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Research article

Efficacy of halfdose aspirin in Kawasaki disease: Insights from a single center experience

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Abstract: Background: Long-term oral aspirin (Asp) therapy poses challenges in children with Kawasaki Disease (KD) complicated by coronary artery aneurysms (CAA), especially when frequent epistaxis is present. Objective: This study seeks to evaluate the efficacy and safety of a reduced-dose aspirin regimen for an antiplatelet therapy during the subacute and convalescent phases of KD. Methods: This retrospective study included 554 pediatric KD patients (350 males, 204 females; median age: 2.5 years). The patients were divided into two groups based on their aspirin dosage initiated one week after fever subsidence: The observation group (OG, n = 253) received low-dose Asp (1.5–2.5 mg/kg/day), while the control group (Ctrl, n = 301) received standard-dose Asp (3–5 mg/kg/day). Results: The incidence of bleeding was significantly lower in the OG compared to the Ctrl group ($p < 0.05$). In both groups, the coronary thrombi either shrank or resolved after one year following alteplase therapy, provided that the international normalized ratio (INR) was maintained at 2.0–3.0 and arachidonic acid (AA) inhibition remained below 20%, with no significant intergroup difference ($p > 0.05$). Aspirin resistance (AR) was observed in 17 OG patients, which resolved after increasing the Asp dose to 3–5 mg/kg/day for one week. Mural thrombosis occurred in six patients (3 per group), none of whom had AR. Conclusion: Reducing aspirin to a half-dose regimen after intravenous immunoglobulin (IVIG) treatment in the subacute and recovery phases of KD is both safe and effective, thereby significantly lowering the risk of bleeding without compromising the antithrombotic efficacy.

Keywords: Kawasaki disease; children; coronary artery aneurysm; thrombus; aspirin; platelet aggregation function

Abbreviations: Asp: Aspirin; A.A.: Arachidonic acid; AHA: American Heart Association; ADP: Adenosine diphosphate; AR: Aspirin resistance; CAL: Coronary artery lesions; CAA: Coronary artery aneurysm; CAN: Normal Coronary artery; COX: Cyclooxygenase; CTCA: CT coronary angiography; CAAT: Thrombus in coronary artery aneurysm; CMR: Cardiovascular magnetic resonance; IVIG-R: Intravenous immunoglobulin resistance; INR: International normalized ratio; ECHO: Echocardiography; GCs: Glucocorticoids; IKD: Incomplete Kawasaki disease; KD: Kawasaki disease; LM: Left main coronary artery; LAD: Left anterior descending branch; LVED: Left ventricular end-diastolic diameter; LVEF: Left ventricular injection fraction; RCA: Right coronary artery; TXA2: Thromboxane A2

1. Introduction

Kawasaki disease (KD) is an acute, self-limited systemic vasculitis of an unknown etiology that primarily affects small and medium-sized arteries, particularly the coronary arteries. First described over 50 years ago by professor Tomisaku Kawasaki in Japan, KD has since become a primary cause of acquired heart disease in children, particularly in developed countries [1] and increasingly in developing regions such as China [2] and India [3]. The global incidence of KD continues to rise, with a marked predilection for children under five years of age, especially those of Asian descent. While KD can cause complications across multiple organ systems, coronary artery lesions (CALs) represent the most serious sequelae. Without timely treatment, 20% to 25% of children with KD may develop CALs. However, this rate significantly drops to 3%–5% with treatments [4–5]. CAL mainly presents alongside coronary artery dilatation, coronary artery aneurysms (CAAs), and thrombus formation within aneurysms (coronary artery aneurysm thrombosis, CAAT). These complications can result in secondary ischemic cardiomyopathy [6], which is a major cause of mortality and long-term disability in affected children. For patients with CALs, Aspirin (Asp) should be taken orally at 3–5 mg/kg/day until the coronary artery recovers to normal [7–10]. However, maintaining long-term aspirin therapy in children with CAAs is challenging, particularly when complications such as epistaxis (nosebleeds) occur. Children are naturally active and often prone to nosebleeds, which can necessitate the temporary cessation of Asp, thereby increasing the risk of thrombosis in aneurysmal segments. This creates a critical therapeutic dilemma: how to effectively prevent thrombosis without exacerbating bleeding risks. Traditionally, due to an uncertainty regarding the protective effect of lower Asp doses, there has been reluctance to reduce Asp below 3 mg/kg/day. Notably, the 2017 American Heart Association (AHA) guidelines state that there is insufficient evidence to confirm that low-dose Asp confers coronary protection in KD [7]. In light of this, beginning in 2020, our team initiated a novel approach to manage KD and incomplete KD (IKD) patients by adjusting the Asp dosage based on platelet function testing using the arachidonic acid (AA) platelet aggregation assay. For patients demonstrating effective platelet inhibition, the Asp dose was tapered to 1.5–2.5 mg/kg/day. This strategy aims to reduce the bleeding risk while maintaining an adequate antiplatelet efficacy.

2. Methods

2.1. Object of study

The inclusion criteria were as follows: (1) Children diagnosed with KD or IKD at Shengjing

Hospital of China Medical University between March 2020 and August 2022; and (2) have a diagnosis made in accordance with the 2017 American Heart Association (AHA) guidelines [7] and the revised 2021 Japanese guidelines for KD [9]. Informed consent was obtained from all guardians prior to enrollment. Those who combined CAL and prolonged Asp usage were followed up until January 2025.

Patients were excluded if they met any of the following criteria: (1) The patients did not continue to follow-up at our clinic; (2) during the observation, patients who either adjusted the Asp dose or stopped Asp for more than one week without consulting with clinicians; and (3) patients who had an AA% more than 20% (aspirin resistance, AR) prior to the Asp dose adjustment.

2.2. Group

The children admitted on Monday, Wednesday, and Friday were classified as the observation group (OG), while those admitted on Tuesday, Thursday, Saturday, and Sunday were classified as the control group (Ctrl). According to the condition of the coronary artery, the patients were divided into the CAL group and the normal coronary artery (CAN) group. 48–72 hours after fever subsided, the Asp dose was reduced to 3–5 mg/kg/day in all patients. In the Ctrl group, the AA test was only performed 2 weeks after the disease. The Asp dose was kept at 3–5 mg/kg/day. In the OG, 2–3 weeks after disease onset, and the fever subsided for about 1 week, the Asp dose was further reduced to 1.5–2.5 mg/kg/day, under the condition that the AA% was < 20%. If the AA% was ≥ 20% after the dose adjustment, then the last dose of Asp was resumed and the AA% was re-tested one week later.

2.3. A.A. test

Venous blood samples (3 mL) were collected from each patient before 9:00 AM at three key time points following their fever resolution: 1 week, 3 weeks, and 6 weeks post-defervescence (approximately 2, 4, and 7 weeks after the disease onset). Each sample was divided equally: 1.5 mL was used for an assessment of platelet aggregation via AA testing, and the remaining 1.5 mL served as a control for internal comparison.

After the initial sampling period, AA testing was performed every 1–2 months during the first year of illness, followed by testing every 3–6 months for the next two years. Then, the testing intervals were extended based on individual patient's status, which continued until the resolution of the CAA or until the end of the follow-up period.

In cases where CALs persisted beyond one month after the disease onset, patients underwent coronary computed tomography angiography (CTCA) to evaluate aneurysmal changes. For patients with distal CAAs, follow-up cyclooxygenase (CTCA) was repeated every 1–2 years to monitor the disease progression or resolution.

2.4. Data collection

A total of 554 patients with KD were enrolled from March 2020 to August 2022. The clinical and laboratory data were retrospectively collected and analyzed. Variables included the following: Sex, age, time of disease onset, duration of intermittent fever, timing of intravenous immunoglobulin (IVIG) administration, presence of IVIG resistance (IVIG-R), and use of glucocorticoids (GCs). Bleeding

events were recorded and categorized as either epistaxis, gingival bleeding, conjunctival bleeding, or subcutaneous bruising with a diameter > 1 cm. The Asp dosage and AA platelet aggregation levels were recorded at approximately 2 weeks, 4 weeks, and 7 weeks after the disease onset. For patients diagnosed with CALs, serial measurements of the Asp dosage and AA inhibition were documented every 2–3 months until the normalization of the coronary artery. In addition, the following cardiovascular data were collected: international normalized ratio (INR) for patients with giant CAAs, incidence and classification of CAL, coronary artery Z-scores, the time to recovery of CAL, and the occurrence of thrombus formation within CAAs.

2.5. Calculation method of Z value

The Canada Z value measurement formula (http://www.pedz. de/en/heart.html) was used to input the height (cm), weight (kg), age, sex, and the left main trunk (LM), left anterior descending branch (LAD), and right trunk (RCA) diameters of the coronary artery, measured by echocardiography (ECHO) and/or CTCA, to automatically generate a Z value.

2.6. Statistical methods

All statistical analyses were conducted using SPSS software for Windows (Version 26.0; IBM Corporation, Armonk, NY, USA). The continuous variables were expressed as medians with interquartile ranges [M (P25–P75)], while categorical variables were presented as frequencies and percentages.

Comparisons of the continuous variables between the observation group and the control group were performed using the Wilcoxon rank sum test. For categorical variables, either the Pearson chi-square (χ^2) test or Fisher's exact test was applied, as appropriate. A two-tailed p-value of < 0.05 was considered statistically significant.

This research was approved by the ethics committee of Shengjing hospital [2022PS050J].

3. Results

3.1. The comparison of general information between two groups

The incidence of bleeding (epistaxis, decayed tooth, sub-conjunctival hemorrhage, and skin bruising larger than 1 cm in diameter) in the OG was significantly lower than that in the Ctrl group ($p < 0.05$). In the CAL group, the median age of onset for the OG was 2.96 years old, which is significantly older (1.21 years) than the Ctrl group ($p < 0.05$). In the CAN group, the median age of onset in the OG was 3.0 years old, which is significantly older (2.25 years old) than the Ctrl group ($p < 0.05$). In patients with a CAL, the Ctrl group presented with significantly higher bleeding symptoms (36.71%) than the OG (17.86%) ($p < 0.05$). In the latter group, all CALs were identified prior to the reduction of the Asp dosage, and no new CALs developed following the dose adjustment (Table 1).

Table 1. The comparison of general information between two groups.

Group	Subgroup	Male (%)	Age (y)	Fever (d)	T-IVIG (d)	IVIG-R n (%)	GCs- IVIG n (%)	IVIG-GCs n (%)	Hemorrhage n (%)
CAL (n = 98)	OG (n = 56)	39 (69.64)	2.96 (1.19–4.00)▲	9.00 (6.00–12.00)	7.00 (5.00–11.00)	12 (21.43)	12 (21.43)	4 (7.14)	10 (17.86)▲
	Ctrl (n = 42)	27 (64.29)	1.21 (0.88–1.56)	8.00 (6.00–10.00)	7.00 (5.00–9.00)	6 (14.29)	10 (23.81)	3 (7.14)	15 (35.71)
CAN (n = 456)	OG (n = 259)	157 (59.10)	2.25 (1.25–3.00)▲	8.00 (6.00–11.50)	7.50 (5.00–9.00)	22 (8.50)	34 (13.10)	10 (4.60)	17 (6.60)
	Ctrl (n = 197）	127 (64.50)	3 (1.67–4.00)	8.00 (6.00–12.00)	7.00 (5.00–11.00)	17 (8.60)	35 (17.80)	9 (3.90)	13 (6.60)

Note: T-IVIG: The time of the first IVIG; OG: Observation group; IVIG-R: IVIG-resist; GCs-IVIG: GCs before IVIG; IVIG-GCs: GCs after IVIG; hemorrhage symptoms: Epistaxis, gingival bleeding, conjunctival bleeding, the diameter of skin bruising larger than 1 cm; compared with the control group, ▲: $p < 0.05$.

3.2. The comparison of CAL recovery between two groups

In the CAL group, some patients had CAAs of varying sizes distributed across multiple coronary artery branches. These patients were subsequently stratified into three subgroups based on the CAA sizes: Large CAA, medium CAA, and small CAA. Each subgroup was further divided into the Ctrl group and the OG for comparison. There was no significant difference in the normalization rate of the CAL between the OG and the Ctrl group within each subgroup ($p > 0.05$) (Table 2).

3.3. Medication usage during thrombosis in children with CAAT

There were 6 children with CAAT, 3 patients in the OG (case 1#, 2#, and 3#) and 3 patients in the Ctrl group (case 4#, 5#, and 6#). Case 1# developed thrombus thrice. In the Ctrl group, all 3 patients took Asp at 3–5 mg/kg/day before the thrombus formed. However, the three patients did not take warfarin at sufficient doses and the INR were all < 2 (Table 3).

Table2. Comparison of CAL recovery between two groups of KD children.

CAA		The time of CAA recovery				
		~1 M (%)	~2 M (%)	~6 M (%)	~1 Y (%)	~2 Y (%)
Large	OG (n = 17)	0 (0.00)	0 (0.00)	2 (11.76)	2 (11.76)	2 (11.76)
	Ctrl (n = 15）	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
p		1.00	1.00	0.49	0.49	0.49
Medium	OG (n = 26)	2 (7.69)	8 (30.77)	12 (46.15)	15 (57.69)	15 (57.69)
	Ctrl (n = 11)	0 (0.00)	1 (9.09)	4 (36.36)	4 (36.36)	4 (36.36)
p		1.00	0.23	0.72	0.30	0.30
Small	OG (n = 59)	31 (52.54)	38 (64.41)	40 (67.80)	41 (69.49)	41 (69.49)
	Ctrl (n = 60)	30 (50.00)	42 (70.00)	43 (76.67)	48 (80.00)	48 (80.00)
p		0.78	0.52	0.65	0.19	0.19

Note: In some CAL children, multiple branches of the coronary arteries were injured, and the degree of injury in each branch was different, which was recorded separately. Hence, n meant number of CAA incidences here.

Table 3. Coronary artery thrombosis in two groups of children with giant CAA.

No.	Group	Age (y)	The during of thrombosis happened							
			Time	Asp (mg/kg)	AA.	INR	warfarin (mg/kg)	PLT ($\times 10^9$)	CRP (mg/L)	Symptoms	MI
#1	OG	6.5	1 m	2.16	2.5	1.5	0.03	336	6.00	0	0
		8	1.5 y	2.17 (100 mg/d)	0.5	1.2–1.7	intermittent	289	5.70	0	0
		10	2.5 y	no	62	1.0	no	320	12.30	Chest pain	Yes
#2	OG	5	1 m	no	no	1.1	no	145	4.65	0	Yes
#3	OG	3	15 d	no	no	1.1	no	521	4.36	0	0
#4	Ctrl	4	3 y	2.08 (100 mg/d)	2.5	1.1–1.7	0.15	343	no	0	0
#5	Ctrl	1.75	8 m	3.33	no	1.1–1.9	0.09	273	no	0	0
#6	Ctrl	6.5	16 d	no	no	1.2	no	505	126.80	0	0
		6.67	2 m	3.01	6.2	1.6	0.06	343	no	0	0

Note: Age: The age of diagnosis; Symptom: The symptom of myocardial ischemia; MI: Myocardial infarction; At the time of diagnosis of KD in #2, #3, and #6, thrombus had already formed in the CAA.

4. Discussion

Asp is a non-selective cyclooxygenase (COX) inhibitor whose antiplatelet effect is primarily achieved through an irreversible acetylation of the serine 529 residue on COX-1. This inactivation of

COX-1 impedes the metabolism of AA, which leads to a reduction in thromboxane A2 (TXA2) synthesis and, consequently, the inhibition of platelet aggregation [11]. Despite its therapeutic benefits, Asp is associated with several adverse effects, including gastritis, epistaxis, gastrointestinal bleeding, loss of appetite, anemia, and, rarely, Reye syndrome in children [12–15]. Previous studies have focused more on the dose comparison of oral Asp in addition to IVIG in the acute stage, and suggested that both high and low doses have no significant difference in the occurrence of CAL [16–19]. Recently, some scholars have proposed that there is no significant difference in the incidence of CAL between using IVIG alone in the acute phase and a combined therapy with oral Asp [20]. These findings indirectly support the rationale behind our use of a reduced Asp dose during the subacute phase, thus reinforcing the potential safety and efficacy of half-dose Asp in maintaining antiplatelet function while minimizing the bleeding risk.

Although current guidelines recommend oral Asp at a dose of 3–5 mg/kg/day starting 48–72 hours after the fever subsides, they do not specify a maximum daily dosage. In our practice, we capped the maximum aspirin dose at 100 mg/day. Throughout this study, no increase in adverse events was observed when the Asp dosage was adjusted based on the AA inhibition monitoring. It remains unclear whether this safety profile is partially attributable to the concurrent use of clopidogrel in all patients with CALs, whose dosages were titrated to maintain an ADP < 40%. Nevertheless, this dual antiplatelet strategy likely contributed to the safe implementation of a half-dose Asp therapy.

The concept of AR has been raised by several researchers, who described a state in which Asp failed to achieve the expected antiplatelet effect despite regular administration. AR may manifest as clinical resistance—defined by the occurrence of thrombotic events during Asp therapy—or as laboratory resistance, which is identified by insufficient platelet inhibition in vitro. Laboratory AR is typically defined by an average aggregation rate exceeding 20% in response to 0.5 mg/mL AA stimulation [21,22]. Due to a variability in salicylic acid concentrations with medium-dose Asp, we elected to monitor AA-induced platelet aggregation beginning in the subacute phase, which is when patients received low-dose Asp (3–5 mg/kg/day). This approach allowed for the early identification and management of laboratory AR, particularly in those receiving half-dose Asp.

In our study, no cases of clinical AR were observed; however, laboratory AR was detected. Prior to the Asp dose reduction (3–5 mg/kg/day), laboratory AR occurred in two patients with CAN in the Ctrl group, both of whom continued Asp at the same dose until seven weeks after the disease onset. Similarly, there were 2 cases of AR in the OG. One case involved a patient with a transient CAL who had 20.4% AA at 3 weeks post onset. The AA% dropped to 7.8% within one week, after which the Asp was tapered to 1.5 mg/kg/day and continued for 17 weeks alongside clopidogrel. AA inhibition was stable at 6.1%, 2.5%, and 8.9% at 5, 9, and 17 weeks, respectively. The second case involved a patient with a persistent CAA and an AA rate of 24% at week 3, which dropped to 7.8% after retesting one week later. The Asp was subsequently reduced to 2.0 mg/kg/day and discontinued at seven weeks. After decreasing the Asp dosage in the OG, a total of 17 patients developed laboratory AR, yet none experienced thrombosis. At four weeks post onset, 9 patients developed laboratory AR, with an average Asp dose of 1.72 ± 0.55 mg/kg/day at that time. Furthermore, at 7 weeks post onset, 7 patients developed laboratory AR, with an average Asp dose of 1.72 ± 0.69 mg/kg/day. One patient developed AR at two years post-onset while taking 2.17 mg/kg/day of Asp.

In this study, six patients developed mural thrombus in CAAs, including three cases in the OG (cases #1–3) and three in the Ctrl group (cases #4–6). Notably, all six patients had INR levels below 2.0, with an AA% < 20% and an adenosine diphosphate-induced platelet aggregation

percentage (ADP%) consistently < 40%. Thus, when KD patients are complicated with a huge CAA, warfarin seems to be the key medicine in preventing thrombosis (INR must over 2 and 2.0–3.0 for efficacy and safety). Patients in the acute phase of KD or of KD complicated with CAL are accompanied by a vascular endothelial cell injury, platelet count increase/activation, and abnormal fibrinolysis, thus leading to a hypercoagulable state that persists through the acute phase and afterwards for a long time. Meanwhile, there are hemodynamic abnormalities in CAA patients, and the blood flow is slow in the CAA, which results in turbulence. Together, these contribute to fibrin formation, platelet aggregation, and blood cell aggregation, which ultimately lead to thrombosis; this further aggravates coronary artery lumen stenosis, obstruction, and even myocardial infarction [23]. Therefore, the main goal in treating KD patients with a CAA is to prevent CAAT. Among the 6 patients, 4 repeatedly used IVIG and additional GCs, and 1 repeatedly applied GCs for 10 days. On the 16th day after the onset of the disease, CAAT was detected and IKD was diagnosed. Another patient was diagnosed with KD 1 month after the onset of the disease. The use of GCs before that was unknown. Our results are consistent with those reported in the literature, which indicate that CAAT is associated with repeated use of IVIG and GCs [24]. Anticoagulation and anti-platelet aggregation are included in the standard treatments for CAA patients, and an adequate dose of warfarin is more important in preventing thrombosis. In this study, Asp combined with clopidogrel were used to antagonize platelet activation mediated by adenosine diphosphate for those with a small and medium CAA, and a combination therapy including antiplatelets and anticoagulation (warfarin) were used to treat patients with a giant CAA.

Children who have a history of thrombus in CAA are prone to recurrence [7], making a long-term and carefully monitored antithrombotic therapy essential. In about 20 children in the OG, the Asp dose was reduced to 1.5 mg/ kg·d^{-1} with an AA% consistently below 1%, and no bleeding events were reported, thus demonstrating that this dosage may be safe and effective for some patients when guided by platelet function testing. However, caution is warranted in further reducing the Asp dose. According to the 2017 AHA guidelines, Asp is typically discontinued at 6–8 weeks if no CAL is present. In our study, among the five CAN cases where the Asp dose was reduced to 0.5 mg/kg/day after six weeks, one patient developed an AA% > 20% within one week. In another five CAN cases, the Asp dose was reduced to 1.0 mg/kg every other day, and four patients exhibited an AA% > 20%, thus indicating a loss of the antiplatelet effect. These findings strongly suggest that the Asp dose should not be reduced below 1.5 mg/kg/day or administered on an every-other-day schedule in the subacute phase; doing so risks undermining platelet inhibition and may contribute to thrombotic events, especially in susceptible individuals. Patients need to take anticoagulant and antiplatelet aggregation drugs and have restricted activities for a long time. Therefore, CALs not only affects the patients' quality of life, but also increases the risk of death if not treated properly. In cases of severe bleeding (e.g., epistaxis), a dose reduction to 1.5–2.5 mg/kg/day may be acceptable, provided the AA% remains below 20%. If bleeding risk precludes the use of warfarin, rivaroxaban may offer a safer alternative [25].

5. Conclusion

Half-dose Asp was not associated with an increased risk of CALs or thrombotic events in this cohort. However, this approach may be associated with a higher incidence of reversible AR.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

H.S.: Data collection, analysis, and editing of the draft of the thesis; Y.C., X.Y., and J.L.: Diagnosis, treatment and follow-up of some patients; H.W.: The design of this project, ethical application; diagnosis, treatment and follow-up of vast majority of patients, the editing of the preface, conclusion and discussion sections of the manuscript; Y.X.: Data, analysis; diagnosis, treatment and follow-up of some patients; editing of the manuscript discussion section and supplementation of references.

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