Original Article
Efficacy of dipyridamole plus IVIG and aspirin on anti-platelet aggregation factors and inflammatory factors in children with Kawasaki disease

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Abstract: Background: While standard therapeutic regimens for Kawasaki disease (KD) in children have exhibited some efficacy, they remain far from ideal. Thus, the pursuit of alternative or improved treatment modalities remis clinically critical. Objective: This study primarily aimed to assess the effect of dipyridamole (DIP) plus human intravenous immunoglobulin (IVIG) and aspirin (ASP) as to efficacy, antiplatelet aggregation factors, and inflammatory markers in children with KD. Methods: A total of 95 pediatric KD patients were selected from February 2021 to July 2024, with 44 cases in the control group treated with IVIG + ASP and 51 cases in the research group given DIP in addition to IVIG + ASP. The efficacy, symptom resolution time (defervescence, limb swelling, mucosal congestion, and cervical lymphadenopathy), coronary artery injury, coagulation function (thrombin time [TT], prothrombin time [PT], and activated partial thromboplastin time [APTT]), antiplatelet aggregation factors (erythrocyte sedimentation rate [ESR], white blood cell count [WBC], and platelet count [PLT]), and inflammatory factors (C-reactive protein [CRP], and tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6]) levels were compared between the two groups. Results: The research group exhibited a higher overall treatment efficacy rate, shorter symptom resolution times, and a significantly lower incidence of coronary artery injury compared to the control group. No significant differences were observed between the two groups or before and after treatment within the same group in coagulation function indices. Markedly reduced levels of anti-platelet aggregation factors and inflammatory markers were observed in the research group versus those in the control group. Conclusion: DIP in combination with IVIG and ASP significantly enhances treatment efficacy and improves levels of antiplatelet aggregation factors and inflammatory markers in children with KD.

Keywords: Dipyridamole, IVIG, aspirin, Kawasaki disease in children, efficacy

Introduction

Kawasaki disease (KD) is the leading cause of acquired heart disease in children in developed countries and is a self-limiting, systemic vasculitis in pediatric patients [1]. KD manifests through a series of characteristic clinical signs, including persistent febrile episodes lasting over five consecutive days, rashes, lymph node enlargement, and limb lesions [2]. Epidemiological data show the highest annual incidence of KD in Asian countries, with a seasonal peak in early spring [3, 4]. The etiology of KD is complex and not fully elucidated, though it is generally believed to be related to coronary artery involvement triggered by an infectious agent, such as a viral infection [5]. The pathologic mechanisms of KD also involve severe inflammation and reactive thrombocytosis caused by immune complexes and the molecular signals they produce, which lead to organ damage [6, 7]. Standard treatment for KD includes intravenous human immunoglobulin (IVIG) and aspirin (ASP), which reduces the risk of coronary artery aneurysms in affected children from 25% to 5% [8]. However, 10% to 38% of patients fail to respond to this treatment or experience recurrent fever [9], possibly due to the development of IVIG resistance, indicating the need for additional intervention to suppress the inflammatory response [10].

Dipyridamole (DIP) is a tetrasubstituted pyrimidine-pyrimidine derivative that acts as an anti-

platelet agent by inhibiting platelet aggregation. It works primarily by increasing adenosine concentration, inhibiting phosphodiesterase activity, and lowering thromboxane A2 (TXA2) levels [11]. In addition to its antiplatelet effects, DIP also exhibits antiviral, anti-inflammatory, and antioxidant properties, making it useful in treating ischemic cerebrovascular disease. When used alongside aspirin (ASP), DIP enhances antiplatelet effects and can increase circulating monocyte-platelet complexes in the body over time [12, 13]. Furthermore, DIP has been shown to reduce the risk of liver cancer in patients with type 2 diabetes [14]. While DIP monotherapy has demonstrated limited efficacy in children with KD, with a platelet suppression rate of only 47% [15], it is often used in combination with other drugs. Research on DIP plus IVIG and ASP in the treatment of KD in children remains scarce, and there is also some controversy regarding the effectiveness of antiplatelet therapy regimens. For instance, the systematic review by Tanoshima et al. [16] noted insufficient evidence to support the clinical effectiveness of antiplatelet agents such as DIP and ASP in treating KD. This study attempts to verify the clinical efficacy of combining DIP, IVIG, and ASP in pediatric KD patients.

Patients and methods

General data

This retrospective study included 95 children with KD admitted to the hospital from February 2021 to July 2024. The patients were divided into a control group of 44 patients treated with IVIG and aspirin (ASP) and a research group of 51 patients who received additional dipyridamole (DIP) alongside IVIG + ASP. No significant differences in general data were observed between the two groups (P>0.05). This study was approved by the Ethics Committee of Kunming Children's Hospital.

Patient selection criteria

Inclusion criteria: Diagnosis of KD in accordance with clinical criteria for children [17]; unexplained fever for more than 5 days; bilateral conjunctival congestion (non-suppurative); acute swelling of the extremities and desquamation during the recovery period; redness and swelling of the lips and oral mucosa; skin rashes and erythema; non-suppurative enlargement of cervical lymph nodes; initial treatment.

Exclusion criteria: Use of IVIG or ASP before admission; congenital heart disease or hematopoietic system diseases; severe infection or secondary bacterial infection; abnormal mental state or malnutrition.

Treatment methods

Both groups of children received routine antipyretic treatment upon admission. The control group was treated with IVIG and ASP: Within 10 days of onset, the child was given IVIG (specification: 2.5 g (50 mL)/bottle; Ningbo Puli Pharmacy Co., Ltd., 1003) at a dose of 1 g/kg each time, completed within 4-6 hours, for 2 days. Additionally, ASP tablets (specification: 0.5 g/tablet; Beijing Kangruina Biotechnology Co., Ltd., A1189) were administered orally at a dose of 30-50 mg/(kg·d), divided into three doses taken in the morning, noon, and evening. After the fever subsided, the dosage was gradually reduced to 3-5 mg/(kg·d). The treatment continued for a total of 2 months.

The research group received additional treatment with DIP (Beijing Biolab Science and Technology Co., Ltd., BP0197-JQB) based on the control group, orally at a dose of 25-50 mg/time, 3 times/day, for a course of 2 months.

Outcome measures

(1) Efficacy. The clinical efficacy was rated as markedly effective (normal body temperature after 5 days of treatment and disappearance of symptoms such as mucosal congestion and swollen lymph nodes), effective (normal body temperature after 5 days of treatment, with improvement in symptoms such as mucosal congestion and swollen lymph nodes), or ineffective (failure to meet the above criteria). Total effective rate = (markedly effective cases + effective cases)/total cases*100%.

(2) Symptom resolution time. The time taken for clinical symptoms to improve was compared between the two groups, including time to defervescence, resolution of limb swelling, mucosal congestion, and cervical lymphadenopathy.

Table 1. Comparison of general data between the two groups

General data	Control group (N=44)	Research group (N=51)	t/x^2	P
Age (years)	3.50±1.05	3.29±1.32	0.849	0.398
Sex			0.051	0.821
Male	24 (54.55)	29 (56.86)		
Female	20 (45.45)	22 (43.14)		
Disease course (d)	7.91±1.75	7.61±2.08	0.754	0.453
Duration of fever (d)	7.11±1.96	7.33±2.35	0.491	0.625
Place of residence			0.039	0.844
Rural	19 (43.18)	21 (41.18)		
Urban	25 (56.82)	30 (58.82)		
Family medical history			1.303	0.254
Without	34 (77.27)	44 (86.27)		
With	10 (22.73)	7 (13.73)		

Table 2. Comparison of treatment efficacy between the two groups

Efficacy	Control group (N=44)	Research group (N=51)	x^2	P
Markedly effective	20 (45.45)	35 (68.63)		
Effective	14 (31.82)	12 (23.53)		
Ineffective	10 (22.73)	4 (7.84)		
Overall effective rate	34 (77.27)	47 (92.16)	4.165	0.041

(3) Coronary artery injury. Ultrasonography was performed to assess coronary artery injury in pediatric patients.

(4) Coagulation function. Fasting venous blood (5 ml) was collected before and after treatment, and the serum was obtained after centrifugation to determine the levels of thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (APTT) by a blood coagulation analyzer (Beijing Meidemikang Biotechnology Co., Ltd., MD-1003).

(5) Antiplatelet aggregation factors. The erythrocyte sedimentation rate (ESR) was tested by a dynamic ESR/hematocrit tester (Zibo Hengtuo Analytical Instrument Co., Ltd., 1111), and the levels of white blood cell count (WBC) and platelet count (PLT) were measured with an automatic blood cell analyzer (Shenzhen EDAN Instruments, Inc., 6944413813403).

(6) Inflammatory factors. The double antibody sandwich method was used to determine changes in serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6).

Statistical methods

SPSS21.0 software package was used for statistical analysis. Counted data were represented by number/percentage (n/%), while measured data were described as mean ± standard error of the mean (mean ± SEM). The comparison of counted data was conducted using a chi-square test. For the comparison of measured data between groups, the independent samples t-test was used; for within-group comparisons before and after treatment, the paired t-test was used. *P*-values <0.05 were considered significant differences. The sample size was determined using the binomial proportion sample size calculation formula. Each group met the minimum sample size requirement, which was calculated to be 40.

Results

Inter-group comparison of general data

The inter-group comparison of general data (**Table 1**) revealed no significant differences in age, sex, disease course, duration of fever, place of residence, or family medical history (all P>0.05).

Inter-group comparison of efficacy and analysis of influencing factors of curative effects

The numbers of markedly effective, effective, and ineffective cases in the control group were 20, 14, and 10 cases, respectively, compared to 35, 12, and 4 cases in the research group. The total effective rate of treatment was significantly higher in the research group compared to the control group (P<0.05; **Table 2**).

Furthermore, a binary logistic multivariate analysis revealed that age, sex, disease course, fever duration, place of residence, and family medical history were not independent risk factors affecting treatment efficacy (all P>0.05); However, the treatment modality was identified as an independent factor (P=0.045; **Tables 2, 3**).

Table 3. Analysis of factors influencing curative effects

Factor	β	S.E.	Wald	P	Exp (β)	95% CI
Age (years)	-0.180	0.263	0.467	0.494	0.835	0.499-1.399
Sex	0.421	0.633	0.433	0.505	1.524	0.441-5.266
Disease course (d)	0.015	0.175	0.008	0.930	1.016	0.721-1.430
Duration of fever (d)	-0.086	0.150	0.327	0.567	0.918	0.683-1.232
Place of residence	0.736	0.615	1.434	0.231	2.088	0.626-6.970
Family medical history	-0.362	0.848	0.182	0.670	0.697	0.132-3.674
Treatment modality	1.302	0.649	4.032	0.045	3.678	1.032-13.114

Table 4. Comparison of time to symptom resolution between the two groups

Symptom resolution time	Control group (N=44)	Research group (N=51)	t	P
Defervescence	2.68±1.09	1.31±0.47	34.490	<0.001
Limb swelling	3.52±1.76	2.73±1.22	2.570	0.012
Mucosal congestion	5.18±1.62	2.49±1.10	9.213	<0.001
Cervical lymphadenopathy	6.16±1.95	2.80±0.98	10.828	<0.001

Table 5. Comparison of coronary artery injury between the two groups

Coronary artery injury	Control group (N=44)	Research group (N=51)	χ^2	P
No injury	25 (56.82)	44 (86.27)		
Severe injury	2 (4.55)	0 (0.00)		
Moderate injury	5 (11.36)	2 (3.92)		
Minor injury	12 (27.27)	5 (9.80)		
Total occurrence	19 (43.18)	7 (13.73)	10.310	0.001

Inter-group comparison of symptom resolution time

The research group showed a markedly shorter time to resolution of defervescence, limb swelling, mucosal congestion, and cervical lymphadenopathy compared to the control group (all P<0.05; **Table 4**).

Inter-group comparison of coronary artery injury

The number of severe, moderate, and minor injuries in the control group was 2, 5, and 12, respectively, while the corresponding cases in the research group were 0, 2, and 5, respectively. The total incidence of coronary artery injury was significantly lower in the research group compared to the control group (P<0.05; **Table 5**).

Inter-group comparison of coagulation function

There were no significant differences in TT, PT, and APTT levels either within groups before and after treatment or between groups (all P>0.05; **Table 6**).

Inter-group comparison of anti-platelet aggregation factors

The two groups did not differ significantly in pre-treatment ESR, WBC, or PLT (P>0.05). An obvious drop in all these indexes was observed in both groups after treatment, with even lower levels of ESR, WBC, and PLT in the research group (P<0.05; **Figure 1**).

Inter-group comparison of inflammatory factors

The two groups exhibited similar CRP, TNF-α, and IL-6 levels before treatment (P>0.05). Both groups showed inhibition of these inflammatory indexes after treatment, particularly in the research group (P<0.05; **Figure 2**).

Discussion

This study identified a statistically higher overall response rate in the research group compared to the control group (92.16% vs. 77.27%), suggesting that the combination of DIP, IVIG, and ASP therapy yields higher clinical efficacy in pediatric KD patients than IVIG and ASP alone. The enhanced therapeutic effect of DIP may be due to its synergistic interaction with IVIG and ASP, thus further improving treatment

Table 6. Comparison of coagulation function between the two groups

Coagulation function	Control group (N=44)	Research group (N=51)	t	P
Thrombin time (s)				
Before treatment	14.09±2.21	14.41±2.12	0.719	0.474
After treatment	14.50±2.42	13.98±2.54	1.017	0.312
Prothrombin time (s)				
Before treatment	12.11±2.18	12.86±2.58	1.517	0.133
After treatment	12.70±1.72	12.37±2.29	0.784	0.435
Activated partial thromboplastin time (s)				
Before treatment	32.73±4.18	34.20±2.76	1.407	0.163
After treatment	32.84±2.62	34.22±5.00	1.645	0.103

outcomes in children with KD. Li et al. [18] confirmed the effectiveness and safety of dual antiplatelet therapy (ASP plus clopidogrel) in the treatment of coronary artery aneurysms caused by KD in children, which aligns with our findings. Further analysis of the factors influencing efficacy revealed that the treatment modality was a significant independent factor, while factors such as age, gender, disease course, fever duration, place of residence, and family medical history had no effect on response to treatment. This suggests that the use of DIP in combination with IVIG and ASP maximizes the therapeutic effect in children with KD. In the study by Sun et al. [19], gender, body mass index, onset time, PLT, and treatment mode were identified as risk factors affecting the short-term prognosis of children with KD. This finding supports the idea that combined treatment including ASP, can help improve the short-term prognosis of these patients. Additionally, the research group also exhibited significantly faster resolution of symptoms such as defervescence, limb swelling, mucosal congestion, and cervical lymphadenopathy, indicating that DIP plus IVIG and ASP for pediatric KD patients offers a more rapid alleviation of clinical symptoms. Furthermore, the total incidence of coronary artery injury in the research group was markedly lower than in the control group (13.73% vs. 43.18%), suggesting that DIP in combination with IVIG and ASP is conducive to reducing the risk of coronary artery injury. However, neither the combination of DIP, IVIG, and ASP nor the IVIG and ASP regimen alone had a significant influence on the coagulation function of children with KD.

We also found that the combination of DIP, IVIG, and ASP significantly down-regulated the levels of ESR, WBC, PLT, CRP, TNF-α, and IL-6, and this down-regulation was significantly more pronounced than that with the IVIG and ASP intervention protocol. This indicates that the antiplatelet aggregation and anti-inflammatory effects of DIP, IVIG, and ASP offer superior treatment for children with KD. In the study by Su et al. [20], it was observed that children with KD typically present with elevated levels of WBC, ESR, PLT, and CRP, and that treatment with IVIG and ASP could significantly ameliorate these abnormalities, supporting our findings. The antiplatelet aggregation mechanism of DIP is related to its down-regulation of phosphodiesterase activity, which in turn elevates the levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [21]. Additionally, DIP inhibits the cellular uptake of adenosine while increasing the extracellular availability of adenosine to balance cardiovascular function [22]. Ramakers B et al. [23] further suggested that DIP can augment the anti-inflammatory effect by elevating the concentration of circulating adenosine, and realize the effective downregulation of TNF-α, IL-6 and other pro-inflammatory factors. Liu et al. [24] also reported that high CRP level remains a risk factor for IVIG resistance in children with KD. In addition to effectively reducing the levels of pro-inflammatory factors such as CRP, TNF-α, and IL-6, DIP has been shown to significantly inhibit matrix metalloproteinase (MMP)-9, a key inflammatory marker, and exert anti-inflammatory effects by inhibiting the p38 mitogen-activated protein kinase (p38 MAPK) and nuclear factor κB (NF-κB) pathways [25]. This study has established that the combination regimen of DIP, IVIG, and ASP provides significant biomedical benefits for the treatment of children with KD. Specifically, it improves
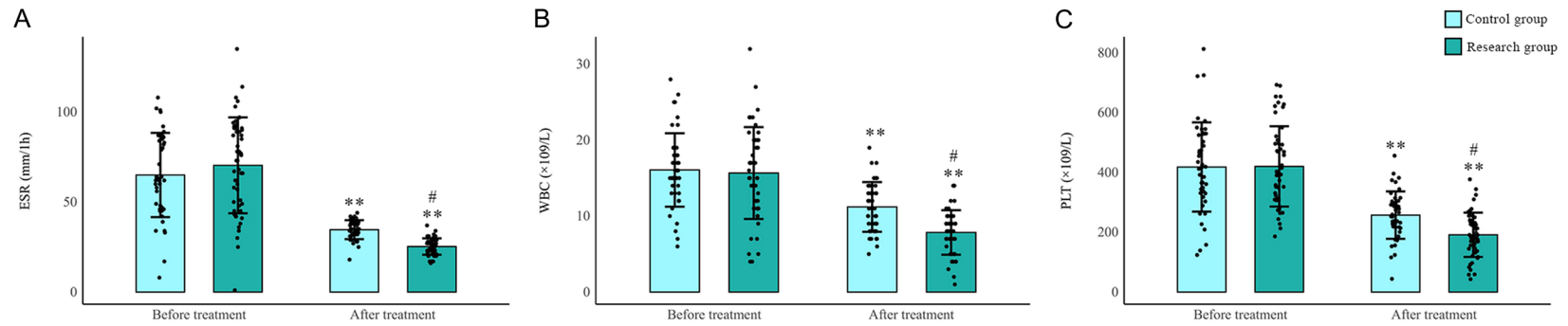
Figure 1. Comparison of antiplatelet aggregation factors between the two groups. A. Changes in the erythrocyte sedimentation rate (ESR) in control and research groups before and after treatment. B. Changes in the white blood cell count (WBC) in control and research groups before and after treatment. C. Changes in the platelet count (PLT) in control and research groups before and after treatment. Note: **$P<0.01$ vs. before treatment; #$P<0.05$ vs. control group.
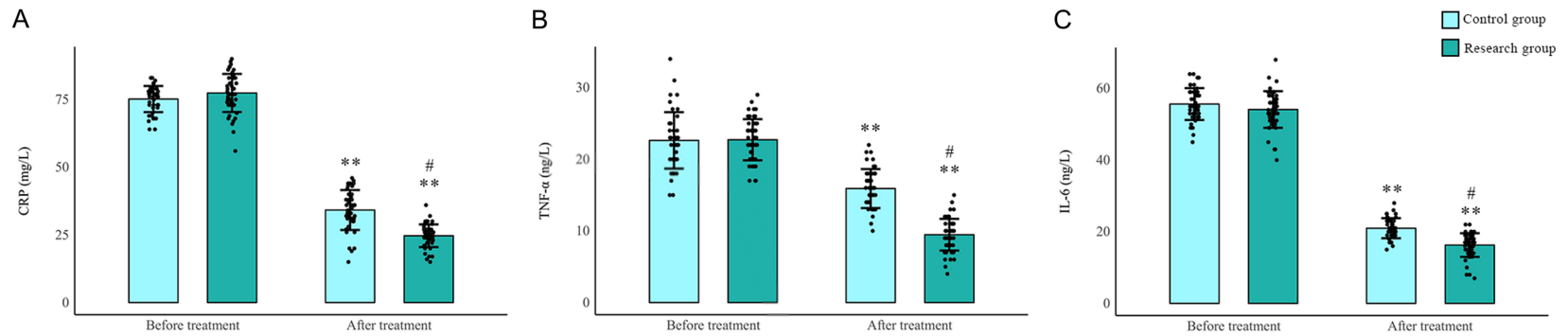

Figure 2. Comparison of inflammatory factors between the two groups. A. Changes in C-reactive protein (CRP) levels in control and research groups before and after treatment. B. Changes in tumor necrosis factor-α (TNF-α) levels in control and research groups before and after treatment. C. Changes in interleukin-6 (IL-6) levels in control and research groups before and after treatment. Note: **$P<0.01$ *vs.* before treatment; #$P<0.05$ *vs.* control group.

therapeutic efficacy, accelerates clinical symptom resolution, mitigates coronary artery damage, modulates platelet aggregation, and dampens inflammatory responses. We hypothesize that this pharmacologic combination may offer additional advantages in the context of immunomodulation. However, the current body of literature pertaining to this aspect is relatively sparse. Further in-depth work is needed to understand fully any potential benefits.

In summary, the combination of DIP, IVIG, and ASP demonstrates good clinical efficacy in treating pediatric KD patients. This treatment regimen accelerates symptom resolution, reduces the incidence of coronary artery injury, and exerts strong anti-platelet aggregation and anti-inflammatory effects. There is a reasonable expectation that this treatment modality may emerge as a reliable alternative to existing therapeutic regimens.

Disclosure of conflict of interest

None.

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