

Intravenous Immunoglobulin – Resistant Kawasaki Disease Treated with Pulsed Doses of Methylprednisolone

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Kawasaki Disease (KD) is usually treated with high doses of Intravenous Immunoglobulin (IVIG) and aspirin. However, 10-15% of children with KD are resistant to IVIG therapy. Corticosteroid therapy remains a controversial alternative in such cases.

We report a case of a four year old boy with KD who was resistant to treatment with high dose IVIG (2 courses of 2g/Kg/day) and aspirin (80mg/Kg/day) and was subsequently treated with pulsed doses of Methylprednisolone (30mg/Kg/day) for three days. The child apparently responded with rapid defervescence, improvement in clinical symptoms, normalization of acute-phase reactants and no progression of coronary artery dilatation or any adverse effects. Pulsed doses of Methyl prednisolone therapy appeared to be a safe and effective treatment for this particular IVIG-resistant KD patient.

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Kawasaki Disease is an acute febrile vasculitis of unknown etiology that occurs predominantly in infants and young children. Coronary artery aneurysms or ectasia develop in 15-25% of untreated children and are the leading cause of long-term morbidity and mortality^{1,2}.

The infusion of intravenous immunoglobulin (IVIG) within 10 days of the onset of KD is known to reduce both the duration of fever and the incidence of coronary artery disease, and thus together with aspirin are the standard treatment^{3,4}. However, 10-15% of children treated with IVIG have a persistent or recurrent fever and a progression of coronary dilatation despite IVIG treatment⁵.

Corticosteroids were used to treat KD before Kato et al reported that steroids might act adversely causing a progression of the coronary lesions⁶. Other studies have revisited this issue in recent years with controversial results. Wright et al showed that pulse steroid therapy could be effective treatment in children with IVIG-resistant KD^{7,8,9}. There is still no established method for treating IVIG-resistant KD patients, which makes this topic the subject of much research.

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To our knowledge, this is the first report from the United Arab Emirates of a patient who was diagnosed with IVIG-resistant KD who, however, responded to pulse methylprednisolone therapy. We also review the literature on the use of pulse steroid therapy for IVIG-resistant KD.

THE CASE

A four-year old boy presented to the hospital in January 2006 with a spiking temperature for four days, skin rash for one day and abdominal pain and vomiting for two days. On admission, the child was acutely ill-looking with extreme irritability but he showed no neck stiffness. His rectal temperature was 40.5⁰ C, heart rate 122/min, blood pressure 85/50mmHg and respiratory rate 25/min. There were polymorphous, maculopapular erythematous rashes on his trunk and extremities. Bulbar conjunctivae were hyperemic bilaterally and his lips were dry, erythematous and fissured. He had a strawberry tongue with diffuse erythema of oropharyngeal mucosa. His neck was supple and no lymphadenopathy was found. His breath and cardiac sounds were normal. The palms and soles were swollen and erythematous without desquamation. His abdomen was slightly distended and tender over the epigastric and right hypochondrial regions with normal bowel sounds. There was no hepatosplenomegaly. There was no erythema or induration of BCG inoculation site and no signs of arthritis or testicular swelling. Perinatal history, past and family histories were irrelevant.

Laboratory investigations showed a leucocyte count of 19,000/mm³ (79% neutrophils, 14% lymphocytes and 7% monocytes), hemoglobin level of 8.4g/dl (normochromic, normocytic) and platelet count of 230,000/mm³. On day ten of admission, platelet count went up to 950,000/mm³. The C-reactive protein was 220mg/dl. Serum Electrolytes were normal. Blood, CSF, urine and stool cultures were negative. Rheumatoid factor, antinuclear antibody and anti DNA titers were negative. C3 and C4 complements were normal. Liver function tests showed total protein 7.5g/dl, Albumin 1.9g/dl, aspartate aminotransferase (AST) and alanine amino transferase (ALT) levels were 312 and 420 U/L. Bilirubin level was normal. ECG showed normal tracing. CXR was normal.

Abdominal U/S showed biliary sludge and dilatation of gall bladder. Base-line 2D Echocardiography on day five of admission and subsequent Echocardiographs on day fourteen and six weeks after discharge showed normal coronary arteries.

This patient had met the American Heart Association endorsed clinical report criteria for the diagnosis of Kawasaki Disease¹⁰. From the second day of admission, he received a dose of IVIG (2g/Kg over 10 hours) in conjunction with a high dose of oral aspirin (80mg/Kg/day). The skin rash soon disappeared but the fever and other symptoms persisted. Mucocutaneous changes and conjunctivitis were still present. A second dose of IVIG (2g/Kg) was given on the fifth day of admission but showed no improvement. He still had a high-grade fever that rose up to 40.5⁰C three days after the second dose. On the tenth day of admission, he received intravenous pulse methyl prednisolone therapy (30mg/Kg/day) over 2 hours for 3 days. His condition improved dramatically as his fever subsided and the skin on his fingertips started to peel. He was given a low dose of aspirin (3mg/Kg/day) after being discharged. He was seen in the clinic six weeks after discharge and found to be afebrile with normal physical examination and normal 2-D Echocardiography.

DISCUSSION

Kawasaki disease is an acute febrile condition, which was first described by Tomisaku Kawasaki in 1967. The self-limiting nature, prevalent age, and regional and endemic nature of KD supports the theory that it has an infectious origin. On the other hand, its involvement of arteries, similar to other immunologic diseases, supports an immunologic origin. The systemic vasculitis in KD is brought about by an activated immune process, whereby cytokines stimulate the production of antibodies against endothelial cells, causing immune complexes to be produced, which subsequently activate the complement system and the platelet system. This leads to the production of inflammatory intermediates and neutrophils activated by anti-neutrophil cytoplasmic antibodies which in turn results in the excretion of cytotoxic substances that attack endothelial cells of blood vessels¹¹.

Patient with KD are seriously ill during the acute phase and 15-25% of children affected may develop coronary artery aneurysms if not appropriately treated^{12,13}. The current standard treatment of KD with IVIG is 2g/Kg within 10 days of the onset of fever plus aspirin, which reduces coronary aneurysm formation to 2-4%^{4,5}. Approximately 10-15% of patients with KD fail to defervesce with initial IVIG therapy^{14,15,16}. Failure to respond usually is defined as persistent or recrudescing fever more than 36 hours after completion of the initial IVIG infusion. Re-treatment with IVIG has been found to be safe, but a subgroup of patients remains unresponsive to IVIG re-treatment¹⁷. Corticosteroids have been used to treat patients who have failed to respond to initial therapy for Kawasaki disease¹⁸. Although an early study by Kato et al suggested that steroids exert a detrimental effect when used as the initial therapy for KD, subsequent studies have shown either no ill effects or possible benefit¹⁶. Wright et al first described the outcome in patients with IVIG-resistant KD who were treated with pulsed doses of corticosteroid. All the patients were treated successfully with pulse methylprednisolone with no adverse effects noted⁷. A recent study in Japan analyzed the outcomes in 299 cases of KD treated with or without corticosteroids and reported that corticosteroids reduced the duration of fever as well as the incidence of coronary artery abnormalities⁸.

This patient was re-treated with 2g/Kg IVIG but remained febrile. Controversy exists regarding the optimal re-treatment dose; some authors re-treat with 1g/Kg and others with 2g/Kg^{7,17,16,19}. One study suggested an improved outcome after re-treatment with 2g/Kg¹⁴. Until further studies are available, re-treating these patients with 2g/Kg IVIG appears to be better choice. Corticosteroids are strong anti-inflammatory drugs that inhibit cytokine production in effector cells²⁰. Because an excess secretion of cytokines may induce endothelial cell activation and injury in the acute phase of KD, corticosteroid therapy may thus be a safe and effective treatment for KD vasculitis²¹. Corticosteroid therapy appears to be more effective than a third dose of IVIG in patients who remain unresponsive after two doses of IVIG therapy^{14,16,17,22}. Until further data from prospective studies are available, pulse methylprednisolone appears to be a safe and effective alternative therapy for patients with IVIG-resistant KD.

CONCLUSION

We present a case of Intravenous Immunoglobulin-resistant Kawasaki Disease who was treated with pulsed doses of methylprednisolone with favorable outcome. To our knowledge, this is the first case to be reported from the United Arab Emirates.

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