Title: Efficacy of Immunoglobulin Plus Prednisolone in Reducing Coronary Artery Lesion in Patients with Kawasaki Disease

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Study Protocol

Trial Design

This is a multicentre, prospective, open-label, randomized controlled trial to evaluate the efficacy of addition of methylprednisolone to conventional initial treatment in children with acute Kawasaki disease. This study will be carried out at ten children’s hospitals in China.

Study Population

Participants will be screened for eligibility if diagnosed with Kawasaki disease (KD) according to the American Heart Association diagnostic guidelines for KD (2017)\(^1\), including incomplete KD. Inclusion criteria: (1) Meeting the above diagnostic criteria for KD; (2) Diagnosed before the tenth day of onset (with the day of onset defined as the first day of fever); (3) Not treated with intravenous immunoglobulin (IVIG) yet; (4) Age ≥1 month to <12 years old; (5) Body weight ≤30 kg.

Exclusion criteria: (1) Z score of any coronary artery before initial treatment ≥10; (2) Receiving steroids or other immunosuppressive agents in the previous 30 days; (3) With a previous history of KD; (4) Afebrile before enrolment; (5) With suspected infectious diseases including sepsis, septic meningitis, peritonitis, bacterial pneumonia, varicella and influenza; (6) With serious immune diseases such as immunodeficiency or chromosomal abnormalities; (7) Refusing to sign the informed consent; (8) Unable to be followed up for at least 3 months.

Randomization and Blinding
After screening for eligibility, participants will be randomly assigned in a 1:1 ratio to the control group or the intervention group through blocked randomization. Randomization sequence is created using Stata (version 15.0, Stata Corp, USA) with varying random block size of 4, 6 and 8. Patients and physicians were not masked to the assignment. Pediatric cardiologists who assess coronary artery lesions (CAL) by echocardiography will be blinded to the assignment.

**Interventions**

Participants in the control group will receive IVIG 2 g/kg and oral aspirin 30 mg/kg per day (given at 3 divided doses) in the initial treatment. Participants in the experimental group will receive IVIG 2 g/kg, oral aspirin 30 mg/kg per day (given at 3 divided doses) and additional prednisolone 2 mg/kg per day in the initial treatment. IVIG is administered within 12 to 24 hours. The dose of aspirin will be reduced to 3 to 5 mg/kg per day when fever subsides for 3 days and C-reactive protein (CRP) is ≤8 mg/L. Aspirin will be continued for at least 6 weeks after onset of KD. Patients in the experiment group will receive intravenous methylprednisolone 1.6 mg/kg per day (given in 2 doses), then changed to oral prednisolone 2 mg/kg when fever subsides for 3 days and CRP is ≤8 mg/L. The oral dose will be reduced every 3 days from 2 mg/kg to 1 mg/kg to 0.5 mg/kg (tapered over 9 days). Then prednisolone will be discontinued.

In both groups, participants resistant to initial IVIG therapy will be given additional treatment, including a second dose of IVIG (2 g/kg), or a high dose of methylprednisolone (10 to 30 mg/kg per day), or infliximab (5 mg/kg), or other
immunosuppressive agents, or a combination with two or more drugs, or even more aggressive treatment such as plasmapheresis, depending on participants’ condition and physicians’ experience.

**Assessment and Outcome Measures**

Baseline characteristics of each participant will be collected, including sex, age of onset, height, body weight, subtype of KD, fever days before initial IVIG, echocardiographic findings at enrolment, and a series of pre-IVIG laboratory tests.

Laboratory tests will be performed at enrolment (before initial treatment), including CRP, erythrocyte sedimentation rate (ESR), white blood cell count (WBC), neutrophil count (NEUT), platelet count (PLT), hemoglobin (HB), serum amyloid A (SAA), serum albumin (ALB), prealbumin, alanine aminotransferase (ALT), aspartate transaminase (AST), creatine kinase-muscle/brain (CK-MB), serum sodium (Na), total bilirubin (TB), N-terminal pro B-type Natriuretic Peptide (NT-proBNP), interleukin-1 (IL-1), interleukin-6 (IL-6), troponin, and D-dimer. CRP and routine blood tests will be measured every 3 days after the completion of initial IVIG infusion until normal. The remaining indicators (except for ESR), if abnormal, will also be measured every 3 days after the completion of initial IVIG infusion until normal.

Axillary temperature (or rectal temperature) will be measured every 6 hours during hospitalization. Participants with an axillary temperature <37.5°C (or rectal temperature <38°C) and remain for at least 24 hours are considered afebrile. Record the time of the initiation of IVIG infusion and the time of the body temperature first becoming normal.
Two-dimensional echocardiography will be performed to evaluate CAL at five time points: at enrolment (before initial IVIG treatment), 10 days to 2 weeks of illness (~ 6 to 8 days after enrolment), 1 month of illness (~ 2 weeks after discharge), 2 months of illness (~ 6 weeks after discharge), and 3 months of illness (~ 10 weeks after discharge). The measurement of each participant included the internal diameter of the left main coronary artery (LMCA), the left anterior descending artery (LAD), the left circumflex coronary artery (LCX), and the proximal and middle segments of the right coronary artery (RCA). Echocardiography will be performed by pediatric echocardiographers at each participating center. Video recordings will be preserved and reevaluated by another two pediatric cardiologists for confirmation.

**Definitions**

IVIG resistance is defined as recurrent or persistent fever (axillary temperature $\geq 37.5^\circ C$ or rectal temperature $\geq 38^\circ C$) after 36 hours of completion of initial IVIG infusion.$^1$

Z score of each coronary artery will be calculated.$^2$ CAL is defined as $z \geq 2$ of any coronary artery of LMCA, LAD, LCX, and the proximal and middle segments of the RCA.$^1$ The severity of CAL is determined based on the maximal z score ($z_{\text{max}}$) and the diameter of all coronary arteries. Dilation only is defined as $z_{\text{max}} \geq 2$ to $<2.5$; small aneurysms are defined as $z_{\text{max}} \geq 2.5$ to $<5$; medium aneurysms are defined as $z_{\text{max}} \geq 5$ to $<10$ and absolute dimension $<8$ mm; giant aneurysms are defined as $z_{\text{max}} \geq 10$ or absolute dimension $\geq 8$ mm. Regression of CAL is defined as $z < 2$ of all coronary arteries (LMCA, LAD, LCX, and the proximal and middle segment of the RCA).
Outcomes

Primary outcome is the occurrence of CAL at 1 month of illness. Secondary outcomes include the need for additional treatment, duration of fever (hours) after initiation of initial IVIG infusion, changes in z scores of LMCA, LAD, LCX, and RCA throughout the study period (from admission to 3 months of illness), changes in serum CRP concentration 72 hours after completion of initial IVIG infusion, and serious adverse events (such as death, hypertension, severe infection, allergic reactions, heart failure, thrombosis, etc.).

Sample Size Calculation

The sample size is calculated using Power and Sample Size Calculations (version 3.1.6). We assume that the difference in the percentage of CAL within 1 to 3 months of illness between the two groups is 4% (12% vs 8% for the control group and the experimental group, respectively). With an $\alpha$ of 0.05 and a power of 0.8, a total of 882 cases in each group would be needed. Given potential drop outs during follow-up, a total of 900 patients in each group are planned to be enrolled.

References


2. Dallaire F, Dahdah N. New Equations and a Critical Appraisal of Coronary