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ORIGINAL ARTICLE

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Efficacy of plasma exchange therapy for Kawasaki disease intractable to intravenous gamma-globulin

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Abstract Kawasaki disease (KD) causes coronary artery lesions (CALs) in 500 Japanese children each year. Intravenous gamma-globulin (IVGG) decreases the incidence of these lesions from 25% to 8% of the total KD cases. We examined whether plasma exchange is a safe and effective prophylaxis against CALs in children with KD intractable to IVGG therapy. Eighty-nine children with KD at high risk of CALs were selected on the basis of increases in fractional changes in inflammatory markers such as white blood cell count, neutrophil count, and C-reactive protein between the baseline and 1–2 days after IVGG treatment. Of 105 children who received a second course of IVGG therapy because the initial course was ineffective, plasma exchange (PE) was performed in 46 children who had not responded to the second IVGG treatment. The outcome was compared with the results when a third course of IVGG therapy was given to the other 59 children. No complications occurred with the plasma exchange therapy. CALs developed in only 8 of the 46 children (17.3%) who underwent plasma exchange, but they occurred in 24 of the 59 (40.7%) who had received a third course of IVGG therapy ($P < 0.0012$). We concluded that PE was a safe, effective prophylactic measure against CALs in children with KD intractable to IVGG therapy. PE should be performed at an early stage, as soon as fractional increases in inflammatory markers are found after IVGG therapy.

Key words Coronary artery lesion (CAL) · Efficacy · Intravenous gamma-globulin (IVGG) · Kawasaki disease (KD) · Plasma exchange (PE)

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Introduction

Kawasaki disease (KD) is an acute, systemic vasculitis of unknown etiology that occurs predominantly in infants and young children.[1] Recent studies have indicated that marked activation of the immune system during the acute phase results in hypercytokinemia,[2,3] which may induce endothelial cell activation and intimal injury, thus triggering systemic vasculitis.[4,5] Studies by our group[6] and others[7,8] have shown that the heat-shock protein HSP65 may induce immune activation.

Without treatment with high-dose intravenous gamma-globulin (IVGG), coronary artery lesions (CALs), i.e., ectasia or aneurysms, develop in 25% to 30% of affected children.[9] The dose of IVGG is gradually increased to 1 g/kg, or 2 g/kg in a single infusion, as recommended in Japan[10] and the United States,[11] respectively. The administration of IVGG in the acute phase of the disease reduces the prevalence of CALS to 3%–10%.[10–12] However, despite this progress in the treatment of KD, about 500–600 children develop CALs every year in Japan.[13] Early diagnosis and prompt treatment are needed for these children, since coronary abnormalities usually develop within 10 days after the onset of the disease.

We have some data that plasma exchange (PE) therapy can markedly improve the hypercytokinemia in the acute phase of KD (unpublished). Thus, in this study we investigated whether PE therapy would be effective for children with KD which was intractable to IVGG therapy.

Patients (Fig. 1)

Two hundred and twenty-five children who had been diagnosed as having KD according to the 1984 revised criteria[14] were enrolled in this study. Approval was obtained from the local institutional review board, and informed consent was given by the parents. After diagnosis, the children received the initial course of IVGG (400 mg/kg for 3–5 days, 1 g/kg

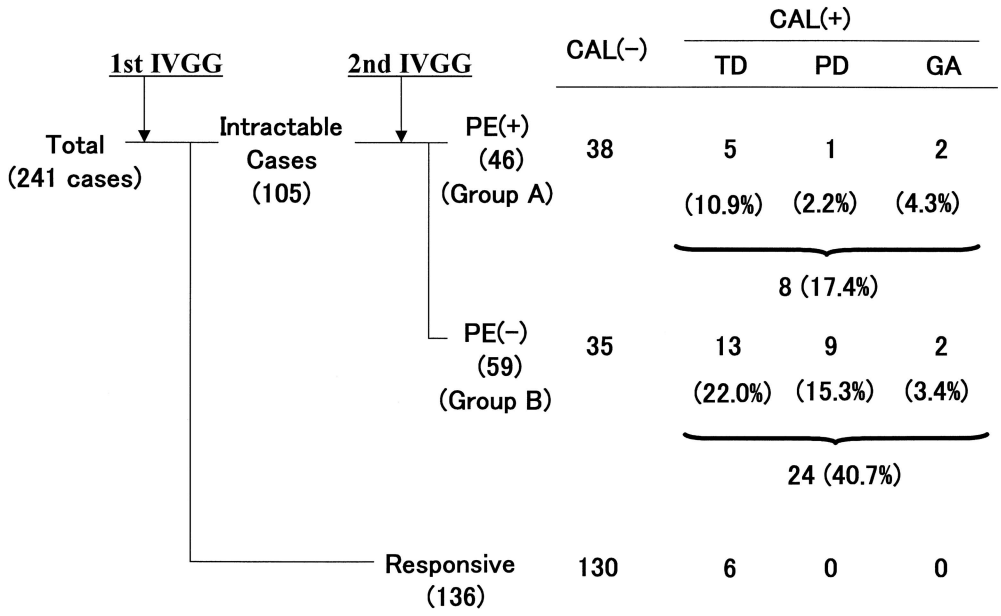

Fig. 1. Outcome in patients with Kawasaki disease (KD). KD was diagnosed in 241 children; 105 were intractable to the initial intravenous gamma-globulin (*IVGG*) treatment based on fractional increases in inflammatory markers. All of these 105 children received additional IVGG, and with the informed consent of their parents, 46 underwent plasma exchange (*PE*) therapy over the three consecutive days following the second IVGG. The remaining 59 children continued to receive additional IVGG after the second course. Of the 46 treated with PE, 38 did not have coronary artery lesions (*CALs*), as shown by serial echocardiography, and 8 children (17.4%) developed CALs: transient dilatation (*TD*) in 5 children, persistent CAL (*PD*) in 1 child, and giant aneurysm (*GA*) in 2 children. In contrast, of the 59 children who did not have PE after the second IVGG, 24 (40.7%) developed CALs: TD in 13, PD in 9, and GA in 2

for 1 or 2 days) together with aspirin (30 mg/kg/day) on days 4–7, followed by a second course of IVGG (500 mg ~ 1 g/kg for 1 or 2 days). We used fractional increases in inflammatory markers (described below) as predictors of the ineffectiveness of each course of IVGG therapy.[15] All children except one were treated within 10 days after the onset of symptoms. Children intractable to the second course of therapy were treated with PE (group A), or without PE and with a third course of IVGG therapy (group B) according to further approval by their parents. PE was performed for children, with the consent of their parents, in the hope of removing any possible etiological agents and excessive proinflammatory cytokines. CALs were routinely monitored by echocardiography on admission and on days 7, 10, 14, and 28–30 by pediatric cardiologists; additional examinations were performed when necessary.[16] The echocardiography was performed by cardiologists who had no knowledge of each child's treatment.

Methods

Definitions

Fractional increases were defined as changes in inflammatory markers, such as white blood cell count, neutrophil count, and C-reactive protein (CRP), between the baseline and 1–2 days after IVGG treatment, as described previously.[15] These changes are useful in evaluating the efficacy of IVGG treatment. Intractable cases were defined as having fractional increases in at least one inflammatory marker and persistent recrudescent fever despite IVGG. A responsive case was defined as one with no fractional increase or with an absence of clinical symptoms, including fever, after IVGG (or with both). CALs were defined as having an internal luminal diameter >3 mm in children below 5 years old, and >4 mm in children of 5 years or older, or as having a diameter >1.5 times that of the adjacent segment of coronary artery.[17] Three types of CALs were recognized: (1) transient dilatation (TD), which regressed to the normal range within 30 days; (2) persistent CALS (PD), with no regression at day 30 and with a lumen diameter <8 mm; (3) giant aneurysms (GA) in which the lumen diameter was ≥8 mm.

Methods of plasma exchange

For blood access during PE, a 22-gauge catheter filled with heparinized saline (heparin, 87.6 ± 28.4 units/ml) was placed in the radial artery as the output line, and another saline-filled 22-gauge catheter was placed in the median vein of the forearm as the input line. If a patient could not sit still during the process of blood access, intravenous sedation was used. For plasma separation, a column of 0.2–0.3 m^2 cross-sectional area (Plasmacute, Kurare, Tokyo, Japan) was used. These dialysis devices are manufactured for children, and are used to monitor blood pressure and blood volume outside and inside the column. The blood volume circulating outside the body was <50 ml. A 5% albumin solution was prepared for plasma replacement instead of

Table 1. Baseline characteristics of patients

	Group A	Group B	*P* value
	PE (+) *n* = 46	PE (−) *n* = 59	
Gender (male:female)	25:21	30:29	0.3812
	Median (1st Qr, 3rd Qr)	Median (1st Qr, 3rd Qr)	
Age at onset (months)	27.0 (19.0, 60.0)	26.3 (14.5, 36.0)	0.1510
Day of initial IVGG	4 (4, 5)	5 (4, 6)	0.0671
	Mean ± SD		
Duration of persistent fever (days)	8.21 ± 1.95	10.33 ± 3.88	0.0337
FC (WBC)	0.804 ± 0.401	0.589 ± 0.231	0.0521
FC (Neutrophils)	0.750 ± 0.438	0.562 ± 0.158	0.0644
FC (CRP)	0.761 ± 0.662	0.568 ± 0.203	0.0673

PE, plasma exchange; IVGG, intravenous gamma-globulin; Qr, quartile; FC, fractional change; WBC, white blood cells; CRP, C-reactive protein

frozen fresh plasma to avoid the risk of infection. When a child had severe anemia, packed red blood cells diluted with an equal volume of 5% albumin solution were added (four cases). The course of PE was performed in an intensive care unit to ensure careful monitoring of weight, blood pressure, temperature, pulse rate, and respiratory rate. In particular, blood coagulation status was observed using the activated coagulation time, which was adjusted to 200–250 s.

PE therapy was performed for three consecutive days, and a replacement volume of 5% albumin solution equal to the patient's circulating plasma volume was calculated each day as follows:

$$CPV = (BW) \times (1 - Hct/100)/13$$

where CPV is the circulating plasma volume (ml), BW is the body weight (kg), and Hct is the hematocrit (%).

Statistical analysis

Quantitative variables, including the time from the onset of the disease to the initial IVGG, the total volume of IVGG, and fractional changes in inflammatory markers were examined for significance using Student's *t*-test. A χ^2 analysis was used for gender, PE performance, and fulfillment of criteria. Multivariate analysis using the logistic model was used to determine whether PE therapy was more effective than further IVGG. All statistical analyses were performed using SPSS for Windows (SPSS, Chicago, IL, USA). A two-tailed *P* value <0.05 was considered to be significant.

Results

Of 241 cases, 105 (43.6%) were found to be intractable to the initial IVGG treatment, and all 105 received a second course of IVGG. Then, with further consent from the parents, 46 of the 105 underwent PE therapy over the 3 days immediately following the second IVGG (day of PE start, 8.45 ± 3.13). The remaining 59 children received a third course of IVGG therapy without PE (day of third IVGG start, 9.12 ± 2.62).

The baseline characteristics of the children with PE (group A) and of those without PE but with a third course of IVGG therapy (group B) are shown in Table 1. No demographic, gender, or fractional change (FC) differences were shown. The children in group B were slightly younger than those in group A. Although group A received a higher dose of IVGG, these cases were still judged to be intractable to IVGG (total dose of IVGG administrated in initial and second course: group A, 2368 ± 723 mg/kg; group B, 2120 ± 480 mg/kg; $P = 0.0715$).

During the 3-day course of PE therapy, high fevers (>38.0°C) subsided promptly in all children. There was a difference in the duration of persistent fever between groups (Table 1). Similarly, inflammatory markers decreased after PE therapy: the white blood cell count decreased from 18400 to 12500/μl, neutrophils decreased from 75% to 57%, and CRP decreased from 14.6 to 4.2 mg/dl. No complications, such as changes in body weight, vital signs, or blood coagulation status, occurred in any patient during PE therapy.

Of the 46 children treated with PE (group A), 38 (82.6%) had no CALs, as demonstrated by serial echocardiography. Unfortunately, 8 children (17.4%) developed CALs: TD in 5, PD in 1, and GA in 2 (see Fig. 1). In group B, the inflammatory changes in 35 children (59.3%) resolved without any coronary complications after the additional IVGG therapy. However, 24 children (40.7%) developed CALs: TD in 13, PD in 9, and GA in 2 (see Fig. 1). Furthermore, the rate of development of clinically severe CALs (PD plus GA) was 3 in 46 patients (6.5%) in group A, and 11 in 59 patients (18.6%) in group B. There was a significant difference between the two groups ($P = 0.022$).

The risk factors for CALs were statistically analyzed to prove the efficacy of PE (Table 2). The odds ratio for PE

Table 2. Statistical analysis of risk factors for CALs

	Odds ratio	95% confidence interval
Univariate analysis		
Age (months)		
<12	1	
12–23	0.839	0.259–2.718
24–35	0.584	0.123–2.782
⩾36	0.390	0.100–1.513
Gender		
F/M	1.319	0.508–3.422
Plasma exchange		
(−)/(+)	0.136	0.036–0.512
Fractional changes (decrease/increase) in		
White blood cells	15.833	1.979–126.705
Neutrophils	4.856	1.280–18.420
C-reactive protein	2.086	0.374–4.151
Fulfilled number in KD criteria		
⩽4	1	
5	2.700	0.474–15.396
6	2.700	0.513–14.207
Day of initial IVGG from onset		
⩽3	1	
4	0.697	0.227–2.141
5	0.327	0.059–1.807
⩾6	0.436	0.098–1.940
Multivariate analysis		
Plasma exchange		
(−)/(+)	0.052	0.007–0.244
Fractional change (decrease/increase) in white blood cells	97.873	7.372–1299.346

CAL, coronary artery lesion; KD, Kawasaki disease; IVGG, intravenous gamma-globulin

versus non-PE for CALs by univariate analysis was 0.136 ($P = 0.0032$), indicating that PE therapy was of benefit. The advantages of PE therapy were also reflected in the fractional changes (FC) in white blood cells ($P = 0.0092$), neutrophils ($P = 0.0202$), and CRP ($P = 0.0817$), but not in age of onset, gender, fulfillment of criteria, total IVGG dose, or day of initial IVGG treatment. Multivariate analysis showed that the most advantageous characteristic was PE therapy (odds ratio 0.052, $P = 0.0012$).

Prognostic factors for CALs formation were estimated. Children with CALs had greater fractional changes in white blood cells ($P = 0.002$), neutrophils ($P = 0.004$), and CRP ($P = 0.048$), confirming the usefulness of the FC calculation for evaluating the efficacy of IVGG. Of the 32 children who developed CALs, only 8 were treated with PE therapy, in contrast to the 24 who received additional IVGG ($P = 0.002$).

Discussion

PE therapy for Kawasaki disease was effective and safe in cases which were intractable to IVGG, and the efficacy was marked. IVGG reduces the frequency of CALs from 25%–30% to 3%–10%; this study indicated that PE therapy may further diminish the prevalence of CALs in KD to 1% or less. Although 17.3% of children treated with PE still developed CALs, their prognosis may have been improved by early diagnosis and the prompt introduction of PE therapy on the basis of fractional increases and persistent recrudescent fever.

In this study, we had two cases with giant aneurysms in spite of PE. A 15-month-old girl (case 1) had fractional increases and persistent fever, and received a total of 3.5 g/kg of IVGG, but her left coronary artery was dilated to 4.8 mm on day 10 when PE therapy was started. Another patient (case 2) was an 18-month-old boy with fractional increases and persistent fever which was intractable to IVGG, and he had a coronary dilatation on day 7 at the start of PE. In addition, in one PD-affected child, PE therapy was started 13 days after the onset of disease. This shows that it may be necessary to provide more sensitive predictors for children at highest risk and to institute early PE therapy.

In previous work we examined the fractional changes in inflammatory markers, such as the white blood cell count, the neutrophil count, and the CRP titer, between the baseline and 1–2 days after IVGG.[15] This study confirmed our finding that the occurrence of coronary artery complications was higher among children with positive fractional changes in these markers. Only about half of the children (42.6%) who were considered to be at highest risk on the basis of fractional changes in inflammatory markers, and who thus received additional IVGG, developed CALs, indicating that our predictors of CALs are still useful.

The mechanism of action of PE therapy is unknown.[18,19] A previous study showed that the pathologic changes in KD were based on endothelial cell activation and subsequent intimal damage to the vessel structure.[4,5] Interleukin-1-β, interferon-γ, and tumor necrosis factor-α may be initiating

factors for endothelial cell activation,[20,21] and the marked increase in coagulation and fibrinolysis may augment the disease process.[22] Factors that trigger the activation of immunocompetent cells, including T-lymphocytes, macrophages, and neutrophils, or which promote the production of proinflammatory cytokines, may initiate the disease. Heat-shock protein HSP65 may be one etiologic agent for KD[6–8]: HSP65 is a highly stable protein with a strong potency for stimulating immunocompetent cells. It may be responsible for reactivation of the Bacille Calmette–Guérin (BCG) injection site, which is the most characteristic symptom of this disease. Thus, the effectiveness of PE therapy could be ascribed to the elimination of excessive proinflammatory cytokines and other etiologic agents such as HSP65 or human cognate HSP60 (unpublished data). However, in a patient with GA despite PE therapy, coronary dilatation was demonstrated at day 7, suggesting that PE had no effect on the CALs already formed. PE may be effective in those pediatric cases that are intractable to IVGG treatment administered in the early stages.

Currently, children with persistent or recrudescent fever after their initial IVGG therapy are often given a second course. The efficacy of steroid pulse therapy was recently investigated as an alternative treatment following its proven efficacy in cases of polyarteritis nodosa.[23] However, it must be kept in mind that steroids increase blood coagulability, and therefore may be risky in KD since they promote fresh embolus formation inside the inflamed vascular structure.[2,3] Steroids, including pulse therapy, need to be reevaluated as options for patients who are intractable to the initial dose of IVGG. We believe that PE therapy is safe. It is easy to carry out for any patient, since 10 infants and 12 children below 10 kg body weight were included in the present study, and this was completed without any technical trouble. Although the published literature has reported complications, including thrombosis, with the PE procedure, we did not experience any problems. Furthermore, the total cost of PE therapy for 3 days was equal to that of additional IVGG (approximately 2 g/kg) in this study, so we believe that PE therapy is never too expensive to perform for patients who are intractable to IVGG therapy.

Finally, there were some limitations to this study: (1) there may be some unknown selection bias because this was a retrospective study; (2) the IVGG regimen used was different from that which was currently standard in other countries, and it also varied from patient to patient.

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