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ORIGINAL ARTICLE

Effectiveness of antiplatelet therapy for Kawasaki disease: a systematic review

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Abstract

Kawasaki disease is an acute systemic vasculitis in children. Antiplatelet medicines are commonly used for Kawasaki disease to attenuate vasculitis and prevent thromboembolism; however, the mechanisms have not been elucidated. The objective of this study is to assess the effectiveness of antiplatelet medications for Kawasaki disease. We used Medline, Embase, Cochrane Central Register of Controlled Trials, and Igaku Chuo Zasshi (Ichushi) from January 1947 to August 2018. Studies describing the platelet functions of antiplatelet drugs for Kawasaki disease were included. Twenty studies met the inclusion criteria. There were no randomized controlled trials. Seven studies compared platelet aggregation ability before and after treatment. Eight studies compared platelet aggregation with that in Kawasaki disease patients without treatment. Four studies compared aggregation among different types of antiplatelet drugs or at different doses. Antiplatelet medications administered in the studies included aspirin, flurbiprofen, dipyridamole, and choline salicylate. Methods for the measurement of platelet aggregation ability varied among studies. The groups with antiplatelet treatment tended to have a decreased platelet aggregation function. The statistical analyses were impossible due to insufficient quantitative data and heterogeneity among the studies.

Conclusion: The present systematic review revealed that there was insufficient evidence for the effectiveness of antiplatelet therapy for Kawasaki disease.

What is Known:
- *Antiplatelet therapy is widely used for Kawasaki disease to mitigate cardiac complications.*
- *The mechanisms of antiplatelet therapy for Kawasaki disease are not clarified.*

What is New:
- *This systematic review showed that the groups with antiplatelet treatment tended to have a decreased platelet aggregation function.*
- *There is insufficient evidence for the effectiveness of antiplatelet therapy for Kawasaki disease.*

Keywords Antiplatelet · Kawasaki disease · Pediatrics · Systematic review

Presentations The results of this study were, in part, presented at the 37th Meeting of Japanese Society of Kawasaki Disease in October, 2017, Tokyo, Japan, and the 12th International Kawasaki Disease Symposium in June, 2018, Yokohama, Japan.

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Abbreviations

ADP	Adenosine diphosphate
CONSORT	Consolidated Standards of Reporting Trials
IVIG	Intravenous immunoglobulin therapy
KD	Kawasaki disease
PGF1	Prostaglandin F1
PGE2	Prostaglandin E2
PDMP	Platelet-derived microparticles
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TXB2	Thromboxane B2
CAL	Coronary artery lesion

Introduction

Kawasaki disease is an acute systemic vasculitis in children with an unknown etiology [1]. Coronary artery aneurysm and subsequent coronary thrombosis are potentially life-threatening complications and determinants of the prognosis of the disease [1]. Suppressing systemic inflammation mitigates the complications; treatments with high-dose intravenous immunoglobulin, corticosteroids, and aspirin have significantly decreased the long-term complications and the fatality rate [1]. Coronary aneurysm and thrombosis are also associated with increased platelet activation and platelet aggregation [2]. Low-dose aspirin was frequently used as an antiplatelet medication. Other antiplatelet medications such as flurbiprofen have also been used. The systematic review by the Cochrane Vascular Group identified only one randomized controlled trial about the effectiveness of adding aspirin on the rate of coronary artery abnormalities [3]; it concluded that there is insufficient evidence to conclude whether children with Kawasaki disease should receive aspirin. The clinical practice guidelines by the American Heart Association in 2017 state that the administration of moderate- to high-dose aspirin is reasonable until the patient is afebrile, although there is no evidence that it reduces coronary artery aneurysms [4]. Moreover, the pharmacodynamics and platelet function during and after antiplatelet therapy in Kawasaki disease have not been completely explicated and no systematic review of the evidence has been conducted. To answer this question, we conducted a systematic search and review about platelet aggregation after administration of antiplatelet medications in patients with Kawasaki disease. The objective of this study was to assess the effectiveness of antiplatelet medications for Kawasaki disease.

Methods

Eligibility

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Included articles were human cohort studies or randomized controlled trials that described platelet aggregation and Kawasaki disease.

A systematic search was conducted regarding the keywords about Kawasaki disease and platelet aggregation, regardless of the presence and absence of the clinical outcomes. The keywords for platelet aggregation included, but were not limited to, thromboxane B2, epinephrine, ADP (adenosine diphosphate), collagen, and ristocetin. The antiplatelet medications for the systematic search included aspirin, dipyridamole, flurbiprofen, ticlopidine, and clopidogrel.

The exclusion criteria were as follows:

1. studies not regarding Kawasaki disease
2. articles which do not describe original research (conference abstracts, case series, editorials, or commentaries)
3. non-human studies (animal studies or in vitro experiments)
4. studies which do not refer to the results about platelet function
5. duplicated studies
6. other reasons that the investigators considered the studies to be irrelevant to the objective

Study identification

We searched Medline, Embase, Cochrane Central Register of Controlled Trials on the Ovid platform, and Japanese literature database Igaku Chuo Zasshi (Ichushi) from January 1946 for Medline, and January 1947 for the other databases to August 2018 without any language restrictions. The experienced librarians at the National Center for Child Health and Development, who are also affiliated with Cochrane Japan, Tokyo, Japan, performed searches with the terms detailed search in Supplemental Table 1.

Study selection

Two investigators reviewed the articles independently. As an initial screening, they went through titles and abstracts of all the articles and excluded the articles clearly meeting the exclusion criteria. As a secondary screening, all articles were reviewed and identified for eligibility. When we found discrepancies of decisions between the two reviewers, a third reviewer hosted a face-to-face meeting to determine the eligibility.

Data collection

The collected data include number of patients, sex, assay of platelet aggregation and values, types of antiplatelet and dose, definition of controls, and clinical outcomes. The data were collected by two investigators independently for validation purpose.

Quality assessment and analysis

The quality assessment was conducted with the Newcastle-Ottawa Scale. Meta-analysis was initially planned when sufficient data was available. A study with a Newcastle-Ottawa Scale of 7 or more was considered to be of high quality.

Results

Literature search and characteristics of the eligible studies

We recognized a total of 1054 articles using three databases, out of which 945 articles were excluded by the titles and abstracts due to apparent ineligibility (Fig. 1). Two reviewers evaluated the entire contents of the remaining 109 articles independently and finally identified 20 articles eligible for our study [2, 5–23].

Summary of 20 studies

None of the studies were randomized controlled trials. Antiplatelet medications in the studies were aspirin, flurbiprofen, dipyridamole, choline salicylate, and vitamin E. The control cohorts were diverse among the studies; seven studies used the same patients' data before antiplatelet treatment as controls [2, 5–10]; nine studies compared the platelet aggregation ability in the antiplatelet therapy group with that of the cohort without treatment [11–19]; three studies compared platelet aggregation between the patients with different types of antiplatelet medications [20–22]; and one study compared antiplatelet function between different doses of the same antiplatelet medications [23]. The median number of total patients per study was 31 (range 5–108). The information on the sex of the patients was available in 12 studies; 177 male patients and 115 female patients participated in those studies. The median Newcastle-Ottawa Scale of the studies was 2 (range 0–5), showing that none of the studies met sufficient quality criteria.

Summaries of the 20 studies are shown in Table 1, Table 2, and Table 3, and the details of the studies are described in the Supplemental Table 2.

Studies with comparison of before and after antiplatelet treatment

Out of seven studies that compared platelet aggregation before and after antiplatelet treatment, six studies used aspirin as the

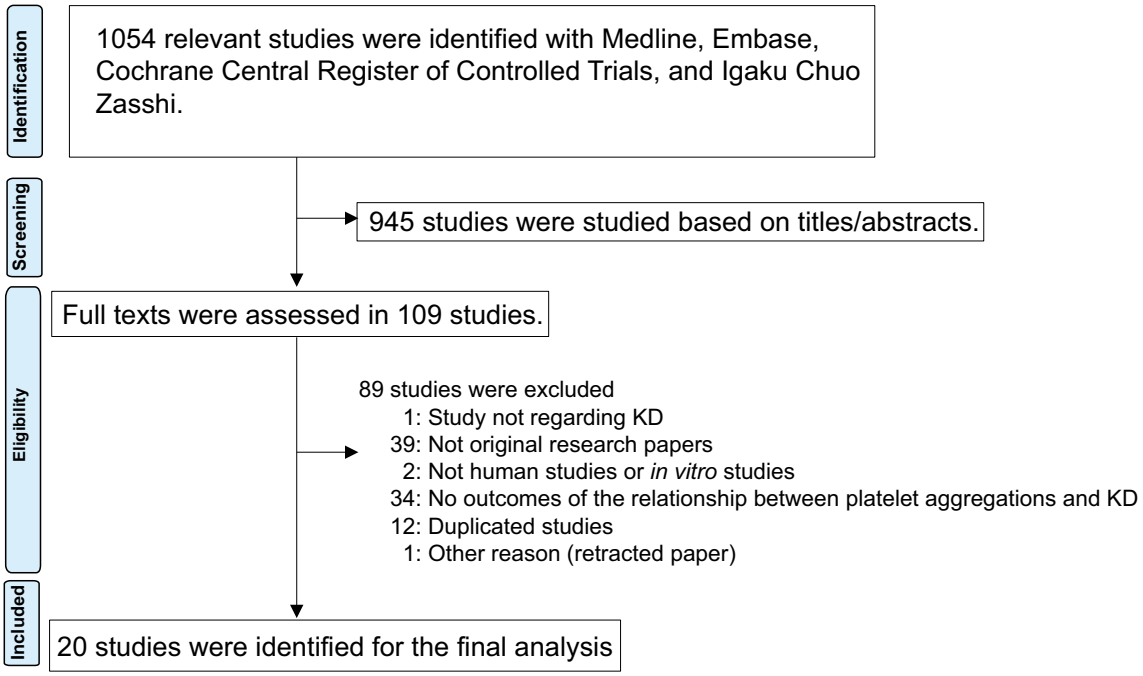

Fig. 1 Study selection flow chart of the study. Out of 1054 studies, 20 studies were finally eligible for the analyses

Table 1 Studies with comparison before and after antiplatelet treatment in patients with Kawasaki disease

No.	First author	Group	No. of patients	Assay and platelet aggregation	Clinical outcomes
1	Inamo [5]	Before treatment Aspirin 50 mg/kg/day	27 32	Thromboxane B2: decrease after treatment (no p value)	N/A
2	Igarashi [6]	Before treatment Aspirin 1–2 mg/kg/day Aspirin 5 mg/kg/day Aspirin ≥ 10 mg/kg/day	2 6 7 9	Thromboxane B2, collagen, and epinephrine: decrease after treatment (no p value)	N/A
3	Shirahata [7]	Before treatment After treatment with aspirin	18 18	ADP, collagen, and epinephrine: decrease after treatment (no p value)	N/A
4	Burns [8]	Before treatment After treatment with aspirin (3–8 mg/kg/day)	31 31	β-Thromboglobulin and platelet factor IV: no details described	16% developed cardiac aneurysm
5	Yamada [2]	Before treatment After treatment	5 5	ADP, collagen, and epinephrine: decrease after treatment (only graph)	N/A
6	Nakamura [9]	Before treatment Aspirin 50 mg/kg/day Before treatment Flurbiprofen 4 mg/kg/day Before treatment Prednisolone 2 mg/kg/day + Dipyridamole 5 mg/kg/day	18 16 2	ADP: no significant change of ADP (only graph) Collagen, epinephrine, thromboxane B2, and 6-keto-PGF1α: no details (only graph)	70% developed CAL 80% developed CAL 0% developed CAL
7	Ichimaru [10]	Before treatment Aspirin 2 mg/kg/day Aspirin 5 mg/kg/day Aspirin 10 mg/kg/day Aspirin 30 mg/kg/day Aspirin 50 mg/kg/day	10 5 9 10 10 9	Collagen and epinephrine: significant reduction ($p < 0.05$, $p < 0.01$) ADP and thromboxane B2: not significant 6-Keto-PGF1α: significant in 30 mg/kg/day, 10 mg/kg/day ($p < 0.05$)	N/A

ADP, adenosine diphosphate; *CAL*, coronary artery lesion

antiplatelet. Platelet aggregation assays included ADP, collagen, epinephrine, and thromboxane B2 (Supplemental Table 2). Six studies showed that platelet aggregation decreased after antiplatelet treatment, but only one of the six showed statistical significance [10], and the other five studies did not present any information about statistical significance (Table 1).

Studies with comparison to cohort without antiplatelet treatment

All nine studies used aspirin as an antiplatelet. The control cohorts were the patients with Kawasaki disease without treatment (number of studies [n] = 6), healthy volunteers ($n = 3$), and Kawasaki disease patients with antibiotic therapy ($n = 1$). Six studies concluded that there were significant decreases in platelet aggregation in the patients treated with antiplatelet drugs (Table 2). Despite the overlap of methodology in several studies, biomarkers used to evaluate platelet aggregation were diverse among the studies, and we were unable to obtain sufficient information to perform further analyses (Supplemental Table 2).

Comparison of multiple antiplatelet medications

Three studies compared platelet aggregation among multiple antiplatelet medications. One study showed that aspirin and flurbiprofen showed significant decreases in platelet aggregation, but the other two did not provide any statistics (Table 3; study number 17–19).

Comparison among doses

One study compared the doses of aspirin (Table 3; study number 20). 6-Keto-prostaglandin F1 (PGF1) alpha was more significantly decreased in the patients with high-dose aspirin (100 mg/kg/day) than in the patients with low-dose aspirin (30 mg/kg/day) ($p \leq 0.05$).

Clinical outcomes

Five out of 20 studies showed clinical outcomes after antiplatelet therapy [8, 9, 12, 18, 23] (Tables 1, 2, and 3, Supplemental Table 2). Coronary artery lesion was included in all five studies, but other outcomes included pericardial

Table 2 Studies with comparison to cohort without antiplatelet treatment

No.	First author	Group	No. of patients	Platelet aggregation by treatment	Clinical outcome
8	Sasai [11]	Healthy children	10	PGE2, thromboxane B2, 6-keto-PGF1 alpha, and TXB2/6-keto-PGF1 ratio: significant decrease after treatment ($p < 0.05$, $p < 0.001$, $p < 0.05$, $p < 0.0001$)	N/A
		Before treatment	16		
		Aspirin 30 mg/kg/day	14		
9	Fulton [12]	KD patients before treatment	16	Thromboxane B2: decrease after treatment (no p value)	3 pts: pericardial effusion
		Afebrile patients with non-KD	10		
		KD patient with aspirin (30–60 mg/kg)	6		3 pts: flattered ventricular septal motion
		KD patients with aspirin (80–120 mg/kg) + IVIG	10		1 pt: right coronary artery aneurysm
10	Suzuki [13]	KD patients without treatment	17	Thromboxane B2, ADP, collagen: decrease after treatment ($p < 0.0001$)	N/A
		Antiplatelet/anticoagulant (mainly aspirin)	20		
11	Taki [14]	Healthy volunteers	9	Spontaneous platelet aggregation: aggregation at the 1st stage is higher than that at other stages($p = 0.02$, $p = 0.02$, $p = 0.01$, $p = 0.04$); aggregation at the 1st stage is higher than that at stages 3, 4, and healthy volunteers ($p = 0.02$, $p = 0.02$, $p = 0.01$, $p = 0.04$)	N/A
		KD patients before treatment	33		
		KD patients until day 20 after IVIG + aspirin	48		
		KD patients from day 21 to 90 after IVIG + aspirin	50		
		KD patients on or after day 91 after IVIG + aspirin	75		
12	Yahata [15]	KD patients without aspirin treatment	8	Platelet-derived microparticles: decrease after treatment ($p = 0.0027$)	N/A
		KD patients with aspirin treatment	6		
13	Yokoyama [16]	KD patients with antibiotic therapy	7	Decrease after treatment with a low dose ($p < 0.01$; no details on assay)	N/A
		KD patients with aspirin (30 mg/kg/day)	9		
		KD patients with aspirin (100–150 mg/kg/day)	7		
14	Shibuya [17]	KD patients without treatment	N/A	ADP: decrease after treatment ($p < 0.05$)	N/A
		KD patients with aspirin (1 mg/kg every day)	N/A	TXB2/6-Keto-PGF1 ratio: decrease in the dose of more than 2 mg/kg ($p < 0.05$)	
		KD patients with aspirin (2 mg/kg every other day)	N/A		
		KD patients with aspirin (3 mg/kg every day)	N/A		
		KD patients with aspirin (5 mg/kg every day)	N/A		
15	Ohga [18]	KD patients without treatment	2	Thromboxane B2, collagen, epinephrine: decrease after treatment (no p value)	
		KD patients with aspirin (1–2 mg/kg/day)	8		aspirin < 9 mg/kg: CAL 35.3%
		KD patients with aspirin (5 mg/kg/day)	11–12		aspirin 10–49 mg/kg: CAL 25.0%
		KD patients with aspirin (> 10 mg/kg/day)	9–10		aspirin > 50 mg/kg: CAL 32.6%
16	Hamasaki [19]	Healthy volunteers	22	ADP, collagen, epinephrine: no significant decrease	N/A
		KD patients with aspirin (1–2 mg/kg/day)	10		
		KD patients with aspirin (5–10 mg/kg/day)	10–16		

ADP, adenosine diphosphate; *CAL*, coronary artery lesion; *IVIG*, intravenous immunoglobulin therapy; *KD*, Kawasaki disease; *pt*, patient

Table 3 Comparison among multiple antiplatelet medications in patients with Kawasaki disease (no. 17–19) and comparison between different doses of aspirin in patients with Kawasaki disease (no. 20)

No.	First author	Group	No. of patients	Platelet aggregation by treatment	Clinical outcome
17	Sato [20]	Aspirin	4	ADP, collagen, epinephrine, ristocetin: no tendency (only graph, no p value)	N/A
		Choline salicylate	4		
18	Inagaki [21]	IVIG 200 mg/day × 4 days aspirin 50 mg/kg/day	8	ADP: decrease after treatment (no p value)	N/A
		IVIG 400 mg/day × 4 days aspirin 50 mg/kg/day	8		
		IVIG 200 mg/day × 4 days aspirin 50 mg/kg/day	4		
		Aspirin 50 mg/kg/day or flurbiprofen 4 mg/kg/day	10		
19	Hoshino [22]	KD patients without treatment	17	ADP: significant decrease in the group with aspirin ($p < 0.01$)	N/A
		Aspirin 30 mg/kg/day	26	Collagen: significant decrease in the group with aspirin and flurbiprofen ($p < 0.01$)	
		Flurbiprofen 4.3 mg/kg/day	18	Ristocetin: no statistical data	
		Vitamin E 4.3 mg/kg/day	28		
		Dipyridamole 5 mg/kg/day	19		
20	Akagi [23]	Aspirin (30 mg/kg/day)	30	Thromboxane B2, 6-Keto-PGF1: decrease at high dose ($p \leq 0.05$)	23% developed CAL
		Aspirin (100 mg/kg/day)	30		17% developed CAL

ADP, adenosine diphosphate; *IVIG*, intravenous immunoglobulin therapy; *KD*, Kawasaki disease

effusion and flattered ventricular septal motion [18]. Only one study demonstrated the statistical analysis, which was not significant [23].

Heterogeneity assessment of the studies

Table 4 summarizes the qualitative and quantitative availability of the demographic information and the results in each eligible study. Blue rectangles indicate that all quantitative data were available. Red rectangles indicate that a part or all quantitative data were missing, and only a description or tendency (e.g., by graph) was obtainable. Gray rectangles indicate the absence of data. Out of 20 studies, 10 studies have at least one missing data. Various assays were used to evaluate platelet aggregation. The most frequent assay was ADP (used in 10 studies, of which five demonstrate quantifiable data), followed by thromboxane B2 and collagen (used in nine studies). Table 4 also shows the diversity of the assays used for platelet aggregation. Finally, this table shows that the studies used various control cohorts. These assessments led us to the conclusion that a quantitative synthesis including meta-analysis was not feasible.

Discussion

In this systematic review, we were not able to perform quantitative analyses due to heterogeneity among studies and the lack of sufficient information. We could not identify any randomized controlled trials, and all the studies were cohort studies with small sample sizes.

There are several reasons for the infeasibility of the quantitative analyses. The diversity of controls is the first hurdle to conducting analyses; the control cohort included the patients before antiplatelet medications, the patients without standard treatment of Kawasaki disease, healthy volunteers, or the patients with different doses of antiplatelet medications. Moreover, the comparison between before and after antiplatelet therapies cannot exclude the possibility of spontaneous reduction in platelet aggregation. The differences in the choice of biomarkers of platelet aggregation used resulted in failure of analyses; only half of the studies used the most frequent biomarker (ADP, 10 out of 20 studies). Moreover, only half of the studies using ADP presented quantifiable information, which is essential for further analyses. Six out of nine studies which chose the patients with Kawasaki disease without standard treatment or healthy volunteers as controls showed statistical significance, but because of the diversity of the biomarker assays, we concluded that the further quantitative analyses are not attainable.

The low quality of the studies is another limitation. The majority of the studies were published more than 20 years ago; only three out of 20 studies were published after 2000, and eight out of 19 articles were published in Japanese only and were not accessible to most readers internationally. Most of the studies published before international consensuses of reporting of clinical studies, such

Table 4 Summary of the qualitative and quantitative availability in each study

		Biomarker of platelet aggregation used in the analyses													
First author	Number of patients	Thromboxane B2	ADP	Collagen	Epinephrine	Ristocetin	(6-keto) PGF1 alpha	Beta-thromboglobulin platelet factor IV	PDMP	TXB2/6-Keto-PGF1 ratio	Spontaneous platelet aggregation	Optical density method	PGE2	No details	Complete quantitative data available?
Inamo[5]															Yes
Igarashi[6]															Yes
Shirahata[7]															No
Burns[8]															No
Yamada[2]															No
Sasai[11]															Yes
Nakamura[9]															No
Ichimaru[10]															Yes
Fulton[12]															No
Suzuki[13]															Yes
Taki[14]															No
Yahata[15]															Yes
Yokoyama[16]															Yes
Shibuya[17]															No
Ohga[18]															No
Hamasaki[19]															Yes
Sato[20]															No
Inagaki[21]															No
Hoshino[22]															Yes
Akagi[23]															Yes

Key:
All quantifiable data are available.
A part of or all data are missing.
Data not analyzed

ADP, adenosine diphosphate; *PGF1*, prostaglandin F1; *PGE2*, prostaglandin E2; *PDMP*, platelet-derived microparticles; *TXB2*, thromboxane B2

as Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [24] or Consolidated Standards of Reporting Trials (CONSORT) [25], were available to researchers. We found a lot of insufficient information, which was the obstacle to performing analyses.

The ultimate goal of treatment of Kawasaki disease is to suppress the inflammation at the acute phase and minimize the incidence of coronary artery aneurysm, thrombosis, and death. Anti-inflammatory and antiplatelet therapies were developed, and aspirin has been used to meet both aims [4]. One of the most epoch-making treatments for Kawasaki disease is intravenous immunoglobulin, initially reported in 1984 [26]; immunoglobulin treatment has dose-dependent effectiveness to prevent coronary artery lesions [27]. Corticosteroids also mitigate the incidence of coronary artery lesions for high-risk Kawasaki disease [1]. Aspirin has been used in combination with immunoglobulin and corticosteroids, but its antiplatelet effect has not been fully elucidated. Although low-dose aspirin is recommended for high platelet count resulting from essential thrombocythemia to reduce the thrombotic risk [28], there has been no indication or recommendation about antiplatelet medications for high platelet count after developing Kawasaki disease. Unfortunately, our study could not elucidate the role of antiplatelet treatment for Kawasaki disease. Seven studies identified decreased platelet aggregation after antiplatelet treatment, but the other studies did not show the significance. Five studies presented the clinical outcomes after antiplatelet, and none of them showed significance. Four studies did not show *p* value, and one study concluded no significant difference was observed between low-dose and high-dose aspirin groups [23]. Therefore, we could not validate the effects of antiplatelet medications on the incidence of coronary artery lesions or mortality rate of Kawasaki disease. Immunoglobulin and corticosteroids have robust evidence of effectiveness. Immunoglobulin and antiplatelet with or within corticosteroids are the standard treatment strategy for Kawasaki disease [4]. Combination of multiple drugs including antiplatelet could be attributable for the effectiveness of the treatment for Kawasaki disease, and it is unknown whether omitting antiplatelet treatment from standard therapy provides comparable treatment outcomes. A multi-center, prospective, randomized controlled trial is underway to determine whether immunoglobulin alone as the primary therapy in Kawasaki disease is as effective as immunoglobulin combined with high-dose aspirin therapy [29].

Conclusion

This systematic review showed that there was insufficient evidence for the effectiveness of antiplatelet therapy for Kawasaki disease. The pharmacodynamics of antiplatelet medications and their clinical effectiveness should be clarified by larger studies.

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Authors' Contributions AI and TK developed the concept of the study. RT, AI, and TK designed the study. RT, RH, and TS selected the eligible studies, collected the data, and summarized the data. RT wrote the initial draft of the manuscript. RH, TS, AI, and TK critically reviewed and revised the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study does not require ethical approval because this is a systematic review of published articles.

Informed consent Informed consent is not necessary for this study because this is a systematic review of published articles.

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