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Case Report

Methylprednisolone as an alternative therapy for Kawasaki disease: case series

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Kawasaki disease (KD), or mucocutaneous syndrome, is an acute, systemic vasculitis of small- and medium-sized arteries that predominantly affects patients younger than five years.[1] KD is the leading cause of childhood acquired heart disease in the developed world.[2] The incidence in those aged under 5 years varies widely throughout the world, accounting for 8.4 per 100,000 in the UK, 17.5 to 20.8 per 100,000 in the USA, and 239.6 per 100,000 in Japan.[2]

The diagnosis of classic KD is based on the simultaneous presence of high fever for 5 or more days with at least four of five other symptoms (bilateral conjunctival hyperemia, ulcerations of the lips and inflammation of the oral cavity, polymorphous rash, edema and desquamation of the extremities, and cervical lymphadenopathy), or fever associated with less than 4 of the diagnostic criteria and echocardiographic abnormalities of the coronary arteries.[3]

In the acute phase, KD treatment aims at reducing the inflammation in the coronary artery wall and preventing coronary thrombosis, whereas long-term therapy, especially in patients with coronary artery ectasias or aneurysms, aims at preventing myocardial damage. Approximately 10% to 20% of patients have persistent fever after standard therapy with intravenous immunoglobulin (IVIG) and oral acetylsalicylic acid, increasing their risk for the development of coronary artery lesions (CAL).[4] The main difficulties for clinicians are performing a timely diagnosis, preventing cardiovascular complications, and treating refractory forms. The incidence of refractory forms has markedly increased, with young age and delayed treatment as major risk factors.[3] In developed countries, IVIG for Kawasaki disease therapy may not be available in every province or rural areas. As such, it is important to have an alternative therapy in such cases. Corticosteroids were used to treat KD long before the first report of IVIG therapy.[5] Here we describe the clinical courses and outcomes of two children with KD who received methylprednisolone therapy. **[Paediatr Indones. 2020;60:283-6 ; DOI: 10.14238/pi60.5.2020.283-6]**.

Keywords: *platelet indices; bacterial sepsis; neonatal sepsis*

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The Cases

The first case was a 16-month-old boy presenting with five days of high fever who was referred from a private hospital in Cilacap to Banyumas District Hospital, Central Java. During the second day of fever, the patient had diarrhea and vomiting more than three times a day. On the fourth day of fever he had generalized erythema on both hands and feet, which spread over the body. On the sixth day of fever, the patient had red lips, strawberry tongue (**Figure 1**), conjunctival injection (**Figure 2**), polymorphous skin rash all over the body , and desquamation of the perineal area (**Figure 3**). On laboratory investigation, leukocyte level was 12,080/μL, with 84.6% neutrophils, hemoglobin 10.9 g/dL, and platelets 345,000/μL. His albumin level was 2.2 g/dL, sodium was 131 mEq/L, and CRP was 300 mg/L. Echocardiography showed minimal pericardial effusion. The patient was treated with methylprednisolone (MP) at 30 mg/kg/day for 3 days, followed by one week of reduced dosage to 1 mg/kg/day, then tapered off. Intravenous immunoglobulin (IVIG) was not given because it was unavailable. The patient was given aspirin at 80-100 mg/kg until his fever was controlled, then the dose was reduced to 3-5 mg/kg/day for 6 weeks. Following reduction of symptoms, the patient was discharged on the fifth day of hospitalization.

The second case was a 22-month-old girl from a private hospital who had been admitted with five days of high recurring fever, cough, rhinorrhea, conjunctivitis, and generalized erythematous rash.

Figure 1. Strawberry tongue (before and after therapy)

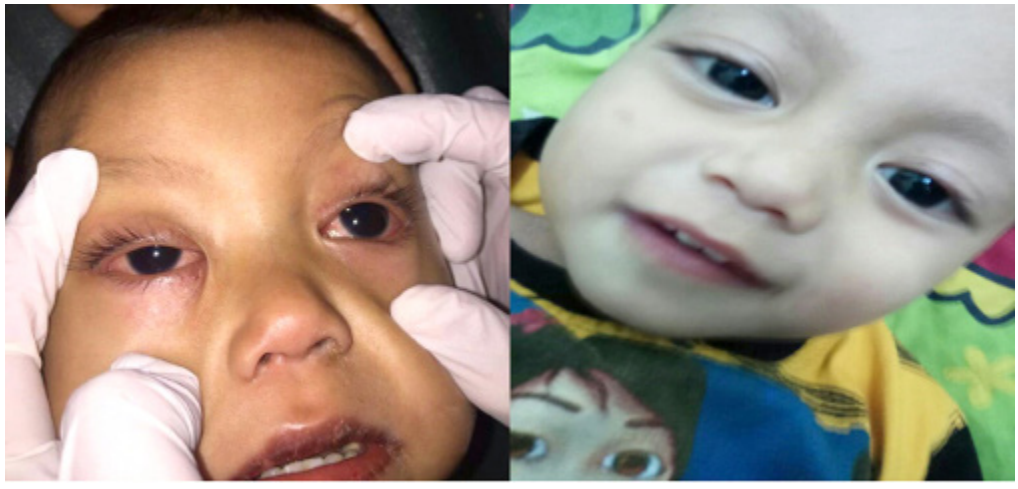

Figure 2. Conjunctival injection **(before and after therapy)**

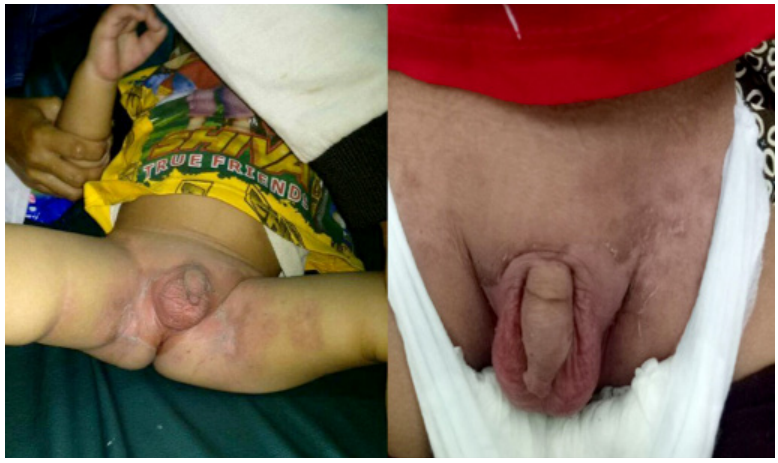

Figure 3. Perineal desquamation (before and after therapy)

She had been diagnosed with measles and discharged after three days. On the second week, the patient was referred to a pediatric cardiologist at Dr Sardjito General Hospital, Yogyakarta, due to desquamated skin all over her body and suspected KD. Laboratory investigations revealed that her leukocyte level was 15,230/μL, neutrophil 59.9%, and platelet count 629,000/μL. Her albumin level was 3.8 g/dL, and CRP was 128 mg/L. Echocardiography showed an aneurysm of the left coronary artery. The patient was treated with methylprednisolone (MP) at 30 mg/kg/day for 3 days and aspirin at 80 mg/day. IVIG was not administered because she was already in the second week of illness. The patient was discharged on the fourth day of hospitalization.

Discussion

Kawasaki disease is an acute, self-limited, febrile illness of unknown cause that predominantly affects children <5 years of age.[6] The disease is characterized by fever ≥ 5 days, bilateral bulbar non-exudative conjunctivitis, erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa, erythema and edema of the hands and feet in the acute phase, and/or periungual desquamation in the subacute phase, rash, and cervical lymphadenopathy.[6,7] In the presence of >4 principal clinical criteria, particularly when redness and swelling of the hands and feet are present, the diagnosis may be made with only 4 days of fever.[6]

The goal of therapy in the acute phase is to reduce inflammation and arterial damage and to prevent thrombosis in those with coronary artery abnormalities.[6] Glucocorticoids are classic anti-inflammatory agents that have been widely used for several pediatric diseases such as asthma, immunoglobulin A (IgA) vasculitis, nephrotic syndrome, leukemia, and collagen diseases.[8] Kawasaki disease is a form of inflammatory vasculitis, therefore, glucocorticoid therapy is an option for inhibiting inflammation. Although corticosteroids are the treatment of choice for other forms of vasculitis, its use has been controversial for children with KD. Intravenous methylprednisolone pulse (IVMP) therapy is often used to treat children with severe or refractory illnesses such as collagen vascular and renal diseases. However, corticosteroids have occasionally been used earlier as the second line therapy for patients unresponsive to initial IVIG treatment, as the routine first line therapy in combination with IVIG, or as the first line therapy in combination with IVIG for selected KD patients at high risk of unresponsiveness to initial IVIG.[9]

According to the 2017 American Heart Association (AHA) guidelines, single dose pulse methylprednisolone should not be administered with IVIG as routine primary therapy for patients with KD, and administration of a longer course of corticosteroids together with IVIG at 2 g/kg and acetylsalicylic acid (ASA) may be considered for treatment of high risk resistance IVIG patients with acute KD, when such high risk can be identified in patients before initiation

of treatment.[6] The addition of glucocorticoids to the initial therapy for KD has been shown to be most efficacious for Japanese children at high risk for IVIG resistance. A retrospective review found that treatment regimens that included prednisolone were associated with significantly shorter fever duration and a lower prevalence of coronary artery aneurysms.[10] Another study reported a lower incidence of coronary artery abnormalities and retreatment, shorter duration of fever, and more rapid decrease in CRP levels in the steroid group.[11] In contrast, a randomized study demonstrated that pulse intravenous methylprednisolone (30 mg/kg over 2 to 3 h) administered before IVIG in primary treatment did not improve coronary artery outcome or reduce the total days of hospitalization or fever.[12] In these patients, the following criteria can be used to select patients for treatment with glucocorticoids: enlarged coronary arteries at presentation (prior to IVIG treatment), age ≤12 months (and particularly age <6 months), KD associated with shock, and KD presenting with macrophage activation syndrome (MAS).[12]

Methylprednisolone therapy for Kawasaki disease in our two patients appeared to be beneficial and effective, but further studies are needed.

Conflict of Interest

None declared.

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