Original Article

Impact of Early Treatment With High-Dose Intravenous Immunoglobulin on Incidence of Kawasaki Disease Complications in Iranian Children

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Abstract

Objective: Kawasaki disease (KD) occurs in five-year-old or younger children. This study aimed to evaluate the impact of high-dose intravenous immunoglobulin plus acetylsalicylic acid therapy on the prevention and treatment of coronary artery lesions and to evaluate the impact of high-dose acetylsalicylic acid (ASA) on the hearing of the patients.

Materials and methods: In this retrospective cohort study, 31 patients with KD were followed from January 2012 to December 2015. The clinical, para-clinical, color Doppler echocardiogram and audiometry results were evaluated.

Results: Overall, seven cases (22.6%) developed coronary artery aneurysm (CAA) in the acute phase of the disease, of whom only two still had CAA at the end of the treatment (6%). One of the five children with CAA recovery had a delay in the onset of treatment and one of two patients with persistent CAA at the end of treatment was admitted within the first 10 days. There was no evidence-based abnormal liver biochemical test. None of the patients developed sensorineural hearing loss (SNHL) on audiometry tests conducted before and after treatment.

Conclusion: Recovery of coronary artery lesions was 71.43% after 28 days of the onset of treatment. The distribution of coronary artery aneurysm was not different in terms of the time of the treatment initiation (P-Value = 0.371). None of the children had a sensorineural hearing loss (SNHL) 48 hours and 4 weeks after treatment.

Keywords: Mucocutaneous Lymph Node Syndrome; Aspirin; Immunoglobulins; Coronary Artery Disease; Hearing disorders

Introduction

Kawasaki disease (KD) is a systemic syndrome of unknown etiology that predominantly occurs in children younger than five years (1). The diagnostic criteria for KD are based on the presence of five or more days of fever and at least four of the five principal clinical features, including bilateral bulbar conjunctival injection, oral mucous membrane

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changes, including injected or fissured lips, injected pharynx or strawberry tongue, polymorphous rash, cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter), and peripheral extremity changes, including erythema of palms or soles, edema of hands or feet (acute phase), and periungual desquamation (convalescent phase) (2). The incidence of KD is ranged widely from 4 to 216 in 100,000, and over 75% of the cases occur in children less than 5 years of age (3).

As the most important complication, coronary artery lesions, if not treated, may lead to myocardial infarction, ischemic heart disease, and sudden death (4). The incidence of central nervous system involvement presenting as aseptic meningitis, seizure, ataxia, transient facial paralysis, sensorineural hearing loss, and subdural effusion ranges from 1.1% (5,6) to 30% (7,8) in KD (9).

Treatment of KD is according to a standardized protocol in most medical institutions. High-dose intravenous immunoglobulin injection (IVIG) (2 g/kg) and oral acetylsalicylic acid (ASA) (80-100 mg/kg/day within 10 days of the start of fever or 24-48 hours after defervescence followed by low-dose ASA (3-5 mg /kg/day)) prevents and reduces coronary artery lesions and damage (10). There are contradictory reports that early detection and treatment compared to delayed treatment would improve the treatment success and prevent complications of Kawasaki's disease, particularly cardiovascular complications (10-12).

It should be noted that the use of high-dose ASA sometimes causes various side effects such as abdominal pain, acute hepatitis, sensorial hearing loss, tinnitus, gastric ulcer, gastrointestinal bleeding, and electrolyte abnormalities (9, 13-16). In this regard, sensorineural hearing loss may develop due to the inflammatory reaction in the acute phase of KD or due to the side effects of high-dose ASA.

The aims of this study were to evaluate the effect of early treatment on the incidence of complications, especially coronary artery complications, and to assess the side effects of treatment on sensorineural hearing loss in Iranian children with Kawasaki disease.

Materials and methods

All pediatrics with a clinical diagnosis of KD who were admitted to Imam Khomeini Hospital, Tehran from January 2012 to December 2015 were included in this retrospective study (n=31). The study was approved by the Ethics Research Committee of Tehran University of Medical Sciences (IR.TUMS.REC.1394.2065) and informed consent was obtained from the parents/legal guardians of the children included in the study. Patients who had a fever for more than 30 days at presentation were not included in the study.

KD was diagnosed when a fever lasted five days or longer and at least four of the five clinical manifestations were observed according to the 2004 American Heart Association criteria (17).

In the acute phase, a combination of intravenous immunoglobulin (Green Cross, 2 g/kg, 12 hours) and oral ASA (80-100 mg/kg/day, three times a day) (Osvah Co, Tehran, Iran) were administered. When a febrile condition continued for 48 hours, low-dose ASA (3–5 mg/kg/day, once daily) was replaced with the previous high-dose regimen for eight weeks. It should be noted that all of the patients were treated with IVIG and ASA immediately after a diagnosis of KD was confirmed.

The laboratory tests included erythrocyte sedimentation rate (ESR), platelet count, C-reactive protein (CRP) and hemoglobin (HGB). In addition, aspartate transaminase (AST) and alanine transaminase (ALT) levels were measured 48 hours after starting treatment.

Color Doppler echocardiography was done at the time of diagnosis, at least 20 days after the end of treatment, and 6-12 months after treatment. Coronary artery abnormality (CAA) was based on a luminal diameter of more than 3.0 mm and an internal diameter of > 1.5 times that of an adjacent segment (18).

Audiometry was done before and 48 hours after starting treatment and at least 20 days after the end of treatment. Hearing was assessed using the auditory brainstem response (ABR) and tympanometry (ICS Charter, Madsen, Denmark). Children older than 3 to 4 years were evaluated by pure-tone audiometry (PTA) as well as tympanometry and ABR. In the ABR test, click and tone burst stimuli (80 dB) were used to evoke abnormal findings.

The Clark classification was applied for determining the severity of hearing loss in PTA using Orbiter 922 as a clinical audiometer at 250, 500, 1000, 2000, 3000, 4000, and 8000 Hz (19).

The SPSS software package version 21.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data at a significant level of $p < 0.05$.

Results

Thirty-one children with KD were enrolled of whom 17 (54.84%) were boys. The mean (SD) and median

(range) age of the patients at the time of KD diagnosis was 43.01 (31.88) and 48 months (10-84), respectively. The season of the KD onset was spring in 41.94 % (13 cases), winter in 32.26 % (10 cases), summer in 12.90 % (4 cases), and autumn in 12.90 % (4 cases) of the patients.

Treatment started within the first 10 days in 17 (54.84%) cases (early detection group) and after 10 days of the disease onset (10-30 days) in 14 cases (46.7%) (Late detection group). Clinical manifestations and laboratory findings are presented in Table 1.

Table 1: Clinical and para-clinical manifestations in the acute phase of Kawasaki disease

Clinical manifestation	Frequency (%)
Oral mucous membrane changes*	28(90.32)
bilateral bulbar conjunctival injection	21(67.74)
Polymorphous rash	19(61.29)
Cervical lymphadenopathy**	17 (54.84)
Fever ≥ 5 days	15(48. 39)
Peripheral extremity changes	17(54.84)
Erythema of palms or soles	6(19.35)
Para-clinical results	
ESR (>40 mm/hr)	23(74.19)
Platelet(> 500,000)	16(51.6)
HGB (<9 gr/dl)	26(83.87)
C-Reactive protein (>+3)	24(80.64)

*Oral mucous membrane changes including injected or fissured lips, injected pharynx or strawberry tongue
**Cervical lymphadenopathy (at least one lymph node >1.5 cm in diameter).
ESR: Erythrocyte sedimentation rate, HGB: Hemoglobin

The mean (SD) and median (IQR) duration of hospital stay were 5.32 (3.094) and 50.0 (4.0) days, respectively. The mean (SD) duration of hospital stay was 5.4 (1.95) days in the early detection and 5.2 (3.98) days in the late detection group, indicating no significant difference (CI 95%: -1.85 to 2.27).

Laboratory findings were compared between admission and discharge (end of treatment) (Table 2). The number of neutrophils, WBC, and lymphocytes increased and CRP decreased significantly at the time of discharge compared to the onset of treatment (P=0.002, P<0.001, P=0.01, and P=0.002, respectively) (Table 2).

Coronary artery aneurysms developed in seven patients (22.6%) in the acute phase of the disease, of whom only two still had an aneurysm at the end of the treatment (6%). One of the five children with CAA recovery had a delay in the onset of treatment and one of two patients with persistent CAA at the end of treatment was admitted within the first 10 days. There was no significant difference in CAA recovery between delayed and early treatment groups (McNemar's test, P=0.371). Demographic and clinical characteristics of the patients with coronary artery abnormality are presented in Table 3.

After defervescence, the mean (SD) AST and ALT were 476 (148) and 53 (44), respectively. There was no evidence-based abnormality in liver biochemical tests (ALT<40 and ALP<120).

None of the 31 patients had SNHL according to ABR and PTA on the first and second audiological assessments. A third audiological assessment was scheduled for all patients at least 20 days after the end of treatment, which was completed by 17 patients (54.84%). All of the cases had normal audiological tests in the follow-up visit.

Table 2: Comparison of lab results between admission and discharge among Kawasaki disease patients

Para-clinical Manifestation*	Median(IQR)		Z (P-Value)
	Admission day	Discharge day	
CRP	35.8(31.75)	7.3(26.8)	2.67(0.008)
ESR	84.0(73.0)	77.0(61.5)	-1.27(0.205)
WBC	14.9(10.59)	9.2(5.91)	-3.11(0.002)
RBC	4.19(0.87)	4.06(0.58)	-.37(0.710)
HGB	16.55(24.2)	10.65(2.0)	-1.25(0.21)
HCT	31.0(6.15)	30.3(8.75)	-.757(0.449)
PLT	397.5(254.7)	490.5(567.75)	-1.74(0.081)
NEUT	53.0(25.6)	40.4(20.45)	-3.323(<0.001)
LYMT	36.0(24.7)	49.5(27.15)	-2.59(0.010)
MON	3.50(5.55)	5.55(6.57)	-1.23(0.218)
EOS	3.39(2.7)	1.5(5.8)	-.562(0.574)

*CRP: C-reactive protein, ESR: Erythrocyte Sedimentation Rate, WBC: White Blood Cell
RBC: Red Blood Cell, HGB: Hemoglobin, HCT: Hematocrit, PLT: Platelet, NEUT: Neutrophil, LYMT: Lymphocyte, MON: monocyte, EOS: Eosinophils

Table 3: Demographic and clinical characteristics of patients with coronary artery abnormality

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age; month	11	40	10	10	12	84	64
Sex	male	male	female	male	male	female	male
Interval between disease onset and start of treatment	8	7	5	16	7	11	14
Fever ≥ 5 days	no	yes	yes	no	yes	no	yes
C-reactive protein (mg/dL)	20.8	50.0	54.5	18.0	64.0	14	84.0
Echocardiogram in acute phase*	LAD	LAD/LCX	LAD	RCA	RCA	LCX	RCA
Response to treatment	Yes	No	No	No	No	Yes	No

*Right Coronary Artery (RCA), Left Circumflex Artery (LCX), Left Anterior Descending (LAD).

Discussion

KD often occurs in five-year-old or younger children (20) with a peak incidence at 18-24 months (21). In the present study, the mean age at disease onset was below four years, which was similar to other studies in Iran (22-23) and some other countries such as Jamaica (24), China (25), Korea (26), and Poland (27).

KD is usually more common with boy to girl ratio of 1.5:1 (28). In this study, this ratio was 1.55:1, which was consistent with studies in Iran and some other countries (23, 29-31).

The incidence of KD has been reported to increase in the winter-spring months in different geographic regions (31-33). Similarly, the disease was more common in the winter and spring in the present study. KD is a systemic vasculitis with unknown etiology. The most important complication of KD is the development of coronary aneurysms in up to 25% of the untreated patients (34). The use of IVIG and aspirin is critical to treat KD and prevent its complications (35).

In a study by K. Bal et al. CA lesions reduced from 17% to 5% after IVIG therapy; this reduction ranged from 3.0% to 11.6% in patients within 10 days of disease onset and from 20% to 40% in patients with a delay in the onset of treatment (36).

In the present study, we compared the impact of early versus delayed treatment on cardiac complications. Arterial aneurysms developed in seven patients (22.6%), of whom only two (6%) still had aneurysms after treatment (at 3-4 weeks). One of the five children with CAA recovery (20%) had a delay in the onset of treatment and one of two patients with persistent CAA at the end of treatment (50%) was admitted within the first 10 days. In the present study, the distribution of artery aneurysms was not significantly different in terms of the timing of treatment initiation, which was consistent with the results of a study by Tse et al. from Canada (10). However, Du et al found that the rate of complications was lower in patients who received the treatment earlier than late treatments (18.3% vs 33.7%) (12). In addition, Kordidarian et al. found that the frequency of coronary artery aneurysms was lower in patients that received IVIG within the first 10 days of referral (11).

As mentioned earlier, high-dose ASA has been hypothesized to be a cause of hearing loss (14). Sensorineural hearing loss after treatment with ASA is known as 20 to 30 dB of mild hearing loss on both sides (37). ASA ototoxicity is reversible within 72 hours upon stopping ASA intake (38). The minimum serum levels of ASA that can change the hearing thresholds are unknown, but there may be a significant correlation between the serum level of ASA and hearing threshold shift (35-39). In the study, none of the patients had SNHL at the time of diagnosis, 48 hours after starting treatment and 20 days after the end of treatment.

The small sample size was one of the limitations of the present study. Another limitation of this retrospective study was the missing data about the type of infection and aneurysm. Furthermore, CAAs were not classified into small, medium-sized, and large (giant) aneurysms.

Conclusion

The results of this study showed 71.43% recovery in coronary artery aneurysms by IVIG and ASA one month after the onset of treatment. Treatment success was independent of time to receiving treatment. None of the children developed SNHL 48 hours and 4 weeks after treatment.

Conflict of Interests

Authors have no conflict of interests.

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