福岡大医紀（*Med. Bull. Fukuoka Univ.*）：33(2), 103-107, 2006

Comparison of C-reactive Protein Improvement in Sulfonated and pH4 Treated Acidic Human Normal Immunoglobulin Treatments for Kawasaki Disease

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Abstract：We administered intravenous human immunoglobulin (IVIG) at a dose of 1g/kg/day in the acute phase of Kawasaki disease and observed changes in C-reactive protein (CRP) before and after administration. We used two human immunoglobulin preparations；namely, freeze-dried sulfonated human normal immunoglobulin (group S) and pH4 treated acidic human normal immunoglobulin (group P), and compared the two preparations. Decreases in CRP were observed in 41 patients (20 in group S, 21 in group P). Neither adverse reactions nor coronary artery aneurysm developed in any patients. The efficacy of the therapy was estimated by the decrease in CRP on day three in comparison to that before the treatment. CRP reduced the value in group P was 26.27±18.49：significantly lower than 41.18±18.82 in group S (P=0.015). In the acute phase treatment of Kawasaki disease, pH4 treated acidic preparation provided a higher degree of improvement in CRP than freeze-dried sulfonated preparation. Therefore, pH4 treated acidic preparation is expected to be faster acting for an improvement of CRP.

Key words：**Kawasaki disease, Intravenous immunoglobulin therapy, Degree of improvement of CRP, Freeze-dried sulfonated immunoglobulin, pH4 treated acidic immunoglobulin**

Introduction

Over twenty years have passed since Furusho et al[1] first reported intravenous human immunoglobulin (IVIG) therapy for acute-phase of Kawasaki disease, and the efficacy of IVIG therapy is now widely recognized.[2] High-dose (1 to 2 g/kg/day) IVIG therapy began to be covered by the national health insurance in 2003 as the standard acute phase treatment of Kawasaki disease in Japan.[3]

The improvement of C-reactive protein (CRP) is a clinically important indicator in evaluating the efficacy of IVIG therapy during acute phase of Kawasaki disease. There have been few comparisons of CRP improvement in different immunoglobulin preparations.[4)-10)] We previously reported a comparison of the duration of fever and the degree of improvement of CRP in IVIG therapy between two immunoglobulin preparations, i.e., freeze-dried sulfonated human normal immunoglobulin or pH4-treated acidic human normal immunoglobulin.[11] There was no difference in the defervescence time between freeze-dried sulfonated preparation and pH4 treated acidic preparation, but the latter provided a higher degree of improvement in CRP. We also enrolled patients to reassess the degree of improvement of CRP.

Subjects and Methods

The subjects consisted of 41 (group S, n=20；

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group P, n=21) of 69 patients that finished treatment with a single administration of 1 g/kg/day of IVIG without a recurrence of fever. Forty-one cases had a baseline CRP value of at least 3 mg/dL, and their CRP values measured three days after administration were also available. To compare the degree of decrease in the CRP values between the two preparations, the day three CRP values were expressed as the adjusted-CRP values, while considering the baseline CRP value to be 100. The lower adjusted-CRP values indicate a more rapid decline in the CRP values. The administering of the S-preparation to one patient and the P-preparation to the next was randomly performed. Statistical analyses were done using the Wilcoxon t-test.

Results

No adverse side effect occurred during the administration of immunoglobulin in any of the 41 patients. The mean age in both groups S and P were around the peak age of onset of Kawasaki disease, and their mean weights were also similar to the average weight of previous patients with Kawasaki disease. Compared with the male/female ratio reported by 17th nationwide survey of Kawasaki disease,[12] the ratio in this study was relatively high, especially in group P (Table 1).

No significant differences were found between the two groups in any of the laboratory parameters before IVIG therapy : WBC count, neutrophil count, CRP, hematocrit, platelet count, albumin, AST, and ALT. No significant differences between the groups were present regarding the administration day, dose, or the infusion rate of IVIG (Table 2).

Table 3 shows the mean WBC counts, mean neutrophil counts, and mean CRP values before and three days after IVIG. The mean WBC and

Table 1. Clinical characteristics in each group

	Group S (N=20)	Group P (N=21)
M/F ratio	1.85	3.20
Age (years)	2.30±1.48 (0.6～1.67)	2.46±2.62 (0.33～11.92)
Weight (kg)	12.18±3.07 (7.5～17.1)	12.33±6.23 (6.6～35.0)

Table 2. Baseline laboratory values and the conditions of gamma globulin administration

	Group S (n=20)	Group P (n=21)
WBC count (/μL)	15,435±3,792 (9,200～22,800)	14,342±3,669 (9,100～22,200)
Neutrophil count (/μL)	9,952±2,974 (5,593～15,392)	8,669±2,631 (5,400～15,096)
CRP (mg/dL)	6.98±3.85 (3.4～19.4)	7.56±2.93 (3.0～13.2)
Ht (%)	32.72±2.43 (26.9～37.6)	33.50±3.29 (27.2～39.8)
PLT ($\times 10^4$/μL)	35.73±11.22 (19.4～61.4)	33.94±9.48 (16.8～53.7)
Alb (g/dL)	3.67±0.35 (3.0～4.3)	3.75±0.41 (3.0～4.4)
AST (IU/L)	42.80±39.58 (24～207)	46.38±42.45 (18～180)
ALT (IU/L)	58.55±62.74 (8～212)	47.57±67.12 (6～285)
Days from onset to admission (day)	4.50±1.40 (1～6)	4.48±1.50 (1～8)
Days from onset to administration of IVIG (day)	5.40±1.27 (2～7)	5.29±1.15 (4～8)
Dose of IVIG (mg/kg)	1,010±60 (899～1,128)	1,032±82 (904～1,149)
Infusion rate of IVIG (mL/kg/min)	0.05±0.01 (0.033～0.061)	0.05±0.01 (0.024～0.063)

Table 3. Comparison of the WBC count and CRP values before and 3 days after of IVIG

	Group S (n=20)	Group P (n=21)
Baseline WBC (/μL)	15,435±3,792 (9,200～22,800)	14,342±3,669 (9,100～22,200)
WBC at day 3 (/μL)	8,470±3,070 (5,700～16,600)	7,967±2,481 (3,500～14,800)
Baseline neutrophil count (/μL)	9,952±2,974 (5,593～15,392)	8,669±2,631 (5,400～15,096)
Neutrophil count at day 3 (/μL)	3,320±1,287 (1,424～6,090)	2,865±1,113 (1,224～4,578)
Baseline CRP (mg/dL)	6.98±3.85 (3.4～19.4)	7.56±2.93 (3.0～13.2)
CRP at day 3 (mg/dL)	2.88±1.89 (1.2～7.3)	1.84±1.02* (0.4～3.8)
Adjusted-CRP at day 3 (%)	41.18±18.82 (16.7～92.4)	26.27±18.49** (4.8～96.7)

*P=0.038 **P=0.015

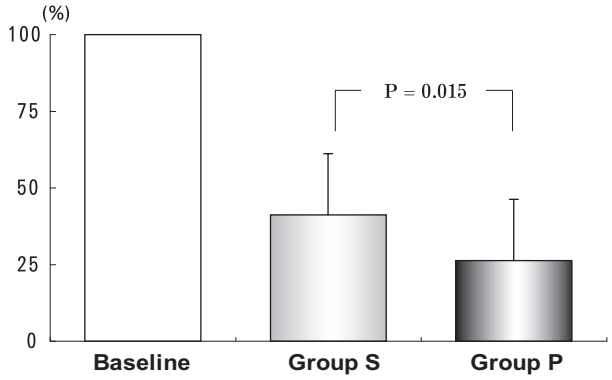

Figure 1. Comparison of the adjusted-CRP values on day 3. The degree of CRP reduction in group P (100→26.27) was significantly greater than that in group S (100→41.18).

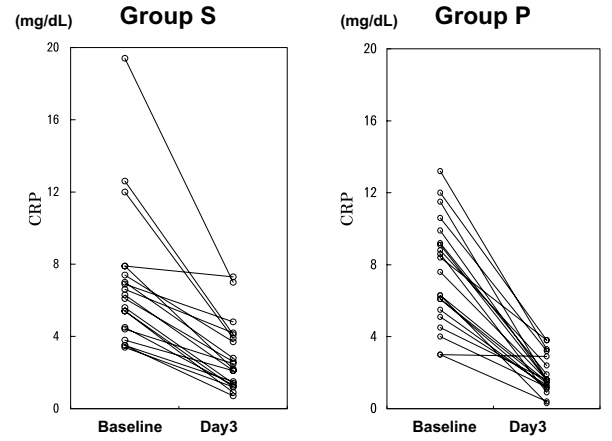

Figure 2. Changes in the CRP values from baseline to day 3 in individual patients in groups S and P

neutrophil counts decreased in both groups, but no significant differences were found between the groups. The mean CRP values of group P at day three were significantly lower than that of group S (p=0.038). The adjusted-CRP values on day three were 41.18±18.82 in group S and 26.27±18.49 in group P, and the degree of CRP reduction was significantly (p=0.015) greater in group P than in group S (Figure 1).

Figure 2 shows changes of CRP values before and after administration in individual patients. Although one patient in each group showed very little improvement of CRP, all of the other patients demonstrated significant decreases in the CRP values on day 3, in comparison to the baseline values.

Discussion

It is important to control severe acute inflammation as early as possible in the acute phase treatment of Kawasaki disease and thereby minimize the incidence of coronary arterial lesions. The treatment of Kawasaki disease should therefore aim to shorten the duration of fever and reduce inflammation within a short period of time. The efficacy of a therapeutic regimen is usually evaluated by its ability to reduce fever or the degree of decrease in either the WBC count, neutrophil count, or CRP value.[3] In order to achieve a clinical response in the shortest possible time, it is important to select a fast-acting preparation.

The immunoglobulin preparations indicated for the treatment of Kawasaki disease can be classified into 3 types according to the IgG modification : namely, sulfonated preparations, pH4–treated acidic preparations, and polyethylene glycol – treated preparations. Ogino et al reported the incidence of side effects to be 0.4% with sulfornated preparations, 0.7% with pH4 acidic treated preparations, and 5.4% with polyethylene glycol treated preparations. Serious complications, such as shock, chills or shivering, cyanosis, or convulsion, were mainly observed in the polyethylene glycol treated preparations.[13] As a result, we selected the former two immunoglobulin preparations and compared them.

In some reports on comparisons of different immunoglobulin preparations, there were no significant differences in the clinical efficacy in the three types of immunoglobulin.[4)–7)]

Muta et al[10] reported no significant differences in the improvement of CRP among the sulfonated preparation, pH4–treated acidic preparation, and polyethylene glycol–treated preparation, however, no detailed data were analyzed regarding the severity of Kawasaki disease. Onouchi et al[8] compared the time course of the neutrophil count as a marker of inflammation, and reported that the pH4 –treated acidic preparation reduced the neutrophil count better than sulfonated preparations during the acute phase of treatment, but it was not statistically significant.

In this study, no significant changes were found in either the WBC or the neutrophil count reduction between the two groups, but the CRP reduction at day three was statistically significantly greater in group P than in group S.

As reported in our previous study,[11] these results indicated that the potency of the pH4–treated acidic preparation in inhibiting inflammation of Kawasaki disease was significantly greater than that of the freeze–dried sulfonated preparation.

However, this study focused on mild cases which finished their treatment with a single dose of 1 g/kg/day of IVIG, further investigations of the efficacies of different preparations should be done in more severe cases.

Conclusions

We compared the administration of the freeze–dried sulfonated preparation with the pH4–treated acidic preparation regarding the improvement in the CRP in the treatment of Kawasaki disease with IVIG. The pH4–treated acidic preparation showed a significantly greater improvement of CRP than the freeze–dried sulfonated preparation during the acute phase. The pH4–treated acidic preparation is therefore considered to act faster than the freeze–dried sulfonated preparation in improving CRP for patients with acute phase of Kawasaki disease with a single dose of 1 g/kg/day IVIG.

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(Received on February 7, 2006,
Accepted on April 3, 2006)