

High-dose gamma globulin plus dipyridamole for Kawasaki disease in children: An investigation of therapeutic effectiveness

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Abstract: The therapeutic efficacy of high-dose (HD) gamma globulin (GG) co-administered with dipyridamole (DIP) was assessed in children with Kawasaki disease (KD). Among 100 enrolled pediatric KD cases, the control group was treated with low-dose (LD)-GG, while the research group received HD-GG. Both groups also underwent standard therapy and oral DIP. Statistical comparisons were conducted for overall effectiveness, safety, coronary artery diameter grading, symptom resolution timelines and serum markers of inflammation. Results indicated the research group achieved higher therapeutic effectiveness than controls while maintaining similar safety profiles. Additionally, the research group exhibited superior coronary artery diameter grading, quicker symptomatic relief and more robust anti-inflammatory effects as measured by serum biomarkers. Conclusively, for pediatric KD, HD-GG+DIP achieves robust therapeutic outcomes while maintaining a safe side-effect profile. Improvements in coronary artery diameter grading, faster symptom relief and regulated serum inflammatory cytokine levels further support its broader clinical application.

Keywords: Dipyridamole; Gamma globulin; Kawasaki disease in children; Therapeutic effectiveness

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INTRODUCTION

Kawasaki disease (KD), essentially a mucocutaneous lymph node syndrome, is a multi-system vasculitis disease commonly found in coronary arteries and also a major inducement of acquired heart disease (Hamwi *et al.*, 2023; Agarwal & Agrawal, 2017; Z. Wang *et al.*, 2021). According to statistics, the disease is most common in children under 5 years of age, with a risk higher in boys than in girls and a relatively higher prevalence in children in Asia and those with a family history (Singh *et al.*, 2015). KD can lead to persistent fever, erythema of the lips and oral mucosa, cervical lymphadenopathy, foot swelling and other typical clinical symptoms, as well as facial paralysis, acute abdomen, seizures and pneumonia and other atypical symptoms, posing varying degrees of threat to the health of children (Rife & Gedalia, 2020; Liu *et al.*, 2021). In addition, patients with the disease will go through three stages: acute stage, subacute stage and convalescent stage. Timely and effective intervention for patients with acute-stage KD will help reduce the risk of coronary artery aneurysm and improve the treatment effect (Marchesi *et al.*, 2018). Although intravenous gamma globulin (GG) plus oral aspirin, the routine treatment for acute KD, can lead to a recovery rate of up to 80%, it may lead to drug resistance and a high risk of complications or death in some patients (Xiong *et al.*, 2022; Noval Rivas & Arditi, 2020). Therefore, this study attempts to further analyze the clinical treatment of KD in children, aiming at providing evidence-based clinical guidance for the management of the disease.

GG is derived from the plasma of healthy subjects. After purification, it can be used as a mixed preparation of immunoglobulin G (IgG), which can play an inflammatory inhibitory role by inhibiting Fc receptors, neutralizing the pathogenic products of unknown infectious factors and maintaining the balance of inflammatory microenvironment (Li & Chen, 2023; Tawfik *et al.*, 2012). In the report of Sun H *et al.* (Sun *et al.*, 2022), GG contributed to obviously higher efficacy and a lower incidence of adverse events than aspirin alone in 90 children with KD, with a positive impact on the improvement of short-term prognosis.

In addition, GG shows a dose-response relationship in KD and high-dose (HD)-GG may bring some side effects to children (Tawfik *et al.*, 2012). Dipyridamole (DIP), as an antiplatelet drug, also has the effect of dilating coronary arteries and can be used for the treatment or preventive intervention of secondary ischemic stroke, preeclampsia and thromboembolic diseases (Florescu *et al.*, 2019; Duley *et al.*, 2019; Surianarayanan *et al.*, 2021). It also has therapeutic value in KD and can be used to reduce the risk of cardiac complications (Tanoshima *et al.*, 2019). DIP has a variety of therapeutic mechanisms, which can play a therapeutic role by inhibiting cAMP-phosphodiesterase, inhibiting platelet reuptake and decomposition of adenosine and enhancing PGI₂ biosynthesis (Kamarova *et al.*, 2022).

Limited data exist regarding the clinical outcomes of HD-GG and DIP combination therapy in childhood KD. The primary objective of this research is to compare the clinical effectiveness of HD versus low-dose (LD) GG, both administered alongside DIP, in pediatric Kawasaki disease

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cases. This systematic comparison covered therapeutic effectiveness, safety, coronary artery diameter grading, symptomatic recovery duration and serum inflammatory cytokine levels. The investigation verified that HD-GG plus DIP yielded better clinical performance without compromising patient safety. These evidence-based conclusions facilitate more informed treatment selection for pediatric KD cases.

MATERIALS AND METHODS

General information

In this retrospective investigation, the study population comprised 100 KD children admitted to our hospital between January 2021 and January 2023, including 49 cases (control group) receiving LD-GG (1.0g/kg) therapy and 51 cases (research group) receiving HD-GG (2.0g/kg) therapy. No statistical inter-group significance was identified in the comparison of general data ($p>0.05$).

Criteria for patient enrollment and exclusion

Inclusion criteria: All the children met the KD diagnostic criteria (Kuo, 2023) and presented with typical symptoms such as fever, lymphadenopathy, mucosal congestion and swelling of hands and feet, with complete medical records and no contraindications to medication.

Exclusion criteria: Children with other skin diseases (Scarlet fever, Stevens-Johnson syndrome, Erythema multiforme, psoriatic disease, Henoch-Schonlein purpura, etc.), serious infectious diseases, congenital pulmonary insufficiency, abnormal coagulation function, or systemic inflammatory syndrome, as well as those with prior use of aspirin and GG before admission were excluded.

Treatment methods

Both groups were given routine symptomatic treatment, such as reducing fever, maintaining electrolyte balance and taking aspirin orally, in addition to DIP (5mg/kg/d, taken in three doses) that was administered orally for 4-8 weeks. The difference is that the control group received LD-GG (1.0g/kg), while the research group was given HD-GG (2.0g/kg). The medication was administered intravenously only once on the first day of treatment. GG dosages, both low and high, were determined based on prior research (Danieli *et al.*, 2023).

Endpoints

(1) Total effective rate (Wang *et al.*, 2024). A marked remission refers to the resolution of clinical symptoms and the disappearance of coronary artery lesions within 5 days of treatment; a remission is translated as the resolution of clinical symptoms and the absence of coronary artery lesions within 5-8 days of treatment; non-remission means that the clinical symptoms have not improved after 12 days of treatment, or coronary artery disease appears. The total effective rate is calculated by dividing the sum of marked

remission and remission cases by the total number of cases.

(2) Safety (Sun *et al.*, 2022). To assess treatment safety, we recorded the number of patients with adverse reactions such as nausea and vomiting, dizziness and headache and diarrhea and calculated the incidence rate.

(3) Coronary artery diameter grading (Xu *et al.*, 2024). The coronary artery diameter of children before and 8 weeks after treatment was detected by echocardiography: 0: the coronary artery diameter was ≤ 2.5 mm in children under 3 years old or ≤ 3.0 mm in those aged 3-9; I: presence of tumor-like expansion and localization, with an inner diameter less than 4 mm; II: presence of single or multiple lesions with an inner diameter of 4-7 mm; III: presence of extensive lesions with an internal diameter ≥ 8 mm, involving more than one coronary artery.

(4) Time of symptom recovery (Lee *et al.*, 2022). The improvement time of clinical symptoms such as fever, swelling of hands and feet, lymphadenopathy and mucosal congestion in both groups was recorded.

(5) Serum inflammatory factors (IFs) (Feng *et al.*, 2024). Fasting venous blood was collected from all patients before and after treatment and serum was obtained after centrifugation to determine IFs such as interleukin (IL)-6, C-reactive protein (CRP) and tumor necrosis factor (TNF)- α by enzyme-linked immunosorbent assays (ELISAs).

Statistical analysis

Measurement data, statistically described by ($X \pm s$), were compared between groups by independent samples t tests and within groups before and after treatment by paired t tests. Counting data were presented in the form of the ratio (percentage) and the inter-group differences were identified using χ^2 tests. The collected experimental data were analyzed by SPSS 21.0, with statistical significance reported at the $p<0.05$ level. Sample size estimation was performed for a two-group proportion comparison, with expected efficacy rates of 60% (control group) and 80% (research group). Using $\alpha=0.05$ (two-tailed) and 80% power, the initial calculation required 41 participants per arm. To compensate for possible 10% attrition, recruitment goals were set at 45 per arm. Final enrollment reached 49 controls and 51 research cases, surpassing the calculated minimum.

RESULTS

Comparative evaluation of patient general data

We found no marked inter-group differences in gender, mean age, course of disease, duration of fever, single parent family, etc. ($p>0.05$). (Table 1).

Comparative evaluation of total effective rate

The total effective rates of the control and research groups

were 69.39% and 92.16%, respectively, revealing markedly higher efficacy in the research group ($p < 0.05$). (Table 2)

Comparative evaluation of side effects of medication

In both groups, the major side effects of medication were nausea and vomiting, dizziness and headache and diarrhea. The incidence of side effects was lower in the research group compared with control group, but with no statistical significance ($p > 0.05$). (Table 3)

Comparative evaluation of coronary artery diameter grading

No statistical inter-group difference was identified in pre-treatment coronary artery diameter grading ($p > 0.05$), but a significant difference was found between groups after treatment ($p < 0.05$). Specifically, the coronary artery diameter grading was milder in the research group versus the control group ($p < 0.05$). (Table 4)

Comparative evaluation of symptom recovery time

The symptom recovery time was primarily evaluated from the following aspects: fever, hand and foot swelling, lymphadenopathy and mucosal congestion. After comparison, notably shorter symptom recovery time was determined in the research group compared to the control group ($p < 0.05$). (Fig. 1)

Comparative evaluation of serum IFs

ELISAs were performed to quantify the levels of the following serum IFs: IL-6, CRP and TNF- α . These serum IFs presented similar levels in the two groups before treatment ($p > 0.05$). Their levels reduced markedly after treatment, with even more notable reductions in the research group ($p < 0.05$). (Fig. 2)

DISCUSSION

The pathogenesis of KD is complex, currently known to involve genetic, infectious and autoimmune factors, with patients presenting high levels of cytokines (such as IL-6 and TNF- α) carrying a higher risk of shock syndrome (Bordea *et al.*, 2022). In addition, the development of the disease will cause multiple injuries to the heart, joints, liver, muscles, kidneys, coronary arteries and central nervous system in children (Cheng *et al.*, 2020). In order to improve the prognosis of KD children and effectively prevent disease progression, it is necessary to continuously explore treatment optimization.

This study identified an evidently higher total effective rate in the research group treated with HD-GG + DIP compared with the control group receiving LD-GG + DIP (92.16% vs. 69.39%), indicating that increasing the GG dosage on the basis of routine therapy can significantly improve curative efficacy in KD children. A potential explanation is that GG intervention's effectiveness in KD children improves

progressively with higher administered doses (Huang *et al.*, 2020). In terms of safety, we observed a similar incidence of side effects of medication (nausea and vomiting, dizziness and headache and diarrhea) between the research and control groups (17.65% vs. 8.16%), suggesting that HD-GG + DIP would not significantly improve the side effects of medication with a reliable safety profile. Then, the results of coronary artery diameter grading revealed that the research group was significantly better than the control group in improving the coronary artery diameter grading after treatment, which indicates the effectiveness of HD-GG + DIP intervention in lowering the coronary artery diameter grade in KD children. According to the statistics of post-treatment recovery time of typical clinical symptoms such as fever, swelling of hands and feet, lymphadenopathy and mucosal congestion in KD children, we found that the recovery of all these clinical symptoms was faster in the research group versus the control group, demonstrating the ability of HD-GG + DIP to effectively accelerate the recovery of clinical symptoms in KD children. This may be related to the fact that a single HD-GG intervention may act faster and effectively alleviate the deterioration of acute vasculitis by significantly increasing serum IgG levels in such children (Fukui *et al.*, 2021).

In the study of Oda T *et al.* (Oda *et al.*, 2019), HD-GG intervention was effective in shortening the duration of fever in KD children, with no serious adverse events, similar to our observations. And as reported by Huang S *et al.* (Huang *et al.*, 2020), HD-GG can also be used to treat newborns with hemolytic disease, which effectively shortened jaundice resolution time and hospitalization stays and improved immunity by increasing the levels of IgA, IgG and IgM after 28 days of treatment. High levels of IL-6, CRP and TNF- α , significantly correlated with the deterioration of serum inflammatory microenvironment, are key markers of KD, among which up-regulated IL-6 and TNF- α are also strongly associated with the insensitivity to GG treatment (Y. Wang *et al.*, 2021). The detection of serum IFs such as IL-6, CRP and TNF- α in this study showed notably decreased levels of all these serum IFs in the research group after treatment, significantly lower than those of the control group, indicating that HD-GG + DIP can effectively inhibit the serum inflammatory environment in KD children.

CONCLUSION

Taken together, for the treatment of KD in children, HD-GG + DIP can validly improve therapeutic effectiveness without significantly increasing the side effects of medication, effectively reduce the internal diameter of coronary arteries to prevent disease deterioration, efficaciously shorten the recovery time of typical clinical symptoms and significantly inhibit the excessive release of serum IFs.

Table1: Comparative evaluation of patient general data

Factors	Control group (n=49)	Research group (n=51)	χ^2/t	p
Sex			0.602	0.438
Male	30 (61.22)	35 (68.63)		
Female	19 (38.78)	16 (31.37)		
Mean age (years)	3.08±1.00	3.49±1.36	1.712	0.090
Course of disease (d)	6.94±1.91	6.69±1.29	0.770	0.443
Duration of fever (d)	6.65±1.91	5.94±2.06	1.785	0.077
Single parent family			0.432	0.511
Yes	8 (16.33)	6 (11.76)		
No	41 (83.67)	45 (88.24)		

Note: "d" represents the time unit in days.

Table 2: Comparative evaluation of total effective rate

Factors	Control group (n=49)	Research group (n=51)	χ^2/t	p
Marked remission	16 (32.65)	33 (64.71)		
Remission	18 (36.73)	14 (27.45)		
Non-remission	15 (30.61)	4 (7.84)		
Total effective rate	34 (69.39)	47 (92.16)	8.418	0.004

Table 3: Comparative evaluation of side effects of medication

Factors	Control group (n=49)	Research group (n=51)	χ^2/t	p
Nausea and vomiting	2 (4.08)	3 (5.88)		
Dizziness and headache	2 (4.08)	4 (7.84)		
Diarrhea	0 (0.00)	2 (3.92)		
Total	4 (8.16)	9 (17.65)	1.987	0.159

Table 4: Comparative evaluation of coronary artery diameter grading

Time point	Grading	Control group (n=49)	Research group (n=51)	χ^2/t	p
Before treatment	0	14 (28.57)	16 (31.37)		
	I	26 (53.06)	28 (54.90)	0.418	0.812
	II	9 (18.37)	7 (13.73)		
After treatment	0	30 (61.22)	43 (84.31)		
	I	15 (30.61)	6 (11.76)	6.802	0.033
	II	4 (8.16)	2 (3.92)		

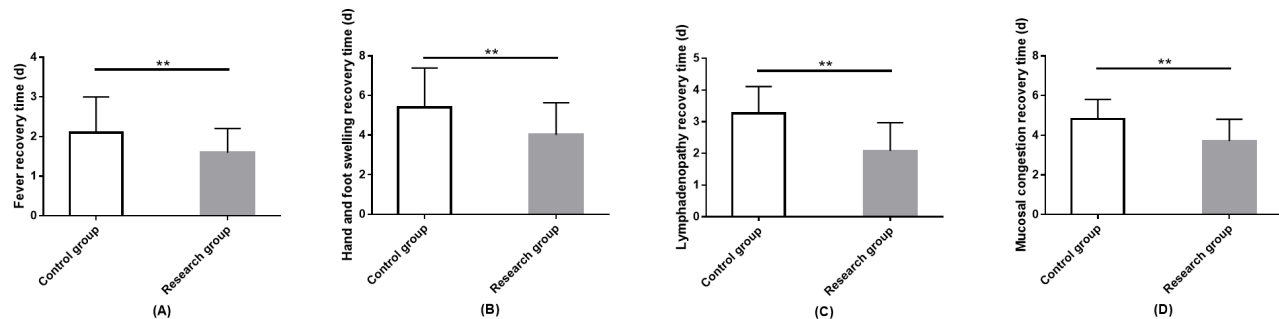


Fig. 1: Comparative evaluation of symptom recovery time

A. The fever recovery time of two groups. B. The hand and foot swelling recovery time of two groups. C. The lymphadenopathy recovery time of two groups. D. The mucosal congestion recovery time of two groups. Note: * and ** represent $p < 0.05$ and $p < 0.01$, respectively.

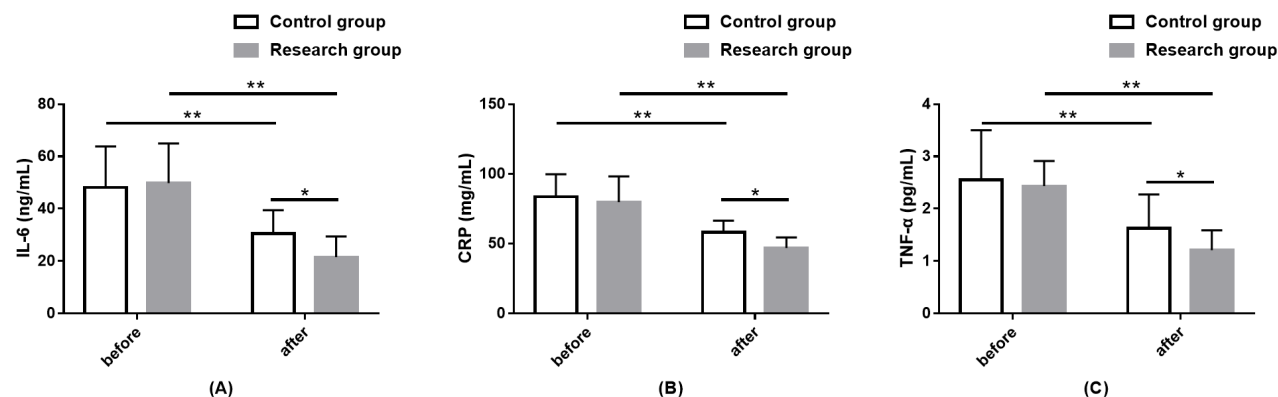


Fig. 2: Comparative evaluation of serum inflammatory factors.

A. The levels of IL-6 in two groups. B. The levels of CRP in two groups. C. The levels of TNF-α in two groups. Note: * and ** represent $p < 0.05$ and $p < 0.01$, respectively.

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Authors' contributions

All work on this manuscript was done by Meng Xie. Meng Xie gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Data availability statement

All data and materials are available from the corresponding author.

Ethical approval

The study was approved by the Ethics Committee of our hospital (No.2022-P2-293-01), this study collected informed consent forms signed by all subjects.

Conflict of interest

There is no conflict of interest.

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