




## Original Article

## Randomized trial of different initial intravenous immunoglobulin regimens in Kawasaki disease

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**Abstract** **Background:** We aimed to assess the efficacy of different initial intravenous immunoglobulin (IVIG) regimens in Kawasaki disease (KD) patients to find more cost-effective therapy options.

**Methods:** A multicenter, open-label, blind-endpoint randomized controlled trial was conducted from January 2014 to December 2015. Patients with KD, within 10 days of illness, were randomly assigned to receive different IVIG regimens (Group A, 2 g/kg once; Group B, 1 g/kg for 2 consecutive days; Group C, 1 g/kg once) and aspirin 30mg/kg/d. Primary outcomes included hours to defervescence and development of coronary artery lesions during the study period. Major secondary outcomes included total fever days, total dose of IVIG, changes of laboratory data, length of stay, and hospitalization expenses. (ClinicalTrials.gov: NCT02439996).

**Results:** A total of 404 patients underwent randomization. No difference was found in the outcomes of defervescence among three groups at 6, 12, 24, and 36 hours after completion of initial IVIG infusion. There were no differences in the incidence of coronary artery lesions during the study period (at week 2, month 1, month 3, and month 6 of illness), changes of laboratory data, total fever days, and length of stay. Group C patients had the lowest total dose of IVIG (mean: 1.2 vs 2.2 vs 2.1 g/kg;  $P < 0.001$ ) and hospitalization expenses (mean: 8443.8 vs 10798.4 vs 11011.4 Chinese Yuan;  $P < 0.001$ ) than other two groups.

**Conclusions:** A single dose of 1g/kg IVIG is a low-cost treatment with the same efficacy as 2 g/kg IVIG and can be an option for the initial therapy of KD patients.

**Key words** coronary aneurysm, cost-benefit analysis, immunoglobulins, intravenous, mucocutaneous lymph node syndrome, treatment outcome.

Kawasaki disease (KD) is a systemic vasculitis occurring predominantly in children under 5 years of age, with coronary artery lesions (CAL) as its main complications.<sup>1</sup> In 1986, a multicenter, randomized trial<sup>2</sup> confirmed that administration of intravenous immunoglobulin (IVIG) plus aspirin could reduce the incidence of CAL in KD patients compared with aspirin alone, with the initial dose of IVIG at 400 mg/kg per day for four consecutive days. In 1991, another multicenter, randomized trial by Newburger *et al.*<sup>3</sup> found that a single high dose of IVIG (2 g/kg once) led to a lower incidence of CAL and a shorter duration of fever without extra adverse effects as compared with the former four-day regimen. Supported by this

clinical trial, a single high dose of IVIG together with aspirin has been adopted as the standard initial therapy for KD in Japanese<sup>4</sup> and American Heart Association (AHA) guidelines.<sup>1</sup>

However, concerning the efficacy of initial IVIG at a single 2 g/kg dose and a single 1 g/kg dose, there was only one randomized prospective study in Japan in 2007.<sup>5</sup> In this study, no difference was found in the incidence of coronary aneurysms between patients receiving a single 2 g/kg IVIG (54 patients) and a single 1 g/kg IVIG (55 patients) as initial therapy. Due to its relatively small number of cases and differences in treating patients resistant to initial IVIG between the two groups, the efficacy of a single 1 g/kg IVIG has not been conclusively confirmed. In 2010, Yeo *et al.* found that medium-dose (1 g/kg) IVIG was also effective in the majority (80%) of KD patients.<sup>6</sup>

Intravenous immunoglobulin is a biological product acquired from thousands of blood donors and is therefore rather expensive for low- and middle-income families in

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China, one of the countries with a quite high incidence of KD (107.3 per 100 000 children under 5 years old in Shanghai in 2016<sup>7</sup>). In Shanghai, the regimens of initial IVIG mainly included 2 g/kg once, 1 g/kg twice, and 1 g/kg once.<sup>7</sup> Aiming to find a more cost-effective therapy option, we conducted a multicenter, randomized controlled trial to assess the efficacy of the three IVIG regimens as initial therapy for KD.

## Methods

### Trial design

We conducted an open-label, multicenter, three-arm randomized controlled clinical trial to compare the efficacy of different IVIG regimens as initial therapy for KD patients: 2 g/kg per day once, 1 g/kg per day for two consecutive days, and 1 g/kg per day once. This study was carried out in three children's hospitals in Shanghai (Children's Hospital of Fudan University, Shanghai Children's Medical Center, and Shanghai Children's Hospital). The study was approved by the institutional review board at each participating center and was performed in accordance with the Declaration of Helsinki. Written informed consents were obtained from all patients or their legal guardians before randomization. This trial was registered at *ClinicalTrials.gov* (identifier: NCT02439996).

### Patient population

Patients were screened if diagnosed with KD according to Japanese guidelines<sup>4</sup> and American Heart Association guidelines<sup>1</sup> for KD, including complete and incomplete KD. Inclusion criteria: (1) within five to ten days of illness (the first day of illness was defined as the first day of fever); (2) 1 month  $\leq$  age of onset <12 years of age.

Exclusion criteria: (i) afebrile before enrolment; (ii) with a previous history of KD; (iii) with CAL before enrolment; (iv) with a history of administration of steroids (oral, intravenous, intramuscular, or subcutaneous) in the previous 30 days or administration of IVIG in the previous 180 days; (v) with severe concomitant medical disorders (chromosomal abnormality, immunodeficiency, complex congenital heart disease, metabolic disorders, nephritis, collagen diseases, etc.); (vi) with suspected infectious diseases including sepsis, septic meningitis, peritonitis, bacterial pneumonia, varicella, and influenza.

### Randomization and blinding

After screening for eligibility, patients were randomly assigned in a 1:1:1 ratio to one of the three study groups, stratified by hospital. Randomization was performed using a simple randomization sequence generated by Microsoft Excel. A set of instructions about correct implementation of the randomized trial was sent to the three participating hospitals. Patients and physicians were not masked to the group assignments, while echocardiologists assessing CAL were blinded.

## Interventions

Patients were randomly assigned to receive IVIG at the dose of 2 g/kg per day once (Group A), 1 g/kg per day for two consecutive days (Group B), or 1 g/kg per day once (Group C). IVIG was administered over 10 h for each regimen. Two IVIG products were used for administration, and both were pH4 and manufactured in Shanghai. In addition, all patients received oral aspirin 30 mg/kg per day, which was reduced to 3 to 5 mg/kg per day when fever subsided for 3 days and C-reactive protein (CRP)  $\leq$ 8 mg/L. Patients admitted before the fifth day of illness were treated with aspirin only and began IVIG treatment between the fifth and tenth day of illness.

Patients resistant to the initial IVIG treatment were given a second dose of IVIG at 2 g/kg. Those resistant to the second dose of IVIG were given methylprednisolone (10 mg/kg for 3 days) or infliximab (5 mg/kg once) according to the American Heart Association guidelines.<sup>1</sup> Initial intravenous immunoglobulin resistance was defined as fever persisting for more than 24 h after completion of IVIG infusion or recrudescence fever associated with at least two symptoms of KD after an afebrile period.

## Measurement

Axillary temperature was measured every 6 h each day during hospitalization. Patients with a temperature  $<37.5^{\circ}\text{C}$  for more than 24 h were considered afebrile. Laboratory tests were performed at enrolment and 72 h after completion of initial IVIG infusion, including full blood count, CRP, alanine aminotransferase (ALT), serum albumin (ALB), and electrolytes. Erythrocyte sedimentation rate (ESR) was measured only before initial IVIG treatment. The serum concentration of aspartate aminotransferase (AST) and percentage of neutrophils prior to initial IVIG treatment were additionally collected to calculate the Kobayashi score for each patient.<sup>8</sup>

Serial evaluation of the coronary arteries was carried out with two-dimensional echocardiography before IVIG administration and at approximately 2 weeks, 1 month, 3 months, and 6 months after onset of illness. Echocardiography was performed by pediatric echocardiologists in each participating center. Video recordings were preserved and reevaluated by another two pediatric echocardiologists. The measurement of each patient included the diameter of left main coronary artery (LMCA), left anterior descending artery (LAD), left circumflex coronary artery (LCX), and the proximal, middle and distal segment of right coronary artery (RCA). The  $z$  score of each artery was also calculated in some patients.<sup>9</sup>

A coronary artery lesion was defined as coronary dilation or aneurysm. A patient was considered to develop CAL when the luminal diameter was  $>3.0$  mm in a child aged younger than 5 years or  $>4.0$  mm in those aged 5 years or older, or when the internal diameter of a segment was 1.5 times or greater than that of an adjacent segment, or  $z$  score  $>2.5$ . A medium aneurysm was defined as an internal luminal diameter from 4 to 8 mm and a giant aneurysm was defined as an

internal luminal diameter >8 mm. The severity of CAL is classified into the following five risk levels on the basis of findings with methods such as echocardiography and selective coronary angiography: Level 1, no coronary artery changes at any stage of illness; Level 2, transient coronary artery ectasia disappears within the first month of onset; Level 3, isolated small to medium (>4 mm but ≤8 mm, or z score between 2.5 and 10.0) coronary artery aneurysm in ≥ 1 coronary arteries; Level 4, ≥1 large or giant coronary artery aneurysm (≥8 mm, or z score ≥10), or multiple aneurysms in a same coronary artery, without obstruction; Level 5, coronary artery obstruction.<sup>1,4,10</sup>

### Outcomes

Primary outcomes included hours to defervescence within 36 h after completion of initial IVIG infusion and the incidence of CAL in week 2. Secondary outcomes included the incidence of IVIG resistance, total fever days, total dose of IVIG, changes in laboratory data 72 h after completion of initial IVIG infusion, incidence of CAL during the whole study period, length of hospital stay, hospitalization expenses, and serious adverse events (including death, severe infection, heart failure, allergic reactions, etc.).

### Sample size calculation

The sample size was calculated using PS Power and Sample Size Calculator (Version 3.0, Vanderbilt University, Nashville, TN, USA) based on the primary outcome parameter (hours to defervescence after completion of initial IVIG). This was a three-arm trial with one control arm (Group A) and two experimental arms (Groups B and C). The hypothesis was to test significant differences between any experimental treatments

with the control arm based on an alpha level of 0.015. According to our previous observations, the outcome in patients receiving Group A intervention was normally distributed with a standard deviation of 18. Therefore, 110 patients in each arm were needed to ensure a statistical power of 0.8 to detect at least 8 h differences between any experimental arm and the control arm.

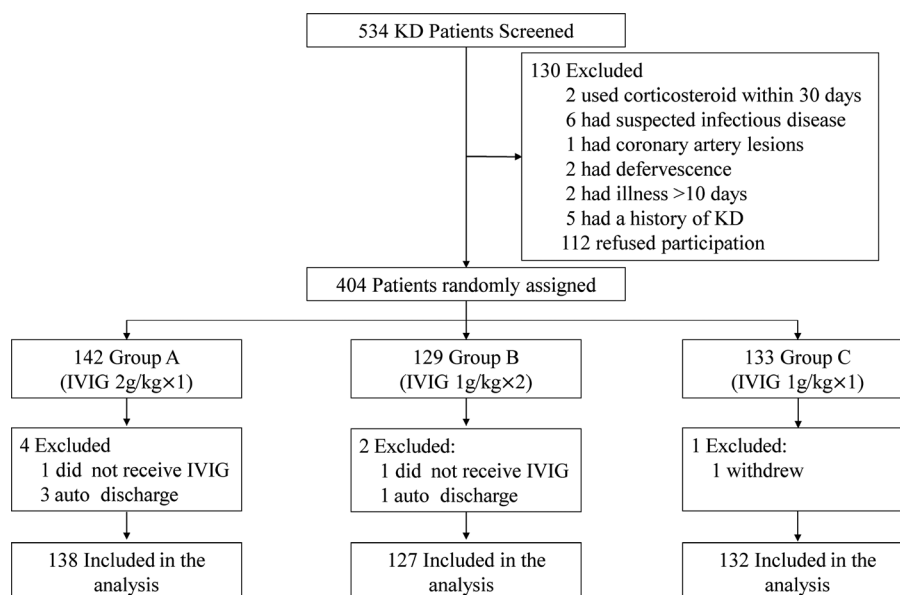
### Statistical analysis

Continuous variables were presented as means ( $\pm$  standard deviation) or medians (interquartile ranges), and compared using a univariate ANOVA or a Wilcoxon rank-sum test. Categorical variables were presented as absolute frequencies (percentages) and compared using the  $\chi^2$  test or Fisher's exact tests. The primary outcome (hours to defervescence) was compared using a univariate ANOVA for the continuous variable, followed by pair-wise *t*-tests if an overall significant difference was found. The variance homogeneity test was performed using the *F* test. Length of hospital stay and hospitalization expenses were analyzed using the rank-sum test (non-normal distribution). An alpha level of 0.015 was adopted according to the Bonferroni adjustment for between-group comparisons. The primary outcome analysis was based on intention-to-treat strategy. All analyses were performed with SPSS 22.0 (IBM Corporation, Armonk, NY, USA).

## Results

### Study population

Between January 2014 and December 2015, a total of 404 patients were enrolled (Fig. 1), of whom 326 were from the Children's Hospital of Fudan University, 63 from Shanghai



**Fig. 1** Enrollment and randomization. IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Children's Hospital, and 15 from Shanghai Children's Medical Center.

Among the patients enrolled, 142 were randomly assigned to Group A (IVIG 2 g/kg once), 129 to Group B (IVIG 1 g/kg for 2 consecutive days), and 133 to Group C (IVIG 1 g/kg once). The numbers of patients with completed primary outcome data were 138 in Group A, 127 in Group B, and 132 in Group C, respectively. Thus, 397 patients were included in the per protocol analysis. Demographics, clinical characteristics, laboratory data, and Kobayashi score at baseline were well balanced among three groups (Table 1).

### Treatment outcomes

There was no difference in the proportion of patients that achieved defervescence within 6, 12, 24, and 36 h after completion of initial IVIG infusion among the three groups (Table 2). Consequently, there was no significant difference in the incidence of initial IVIG resistance (10.1%, 5.5%, and 9.1% for Group A, Group B and Group C, respectively;  $P = 0.364$ ). The proportion of patients resistant to the second dose of IVIG was 0 of 14 in Group A, 1 of 7 in Group B (responsive to further treatment of infliximab 5 mg/kg), and 5 of 12

**Table 1** Baseline characteristics of patients among three groups

	Group A ( <i>n</i> = 138)	Group B ( <i>n</i> = 127)	Group C ( <i>n</i> = 132)	<i>P</i>
<b>Demographics</b>				
Age (month), mean ± SD	26.4 ± 22.7	28.8 ± 22.3	26.1 ± 20.0	0.551
Bodyweight (kg), mean ± SD	12.5 ± 4.4	13.2 ± 5.2	13.0 ± 5.7	0.488
Male sex, <i>n</i> (%)	90 (65.2%)	82 (64.6%)	77 (58.3%)	0.441
Incomplete KD, <i>n</i> (%)	13 (9.4%)	15 (11.8%)	15 (6.5%)	0.799
<b>Principal clinical findings, <i>n</i> (%)</b>				
Exanthema	136 (98.6%)	122 (96.1%)	129 (97.7%)	0.424
Cervical lymphadenopathy	45 (32.6%)	43 (33.9%)	46 (34.9%)	0.927
Bilateral conjunctival congestion	110 (79.7%)	104 (81.9%)	111 (84.1%)	0.647
Reddening of lips	137 (99.3%)	123 (96.9%)	130 (98.5%)	0.314
Strawberry tongue	133 (96.4%)	117 (92.1%)	125 (94.7%)	0.316
Reddening and oedema of palms and soles	91 (65.9%)	80 (63.0%)	87 (65.9%)	0.849
Membranous desquamation	114 (82.6%)	98 (77.2%)	110 (83.3%)	0.383
<b>Laboratory data (mean ± SD)</b>				
WBC ( $\times 10^9/L$ )	15.3 ± 5.5	15.0 ± 5.8	15.7 ± 5.5	0.644
CRP <sup>†</sup> (mg/L)	85 (42–134)	75 (42–120)	72 (45–112)	0.147
ESR (mm/h)	66.2 ± 22.9	62.1 ± 23.7	64.3 ± 24.7	0.389
Hb (g/L)	108.8 ± 11.9	111.0 ± 11.4	110.5 ± 13.5	0.332
PLT ( $\times 10^9/L$ )	332.2 ± 107.1	340.0 ± 121.0	357.9 ± 135.2	0.208
ALB (g/L)	35.5 ± 4.0	36.3 ± 3.3	35.7 ± 3.3	0.190
ALT (IU/L)	30.8 ± 44.4	34.6 ± 45.3	32.9 ± 36.5	0.770
Na <sup>+</sup> (mmol/L)	136.5 ± 3.4	136.7 ± 3.4	136.1 ± 3.2	0.349
Kobayashi score (points), mean ± SD	1.68 ± 1.39	1.53 ± 1.38	1.59 ± 1.40	0.640

ALB, serum albumin; ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; KD, Kawasaki disease; Na<sup>+</sup>, serum sodium; PLT, platelet count; WBC, white blood cell.

<sup>†</sup>Median (interquartile range), based on tobit regression. Left-censored observation at 8 mg/L, right-censored observation at 160 mg/L.

**Table 2** Treatment outcomes among the three groups

	Group A ( <i>n</i> = 141)	Group B ( <i>n</i> = 128)	Group C ( <i>n</i> = 132)	<i>P</i>
<b>No. of patients achieved defervescence by 36 h after completion of initial IVIG</b>				
6 h, <i>n</i> (%)	45 (31.2%)	42 (29.1%)	33 (22.7%)	0.277
12 h, <i>n</i> (%)	98 (71.0%)	94 (74.0%)	100 (76.8%)	0.670
24 h, <i>n</i> (%)	127 (92.0%)	113 (89.0%)	120 (90.9%)	0.690
36 h, <i>n</i> (%)	136 (98.6%)	124 (97.6%)	128 (97.0%)	0.646
Fever duration before initial IVIG infusion (days), mean ± SD	5.9 ± 1.9	5.9 ± 2.0	5.9 ± 2.0	0.960
Second dose IVIG, <i>n</i> (%)	14 (10.1%)	7 (5.5%)	12 (9.1%)	0.364
Resistance to second IVIG, <i>n</i>	0	1	5	0.030*
Overall duration of fever (days), mean ± SD	7.9 ± 2.3	7.5 ± 1.8	7.8 ± 2.3	0.345
Total dose of IVIG used for each patient (g/kg), mean ± SD	2.2 ± 0.6	2.1 ± 0.4	1.2 ± 0.6	<0.001

IVIG, intravenous immunoglobulin.

\*Fisher exact test.

in Group C (all responsive to further treatment of methylprednisolone 10 mg/kg for 3 days), respectively ( $P = 0.030$ ). The overall duration of fever was not significantly different among three groups ( $P = 0.345$ ). As compared with Group A and Group B, the total dose of IVIG was the lowest in Group C (mean: 2.2 vs 2.1 vs 1.2 g/kg per patient;  $P < 0.001$ ).

### Coronary artery lesions

There was no difference in the incidence of CAL among the three groups at week 2 of illness (15.2%, 15.0%, and 12.9% for Group A, Group B and Group C;  $P = 0.837$ ; Table 3). Similarly, no difference was found in the incidence of CAL at month 1, month 3, or month 6 of the illness ( $P = 0.634$ , 0.487 and 0.415, respectively; Table 3). The occurrence or progression of CAL after week 2 was not found in any treatment group.

### Laboratory data

White blood cell counts, CRP level, hemoglobin concentrations, and platelet counts were not different among the three groups 72 h after completion of initial IVIG infusion ( $P = 0.744$ , 0.938, 0.263 and 0.341, respectively; Table 4). Alanine aminotransferase was also measured 72 h after completion of initial IVIG infusion in 67 patients (20 for Group A, 26 for Group B, and 21 for Group C, respectively) with abnormally

elevated levels before IVIG administration, showing no difference among three groups ( $P = 0.469$ ; Table 4).

### Length of stay and hospitalization expenses

No difference was observed in the length of hospital stay among the three groups (mean  $\pm$  SD: 8.3  $\pm$  2.7 days for Group A, 8.4  $\pm$  2.5 days for Group B, and 8.3  $\pm$  3.4 days for Group C;  $P = 0.989$ ). However, hospitalization expenses were the lowest in Group C as compared with Group A and Group B (mean  $\pm$  SD: 8443.8  $\pm$  4,256.8 vs 10 798.4  $\pm$  4,631.1 vs 11 011.4  $\pm$  4,624.8 Chinese Yuan;  $P < 0.001$ ).

### Adverse events

Only one patient in Group B had adverse events. The patient contracted chickenpox nine days after onset of fever but recovered without complications. Intravenous immunoglobulin resistance or CAL did not occur in this patient during the study period.

### Discussion

In this randomized controlled trial, we compared the effectiveness of three IVIG treatment regimens (1 g/kg once, 1 g/kg twice, 2 g/kg once) as initial therapy in acute KD patients. No

**Table 3** Coronary artery lesions among the three groups during the study period

	Group A (n = 138)	Group B (n = 127)	Group C (n = 132)	P
Week 2, n (%)	21 (15.2%)	19 (15.0%)	17 (12.9%)	0.837*
Level 2, n (%)	12 (8.7%)	7 (5.5%)	10 (7.6%)	
Level 3, n	9	10	6	
Level 4, n	0	2	1	
Month 1, n (%)	9 (6.5%)	12 (9.5%)	7 (5.3%)	0.634
Level 3, n	9	10	6	
Level 4, n	0	2	1	
Month 3, n (%)	3 (2.2%)	6 (4.7%)	4 (3.0%)	0.487
Level 3, n	3	4	3	
Level 4, n	0	2	1	
Month 6, n (%)	1 (0.7%)	5 (3.9%)	2 (1.5%)	0.415
Level 3, n	1	3	1	
Level 4, n	0	2	1	

\* $P = 0.712$  based on intention-to-treat analysis.

**Table 4** Laboratory data 72 h after completion of initial IVIG infusion

	Group A (n = 138)	Group B (n = 127)	Group C (n = 132)	P
WBC ( $\times 10^9/L$ ), mean $\pm$ SD	8.9 $\pm$ 3.8	8.7 $\pm$ 3.4	9.0 $\pm$ 3.9	0.744
CRP (mg/L), median (IQR)	9 (7–15)	8 (7–14)	9 (7–15)	0.938 <sup>†</sup>
Hb (g/L), mean $\pm$ SD	108.0 $\pm$ 11.9	109.5 $\pm$ 11.6	110.4 $\pm$ 13.7	0.263
PLT ( $\times 10^9/L$ ), mean $\pm$ SD	550.2 $\pm$ 155.1	529.2 $\pm$ 144.1	557.0 $\pm$ 174.1	0.341
ALT (IU/L) <sup>‡</sup> , mean $\pm$ SD	35.1 $\pm$ 32.2	31.8 $\pm$ 29.0	52.6 $\pm$ 97.4	0.469

ALT, alanine aminotransferase; CRP, C-reactive protein; Hb, haemoglobin; PLT, platelet count; WBC, white blood cell.

<sup>†</sup>Based on tobit regression. Left-censored observation at 8mg/L, right-censored observation at 160 mg/L.

<sup>‡</sup>Data were available for 20, 26 and 21 for Groups A, B and C, respectively.

difference was found in the hours to defervescence after completion of initial IVIG infusion, incidence of IVIG resistance, incidence of CAL at any stage during the study period (week 2, month 1, month 3, and month 6 of illness), total fever days, laboratory data 72 h after completion of initial IVIG infusion, and length of stay among three treatment groups. These findings suggest that a single dose of IVIG at 1g/kg is able to improve the KD symptoms during the acute phase.

Early studies of the IVIG dose in 2003 and 2004 mainly focused on comparisons of 2 g/kg once versus 400 mg/kg/day for five days and 400 mg/kg/day for 4 days, and showed an apparent therapeutic advantage for 2 g/kg IVIG, including the reduction in proportion of CAL and shortening of fever duration.<sup>11,12</sup> However, comparisons between a single 2 g/kg dose and a single 1 g/kg dose were not mentioned in these studies.

Since 2007, there have been several studies with similar findings to ours, including the prospective study in Japan on the use of 2 g/kg or 1 g/kg IVIG and Yeo's study on the effectiveness of the medium-dose (1 g/kg) IVIG in Korea.<sup>5,6</sup> Besides, in 2012, a meta-analysis of 28 randomized clinical trials involving 2,596 KD cases revealed no significant differences in the incidence of CAL in the acute phase (relative risk = 1.16, 95% CI: 0.88 to 1.54) and subacute phase (relative risk = 0.50, 95% CI: 0.20 to 1.27), and the proportion of fever disappearance within 2 days (mean difference = 0.6, 95% CI: -0.03 to 0.16;  $P = 0.18$ ) between the IVIG treatment groups at the doses of 1 g/kg for 1–2 days (mainly 1 g/kg for 2 days) and 2 g/kg for single use.<sup>13</sup> In 2020, Suzuki *et al.* compared clinical outcomes between 2 g/kg and 1 g/kg IVIG in KD children with higher bodyweight (25 kg or more) using a national inpatient database. The study showed no significant differences in the proportions of coronary artery aneurysms (5.3% vs 4.1%;  $P = 0.587$ ), IVIG resistance (20.3% vs. 14.2%;  $P = 0.054$ ), and length of stay (median: 11 vs 11 days;  $P = 0.476$ ).

Furthermore, according to our previous two epidemiologic surveys of KD in Shanghai from 2008 to 2017 (once every 5 years), treatment dose of IVIG, including 2 g/kg once, 1 g/kg once, or 1 g/kg twice, was not the independent risk factor for CAL in the multivariate analysis (involving 2,302 cases and 3,627 cases, respectively).<sup>7,14</sup> All of these studies suggest that a single dose of 1 g/kg IVIG as initial therapy is also an effective treatment for KD patients and could be an alternative treatment option.

In our study, administration of 1 g/kg IVIG once as initial therapy significantly reduced the total dose of IVIG per patient (mean: 2.2 vs 2.1 vs 1.2 g/kg for Group A, Group B, and Group C, respectively;  $P < 0.001$ ) and hospitalization expenses (mean: 10798.4 vs 11011.4 vs 8443.8 Chinese Yuan for Group A, Group B, and Group C, respectively;  $P < 0.001$ ). Considering the similar clinical outcomes and lower medical costs, the initial therapy of 1 g/kg IVIG is better than 2 g/kg IVIG from an economic view. Intravenous immunoglobulin is a blood product manufactured from pooled human plasma, and its high cost is hardly affordable for people in low- and middle-income families. In China, for example, 1 g of

immunoglobulin costs approximately 230 Chinese Yuan (about 35 US dollars), equivalent to a day's salary for an ordinary employee in the cities, and a month's income for a family in rural areas. In such a populous country with a high incidence of KD,<sup>7</sup> it is therefore particularly important to find a low-cost treatment with the same efficacy to reduce the financial burden.

While high dose (2 g/kg) IVIG are generally well tolerated in KD patients, there are still some concerns. Hemolysis is a rare but serious side effect of IVIG and is more common in patients who receive high-dose IVIG, for example, in IVIG-resistant patients who receive a second or more doses of IVIG and obese KD patients whose total dose of IVIG is higher.<sup>15,16</sup> The possible mechanism is that erythrocytes are destroyed and cleared due to the high titers of antibodies against blood groups A and B contained in IVIG preparations.<sup>17</sup> It is also reported that a single high-dose regimen increases blood viscosity and therefore might increase the risk of thromboembolism.<sup>18,19</sup> Reducing the dose of IVIG therefore helps to prevent the occurrences of these serious complications.

Notably, we found that Group C patients (receiving 1 g/kg IVIG) were more likely to be resistant to a second dose of IVIG (2 g/kg), as compared with the other two groups (5/12 vs 0/14 vs 1/7;  $P = 0.030$ ). If KD patients who receive 1 g/kg IVIG as initial treatment develop IVIG resistance, more aggressive additional treatment could therefore be given such as infliximab. Infliximab, a monoclonal antibody against tumor necrosis factor  $\alpha$ , is more effective in fever resolution compared to a second IVIG dose.<sup>20,21</sup> Further studies are needed to determine the efficacy of infliximab in KD patients who do not respond to the initial 1 g/kg IVIG. If this problem is properly handled, 1 g/kg IVIG could be a cost-effective treatment option for KD patients.

Considering the possible different effectiveness of IVIG manufactured by different processes,<sup>22</sup> we only adopted human immunoglobulin (pH4) for intravenous injections that were made in Shanghai. One limitation of our study is that one of the three centers contributed the majority of the sample size (80.3%). However, bias is minimized because stratified randomization by hospital was performed. Another limitation is that we used either exact diameter of coronary artery or z score in the definition of CAL as z scores could not be calculated in all patients due to lack of height. However, no matter which method was used, we strictly followed the criteria to define CAL.

In summary, based on the analysis of the fever duration, occurrences of CAL, changes in laboratory tests, adverse events, and hospital expenses, our current study indicates that a single dose of 1g/kg IVIG could be an effective and low-cost initial treatment option for KD patients.

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## Disclosure

The authors declare no conflict of interest.

## Author contributions

G.Y. Huang and F. Liu contributed to the conception and design of this study. L. He, M. Huang, M.R. Huang, L.J. Xie, Y. Guo, X.Y. Xu, C. Chu, L. Wu, X.C. Liang, S.N. Sun, F. Wang, L. Zhao, Q.M. Zhao, X.J. Ma and L.P. Xie were responsible for the patient recruitment and data collection. L. He and W.L. Yan performed the statistical analyses. L. He and F. Liu drafted the manuscript. G.Y. Huang critically reviewed the manuscript and supervised the whole study process. All of the authors read and approved the final manuscript.

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