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RANDOMIZED-PROSPECTIVE STUDY OF A SINGLE INFUSION OF 1G/KG GAMMAGLOBULIN FOR REDUCING A TOTAL DOSE OF GAMMA-GLOBULIN IN KAWASAKI DISEASE TREATMENT

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A high-dose (2g/kg) gammaglobulin (IVIG) treatment has been well established as a standard therapy for Kawasaki disease (KD). However, it has been clinically and economically expected to reduce a total dose of IVIG because the gammaglobulin is a blood preparation and very expensive. To assess the efficacy of a single infusion therapy of 1g/kg IVIG for preventing the cardiac sequelae, we attempted a multicentral prospective study using our own protocol. Method: 77 KD patients in the acute phase were randomly divided into 2 groups as follows: Group A, a single infusion of 2g/kg IVIG (an additional therapy: 2g/kg), Group B, a single infusion of 1g/kg IVIG (1st additional therapy: 1g/kg, and 2nd 2g/kg). The initial IVIG therapy was started in the 5-7th day of illness in all patients. The additional IVIG was performed in the cases who satisfied with 2 or more items of the following criteria at 24-36h after the first treatment: 1) body temperature >= 37.5 ^{o}C, 2) CRP >= 3.0g/dl, 3) neutrophils >= 7500/mm^3. Serial echocardiograms were taken until 60 days of illness. Results: 36 were assigned to Group A and 41 to Group B. At enrollment the patients in each group had similar demographic characteristics and laboratory data before treatment. In Group A, no coronary arterial involvement was observed. In Group B, 2 patients with additional 2nd therapy showed temporary coronary dilatation (N.S. vs. Group A, X^2 test). 32% in Group B patients were treated only with a single infusion of 1g/kg gammaglobulin. Conclusion: This prospective study suggests that a single infusion of 1g/kg gammaglobulin is clinically effective to prevent coronary sequelae as well as 2g/kg IVIG.

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RANDOMIZED CONTROLLED STUDY OF INTRAVENOUS GAMMA-GLOBULIN PRODUCTS IN TREATMENT OF KAWASAKI DISEASE

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Background: The efficacy of high-dose intravenous gamma-globulin (IVGG) treatment in Kawasaki disease (KD) is well known. But it is unclear whether the IVGG products manufactured by various companies are equally efficacious in treatment of KD and whether they are equally safe. **Purpose:** To compare the efficacy and safety of various IVGG products in patients with KD. **Methods:** We studied 142 patients with KD who had no coronary artery complications on admission and within the first 9 days of illness. Using a random number table, 50 patients were selected to receive freeze-dried, sulfonated product (Venilon-I; product A), 56 patients were selected to receive pH4-treated product (Polyglobin-N; product B), and the remaing 36 patients were selected to receive polyethyleneglycol-treated product (Venoglobulin-IH; product C). The doses of IVGG (2g/kg X 1 day or 1g/kg X 1 day) were determined by Harada's score. All patients were treated with IVGG in combination with aspirin. **Results:** There were no significant differences among the 3 groups in regard to age, gender, Harada's score, and illness days when IVGG was initiated. The incidence rate of patients who needed additional IVGG treatment was similar in all groups (product A.26.0%, B 21.4%, C 30.6%). The incidence of coronary artery complications was similar in all groups (product A 10.0%, B 8.9%, C 2.8%). The adverse effects of IVGG were seen in 4 patients, but all patients recovered after IVGG was discontinued. There were no significant differences among the 3 groups in regard to adverse effects (product A 0%, B 1.8%, C 5.6%). **Conclusion:** We concluded that there are no significant differences among 3 IVGG products in regard to their efficacy and safety.

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SELECTION OF ACUTE KAWASAKI DISEASE PATIENTS WHO CAN BE TREATED BY 1G/KG INTRAVENOUS GAMMA GLOBULIN

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Although, the efficacy of 2g/kg IVGG has been widely accepted, 1g/kg single administration of IVGG(1g-IVGG) alone is also effective in a certain number of acute Kawasaki disease(KD) patients(pts). To investigate the efficacy of 1g-IVGG in acute KD pts, we reviewed 136 pts started with IVGG (108 pts started with 1g/kg, and 28 pts started with 2g/kg).

Among 108 pts, 1g-IVGG alone was effective in 68 pts(63%)(CRP: 7.7+/-3.7mg/dl), and 35(32%) of 40 pts(CRP:10.7+/-6.5mg/dl,p<0.05)) who required additional therapy(AT) such as IVGG, Predonisolone or Ulinastatin, responded well. 2g-IVGG was started in 28 pts(21%) and effective in 10 pts(7%). The other 18 pts(13%) required AT. Coronary arterial sequelaes were recognized in 5 pts(3.7%) in 1g-IVGG plus AT and 1 pts (0.7%) in 2g-IVGG plus AT. If initial CRP is <12 mg/dl and WBC <15,000/μl, 1g-IVGG alone seemed to be effective in 35/48(73%) of pts(CRP: 6.6 vs 11.7 mg/dl,p<0.05). WBC/neutrophil counts reduced by –34%/-60% and CRP by –36% after 48 hrs. In pts requiring 1g-IVGG plus AT, WBC/neutrophil decreased only by –7.3%/-34% and CRP by –34%.

We conclude that approximately 50%(68/136 pts) of acute KD pts can be treated with 1g-IVGG alone. CRP<12.0mg/dl and WBC<15,000μl seem to be good parameters that can predict the 73%response rate. Reduction of WBC/neutrophil and CRP may be hallmarks of the effectiveness.

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ESTIMATION OF "SELECTIVE" INTRAVENOUS GAMMA GLOBULIN TREATMENT INDICATED BY HARADA SCORE

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Harada score, which was originally constructed as a guideline for indication of intravenous gamma globulin (IVGG) in research group of Kawasaki disease promoted by the Ministry of Health (Kouseishou), had been applied to consecutive 258 cases of Kawasaki disease between 1989 and 1998. Each item of score are regarded as positive when patient is male, 12-month-old or younger, white blood cell count is 12,000/mm^3 or more, platelet count is less than 350,000/mm^3, C-reactive protein is 4.0mg/dl or more, hematocrit is less than 35%, serum albumin is less than 3.5g/dl. Concerning to these items, 203 cases (78.7%) fulfilled 4 or more items and were treated with IVGG. Among them, coronary artery lesion (CAL) developed in 28 cases (13.8%) at 30th day after onset and remained after 1 year in 19 cases (7.4%). Giant aneurysm larger than 8mm in diameter developed in 3 cases (1.5%). Fifty-five cases fulfilled 3 or fewer items and were not treated with IVGG. CAL developed in 2 cases (3.6%) at 30th day and both of them regressed to discontinue medication until 1 year after onset. Frequency of blood examinations while patient is in hospital were done every 3.13±0.87 days in cases during 3 years from 1986 to 1988 before Harada score was evaluated, while during 10 years of this study examinations were done every 3.06±0.46 days in cases that IVGG was indicated, and 2.81±0.68 days in cases that IVGG was not indicated. Harada score has utility with 93.3% and 100% of sensitivity at 30th day and over 1 year respectively, for selection of cases which IVGG is absolutely necessary for prevention of CAL. Though frequency of blood tests tends to increase, statistics concerning to it was not significant.

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A CASE OF KAWASAKI DISEASE IN NICU

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[Background] Kawasaki disease (KD) in children younger than 3 months of age is rarely observed. The rarity of disease in early infants may be due to protective effects of transplacental immunity and/or low level of exposure to infectious agent. We report a case of an infant who developed KD in a neonatal intensive care unit (NICU). [Case report] A male infant was born at 31 weeks of gestation; weighed 1772g, and admitted to our NICU. At 84 days of age, he presented with high fever, exanthema and dyspnea. He was diagnosed with pneumonia and treated with intravenous antibiotics and gammaglobulin (150 mg/kg/day, 3 consecutive days). The high fever lasted even after improvement of respiratory lesions, which were followed by bilateral conjectival injection, bright red lips and edematous changes in palms and soles. He was diagnosed with KD at 93 days of age (9 days of illness). Right and left coronary arteries were dilated up to 2 mm. He was treated with high-dose gammaglobulin (1500 mg/kg/dose), however, fever and other symptoms persisted. He developed pericardial effusion and bilateral coronary arterial aneurysms (4.5 mm), despite 4 additional gammaglobulin injections (1000 mg/kg/dose, respectively). Beginning at 24 days of illness, he was treated with intravenous ulinastatin (15000 U/kg/day) for 5 days, and fever and all other symptoms disappeared. He was discharged at 63 days of illness. Follow-up cardiac catheterization and angiography at 2 months after discharge confirmed bilateral coronary arterial aneurysms. [Discussion] The present case developed KD even in extremely isolated environment as NICU. One possible explanation is that premature infants receive insufficent passive immunity from their mothers. In this infant, ulinastatin therapy was effective. Thus this treatment should be considered for young infants who are resistant to intravenous gammaglobulin therapy

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TREATMENT OF ACUTE PHASE OF KAWASAKI DISEASE WITH PREDNISOLONE

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Treatment of the acute phase of Kawasaki disease (KD) remains controversial. Although aspirin plus intravenous gamma globulin (IVGG), the current treatment of choice, reduces coronary aneurysm formation to less than 5%, some children still develop aneurysms despite the use of high-dose IVGG. In our hospital, prednisolone (PSL) has been used for many years, and it was reported that it tended to reduce the duration of fever and the incidence of coronary arterial abnormalities. We concluded that steroids did not make coronary lesions worse. Our data suggest that PSL may have an additional benefit when used with IVGG. Since 1992, 97 cases (62 male and 35 female) of KD were treated with a predetermined protocol including PSL. Treatment with aspirin (30 mg/kg/day), dipyridamole (2 mg/kg/day), propranolol (1 mg/kg/day) and PSL (2 mg/kg/day) was started within 9 days of the onset of illness. PSL was administered over 3 weeks, during which the dose was reduced about every week. In severe cases (n=54) we added IVGG (200 mg/kg/day for 5 days). (Cases were severe if they met the following criteria: (1) younger than 13 months of age, (2) matched Harada's guideline, (3) development of a coronary abnormality was expected, or (4) persistent or relapsing fever at 48 hours after treatment with PSL.) Only one case (1.0%) had a moderate abnormality (maximal diameter was 4.2 mm in RCA). None of the patients had giant aneurysms. The duration of PSL administration was 25.7 ± 8.4 days (mean ± SD, maximal duration was 56 days). We consider that PSL should be used as early as possible and not be stopped early or suddenly. This protocol in which high-risk patients were treated with PSL and IVGG showed a satisfactory result.