KD, similar to previous studies. [16,17] The mean age of our children with KD (43 mon) was higher than that in many studies such as those by Samadli et al [18] and Kil et al. [17] Concordant with a study by Singh et al, [2] all our patients had a fever, which declined after medication such that 78.9% had a significant decrease in fever within 48 hours of medication. Additionally, 14.4% of our patients had fever reduction within the third day, 1 patient within the fourth day, and 3 patients within the fifth day. In 2 patients, fever decreased on the sixth and the eighth days, comparable with the results reported by Bal et al. [19] Considering these issues, patients with KD who had a decline in fever levels after the normal period (48 h) showed treatment resistance. Binder et al [20] found that more than four-fifths and nine-tenths of their patients with KD had elevated CRP and ESR, respectively, and half had leukocytosis and two-fifths developed thrombocytosis during hospitalization. They also reported that the most common symptoms were fever (100%), non-purulent conjunctivitis and exanthema. Moreover, three-fourths of their patients had changes in lips and oral cavities, including cracked lips and strawberry tongue. Cervical lymphadenopathy was observed in 70%, and nearly half of the studied patients experienced changes in extremities, including palmar or plantar erythema. About one-fifth complained of gastrointestinal symptoms such as diarrhea, stomach ache, and vomiting. Binder and colleagues also found an increase in ESR in their KD patients with coronary artery abnormalities compared with those without abnormalities

in the coronary arteries, although the difference was not statistically significant. Kil et al [17] reported no changes in ALT in their KD patients; still, they found elevated neutrophil/lymphocyte differential, CRP, Alb, PLT count, and Hb.

Asadi-Pooya et al [7] reported that one-fourth of their patients had high ESR. The other observed features in their study population were common changes in the lips (eg, fissuring, cracking, and bleeding), conjunctivitis with a similar trend in oral changes, erythema, edema, and desquamation. They also found maculopapular, scarlatiniform, and morbilliform rashes in four-fifths of the studied patients.

Li et al [21] reported changes in oral mucosa, cervical lymphadenopathy, swelling of the extremities, polymorphous rashes, strawberry tongue, desquamation, conjunctivitis, skin rashes, and indurative edema in their patients, while only half had lymphadenopathy.

In a report from Pakistan, all patients with KD had fevers and eye changes. Additionally, almost all had changes in the lips and oral cavities, and more than half had cervical lymphadenopathy and rashes. [22]

In the present study, more than half of the patients had cervical lymphadenopathy, less than half had conjunctivitis, 86.7% had strawberry tongue, 72.2% had desquamation, 80% had skin rashes, 60% had indurative edema, 43.3% had pyuria, 4.4% had diarrhea, and 2.2% had arthritis. Our results demonstrated that coronary artery abnormalities changed in tandem with the timing of IVIG. Of 19 patients with late diagnoses, 31.6% and 26.30% had abnormal left and right coronary arteries, respectively. Among those diagnosed early, the trends of abnormality were 21.10% and 11.30%, respectively. The initial treatment was done on 21 patients with abnormalities in the left coronary artery; however, the numbers decreased 5, 2, and 1 after 2, 6, and 12 months. Prior to IVIG administration, abnormal right coronary arteries were reported in 13 patients. Nonetheless, 2, 6, and 12 months after IVIG administration, the number of patients with right coronary artery abnormalities fell to 5, 1, and 1, respectively. Accordingly, all our patients with coronary artery abnormalities recovered 1 year after the initial medication. Bal et al [19] showed that the risk for coronary artery abnormalities was significantly lower among patients who received treatment early than in those who received treatment late. They also concluded that the resolution of coronary artery abnormalities was significantly shorter in patients who received treatment early.

Samadli et al [18] reported that 10 patients with KD had coronary artery abnormalities in the acute stage. Of these patients, 7 received treatment early: 2 cases on day 5, 2 cases on day 6, 1 case on day 8, and 2 cases on day 9. In addition, there were still 3 cases receiving IVIG late. They concluded that the resolution of coronary artery abnormalities was associated with the timing of treatment. Subsequent use of IVIG may result in a higher occurrence rate of coronary artery abnormalities, and more severe vasculitis requires more aggressive therapy. In a prior investigation, the incidence of coronary artery abnormalities during the convalescent phase was significantly higher in the late IVIG treatment. [23] A recent randomized clinical trial showed a lower rate of coronary artery abnormalities in high-risk patients treated with 3 to 5 weeks of oral steroids in addition to conventional IVIG. [24] Therefore, the early IVIG treatment is considered effective for suppressing systemic inflammation and preventing coronary artery abnormalities. Although IVIG is highly effective in KD, approximately 10% to 20% of patients with KD develop recrudescent or

persistent fever at least 36 hours after the end of their IVIG infusion. [25]

Regarding the decrease in coronary artery abnormalities based on early or late IVIG treatments, Bal et al [19] reported that 81.1% of their patients received the first dose of IVIG early and 18.9% late. Overall, resolution in coronary artery abnormalities within 9 weeks was recorded in 65.2% of 23 children. Among the children with KD and coronary artery abnormalities who received IVIG late, 50% showed resolution, as opposed to 76.9% of the children who received IVIG early. In the present study, resolution in coronary artery abnormalities occurred in 95.65% of the studied patients within 6 months after disease onset. Among the study population, 10 children received IVIG late: 1 patient received the medication on the 14th day, 2 received medication on the 13th day, 3 received medication on the 12th day, and 4 received medication on the 11th day after KD onset.

The duration of fever decreases dramatically after the initial IVIG treatment, which is attributed to depressed systemic inflammation. Further, the potential mechanisms of IVIG treatment may include several immune regulatory processes. [19]

Persistent fever after IVIG therapy is one of the risk factors predicting coronary artery abnormalities. [18]

Kil et al [17] reported that most of their patients with KD presented with incomplete KD, with a lower incidence rate of coronary artery abnormalities. Asadi-Pooya et al [7] reported that the median ESR in the cardiac group was 64 mm/h, which was not statistically significantly different from that of the noncardiac group. Li et al [21] concluded that higher CRP and PLT and lower Alb and Hb were associated with IVIG resistance and the risk of coronary artery abnormalities. [26] In an investigation by Bal et al, [19] 3 patients did not respond to the first dose of IVIG and received a second dose. In the present study, before IVIG administration, abnormal left coronary arteries were reported in 21 patients. nonetheless, 2, 6, and 12 months following IVIG administration, the number of children with left coronary artery abnormalities declined to 5, 2, and 1, respectively. The patient who had an abnormal left coronary artery 1 year from the initiation of medication was a 13-month-old boy whose left coronary artery size at initial medication was 2.7 mm, which decreased to 2.1 mm after 1 year. He received IVIG early (6 days after fever onset). When undergoing echocardiography 12 months after IVIG treatment, the patient was 25 months of age, and the size of 2.1 mm for this age is normal when our categorization of age was based on the admission time. Moreover, prior to IVIG administration, abnormal right coronary arteries were reported in 13 patients. Nevertheless, 2, 6, and 12 months after IVIG administration, the number of patients with right coronary artery abnormalities dropped to 5, 1, and 1, respectively. The latter patient had a resolution in the right coronary artery 12 months after medication. The resolution of coronary artery abnormalities is associated with late or early IVIG administration. The risk for coronary artery abnormalities and the resolution time of coronary artery abnormalities are significantly shorter in patients who receive medication early than in those who receive IVIG late. [19]

It has been suggested that earlier treatment, particularly before the fifth day of the disease, is associated with a decreased risk of non-response to IVIG. [27] IVIG is administered in high doses, with marked improvements usually noted within 24 hours. If the fever does not respond, an additional dose may have to be considered. In rare cases, a third dose may be given to the child. IVIG by itself is most useful within the first 7 days of the onset of fever

in terms of preventing coronary artery aneurysms. IVIG given within the first 10 days of the disease reduces the risk of damage to the coronary artery in children, without serious adverse effects. [28] In a study by Binder et al, [20] 6 patients had cardiac complications; 5 patients experienced tubular dilatation in the coronary artery and 1 patient suffered an aneurysm. In addition, pericardial effusion was observed in 1 patient. The patients with tubular dilatation in the coronary artery had a fever lasting for 5 to 15 days. These findings suggest that there may be etiologic substances that induce continuous inflammation in the pathologic lesions of the coronary arteries, and the severity and chronicity of the lesions may depend on the immune status of the host against KD insults. The immune status of patients with giant aneurysms may not control the etiologic substances properly and may induce ongoing inflammation in coronary artery pathologic lesions. Therefore, immune-modulators such as IVIG and corticosteroids may be limited in ability to remove substances inducing sustained coronary artery injuries. [17] Noguchi et al [13] demonstrated that plasma exchange with 5% Alb was effective for refractory KD in patients resistant to other treatments for KD. In conjunction with IVIG, our data suggested that the use of low-dose ASA during acute KD was not inferior to high-dose ASA in reducing the risk of coronary artery abnormalities. Notably, ASA at any dose has never been shown to reduce the risk of coronary artery abnormalities.

The limitations of the current study were a lack of proper information in the patients' profile regarding the second echocardiographic examination for detecting changes in the coronary artery diameter and the low number of patients for the generalization of the results.

CONCLUSIONS

According to the results of the present study, IVIG plus ASA in patients with KD has a significant effect on left and right coronary artery abnormalities within 6 months, with the effect being stronger in the left coronary artery in patients diagnosed early. Although some of our patients with KD did not respond to IVIG treatment after 48 hours, medication with a second dose of IVIG and corticosteroids proved efficacious. Our findings suggest that ASA at a dose above 3 to 5 mg/kg/d may not be indicated in acute KD. It is necessary to develop a diagnostic test for KD and to provide more education to healthcare providers for the early recognition of KD.

Acknowledgments

The authors would like to thank the recruited patients and their parents for their participation in the present study.

Conflict of Interest

The authors declare no conflicts of interest.

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