Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis

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ABSTRACT

Objective To summarise clinical trials that compared the incidence of coronary abnormality between intravenous immune globulin (IVIG) plus corticosteroid therapy and IVIG therapy alone, and to determine the overall efficacy and safety of IVIG plus corticosteroid therapy for the initial treatment of Kawasaki disease.

Background Although use of IVIG as initial therapy has been established in Kawasaki disease, the role of corticosteroids therapy is controversial.

Methods Medline, The Cochrane Library, The Clinical Trials, and Embase Database were searched for published clinical studies up to 31 March 2012. Studies that compare the efficacy of IVIG plus corticosteroid with that of IVIG in treating Kawasaki disease were included. The coronary outcome and adverse events were analysed by meta-analysis.

Results 9 clinical studies with a total of 1011 patients were identified. Meta-analysis of the 9 studies showed that IVIG plus corticosteroid therapy significantly reduced the risk of coronary abnormality (OR: 0.3; 95% CI 0.20 to 0.46). Similar results were observed in subgroup analyses of randomised controlled studies (OR: 0.3; 95% CI 0.18 to 0.5), studies focused on patients with a high risk of IVIG resistance (OR: 0.2; 95% CI 0.1 to 0.36) and studies with blinded-endpoint manner (OR: 0.32; 95% CI 0.19 to 0.55). There was no significant difference in the incidence of severe adverse events between the IVIG plus corticosteroid group, and the IVIG group (OR: 1.24; 95% CI 0.33 to 4.67).

Conclusions Combination of corticosteroid with the conventional regimen of IVIG as an initial treatment strategy could reduce the risk of coronary abnormality.

INTRODUCTION

Kawasaki disease is often complicated by an acute, self-limited vasculitis that occurs predominantly in infants and young children. Coronary artery aneurysms, or ectasia, develop in 15%–25% of untreated children with the disease and lead to myocardial infarction, ischaemic heart disease or sudden death. In the USA, Kawasaki disease has surpassed acute rheumatic fever as the leading cause of acquired heart disease in children. Since it was first described in Japan in l967 by Tomisaku Kawasaki, the disease has been known to occur in both endemic and community-wide epidemic forms in the Americas, Europe and Asia, in children of all races.[1–4]

The treatment with intravenous immunoglobulin plus aspirin has been proved to resolve inflammation, and reduces the occurrence of coronary artery abnormalities.[5–7] However, about 20% of patients have persistent or recurrent fever after completion of intravenous immunoglobulin, and these patients have a particularly high risk of developing coronary artery abnormalities.[8 9] Although corticosteroid is a useful treatment option for various forms of vasculitis, many physicians hesitate to use them because a report showed a high incidence of coronary artery abnormalities in patients who received a prolonged course of oral prednisolone.[10]

Several clinical trials have been performed to investigate the efficacy of corticosteroid in Kawasaki disease[11–27]; however, the role of a corticosteroid in the initial treatment of Kawasaki disease has not been established. In 2007, a multicentre, mixed ethnic group, prospective, blinded-endpoint, randomised, controlled trial reported that the efficacy of pulsed intravenous methyprednisolone added to conventional therapy did not improve coronary artery outcomes.[24] Recently, we noted in a Japanese study conducted in a prospective, randomised, blinded-endpoints, controlled design, that primary treatment with IVIG plus prednisolone significantly reduced the risk of coronary abnormality in patients with severe Kawasaki disease.[27] Based on the controversial results, in order to further investigate the potential benefit of corticosteroid in an enlarged population, we performed the present study to systematically identify clinical trials that compared the efficacy of IVIG plus corticosteroid therapy, and IVIG therapy, for the initial treatment with respect to the coronary artery outcome.

METHODS

To perform a meta-analysis of clinical trials is still challenging because of different study designs and potential biases. Hence, we conducted this study according to the guideline of PRISMA Statement (The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate healthcare interventions: explanation and elaboration).[28]

Inclusion criteria

Studies were included if they met the following criteria: (1) subjects had a stated diagnosis of Kawasaki disease[4 29 30]; (2) studies parallelly compared the efficacy of IVIG plus corticosteroid and IVIG alone therapy; (3) two-dimensional echocardiography, or coronary artery catheterisation, was performed to detect the presence of coronary artery abnormality during study follow-up.

Information source and study selection

Two investigators independently performed the data search, employing the search theme, 'Kawasaki, clinical study'. Searches of published

studies were performed by Medline, The Cochrane Library, The Clinical Trials and Embase Database up to 31 March 2012. The reports were screened using the titles and abstracts, and articles relevant to our subject were reassessed by reviewing the full text. Disagreement about studies selection was resolved by consensus, when necessary. Detailed characteristics of included studies were recorded on our original information table. Primary outcome was incidence of patients with coronary artery abnormality per group during follow-up assessment. The severe adverse events per group during the study period were also estimated.

Quality assessment

The quality of each study was rated by using the following schema[31]:

1. Were the criteria for the diagnosis of Kawasaki disease stated explicitly? (defined as: (a) a statement that all patients met the diagnostic criteria of the American Heart Association; (b) a statement that all patients met the diagnostic criteria of the Japanese Ministry of Health or (c) fever for 5 days plus any four of the following: conjunctivitis, mucositis of the oral pharynx, peripheral oedema, unilateral lymphadenopathy, and rash) (score: yes = 1; no = 0).
2. Was an experimental study design used? (score: randomised, controlled, prospective study with defined protocol = 2; controlled, defined protocol = 1; none = 0).
3. Was follow-up coronary imaging performed after enrolment? (score: ≥4 weeks = 2; 2≤ weeks<4=1; not stated = 0).
4. Was coronary imaging interpreted in a blinded manner? (score: yes = 1; no or not stated = 0). Each study was scored by the investigators. Conflicts about quality scoring were resolved by consensus.

STATISTICAL ANALYSIS

All the statistical analyses in this meta-analysis were performed on the basis of intention-to-treat principle. The significance between two groups of this meta-analysis was estimated by OR with a two-tailed 95% CIs. A fixed-effects model was employed for consistent outcome variables, and a random-effects model for inconsistent outcome variables. Heterogeneity was assessed by means of a Cochran Q test. Statistic value I^2 represented the degree of inconsistency with a score of 25%, 50% and 75%, representing low, moderate and high levels of inconsistency, respectively. p Value for the test of heterogeneity less than 0.01 was considered significantly heterogeneous between studies. If heterogeneity was observed between pooled studies, further sensitivity analyses were performed to detect potential confounding variables. Statistical analyses procedures were performed using the Revman software package (Review Manager, Version 5.0, The Cochrane Collaboration, Oxford, UK).

RESULTS

Studies selection

The study selection process is illustrated in figure 1. A total of 1753 items of literature was retrieved in our primary search. After screening titles and abstracts, 1736 were excluded due to irrelevance. The remaining 17 clinical studies relevant to corticosteroid treatment were selected for further assessment. Eight studies were excluded. Of these studies, one study compared a corticosteroid treatment group with a non-corticosteroid treatment group,[11] one study had equivocal treatment allocation process,[12] one study enrolled patients who were all treated with corticosteroid, and performed a before/after comparison,[13] five studies compared IVIG with corticosteroid alone therapy.[14–18] Consequently, nine clinical studies were enrolled in this meta-analysis.

Baseline characteristics of included study

As shown in table 1, seven of the nine studies were conducted in Japan,[19 21–23 25–27] the other two were in the USA.[20 24] The time of publication ranged from 1999 to 2012. The overall study population included in this study was 1011; 59% were men, 536 were allocated to the IVIG plus corticosteroid group and 475 to the IVIG group. The mean age ranged from 1.7 years to 4.5 years. The mean severity score[32] ranged from 3.7 to 4, whereas, three studies[25–27] enrolled a high-resistant risk[33–35] of IVIG therapy patients. All studies initiated primary treatment at an early clinical stage (within the first 10 days). For the drug administration during study period, all patients enrolled in the included studies received aspirin. The usage of aspirin was 30 mg/kg/day in seven studies[19 21–23 25–27] 20–25 mg/kg/day in one study[20] and 80–100 mg/kg/day in one study.[24] There were four studies using prednisolone 2 mg/kg/day,[19 21 23 27] four studies using intravenous methyprednisolone (IVMP) 30 mg/kg/day[20 24–26] and one study using dexamethasone 0.3 mg/kg/day[22] as corticosteroid agents. Five studies administrated IVIG 2 mg/kg/day for one dose,[20 24–27] two studies 1 mg/kg/day for two doses,[21 23] one study 200–400 mg/kg/day for five doses[19] and one study 0.4 or 0.5 mg/kg/day for four or five doses.[22] Two-dimensional echocardiogram was used in all studies to detect coronary abnormality during study follow-up.

Quality assessment

The quality assessment of nine studies selected in the meta-analysis is shown in table 2. All the included studies

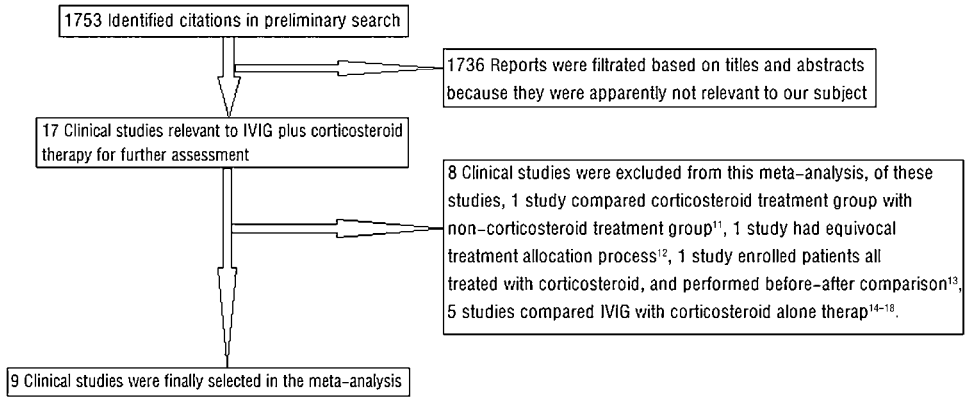


Figure 1 Flow diagram of studies selection process.

Table 1 The demographic, clinical treatment and outcome characteristics of nine studies included in the meta-analysis

Study	Publication year	Study type	Excluded patients with coronary abnormality at baseline?	Sample size in IVIG +CORT/IVIG alone group (n/n)	Gender (male %)	Mean age (years)	Mean severity score or risk of IVIG resistance at baseline	Clinical stage when treatment initiated
Shinohara *et al*[19]	1999	Retrospective	Coronary abnormality was excluded	62/25	59	1.7	Severity score 3.7[32]	Early stage
Sundel *et al*[20]	2003	RCT	Coronary aneurysm was excluded	18/21	69	4.4	Not reported	Early stage
Okada *et al*[21]	2003	RCT	Coronary aneurysm was excluded	14/18	56	2.8	Severity score 4[32]	Early stage
Jibiki *et al*[22]	2004	Non-randomized controlled study	Coronary abnormality was excluded	46/46	49	2.3	Not reported	Early stage
Inoue *et al*[23]	2006	RCT	Coronary abnormality was excluded	90/88	57	4.5	Severity score 3.7[32]	Early stage
Newburger *et al*[24]	2007	RCT	Coronary aneurysm was included	101/98	62	2.9	Not reported	Early stage
Okada *et al*[25]	2009	Non-randomized controlled study	Coronary abnormality was excluded	62/32	77	2.8	High risk of IVIG resistance[33]	Early stage
Ogata *et al*[26]	2012	RCT	Coronary abnormality was excluded	22/26	50	3.5	High risk of IVIG resistance[34]	Early stage
Kobayashi *et al*[27]	2012	RCT	Coronary abnormality was excluded	121/121	56	2.6	High risk of IVIG resistance[35]	Early stage

	Drug administration						Outcomes assessment			
Study	Usage of aspirin mg/kg/day	Agent of CORT	Usage of CORT (mg/kg/day)	Duration of CORT therapy (day)	Usage of IVIG (mg/kg/day)	Dose of IVIG (n)	Method to detect coronary lesion	Criteria of coronary abnormality	Patients had coronary lesion in IVIG+CORT/IVIG group (n/n)	Severe adverse events in IVIG +CORT/IVIG group (n/n)
Shinohara *et al*[19]	30	Prednisolone	2	Defervescence	200–400	5	Echocardiography and angiography	Dilation ≥4 mm[29]	1/6	0/0
Sundel *et al*[20]	20–25	IVMP	30	1	2	1	Echocardiography	Z score ≥3[36]	0/1	0/0
Okada *et al*[21]	30	Prednisolone	2	3	1	2	Echocardiography	Dilation ≥3 or 4 mm §[29]	0/0	0/0
Jibiki *et al*[22]	30	Dexamethasone	0.3	3	0.4 or 0.5	4 or 5	Echocardiography	Dilation ≥3 mm[29]	2/2	0/0
Inoue *et al*[23]	30	Prednisolone	2	3	1	2	Echocardiography	Dilation≥3 or 4 mm §[29]	2/10	0/0
Newburger *et al*[24]	80–100	IVMP	30	1	2	1	Echocardiography	Z score ≥2.5,[29 36]	30/28	2/2
Okada *et al*[25]	30	IVMP	30	1	2	1	Echocardiography	Z score ≥3[36]	15/15	0/0
Ogata *et al*[26]	30	IVMP	30	1	2	1	Echocardiography	Z score ≥2.5[36]	2/10	0/0
Kobayashi *et al*[27]	30	Prednisolone	2	5	2	1	Echocardiography	Dilation ≥3 or 4 mm* [29]	4/28	3/2

*Dilation ≥3 or 4 mm: a coronary artery was defined as abnormal if the internal lumen diameter was >3 mm in a child <5 years, or >4 mm in a child ≥5 years according to Japanese Ministry of Health and Welfare.
RCT, randomized controlled trial; IVIG, intravenous immunoglobulin; CORT, corticosteroid; IVMP, intravenous methyprednisolone; IVIG, intravenous immunoglobulin; CORT, corticosteroid;

defined their diagnostic criteria for Kawasaki disease. Of the nine eligible studies, six studies used a prospective, randomised, controlled method,[20 21 23 24 26 27] two studies were non-randomized-controlled trials[22 25] and one study was a retrospective report.[19] Seven studies had coronary imaging follow-up of 4 weeks or more,[19–21 23 24 26 27] whereas, two studies had coronary imaging follow-up less than 4 weeks.[22 25] Four studies reviewed the coronary image in a blinded

Table 2 Quality assessment of nine studies included for the meta-analysis

Study	Diagnostic criteria	Study design	Imaging follow-up	Blinded outcome	Total score
Shinohara *et al* 1999[19]	1	1	2	0	4
Sundel *et al* 2003[20]	1	2	2	1	6
Okada *et al* 2003[21]	1	2	2	0	5
Jibiki *et al* 2004[22]	1	1	1	0	3
Inoue *et al* 2006[23]	1	2	2	0	5
Newburger *et al* 2007[24]	1	2	2	1	6
Okada *et al* 2009[25]	1	1	1	0	3
Ogata *et al* 2012[26]	1	2	2	1	6
Kobayashi *et al* 2012[27]	1	2	2	1	6

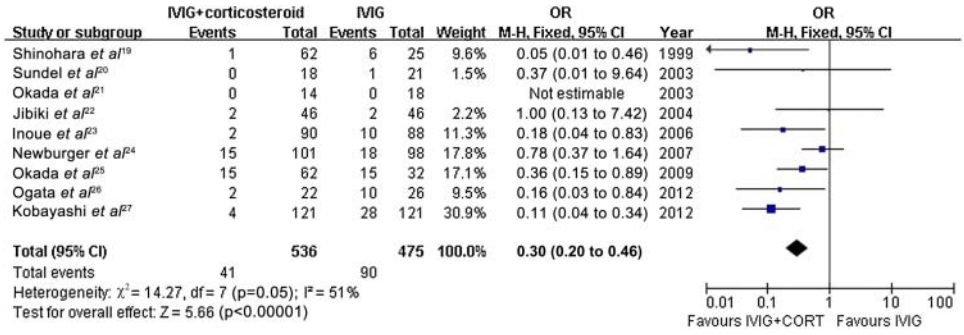


Figure 2 Meta-analysis of nine included studies.

manner,[20 24 26 27] while no statement about blinded manner of outcome assessment was noted in the remaining studies.

Meta-analysis

When outcome of the nine included studies were combined, significantly fewer patients who received IVIG plus corticosteroid therapy experienced coronary artery abnormality than those who received IVIG therapy alone (7.6% vs 18.9%; OR: 0.3; 95% CI: 0.20 to 0.46; p<0.001), the test for heterogeneity (I^2=51%; p=0.05) (figure 2).

Sensitivity analyses

To explore and control possible confounding variables, we also performed subset analyses. There were six prospective randomised controlled studies.[20 21 23 24 26 27] When outcomes of these studies were combined, the IVIG plus corticosteroid group still had significantly fewer coronary artery abnormalities compared with the IVIG alone group (6.3% vs 18%; OR: 0.3; 95% CI 0.18 to 0.5; p<0.001), the test for heterogeneity (I^2=61%; p=0.04) (figure 3).

Three studies enrolled patients with a high risk for IVIG resistance.[25–27] When outcomes of these studies were combined, the benefit of lower incidence of coronary abnormality in the IVIG plus corticosteroid group seemed more significant (10.2% vs 29.6%; OR: 0.2; 95% CI 0.1 to 0.36; p<0.001) with the test for heterogeneity (I^2=29%; p=0.25) (figure 3).

Patients in four studies received prednisolone,[19 21 23 27] while patients in another four studies received IVMP[20 24–26] as corticosteroid agents. To control different corticosteroids preparation as confounding variable, we included four studies administering prednisolone. Patients in the IVIG plus prednisolone group experienced significantly lower incidence of coronary artery abnormalities compared with the IVIG alone group (2.4% vs 17.5%; OR: 0.12; 95% CI 0.05 to 0.26; p<0.001) with the test for heterogeneity (I^2=0%; p=0.67) (figure 3). When four studies administrating IVMP were included, patients in the IVIG plus IVMP group still experienced significantly lower incidence of coronary artery abnormalities compared with the IVIG alone group (15.8% vs 24.9%; OR: 0.48; 95% CI 0.28 to 0.81; p=0.006) with the test for heterogeneity (I^2=18%; p=0.3) (figure 3).

Four studies in this meta-analysis reviewed and analysed the coronary images in a blinded manner,[20 24 26 27] while the remaining studies did not state anything about the blinded manner of coronary outcome assessment. The risk of coronary abnormality was significantly lower in the IVIG plus corticosteroid group when blinded-endpoint studies were included (8% vs 21.4%; OR: 0.32; 95% CI 0.19 to 0.55; p<0.001) with the test for heterogeneity (I^2=68%; p=0.02) (figure 3), and meta-analysis for non-blinded-endpoint studies (7.3% vs 15.8%; OR: 0.27; 95% CI 0.14 to 0.52; p<0.001) with the test for heterogeneity (I^2=34%, p=0.21) (figure 3).

Seven studies had coronary image follow-up ≥4 weeks.[19–21 23 24 26 27] When we included only these studies, the patients in the IVIG plus corticosteroid group still experienced significantly lower incidence of coronary abnormality compared with the IVIG group (5.6% vs 18.4%; OR: 0.27; 95% CI 0.17 to 0.44; p<0.001) with the test for heterogeneity (I^2=61%, p=0.02) (figure 3).

Assessment of adverse events

All patients in the included studies were monitored clinically for adverse events daily during administration of the study therapy, and then for the study period. Safety assessments included recording of all severe adverse events, conducting physical examinations and laboratory assessments. During the study period, five patients (0.93%) in the IVIG plus corticosteroid group experienced severe adverse events (including: one hypotension, one respiratory dysfunction, two high cholesterol, one neutropenia), whereas, four patients (0.84%) in the IVIG group experienced severe adverse events (including: two non-occlusive thrombus in the coronary artery, one anaphylaxis to IVIG, one high cholesterol). No death was reported in the included studies during their study periods. The incidence of severe adverse events in the IVIG plus corticosteroid group and the IVIG group were similar (0.93% vs 0.84%; OR 1.24; 95% CI 0.33 to 4.67; p=0.75) with the test for heterogeneity (I^2=0%; p=0.75) (figure 4).

DISCUSSION

The combined data presented in this meta-analysis showed that adding corticosteroid to IVIG therapy as primary management option had the advantage of reducing the risk of coronary artery abnormality when compared with IVIG alone therapy. The overall risk of adverse events was relatively low, and no significant difference of severe adverse events was observed between the two groups during study follow-up, suggesting that IVIG-combined corticosteroid therapy strategy is safe and effective in the initial treatment for patients with Kawasaki disease.

An acute febrile disorder with systematic vasculitis that predominantly occurs in infancy and early childhood is the characteristic of Kawasaki disease, and coronary lesions carry the greatest risk of mortality in notable determinants of its outcome. Later in adulthood, angiographic and postmortem studies demonstrated that coronary sequelae, persisting long after acute Kawasaki vasculitis, result in arteriosclerotic changes, which increase the risk of serious coronary events.[37 38] Acute and chronic inflammation has been recognised as the pathophysiological basis which is closely associated with coronary artery disease during the course of Kawasaki disease and afterwards.[39] Therefore, adding corticosteroid to the standard

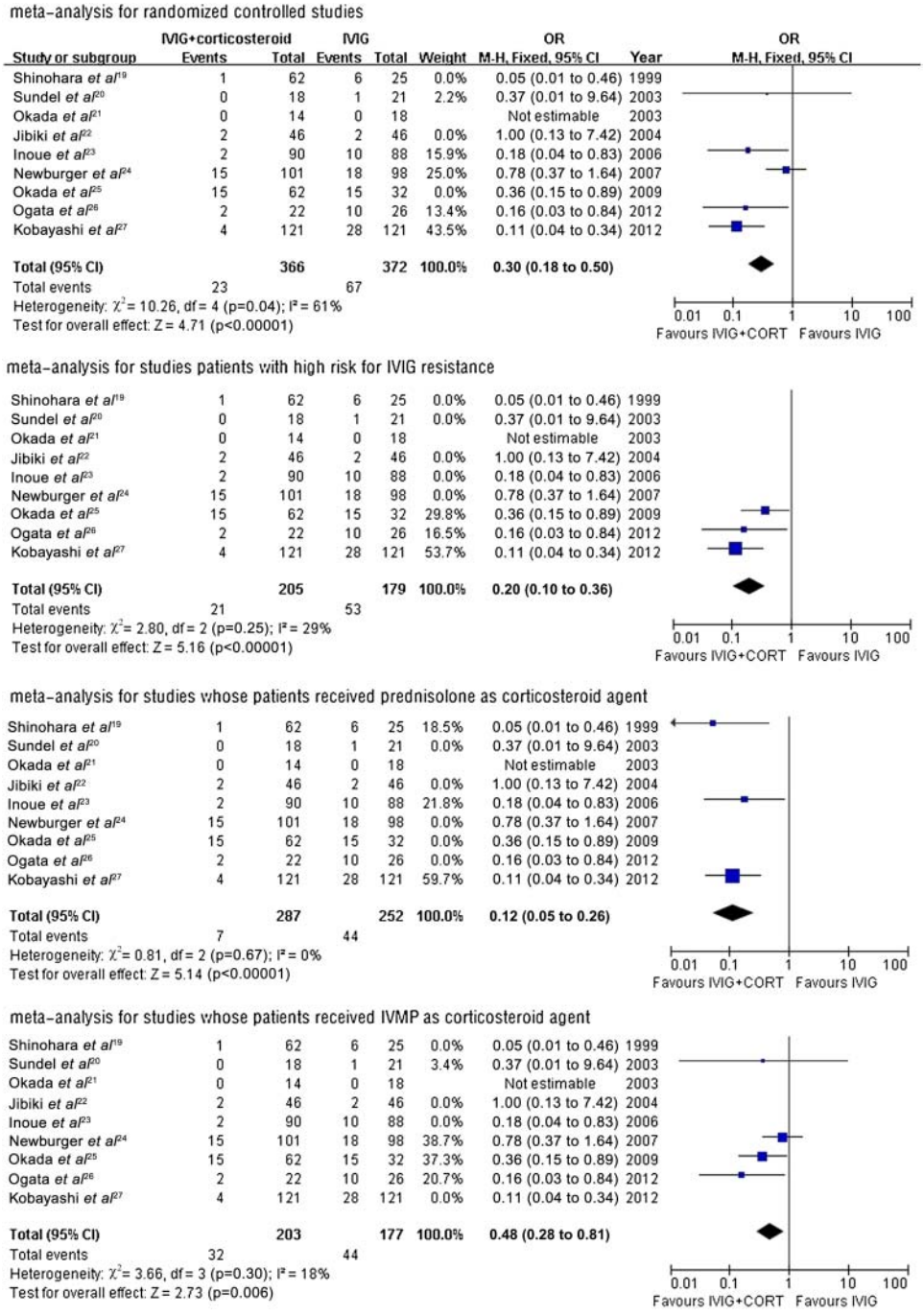


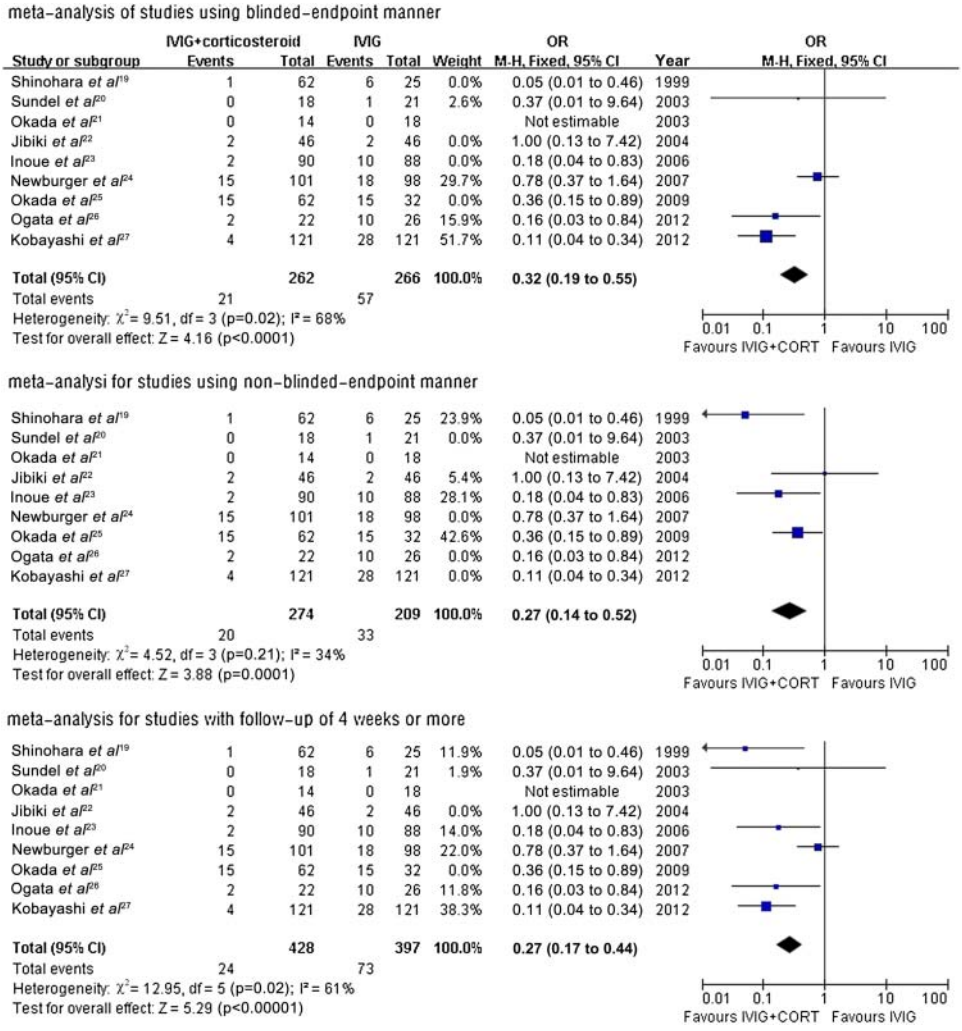
Figure 3 Sensitivity analyses and subgroup meta-analysis. Sensitivity analyses and subgroup meta-analysis.

therapy as an initial therapy strategy to reduce the risk of coronary sequelae seems reasonable.

Several studies suggest that corticosteroids improved the laboratory findings, shorten the duration of fever, made C-reactive protein and cytokines levels decrease rapidly and reduced the number of patients requiring rescue treatment.[16 19–21 23–25 27] However, the promising results of corticosteroid noted that these clinical studies were also challenged by some negative reports. An early Japanese study first showed that corticosteroid therapy exposed a serious detrimental effect on coronary artery in patients with Kawasaki disease, but later on, this study was reported to have potential methodological flaws.[10] Recently, a prospective, multicenter, controlled study demonstrated that corticosteroid therapy was useful for the clinical outcome, but it could not reduce the risk of coronary aneurysm when compared with IVIG therapy.[15] Moreover, a Canadian retrospective report revealed that the use of corticosteroid in the acute stage for patients with evolving coronary artery lesions worsened the clinical and coronary outcome.[11] Although an early meta-analysis including corticosteroid in regimens containing aspirin for primary treatment of Kawasaki disease, reduced the incidence of coronary aneurysm. The results may be overestimated due to small sample size, lack of randomised controlled trials and potential bias.[31]

In 2007, a multicenter and multi-ethnic group study conducted in the USA by Newburger and colleagues prospectively observed no improvement in coronary abnormality when corticosteroid treatment was combined with IVIG therapy.[24] Possible reasons might be the patient's enrolment and time to initiate treatment. The median time until start of treatment was

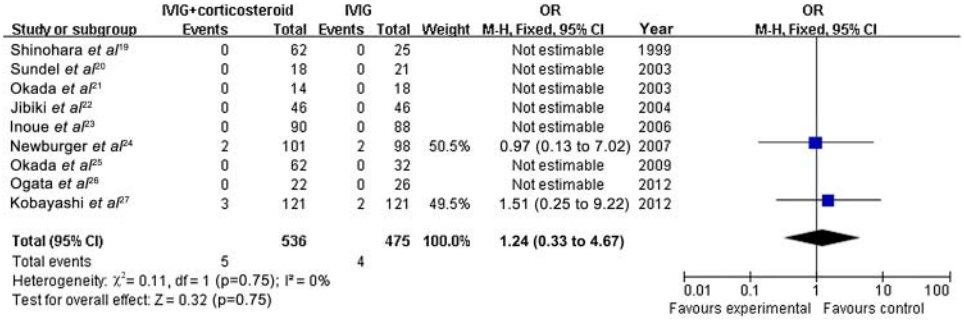
Figure 3 Continued.



relatively late, and the patients who already had coronary artery abnormality at baseline were also considered eligible in their study. A major benefit from early suppression of vasculitis would result if the corticosteroid therapy administrated precedes vascular remoulding,[40 41] and this explanation may also partially interpret the results shown by Millar *et al*[11] and Otaga *et al*'s[15] studies. In a Japanese nation-wide study in 2012, Kabayashi and colleagues demonstrated that prednisolone treatment combined with IVIG therapy at a relatively earlier stage improved coronary and clinical outcomes in patients with severe Kawasaki disease, but their results and score system might be potentially restricted in minority ethnic groups.[27] Interestingly, results from their subset study suggested that primary treatment with IVMP therapy did not improve coronary outcome in patients with high risk for IVIG resistance. Thus, an intriguing concern whether different corticosteroid preparations had disparate effects on clinical or coronary outcome was raised.

In an effort to obtain a better understanding of IVIG plus corticosteroid therapy among an enlarged population, nine eligible clinical studies were finally included in this meta-analysis, different from our previous study. Six of them performed prospective, randomised, controlled design to compare our subjects. The result of the subset analysis that merely included prospective, randomised, controlled trials still showed significant beneficial effect of corticosteroid-combined standard therapy on coronary outcome. During this process, a moderate, but not strong, heterogeneity was detected by Q test. Further sensitivity analyses revealed that the disparate study design, different patient enrolments, drug administration, non-blinded-endpoint manner and different follow-up duration may be potential sources of

Figure 4 Meta-analysis for adverse events.



inconsistence, but these factors ultimately did not alter the primary result of the present meta-analysis. Nevertheless, potential bias could not be avoided because of intrinsic differences in study design, a large-scale, multicenter, better-designed, international study may be needed.

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Notes