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Original Article

A meta-analysis of re-treatment for intravenous immunoglobulin-resistant Kawasaki disease

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Abstract *Objective:* To determine the optimal drug therapy for intravenous immunoglobulin-resistant Kawasaki disease. *Methods:* Studies regarding drug therapy for intravenous immunoglobulin-resistant Kawasaki disease were selected from medical electronic databases including PubMed, Medline, Elsevier, and Springer Link. The effectiveness in terms of temperature recovery and coronary artery damage was compared between a second intravenous immunoglobulin treatment and glucocorticosteroid treatment for children with intravenous immunoglobulin-resistant Kawasaki disease using meta-analysis with Review Manager 5.3 software. Indices to evaluate the effects were body temperature, biomarker levels, and coronary artery lesions detected by echocardiography. Results are reported as relative risks or odds ratio with a 95% confidence interval and $p < 0.05$. *Results:* Meta-analysis included 52 patients in the second intravenous immunoglobulin treatment group and 75 patients in the glucocorticosteroid treatment control group from four studies that met our inclusion criteria. Temperatures of patients who received glucocorticosteroid treatment were effectively controlled compared with those who received a second intravenous immunoglobulin treatment (relative risk = 0.73, 95% confidence interval: 0.58–0.92, $p = 0.007$). There were no differences, however, in the incidence of coronary artery lesions between the two groups (odds ratio = 1.55, 95% confidence interval: 0.57–4.20, $p = 0.39$). *Conclusions:* Glucocorticosteroids are more effective in controlling body temperature compared with intravenous immunoglobulin re-treatment in intravenous immunoglobulin-resistant Kawasaki disease children; however, glucocorticosteroids and intravenous immunoglobulin re-treatment showed no difference in the prevention of coronary artery lesions.

Keywords: Mucocutaneous lymph node syndrome; Kawasaki disease; intravenous immunoglobulin; glucocorticosteroid; meta-analysis

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KAWASAKI DISEASE IS AN ACUTE FEBRILE RASH illness of unknown cause, characterised by systemic vasculitis. Kawasaki disease most commonly affects young children under the age of five, and involves mainly the small arteries, especially the coronary arteries, which can result in coronary artery aneurysms.[1–3] Over the past 10 years, the incidence of Kawasaki disease as well as coronary artery lesions has significantly increased,[4] and coronary artery lesions have become the most common cause for acquired heart disease in children in developed countries.[5] Recent studies have shown that Kawasaki disease can cause coronary atherosclerosis in adults, even leading to sudden death.[6,7] The standard treatment regimen for the acute phase of Kawasaki disease involves administering intravenous immunoglobulin 2 g/kg within 10 days of onset and aspirin 50 mg/kg to effectively decrease in duration of fever and reduce the incidence of coronary artery disease.

It is important to note that, according to the literature, 10–25% of children with Kawasaki disease

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still have fever or recurrence of fever after being relieved, within 36 hours, of the initial intravenous immunoglobulin treatment. Such cases are classified as intravenous immunoglobulin-resistant Kawasaki disease.[8] The treatment regimen for children with intravenous immunoglobulin-resistant Kawasaki disease is still controversial. The American Heart Association recommends a second administration of 2 g/kg intravenous immunoglobulin to treat children with initial intravenous immunoglobulin-resistant Kawasaki disease;[9] however, this is based on evidence from serial case analyses and case–control studies of poor quality, and is only of evidence level C. Other existing therapies include glucocorticoids therapy, biological agents such as plasmapheresis, protease inhibitors – ulinastatin for injection – infliximab, and other drugs;[10] however, there is no standard therapy for intravenous immunoglobulin-resistant Kawasaki disease. In this study, we performed a meta-analysis of published studies in order to evaluate the effects of a second intravenous immunoglobulin dose compared with glucocorticoids as clinical treatments for intravenous immunoglobulin-resistant Kawasaki disease.

Materials and methods

Inclusion criteria

Studies meeting all of the following inclusion criteria were included: study participants were children with initial intravenous immunoglobulin-resistant Kawasaki disease; the study evaluated comparative effectiveness of re-treatment with intravenous immunoglobulin at 1–2 g/kg versus treatment with glucocorticosteroids; studies contained detailed descriptions regarding basic information of patients, study design, efficacy determination, and whether follow-up was available before drug use; and indications used to evaluate effects included change in body temperature, biomarker levels, and coronary artery lesions detected by ultrasonic cardiogram.

Exclusion criteria

Studies meeting any of the following criteria were excluded: study participants did not have intravenous immunoglobulin-resistant Kawasaki disease; the control group continuously received intravenous immunoglobulin with modified dosing; design was of retrospective nature without a control group or retrospective controlled study without randomised studies; and the intravenous immunoglobulin-resistant patients received other treatments after being treated with intravenous immunoglobulin or steroids.

Efficacy evaluation

Following non-responsiveness to a first intravenous immunoglobulin dosing, the following conditions were considered to be effective during re-treatment: temperature dropped to normal within 3 days without repeatedly rising; and re-examined ultrasonic cardiogram results during follow-up period suggested no coronary artery lesion or coronary artery lesion was alleviated. In this study, a meta-analysis was performed to analyse body temperature change 1-week after treatment and to observe changes in coronary artery aneurysm incidence within 4 weeks after a second intravenous immunoglobulin or glucocorticosteroid re-treatment in children with resistant Kawasaki disease.

Retrieval of literature

Databases used in this study included PubMed (1968–2014), Medline (1950–2014), Elsevier (1998–2014), Springer Link (as of 2014), Ovid (2000–2014), BlackWell (1999–2014), BMJ Journals online (as of 2014), Karger (1890–2014), John Wiley (1999–2014), and Chinese Journal Full-text Database (1990–2014). The cut-off time for all the literature retrieved was February, 2014.

Retrieval strategy involved searching for the following key words in full-text databases in English: Kawasaki disease/mucocutaneous lymph node syndrome/Kawasaki disease/mucocutaneous lymph node syndrome *AND intravenous immunoglobulin/intravenous gamma-globulin/intravenous immunoglobulin/intravenous gamma globulin/immunoglobulin AND resistant/unresponsive/refractory/intractable/failure AND treatment/re-treatment/therapy/management. In order to search for the articles containing therapy for intravenous immunoglobulin-resistant Kawasaki disease, the following key words were also included in searches: Kawasaki disease AND initial intravenous immunoglobulin treatment failure/fail to respond to initial treatment with intravenous immunoglobulin/additional gamma-globulin AND intravenous methylprednisolone/intravenous methylprednisolone/steroid AND treatment/re-treatment/therapy/management.

Original texts were obtained from full-text databases of electronic periodicals.

Quality assessment of literature

Investigators used abstracts to screen literature, extracting and evaluating articles based on basic information, study subjects, design, implementation, and analysis methods.

The sample size, age, diagnostic criteria of Kawasaki disease, the initial treatment, diagnostic criteria of intravenous immunoglobulin-resistant Kawasaki

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disease, and re-treatment after non-response to intravenous immunoglobulin were obtained from the data extracted from the selected articles.

The quality of included literature was assessed using the Juni scale, according to the following four evaluation criteria of randomised controlled trials: correct randomised method; allocation concealment to avoid selective bias due to random allocation influenced by various factors; blind design; and intention-to-treat analysis when needed. Those studies fully meeting the above-mentioned four requirements were ranked grade A with the possibility of minimum bias; studies partially satisfying any or several of the criteria were ranked grade B with the possibility of moderate bias; failure to meet several or many of the requirements were ranked grade C with the possibility of high bias.

Statistical analysis

Review Manager 5.3 software was used for statistical analysis. Comprehensive analysis of orientation was performed for the results of the selected studies. χ^2-test was used for heterogeneity analysis, and $p > 0.05$ showed that no heterogeneity existed among studies. For studies involving enumerated data, the results were stated with relative risk and 95% confidence intervals. The difference was considered to be statistically significant when $p < 0.05$.

Results

General information of study subjects

From the medical literature, six studies of intravenous immunoglobulin-resistant Kawasaki disease were identified.[11–16] Of these, the Hashino et al study[11] and Teraguchi et al[16] study were excluded because of the following reasons: the control group continuously applied intravenous immunoglobulin with modified dosing[11] and the intravenous immunoglobulin-resistant patients received other treatments after being treated with intravenous immunoglobulin or steroids.[16] Ultimately, four trials were selected, of which two were randomised controlled trials and the other two were comparative effectiveness studies that did not involve randomisation.[12–15] An overview of the selected studies is listed in Table 1. Participants ranged from 1 to 141 months of age, and in total there were 52 patients in the second intravenous immunoglobulin treatment group and 75 patients in the glucocorticosteroid treatment control group. Kawasaki disease diagnosis was described in detail in each of the selected studies. All the children were diagnosed in accordance with Kawasaki disease criteria established by the "Japanese Kawasaki disease research committee", and diseases with similar clinical manifestations of Kawasaki disease were excluded. All the studies observed normalisation of body temperature within a specific time frame and the occurrence of coronary artery aneurysms. A 50% decrease in C-reactive protein following 1-week re-treatment was regarded as the index in one article,[15] as shown in Table 1. Associated covariates such as age, gender, and duration of illness are shown in Table 2.

Quality of the selected studies

Of the two randomised controlled trials and two comparative effectiveness studies, each contained a control group. Of all, two trials did not adopt the blind method, and one did not have allocation concealment; neither blind method nor allocation concealment was mentioned in the remaining two trials. No patients were lost to follow-up or withdrawal; two studies were ranked grade B, and the other two studies were ranked grade C. See Table 3.

Meta-analysis results

Body temperature recovery. Comprehensive analysis of the selected studies indicated that, following the first dose of intravenous immunoglobulin treatment, body temperatures were more effectively restored in intravenous immunoglobulin-resistant Kawasaki disease patients in the glucocorticosteroid treatment group (62/75, 82.7%) in comparison with patients in the second intravenous immunoglobulin treatment group (32/52, 61.5%), and the difference was statistically significant (relative risk = 0.73, $p = 0.007$). See Figure 1.

Coronary artery lesions. Comprehensive analysis indicated that, after the first dose of intravenous immunoglobulin treatment, no statistically significant difference (odds ratio = 1.55, $p = 0.39$) existed between the incidence of coronary artery lesions in the glucocorticosteroid re-treatment group (9/75, 12%) compared with the second intravenous immunoglobulin treatment group (10/52, 19%). See Figure 2.

Adverse reactions. Patients undergoing methylprednisolone pulse therapy showed adverse reactions including hypertension, hypothermia, and bradycardia. The adverse reactions of glucocorticosteroids in the studies are detailed in Table 4.

Discussion

Coronary artery lesions are the most common and serious cardiovascular complication of Kawasaki disease, and they often persist after the acute phase. They are a major cause of death in children with Kawasaki disease. The occurrence rate of intravenous

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Table 1. Initial treatment and re-treatment in the four selected studies.

		Initial treatment				Re-treatment			
Literature	Design of study	Course of disease (days)	Coronary artery	Treatment	Diagnostic standard of non-response to IVIG	Re-treatment regime	Restoration of body temperature	Decrease in CRP	No. of CAA
Furukawa et al[14]									
IVIG re-treatment (19 cases)	Subjects that refused steroids assigned to re-treatment with IVIG, no blinding	Not mentioned	Normal	IVIG 2 g/kg + ASA 30 mg/kg	Fever persisted or relapse within 36 hours	IVIG 2 g/kg	Rapid drop to normal, without relapse	Not mentioned	2
GCS treatment group (44 cases)						IVMP 30 mg/(kg day), heparin 10–20 U/kg, for consecutive 3 days	Rapidly dropped to normal, the body temperature rose again in 10 cases in 1 week after re-treatment	Not mentioned	5
Ogata et al[15]									
IVIG re-treatment (14 cases)	Subjects assigned to IVIG versus steroids based on location of care, no blinding	<9	Normal	IVIG 2 g/kg + ASA 30 mg/kg	Temperature ⩾37.5°C or CRP drop < 50% within 48 hours	IVIG 2 g/kg	Drop to normal in 3.0 ± 2.4 days	(17 ± 49) mg/L	3
GCS treatment group (13 cases)						IVMP 30 mg/(kg day), for consecutive 3 days	Drop to normal in 1.0 ±1.3 days	(6 ± 14) mg/L	0
Miura et al[12]									
IVIG re-treatment (11 cases)	RCT for which the blind method was not mentioned	Not mentioned	Normal	IVIG 2 g/kg	Temperature ⩾37.5°C within 48 hours	IVIG 2 g/kg	Drop to normal in only 3 cases on the third day, later 5 cases relapsed	Not mentioned	3
GCS treatment group (11 cases)						IVMP 30 mg/(kg day), for consecutive 3 days	Drop to normal in 10 cases in first 3 days, later 5 cases relapsed	Not mentioned	2
Miura et al[13]									
IVIG re-treatment (8 cases)	RCT for which blind method was not mentioned	5	Normal	IVIG 2 g/kg	Temperature ⩾37.5°C within 48 hours	IVIG 2 g/kg	The body temperature dropped to normal in 5 cases in the first 2 days, later total 4 cases relapsed	(0.22 ± 0.10) mg/L	2
GCS treatment group (7 cases)		4				IVMP 30 mg/(kg day), for consecutive 3 days	The body temperature dropped to normal in all cases on the second day, later total 3 cases relapsed	(0.38 ± 0.17) mg/L	2

ASA = acetylsalicylic acid; CAA = coronary artery aneurysm; CRP = C-reactive protein; GCS = glucocorticosteroid; IVIG = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; RCT = randomised controlled trial

Table 2. Age, gender, and duration of illness on admission.

	Age			Gender			Duration of illness		
Studies	IVIG	Glucocorticoid	p	IVIG	Glucocorticoid	p	IVIG	Glucocorticoid	p
Miura et al[12]	Not mentioned			Not mentioned			Not mentioned		
Miura et al[13]	31 ± 26 months	32 ± 19 months	ns	5:3	5:2	ns	4(4–4) days	5(4–7) days	ns
Ogata et al[15]	33 ± 24 months	14 ± 17 months	ns	9:4	7:5	ns	4 ± 1.3 days	5 ± 0.3 days	ns
Furukawa et al[14]	31.3 ± 23.8 months	28.1 ± 21 months	ns	11:8	23:21	ns	Not mentioned		

IVIG = intravenous immunoglobulin; ns = no significant difference.

Table 3. Quality assessment of the four selected studies.

Studies	Randomisation	Allocation concealment	Blind method	Loss to follow-up/withdrawal	Grade
Miura et al[12]	Yes	Not mentioned	Not mentioned	No	B
Miura et al[13]	Yes	Not mentioned	Not mentioned	No	B
Furukawa et al[14]	No	No	No	No	C
Ogata et al[15]	No	Not mentioned	No	No	C

immunoglobulin-resistant Kawasaki disease reported in the United States this year was 18 to 22%.[17] A highly activated immune system and vasculitis are marked features of Kawasaki disease.[18,19] Intravenous immunoglobulin can reduce the abnormal immune response; reduce cytokine levels; suppress endothelial cell activation, immune regulation, and Fc receptor blockers; inhibit antibody formation; neutralise super-antigens of bacteria and viruses; improve clinical symptoms; and alleviate coronary injury.[20,21] Intravenous immunoglobulin remains the most important and widely used therapeutic to reduce coronary artery lesion incidence. Intravenous immunoglobulin dosing is negatively correlated to coronary artery lesion incidence.[22,23]

At present, most doctors advocate administering a second intravenous immunoglobulin treatment for patients who are non-responsive to the first dose of intravenous immunoglobulin, but specific re-treatment dosage is inconclusive. Teraguchi et al[16] conducted a prospective trial to evaluate the effectiveness of methylprednisolone pulse therapy compared with an additional intravenous immunoglobulin therapy for intravenous immunoglobulin-resistant Kawasaki disease patients. They found that clinical symptoms and laboratory parameters in two-thirds of patients were significantly improved after the second dose of immunoglobulin, whereas methylprednisolone pulse therapy had more treatment failures, characterised by persistent fever or recrudescence of fever. The above findings were very meaningful and informative and would attract further clinical trials in the field, although this study was not included in this meta-analysis, as intravenous immunoglobulin-resistant patients received other treatments after being treated with intravenous immunoglobulin or steroids in the study.[16]

Our present study revealed that in 52 cases of second immunoglobulin treatment for intravenous immunoglobulin-resistant Kawasaki disease, the body temperatures of 32 cases dropped to normal within 72 hours, but 20 cases did not respond to treatment, and 10 cases showed the occurrence of coronary artery lesions. Even after following a third round of intravenous immunoglobulin treatment, there still remained cases of non-responsiveness. This may be due to various factors[24] such as levels of blood neutrophils, C-reactive protein, white blood cells, serum cholesterol, sodium, potassium, etc. before treatment.

At present, a therapeutic regimen of glucocorticoid drugs for patients with intravenous immunoglobulin-resistant Kawasaki disease has been generally accepted.[25] Similar to other vasculitis syndromes, the occurrence of vasculitis in Kawasaki disease patients is associated with vascular endothelial injury and vascular wall damage due to an abnormal immune response. Some humoral factors, especially anti-neutrophil cytoplasmic antibodies, can activate neutrophils, resulting in early vascular injury of Kawasaki disease. Glucocorticosteroids may suppress NF-κB, improve IκB activation, inhibit a variety of cytokines and COX_2, and block inflammation.[26] This is primarily attributable to the fact that glucocorticosteroids act directly on the glucocorticoid receptor in the cell membrane, playing a role in stabilising the membrane and blocking receptor activation. Decreased in vivo cortisol levels in Kawasaki disease children during the acute period provided the

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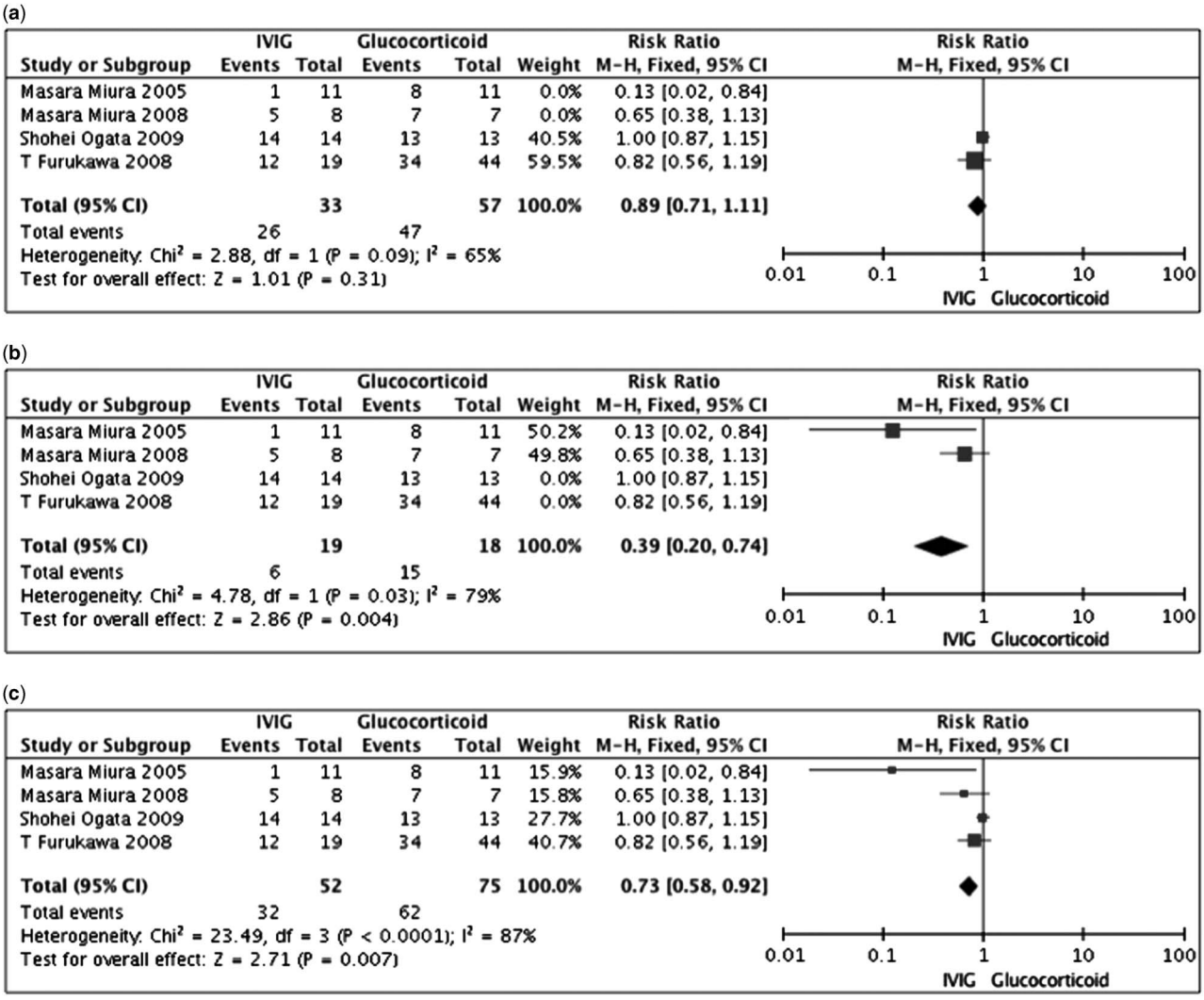

Figure 1.
*Forest plot of body temperature recovery with a second intravenous immunoglobulin treatment versus glucocorticoid treatment in children with intravenous immunoglobulin-resistant Kawasaki disease. In these studies, efficacy was measured as body temperature returning to normal without longer relapse. Each ■ represents the relative risk of each study; the horizontal line across represent 95% confidence intervals; ◆ represents comprehensive analysis of the results. In the figure, ◆ having no intersection with a vertical line suggests that the temperatures of intravenous immunoglobulin-resistant Kawasaki disease patients who received glucocorticosteroid re-treatment were more effectively improved compared with intravenous immunoglobulin-resistant Kawasaki disease patients who received a second intravenous immunoglobulin treatment, and the difference between both groups was statistically significant (relative risk: 0.73, 95% confidence interval: 0.58–0.92, p = 0.007). (**a**) The results of two comparative effectiveness studies, (**b**) the results of two randomised controlled trials (RCTs), and (**c**) the results of all the four studies.*

theoretical basis for applying glucocorticosteroid treatment in children with Kawasaki disease.[27] Miura et al believe that as soon as Kawasaki disease patients display non-responsiveness to immunoglobulin, glucocorticosteroid therapy should be used to rapidly relieve inflammation in patients. Delayed treatment could lead to the persistence of inflammatory cytokines, causing sustained coronary lesions; on the other hand, glucocorticosteroid can further suppress the inflammatory response that immunoglobulins are unable to suppress.[28]

Hung and Chiu[29] found that methylprednisolone showed significantly greater efficacy than a third intravenous immunoglobulin treatment in children who were unresponsive to two consecutive intravenous immunoglobulin treatments. Sundel et al[30] found that when methylprednisolone was administered at 30 mg/kg day for 3 days during a standard treatment regimen, patient body temperature returned to normal faster, C-reactive protein and erythrocyte sedimentation decreased more quickly, and length of hospital stay was shortened, with no

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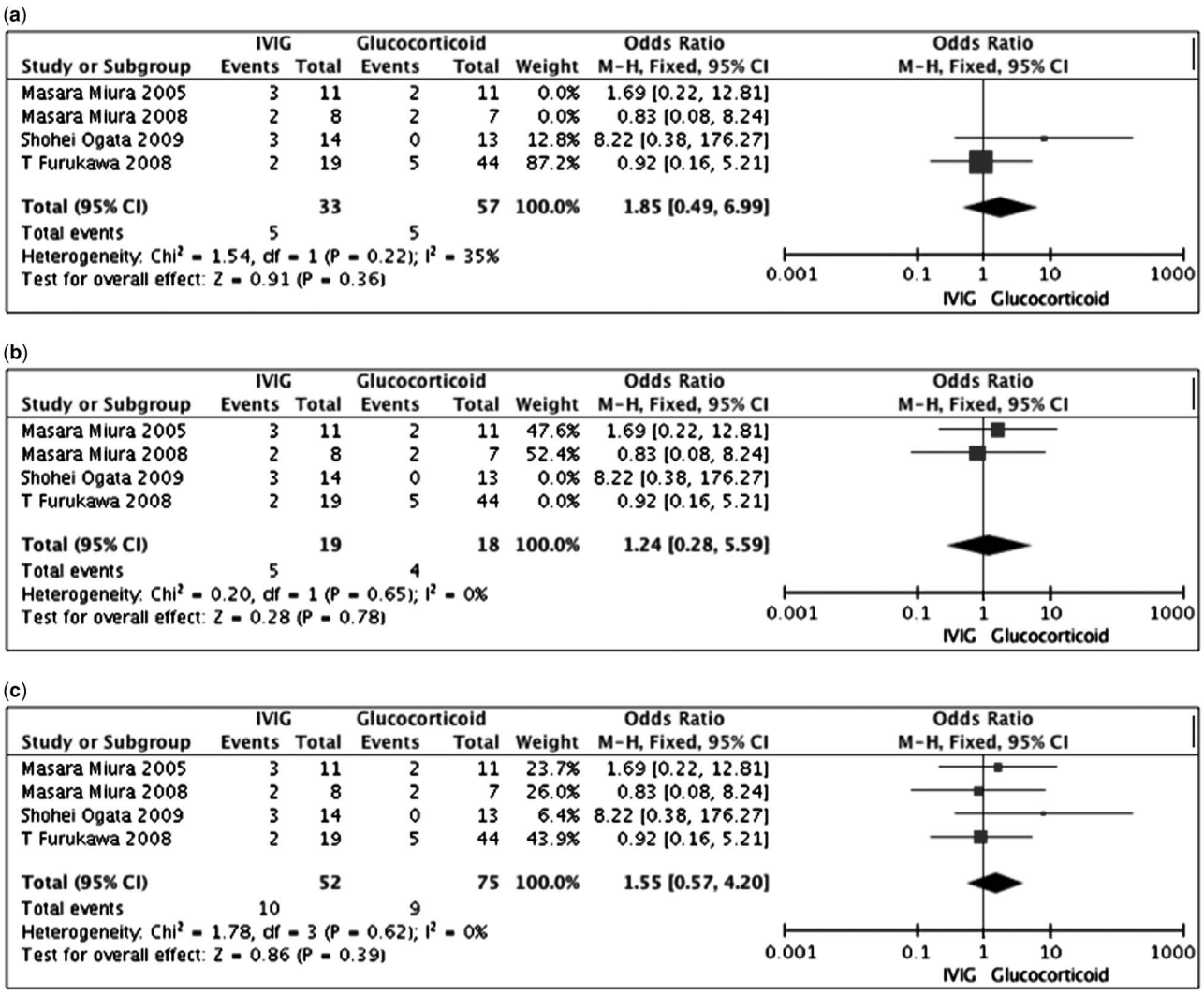

Figure 2.
*Forest plot of coronary artery lesions with second intravenous immunoglobulin treatment versus glucocorticoid treatment in intravenous immunoglobulin-resistant Kawasaki disease in children. In these studies, efficacy was determined by the occurrence of coronary lesions. Each ■ represents the odds ratio of each study, and the horizontal line across represents 95% confidence intervals. ◆ represents comprehensive analysis of the results. ◆ having no intersection with a vertical line suggests that there was no statistical difference in the occurrence of coronary lesions between glucocorticosteroid re-treatment and the second intravenous immunoglobulin treatment (odds ratio: 1.55, 95% confidence interval: 0.57–4.20, p = 0.39). (**a**) The results of two comparative effectiveness studies, (**b**) the results of two randomised controlled trials (RCTs), and (**c**) the results of all the four studies.*

Table 4. Occurrence of adverse reactions of glucocorticoid therapy in the four selected studies.

Studies	Hypertension	Hypothermia	Bradycardia	Thrombosis	Gastrointestinal bleeding	Hyperglycaemia	Nerve palsy
Miura et al[12]	10 (91%)	9 (82%)	9 (82%)	0	0	6 (55%)	–
Miura et al[13]	5 (71%)	1 (14%)	6 (86%)	0	0	–	–
Furukawa et al[14]	5 (10%)	3 (6%)	3 (6%)	0	0	–	1 (2%)
Ogata et al[15]				Not mentioned			

significant adverse reactions. Ogata et al[15] pointed out that, following non-responsiveness to initial immunoglobulin treatment in children with intravenous immunoglobulin-resistant Kawasaki disease, the use of glucocorticoid drugs could significantly shorten fever time, reduce C-reactive protein levels, and cause

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high recovery rate of coronary artery aneurysms compared with further immunoglobulin treatment. The present study found that after administration of glucocorticoid re-treatment in 75 initial intravenous immunoglobulin non-responsiveness cases, the body temperatures of 62 patients dropped to normal ranges within 72 hours, but non-responsiveness persisted in 13 cases, and coronary artery lesions occurred in nine cases. Comparisons of the groups suggest that glucocorticosteroids are better for fever reduction compared with the second dose of intravenous immunoglobulin.

Many researchers propose that glucocorticosteroids could help in restoring dilated coronary arteries, but studies also suggest that glucocorticosteroids could facilitate coronary artery lesions.[25,31] The present study, however, showed that coronary artery lesions occurred in nine out of 75 cases after glucocorticosteroid treatment with non-response to initial intravenous immunoglobulin treatment. There was no significant difference in the occurrence of coronary artery lesions between the glucocorticosteroid re-treatment group and the second intravenous immunoglobulin re-treatment group.

Methylprednisolone pulse therapy involves some adverse reactions[32] such as hypertension, hypothermia, bradycardia, thrombosis, and even gastrointestinal bleeding. These adverse reactions, however, are mostly temporary, and the majority of children recover without special treatment. In the present analysis, common adverse reactions concomitant with glucocorticoid usage included hypertension, hypothermia, bradycardia, and some rare reactions including gastrocnemius nerve palsy. Most of these patients recovered without special treatment.

The meta-analysis of currently published comparative trials demonstrates that glucocorticosteroids are more effective in restoring body temperature than a second intravenous immunoglobulin treatment in children with intravenous immunoglobulin-resistant Kawasaki disease; however, no statistical difference was found in the incidence of coronary artery lesions between the two groups. Further studies are still needed to confirm the safety and efficacy of corticosteroids.

Nevertheless, the meta-analysis in this study has some limitations. First, there was a limited number of randomised controlled trial studies investigating the re-treatment for children with intravenous immunoglobulin-resistant Kawasaki disease, and each sample size was small. Second, the follow-up periods of each study were relatively short, which resulted in the fact that the defervescence might be only a surrogate outcome for control of the inflammatory response. Therefore, whether glucocorticoid therapy should be used routinely to treat children with intravenous immunoglobulin-resistant Kawasaki disease still needs multi-centre and large sample-sized studies to further evaluate its safety and efficacy.

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Conflicts of Interest

None.

Ethical Standards

This study was in line with the ethical standards and approved by the Ethical Committee of Peking University First Hospital.

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