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Use of Corticosteroid in Children with Unresponsiveness to Intravenous Immunoglobulin in Kawasaki Disease

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Abstract

Background
Kawasaki Disease (KD) is a vasculitis with multi-organ involvement of unknown etiology; it is the most common cause of pediatric-heart diseases in developed countries. Treatment with Intravenous Immunoglobulin (IVIG) prevents coronary artery lesions; although there are some IVIG-resistant cases, combination therapy with corticosteroids and IVIG is one of the recommendations for treatment of these cases. The aim of this study was to compare these three options for treatment of Kawasaki Disease and to evaluate their ability to deal with coronary artery complication of Kawasaki Disease.

Materials and Methods
A prospective cross- sectional study of hospitalized cases of Kawasaki Disease, conducted in pediatric department of Imam Reza hospital, Mashhad-Iran, during 2013 to 2015 (18 months). Based on demographic and clinical data of these patients, children with high risk of unresponsiveness to IVIG therapy (based on Harada score), were determined and treated with IVIG and corticosteroids-combination initially. Follow-up patients for heart complications were 6 weeks.

Results
Twenty five patients (89.2%) out of total 28 hospitalized patients in this period of time who fulfilled diagnostic criteria were considered as complete Kawasaki Disease. Coronary Artery Lesions (CALs) were shown in 4 patients during the follow-up period, with high risk in patients with incomplete presentation (33.3% versus 12%, $P<0.05$). None of the children were treated with IVIG and corticosteroids combination therapy at the onset showed coronary artery lesions.

Conclusion
The current study showed that IVIG plus intravenous methylprednisolone (IVMP) combination therapy is a safe and effective treatment regimen in prevention of CALs.

Key Words: Children, Coronary artery lesions, Corticosteroid, Kawasaki.

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1- INTRODUCTION

Kawasaki disease a systemic vasculitis of unknown etiology (1, 2) that predominantly affects medium sized arteries, with a striking predilection for coronary arteries, and it is the most common cause of pediatric-heart diseases in developed countries (3, 4). Kawasaki disease has more tend to involve children younger than 5 years old, especially those who live in Asian countries (2). Complete Kawasaki disease diagnosis is based on presence of fever (temperature exceeding 38° c) lasting for more than 5 days accompanied by the presence of at least 4 major criteria contains; diffuse mucosal inflammation, strawberry tongue and fissure lips appeared in site of mouth, Bilateral non-purulent conjunctivitis signed in eyes.

Another sign present in the neck lymph nodes may changes in the extremities also be found on the indurative angioedema over both hands and feet and polymorphous exanthema occur as Skin rash (5); incomplete Kawasaki is diagnosed based on presence fever lasting for more than 5 days accompanied by the presence of at least 2 major criteria with at least 3 additional laboratory criteria such as serum albumin ≤ 3.0 g/dl, Anemia for age, elevation of alanine aminotransferase, Platelets after 7 days ≥ 450 000/mm3, White blood cells (WBCs) ≥ 15 000/mm3 and Urine WBC ≥ 10/ high power field (HPF) (6).

It is important to treat this disease within 10 days of the onset of fever; IVIG prevents coronary artery lesions (CALs) such as coronary artery fistulas, coronary artery aneurysms and dilatations in 25% of untreated patients; following IVIG-therapy, risk of coronary artery lesions is reduced from 25% to 3-5% (7, 8); these lesions can lead to long term sequelae e.g. stenosis or obstruction (2, 3, 9). Based on recent studies some groups of risk factors e.g. Harada score which contain WBC >12 000/μL, Platelets < 350 000/μL, C-reactive protein > 3 mg/dL, Hematocrit < 35% (our cut off hemoglobin < 11.6 g/dL), Albumin < 3.5 g/dL in male with age of ≤ 12 years is considered which is associated with unresponsiveness to IVIG in Japanese patients with typical Kawasaki disease, but acceptance of these factors in non-Japanese populations and (or) atypical or incomplete Kawasaki disease needs more study. There can be three modes of therapy using corticosteroids for treatment of Kawasaki disease:

- For patient unresponsive to IVIG,
- In combination with IVIG for all patient and
- In combination with IVIG for selected patient who are expected to be unresponsive to IVIG (10);

The combination of corticosteroid and IVIG administration for all patient as routine first line therapy is not reasonable treatment, because there is not sufficient evidence, in addition we need future investigation to determine predictive models for unresponsiveness to IVIG. Failure of treatment with IVIG as the first line therapy is reported in 6.8% to 38.3% (11, 12); these patients who are unresponsive to IVIG have a high risk for CALs (12, 13), since the failure rate with IVIG alone as the second line therapy (22.2% to 48.6%), is similar to IVIG as the first line (12, 14, 15), use of a combination therapy with IVIG in unresponsive cases is reasonable; however, based on the 2004 guideline of American Heart Association (AHA), Kawasaki disease treatment with corticosteroids is recommended only for patients whom have shown persistent fever for more than 36 hours spite of receiving two or more IVIG infusions. The aim of this study was to compare these three options for treatment of Kawasaki disease and to evaluate their ability to deal with coronary artery complication of Kawasaki disease.

2- MATERIALS AND METHODS

This prospective cross-sectional study reviewed medical records of Kawasaki disease patients who were hospitalized in our pediatric department of Imam Reza hospital in Mashhad-Iran, from October 2013 to March 2015. In this period of 18 months, 28 patients with complete (n=25) and incomplete (n=3) Kawasaki Disease were admitted. The patients were undergoing treatment in three groups which included only intra venous methylprednisolone group, methylprednisolone group, and combination group.

The study was approved by the local Ethical Committee of the Mashhad University of medical sciences, and subjects gave their informed written consent. Our criteria for diagnosis of complete Kawasaki disease were compliant with the diagnostic guidelines for Kawasaki disease (5); incomplete Kawasaki was diagnosed based on clinical and laboratory criteria (**Table.1**) (6). Demographic and laboratory data were collected by physician; among these patients 4 of them had positive Harada score and received corticosteroid and IVIG combination therapy. Unresponsiveness to IVIG was demonstrated by persistence or recurrence of fever 36-48 hours after completion of the initial IVIG therapy (2gr/kg/infusion in 12 hours) (16); patients who were unresponsive to IVIG were treated by additional dose of IVIG plus high dose intravenous methylprednisolone (IVMP) (25mg/*kg* (max1gr) 3days.

All of the patients were followed for 6 weeks; in this period laboratory and echocardiographic monitoring was done; three echocardiogram (Accuvix V10, Samsung Medison) were performed by a pediatric cardiologist, once at the time of diagnosis, and then at 2 weeks and 6 weeks after diagnosis. According to clinical and laboratory monitoring patient's response to medication was evaluated.

Table-1: Diagnostic criteria for Kawasaki Disease (6)

Symptoms	Laboratory data
Fever ≥ 5 days (± 4 signs of bellow)	Leukocytosis, increased polymorphonuclear neutrophil (PMN)
Bilateral non purulent conjunctivitis	↑ Erythrocyte sedimentation rate (ESR), platelet
Rash (morbilliform)	Echo finding
Edema in hand and foot	Bladder hydrops
Unilateral neck lymph adenopathy	↑ Aspartate aminotransferase (AST or SGOT), ↑Alanine aminotransferase (ALT or SGPT)
Lips Fishing	Streel pyuria
Strawberry thong	Aseptic meningitis

3- RESULTS

In this cross-sectional study, there were 28 patients (20 males, 8 females), ranging from 6 to 36 months of age. Most of them met criteria for complete type of Kawasaki disease and only 3 of them showed incomplete type of disease. Four Kawasaki disease patients were assigned to the predicted IVIG-resistant group based on the Harada score at the time of diagnosis who received combination the Intravenous Immunoglobulin therapy plus IVMP. Two weeks after disease onset CALS was diagnosed in 4 cases based on American

Heart Association (AHA) echocardiographic criteria (6); two of these patients received IVMP because of unresponsiveness to initial IVIG and the remaining two cases were treated with IVIG alone. Among cases who were treated with IVIG alone 12.5% (2 cases) showed CALs, while in unresponsive patients who were treated with IVIG plus IVMP, 25% (2 cases) showed CALs; this difference was statistically significant (P <0.005). None of the cases who were receiving IVIG and IVMP combination therapy at the time of diagnosis showed CALs. There wasn't any case of adverse events such as bradycardia, hypothermia, and hypertension among patients who received corticosteroid.

Patients with incomplete KD had a higher risk for developing CALs (33.33% versus 12%). All of patients became afebrile after therapy with IVMP in comparison to IVIG alone. A shorter period of time was needed for hospitalization and serum albumin levels, ESR, neutrophil and platelet count to become normal following corticosteroid administration.

4- DISCUSSION

Management of Kawasaki disease with IVIG decreases CALs from 25% to 3- 5% (7, 8); in our study 14.28% of cases developed CALs spite of therapy. IVIG would be administered only for Japanese children suffering from Kawasaki disease with positive Harada score; IVIG was administered for all KD patients in our study, and children who had positive Harada score received intravenous methylprednisolone, in addition from the beginning of therapy.

In a study by Tewelde et al., the positive predictive value of high Harada score and the negative predictive value of low Harada score for CALs were 19% and 98%, respectively; and most of patients who were developing CALs had positive Harada score (90%) (17); but in our study none of the cases with positive Harada score developed CALs, and 16.66% of cases negative Harada score developed CALs; this difference might be due to beneficial effects of IVMP use for patients with positive Harada score as the primary treatment in our study.

In a study by Chen et al, CALs was reported significantly fewer in patients receiving IVIG and IVMP combination therapy in comparison to those whom received IVIG alone (7.6% versus 18.9%) which is comparable to the results of present study (18). Athappan et al., demonstrated that patients who received IVIG plus IVMP therapy, were retreatment less than patients receiving standard therapy regimen, however, no significant reduction in the incidence of (CALs) were reported; in this study combination therapy was not performed only for high risk patients (e.g. Harada score), that is different results in comparison to our results (19).

In a meta-analysis by Zhu et al., duration of fever and the time required for C-reactive protein (CRP) to return to normal reduced following corticosteroid therapy, were similar to the results of present study (20). Improvement in normalization of neutrophil count and CRP levels following corticosteroid administration can reduce the risk of CALs development due to endothelial injury reduction (21, 22).

4-1. Limitations of the study

Harada score is a highly sensitive and relatively specific criterion in Japanese children, but this isn't clear whether it is a suitable criterion for other populations; which was one of the limitations of our study. Present study was not a blind multi-centered study which can be another limitation to our study. More investigation will be necessary in order to confirm safety and efficacy of this therapeutic strategy.

5- CONCLUSION

At current study, it seems that Intravenous Immunoglobulin (IVIG plus IVMP) combination therapy is a safe and effective treatment regimen in prevention of CALs. This strategy is recommended as initial therapy in positive Harada score patients. Inflammatory markers and duration of fever were decreased following corticosteroid administration.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

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