Evaluation of high-dose aspirin elimination in the treatment of Kawasaki disease in the incidence of coronary artery aneurysm

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ABSTRACT

Background : Standard first-step therapy for Kawasaki disease consists of Intravenous immunoglobulin and high dose Aspirin (80-100 mg/kg/day). The standard dose of Intravenous immunoglobulin (2gr/kg) is strongly effective in reducing the risk of coronary arteries abnormalities. So, the proper dose and efficacy of Aspirin to decrease the risk of coronary arteries abnormalities is a controversial issue. In this study, it is tried to assess the result of eliminating high-dose Aspirin in the treatment of the acute phase of Kawasaki and observe the incidence rate of coronary arteries abnormalities when only Intravenous immunoglobulin was administered.

Methods : This study is a prospective randomized, open-label, blinded end-points clinical trial performed in Afzalipour hospital in Kerman University of Medical Sciences from September 2017 to September 2018 in 62 patients with typical and atypical Kawasaki disease. The study group received Intravenous immunoglobulin (2 g/kg) and the control group get the same dose of Intravenous immunoglobulin plus Aspirin with the dose of 80-100 mg/Kg/day until they were afebrile for 48 hours. Afterward, both groups received a daily single dose (3-5 mg/kg) of Aspirin for six weeks. Echocardiography was done after two weeks, six weeks, and six months. Internal diameter of the left and right main coronary arteries was measured and then the corresponding Z-score was calculated.

Results : In the study group, coronary arteries abnormalities decreased from 38.7% in the 2nd week to 16.1% in the 6th month. In the control group, it declined from 54.8% to 22.6%. There was no statistically significant difference between the groups in term of frequency of abnormal coronary arteries at the study period (P=0.151).

Conclusions : We concluded that high dose Aspirin does not have a significant role in preventing coronary arteries abnormalities in Kawasaki disease and giving standard 2 gr/kg/day Intravenous immunoglobulin without high-dose Aspirin in acute-phases therapy does not increase the risk of coronary arteries abnormality.

Keywords : Coronary arteries abnormalities, high-dose aspirin, intravenous immunoglobulin therapy, Kawasaki disease

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INTRODUCTION

Kawasaki disease (KD) is a type of acute febrile vasculitis, which is typically a self – limited condition mostly involving medium-sized blood vessels resulting in coronary artery abnormalities (CAA) in children in developed countries.[1-3] Standard first-step therapy for KD consists of intravenous immunoglobulin (IVIG) and high-dose aspirin (HDA) (80–100 mg/kg/day). According to recommendations of the American Heart Association criteria (AHA), this therapy has a synergic generalized anti-inflammatory effect. In this regard, HDA has anti-inflammatory effects, but in lower doses, it mainly acts as an antithrombotic agent.

Studies have shown that IVIG with a dose of 2 g/kg/day is strongly effective in reducing the risk of CAA in patients with KD[4-9] On the other hand, the proper dose and efficacy of aspirin to decrease the risk of CAA is mostly unknown and controversial.[4,10-12] Two meta-analyses have shown that HDA is not effective in reducing the risk of CAA in KD, and it solely depends on IVIG dose.[8,9]

This study was conducted to assess the results of eliminating HDA in treatment of acute phase of KD on erythrocyte sedimentation rate (ESR), hemoglobin (Hb) level, platelet count, coronary arteries diameter, and the incidence rate of CAA when only IVIG was administered in study groups.

METHODS

This is a prospective randomized, open-label, blinded end points clinical trial that was performed in Afzalipour Hospital in Kerman University of Medical Sciences from September 2017 to September 2018. Participants included children who were admitted with typical and atypical KD according to the AHA criteria for KD. Inclusion criteria were younger than 18 years and confirmed KD. Exclusion criteria included the presence of structural heart disease, fever for more than 10 days, and the presence of other possible infections. The participants were assigned to study and control groups using a simple sampling method. The study group received IVIG with a dosage of 2 g/kg over 10–12 h and the control group received the same dose of IVIG plus acetylsalicylic acid (ASA) with a dose of 80–100 mg/kg/day in every six hours until they were afebrile for 48 h. Next, they received a daily single dose of 3–5 mg/kg ASA for 6–8 weeks or until the coronary aneurysm is completely healed. The treatment was started before day 10 of fever onset for all the participants.

Echocardiography was done after 2 weeks, 6 weeks, and 6 months. The internal diameter of the left and right main coronary arteries and left anterior descending (LAD) artery was measured by echocardiography and then the Z-score of these arteries was calculated. CAA was defined as a *Z*-score 2.5 or higher. Furthermore, laboratory tests including Erythrocyte sedimentation rate (ESR), Hemoglobin (Hb), and platelet count were done for all the patients three times. Furthermore, individual characteristics such as age, sex, height, and weight were assessed.

We obtained informed consent from the patients and their parents. Furthermore, the protocol of this study was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethics code: IR.KMU.AH.REC.1396.1844). Data were analyzed using IBM SPSS Statistics package version 22.0(SPSS Inc., Chicago, U.S.A). Descriptive results were presented by mean, standard deviation, and frequency tables. Chi-square test, Independent *t*-test, generalized Estimating Equation Model, and repeated measure analysis of variance (ANOVA) were performed for the data analysis. For all the statistical tests, Cronbach's alpha level of 0.05 was set as the significance level.

Table 1: Comparison of mean or frequency of various characteristics between the study group and control groups at the baseline time

Variable	Mean±SD			*P*
	Total	Control group	Study group	
Age (years)	3.75 ± 1.23	3.77 ± 1.20	3.74 ± 1.29	0.919
Weight (kg)	15.11 ± 3.77	15.19 ± 3.64	15.03 ± 3.96	0.868
Body surface	0.63 ± 0.12	0.64 ± 0.11	0.63 ± 0.12	0.853
ESR	77.04 ± 22.27	80.40 ± 19.05	73.80 ± 24.88	0.251
Hb	10.36 ± 1.37	10.64 ± 1.38	10.05 ± 1.31	0.100
Platelet count	504.72 ± 185.97	496.83 ± 182.85	512.61 ± 191.72	0.741
LMCA diameter	3.25 ± 0.62	3.33 ± 0.67	3.16 ± 0.57	0.277
LAD artery diameter	2.48 ± 0.52	2.42 ± 0.58	2.54 ± 0.45	0.36
RCA diameter	2.37 ± 0.62	2.41 ± 0.66	2.32 ± 0.59	0.582
Sex, *n* (%)				
Male	41 (66.1)	22 (71)	19 (61.3)	0.296
Female	21 (33.9)	9 (29)	12 (38.7)	

ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, SD: Standard deviation, LMCA: Left main coronary artery, RCA: Right coronary artery, LAD: Left anterior descending

RESULTS

Of 62 participants in the study, 31 patients were assigned to the study group and 31 to the control group. Table 1 shows the baseline characteristics of the two groups. About 71% (n = 22) of the control group and 61.3% (n = 19) of the study group were males. However, sex distribution had no significant difference between the groups. The two groups did not show a significant difference in terms of mean weight (P = 0.868) and body surface (P = 0.853). The median and interquartile range of age for both the groups were 4 years and 3–5 years, respectively. Furthermore, the mean of age of them did not show significant difference (P = 0.919). Furthermore, means of ESR level (P = 0.251), Hb level (P = 0.100), and platelet count (0.741) were not significantly different in terms of the groups at baseline time. The mean left main and right coronary artery (RCA) and LAD artery diameter and *Z*-sore were the same in both groups (P = 0.277, P = 0.582, and P = 0.36) [Table 1].

The mean (±standard deviation [SD]) of the ESR level for the study period was 47.07 (±30.45). The total mean (±SD) of ESR the level at baseline, after 6 weeks, and after 6 months was 77.41 (±22.27), 48.53 (±14.41), and 15.75, respectively, indicating a reduction trend at the study period. The repeated measures ANOVA test revealed that the mean ESR level did not vary between the control and study groups significantly (P = 0.590), but it varied significantly across the study time period (P < 0.001). Moreover, there was no interaction effect between time and group type for ESR level (P = 0.227). Overall, the mean (±SD) Hb level was 10.62 (±1.30) and had an increasing trend in the studied period. The mean (±SD) Hb level in the control group was 10.83 (±1.30), which was significantly higher compared to the study group (mean = 10.38). Although the mean Hb level between the two groups (P = 0.031) and in terms of time (P < 0.001) had significant variations, there was no interaction effect between time and group type (P = 0.087). Overall, the mean platelet count did not show a significant difference (P = 0.392) between the study group (mean = 428.21 × 10^3/μL) and control group (mean = 407.75 × 10^3/μL). Generally, platelet count had a significant decreasing trend over time (P < 0.001) and both groups showed the same pattern; nevertheless, there was no significant interaction effect between (P = 0.076) time and the treatment group [Table 2].

The total mean of left main coronary artery (LMCA) diameter at baseline time, after 6 weeks, and after 6 months was 3.23, 3.08, and 2.69, respectively, indicating a significant reduction over the study period (P = 0.001). The pattern of LMCA diameter reduction was similar in both groups. The mean LMCA diameter in the study group (mean = 3.01) and control group (mean = 3.01) did not show the difference (P = 0.995), and there was no significant interaction effect between time and groups (P = 0.073). The mean RCA diameter over time (baseline = 2.39, after 6 weeks = 2.33, and after 6 months = 2.08) showed a significant reduction (P < 0.001) with the same reduction

Table 2: Repeated-measures analysis of variance of the effects of treatment in terms of the group, time, and their interaction

Variable	Time	Mean±SD			*P**	*P***	*P****
		Control group	Study group	Total			
ESR	Baseline	81.27±18.76	73.80±24.88	77.41±22.27	0.590	<0.001	0.277
	After 6 weeks	49.24±13.47	47.87±15.43	48.53±14.41			
	After 6 months	15.51±13.10	15.96±14.03	15.75±13.47			
	Overall	48.32±30.87	45.88±30.15	47.07±30.45			
Hb	Baseline	10.83±1.38	10.10±1.29	10.50±1.37	0.031	<0.001	0.087
	After 6 weeks	10.81±1.28	10.21±1.18	10.53±1.26			
	After 6 months	11.09±1.23	10.97±1.15	11.03±1.18			
	Overall	10.83±1.30	10.38±1.27	10.62±1.30			
Platelet count	Baseline	513.57±183.38	547.07±181.12	529.70±181.36	0.392	<0.001	0.076
	After 6 weeks	410.78±99.62	382.23±93.70	397.03±96.98			
	After 6 months	369.67±101.29	308.26±113.19	340.11±110.59			
	Overall	428.21±144.61	407.75±165.93	418.22±155.26			
LMCA diameter	Baseline	3.33±0.67	3.13±0.56	3.23±0.62	0.955	0.001	0.073
	After 6 weeks	3.13±0.57	3.03±0.60	3.08±0.58			
	After 6 months	2.55±0.56	2.84±1.39	2.69±1.06			
	Overall	3.01±0.68	3.01±0.93	3.01±0.81			
RCA diameter	Baseline	2.44±0.65	2.33±0.60	2.39±0.62	0.239	<0.001	0.905
	After 6 weeks	2.38±0.58	2.27±0.54	2.33±0.56			
	After 6 months	2.14±0.41	2.03±0.35	2.08±0.38			
	Overall	2.31±0.57	2.21±0.51	2.26±0.54			
LAD artery diameter	Baseline	2.42±0.58	2.54±0.45	2.48±0.52	0.095	<0.001	0.017
	After 6 weeks	2.26±0.53	2.38±0.45	2.32±0.49			
	After 6 months	1.70±0.43	2.04±0.49	1.87±0.49			
	Overall	2.13±0.60	2.32±0.50	2.22±0.56			

*Difference between two group, **Difference between the three times, ***Interaction effect between time and group. ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, SD: Standard deviation, LAD: Left anterior descending, LMCA: Left main coronary artery, RCA: Right coronary artery

patterns for both groups; however, no interaction effect was observed for time and group [Table 2]. About 29% of the patients in the study group and 38.7% in the control group had an aneurysm of LMCA at baseline time of the study. After 6 months, these percentages declined to 12.9% and 6.5% for study and control groups, respectively. There was no difference between the groups in terms of the decreasing trend of the frequency of LMCA aneurysm ($P = 0.527$). The frequency of LMCA aneurysm at the 6th week had no significant difference ($P = 0.253$) compared to the baseline time, but the frequency showed a significant reduction at the 6th month of the disease period ($P = 0.001$).

Furthermore, 16.1% and 25.8% of the patients in the study and control groups had abnormal RCA diameter, respectively, at the baseline time. However, it decreased to 6.5% and 16.1% after 6 months, although there was no difference between the groups ($P = 0.250$). The RCA aneurysm had a significantly decreasing trend in the 6th week ($P = 0.039$) and the 6th month ($P = 0.001$) compared to the baseline time.

Furthermore, frequency of LAD abnormality showed significant decreasing at the 6th week ($P = 0.002$) and the 6th month ($P < 0.001$) compared to the baseline time, but there was no significant difference between the groups ($P = 0113$).

Overall, 58.1% and 54.8% of the patients in study and control groups had abnormal coronary arteries diameter (Z score >2.5) in at least one of the three coronary arteries at the baseline time that it decreased to 25.8% and 22.6% at the 6th month, respectively. There were not differences between the groups in terms of frequency of abnormal coronary arteries abnormality at study period ($P = 0.907$). The frequency of coronary arteries aneurysm at the 6th week had no significant difference ($P = 0.592$) than the baseline time, but the frequency showed significant decrease at 6th month of the disease period ($P < 0.001$) [Table 3].

DISCUSSION

CAA is the most serious complication of KD, so it is critical to find the most effective aspirin dose to prevent this complication. Although HDA does not seem effective in preventing the CAA in KD,[7,9,10] still aspirin is a part of the standard first-step therapy of KD. The meta-analysis of Durongpisitkul *et al.*[8] shows that the incidence of CAA was almost the same in KD patients who received 2 g/kg/day IVIG with a high dose of aspirin (80–100 mg/kg/day) compared with patients who received IVIG with a lower dose of aspirin (<80 mg/kg/day), which is consistent with our study. Hsieh *et al.*[4] discussed that aspirin does not have a significant role in preventing CAA in KD patients, which is also consistent with our study.

Ito and Kiyosawa[13] argued that the occurrence of CAA in patients treated with both aspirin and IVIG was different from patients who were given only IVIG. However, its conclusion is inconsistent with ours as Ito and Kiyosawa used IVIG with doses of 400 mg/kg/day during 5 days of the acute phase of KD, which is different from the standard therapeutic dose of 2 g/kg/day. Hence, if the standard doses of IVIG were used in the Ito trial, it might be consistent with our conclusion that aspirin does not have a critical role in the prevention of CAA in the KD patients.

In this clinical trial study, the effect of eliminating HDA (80–100 mg/kg/day) was studied on CAA incidence in the treatment of acute phase of KD in a pair of case and control groups. The result of the study showed that eliminating HDA did not have any significant effect

Table 3: Comparison frequency of abnormal coronary arteries diameter in term of groups type and time

Aneurysm	Group	Abnormal (Z score>2.5)	Baseline	At 6th week	At 6th months	*P*
LMCA	Study	Yes	9 (29.0)	7 (22.6)	4 (12.9)	0.527
		No	22 (71.0)	24 (77.4)	27 (87.1)	
	Control	Yes	12 (38.7)	11 (35.5)	2 (6.5)	
		No	19 (61.3)	20 (64.5)	29 (93.5)	
	P-value		Ref	0.253	0.001	
RCA	Study	Yes	5 (16.1)	3 (9.7)	2 (6.5)	0.250
		No	26 (83.9)	28 (90.3)	29 (93.5)	
	Control	Yes	8 (25.8)	6 (19.4)	5 (16.1)	
		No	23 (74.2)	25 (80.6)	26 (83.9)	
	P-value		Ref	0.039	0.011	
LAD	Study	Yes	17 (54.8)	12 (40)	4 (12.9)	0.113
RCA		No	14 (45.2)	18 (60)	27 (87.1)	
	Control	Yes	13 (41.9)	7 (22.6)	1 (3.2)	
		No	18 (58.1)	24 (77.4)	30 (96.8)	
	P-value		Ref	0.002	<0.001	
Overall	Study	Yes	18 (58.1)	16 (51.6)	8 (25.8)	0.907
		No	13 (41.9)	15 (48.4)	23 (74.2)	
	Control	Yes	17 (54.8)	17 (54.8)	7 (22.6)	
		No	14 (45.2)	14 (45.2)	24 (77.4)	
	P-value		Ref	0.592	<0.001	

LMCA: Left main coronary artery, RCA: Right coronary artery, LAD: Left anterior descending

on CAA incidence and even without ASA we can treat the acute phase of KD. The incidence of CAA declined in both study and control groups at the time of the study. In the study group, CAA decreased from higher in males than females (66.1% and 33.9%, respectively), which is compatible with older trials [13-16] In this trial, CAA rates (*Z*-score ≥2.5) were seen in 56.45% of the studied population, which is higher than that reported in previous trials.[9,14,15]

Tang *et al.*[17] conducted a clinical trial on 661 patients with KD and 141 (21.3%) had CAA at the time of diagnosis. Friedman *et al.*[18] performed a meta-analysis on 2860 KD patients from 1979 to 2014. In this study, 500 (17%) of participants had CAA and 90 of these 500 had CAA incidence with *Z*-scores larger than 10. CAA incidence in Friedman *et al.* meta-analysis was lower than our study. However, in the study of Hamza *et al.*,[19] the CAA incidence was 53.8%, and in Zhang's coherent study,[20] the incidence was 63.3%. Hence, Zhang's coherent trial had a higher CAA incidence than our study.

Our study was performed in a referral hospital, where most patients have severe complications or came with late diagnosis, these factors can be attributed to an increase of CAA incidence in the trial. Besides, this is the first KD trial that has been done in this geographic area, Hence, the race of patients also might be a factor for higher CAA incidence.

Limitations

Using a larger sample size and eliminating the effects of a late diagnosis of KD may lower the CAA incidence in this trial.

CONCLUSIONS

In this clinical trial study, 6 months after KD diagnosis, CAA incidence in the study group (treated with only IVIG with standard dose in acute phase) was 25.8%. Meanwhile, in the control group (treated with both standard dose of IVIG and HDA 80–100 mg/kg/day in acute phase), it was 22.6% and this difference is nonsignificant (P = 0.907). We concluded that HDA does not have a significant role in preventing CAA in KD patients and giving standard 2 g/kg/day IVIG without HDA (80–100 mg/kg/day) in KD acute phase therapy does not increase the risk of CAA, as the main reason of morbidity and mortality in KD patients. Hence, even without ASA you can treat acute phase of KD.

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Conflicts of interest

There are no conflicts of interest.

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