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Intravenous immunoglobulin for the treatment of Kawasaki disease in children (Review)

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[Intervention Review]

Intravenous immunoglobulin for the treatment of Kawasaki disease in children

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Editorial note: This review has been superseded by Cochrane Review 'Intravenous immunoglobulin for the treatment of Kawasaki disease': https://doi.org/10.1002/14651858.CD014884

ABSTRACT

Background

Kawasaki disease is the most common cause of acquired heart disease in children in developed countries. The coronary arteries supplying the heart can be damaged in Kawasaki disease. The principal advantage of timely diagnosis is the potential to prevent this complication with early treatment. Intravenous immunoglobulin (IVIG) is widely used for this purpose.

Objectives

The objective of this review was to evaluate the effectiveness of IVIG in treating, and preventing cardiac consequences, of Kawasaki disease in children.

Search methods

Electronic searches of the Cochrane Peripheral Vascular Disease Group Specialised Register, CENTRAL, MEDLINE, EMBASE, and CINAHL were performed (last searched March 2003). We also searched references from relevant articles and contacted authors where necessary. In addition we contacted experts in the field for unpublished works.

Selection criteria

Randomised controlled trials of intravenous immunoglobulin to treat Kawasaki disease were eligible for inclusion.

Data collection and analysis

Fifty-nine trials were identified in the initial search. On careful inspection only sixteen of these met all the inclusion criteria. Trials were data extracted and assessed for quality by at least two reviewers. Data were combined for meta-analysis using relative risk ratios for dichotomous data or weighted mean difference for continuous data. A random effects statistical model was used.

Main results

The meta-analysis of IVIG versus placebo, including all children, showed a significant decrease in new coronary artery abnormalities (CAAs) in favour of IVIG, at thirty days RR (95% CI) = 0.74 (0.61 to 0.90). No statistically significant difference was found thereafter. A subgroup analysis excluding children with CAAs at enrolment also found a significant reduction of new CAAs in children receiving IVIG RR (95%) = 0.67 (0.46 to 1.00). There was a trend towards benefit from IVIG at sixty days (p=0.06).

Results of dose comparisons showed a decrease in the number of new CAAs with increased dose. The meta-analysis of 400 mg/kg/day for five days versus 2 gm/kg in a single dose showed statistically significant reduction in CAAs at thirty days RR (95%) = 4.47 (1.55 to 12.86). This comparison also showed a significant reduction in duration of fever with the higher dose.

There was no statistically significant difference noted between different preparations of IVIG.

There was no statistically significant difference of adverse effects in any group.

Authors' conclusions

Children fulfilling the diagnostic criteria for Kawasaki disease should be treated with IVIG (2 gm/kg single dose) within 10 days of onset of symptoms.

PLAIN LANGUAGE SUMMARY

Intravenous immunoglobulin for the treatment of Kawasaki disease in children

Good evidence that intravenous immunoglobulin treatment within the first 10 days of symptoms reduces coronary artery abnormalities (heart damage) in children with Kawasaki disease. Kawasaki disease is a disease that primarily affects children under five years old. The cause of Kawasaki disease is not known. Its symptoms are persistent fever, red eyes and lips, strawberry tongue, rash and swollen lymph nodes. If not detected and treated immediately, Kawasaki disease can result in heart damage and occasionally death. Intravenous immunoglobulin involves injecting antibodies purified from donated blood. The review of trials found that intravenous immunoglobulin given within the first 10 days of the disease reduces the risk of damage to the coronary arteries of the heart in children, without serious adverse effects.

BACKGROUND

Description of the condition

Kawasaki disease, or mucocutaneous lymphnode syndrome is a systemic vasculitis (inflammation of the blood vessels), which predominantly affects children under the age of five years (Royle 1998). It was first described by Dr Tomisaku Kawasaki in 1967 (Kawasaki 1967). Despite subsequent advances in treatment and research exploring a superantigen-mediated role in the development of Kawasaki disease (Leung 1993; Curtis 1995; Leung 1995), its cause remains unknown. However, epidemiological studies support an infectious agent inducing the disease in a genetically susceptible minority (Harnden 2002). Reported incidence rates differ considerably throughout the developed world with rates in Japan 10 times those in the United States and 30 times those in the United Kingdom and Australia (Dhillon 1993; Royle 1998; Yanagawa 2001). World wide mortality rates also vary between 0.08% in Japan to 3.7% in the UK (Dhillon 1993). It is unclear whether mortality reflects intrinsic severity of disease and/or early recognition and delivery of effective treatment.

The most important complication, inflammation of the coronary arteries leading to formation of aneurysms, occurs in 20-30% of untreated patients (Kato 1995). Thrombosis within an aneurysm, myocardial infarction, and dysrhythmias (disordered rhythm of the heart) may occur in the acute phase of the illness. Patients may also suffer long term morbidity as a result of scarring of coronary arteries, thickening of the inner wall of the arteries, and accelerated atherosclerosis.

There is no diagnostic test for the disease, and many cases are missed (Curtis 1995). Diagnosis is based on clinical criteria such as that summarized by the American Heart Association (AHA) in 1993 (Dajani 1993). These include fever for five or more days, polymorphous exanthem (a rash of indefinite or variable appearance), nonpurulent conjunctivitis, changes in the lips or oral cavity, redness and oedema with later desquamation (peeling of the skin) of the extremities, and at least one cervical lymph node that is >1.5 cm in diameter. The diagnosis is made when the child has five days of fever, four of the other five findings, and no evidence of another disease with similar clinical features. However, many common childhood infections do have similar clinical features. Furthermore, the diagnostic features of Kawasaki disease may appear sequentially rather than simultaneously. The two features that doctors most often remember are desquamation of the rash and increased numbers of platelets in the blood stream (thrombocytosis). Unfortunately, these features are the least useful in reaching an early diagnosis because they usually occur later in the disease (Curtis 1997). Moreover, the clinical diagnostic criteria do not identify every case; "incomplete" or "atypical" cases have come to light because coronary artery aneurysms have been found on echocardiography or at autopsy (Rowley 1987). One study has shown that more patients with partial findings developed coronary artery abnormalities than did those with the full clinical picture (Witt 1999). As a result of this, many feel justified in making a diagnosis of Kawasaki Disease even when children do not meet all the AHA criteria.

Description of the intervention

The principal advantage of timely diagnosis of Kawasaki disease is the potential to prevent the complication of coronary artery abnormalities by early treatment. Intravenous immunoglobulin (IVIG) is widely used for this purpose.

Why it is important to do this review

The review will examine the effectiveness of IVIG. Two further Cochrane systematic reviews on the treatment of Kawasaki disease are also underway; 'Salicylate for the treatment of Kawasaki disease in children' (currently being prepared by the authors of this review) (Love 2003), and 'Steroid hormone treatment for Kawasaki disease in children' (Liu 2003).

OBJECTIVES

The objective of this review was to evaluate the effectiveness of intravenous immunoglobulin (IVIG) in treating, and preventing longterm cardiac consequences, of Kawasaki disease in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised studies examining the effectiveness of IVIG in the treatment of Kawasaki disease in children were eligible for inclusion.

Types of participants

Children between the age of 0-18 diagnosed with Kawasaki disease.

Types of interventions

- IVIG versus placebo or no treatment
- IVIG of differing doses
- IVIG and salicylate versus salicylate alone
- Single dose IVIG versus multiple dose IVIG
- Different types of IVIG

Types of outcome measures

Primary Outcomes

- Death
- Coronary artery abnormalities (CAAs) (dilatations and aneurysms, diagnosed by echocardiography, coronary angiography or autopsy)
- Myocardial function abnormalities (diagnosed by echocardiography, coronary angiography or autopsy)

Secondary Outcomes

- Duration of fever
- Adverse effects
- Duration of hospital stay

Search methods for identification of studies

Publications in the literature that described, or may have described, the use of intravenous immunoglobulin for the treatment of Kawasaki disease in children were sought. No restrictions on language of publication were made.

1. The Cochrane Peripheral Vascular Diseases Group searched their Specialised Register (last searched March 2003) for publications

describing randomised controlled trials of the use of intravenous immunoglobulin for the treatment of Kawasaki disease in children. See the 'Search strategies for the identification of studies' section within the editorial information about the Cochrane PVD Group in *The Cochrane Library,*

http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/PVD/frame.html for more details on the Specialised Register.

2) The following electronic databases were searched using Ovid software;
Electronic Databases
MEDLINE - 1966 to April 2003
EMBASE - 1980 to April 2003
CINAHL - 1982 to April 2003

For details of the search strategy used to search these databases see Appendix 1.

3) The Cochrane Central Register of Controlled Trials (CENTRAL), was searched. For details of the search strategy used see Appendix 2.

4) The following Trial Registers were searched:
National Health and Medical Research Council (NHMRC) Clinical Trials Register
Meta-Register

Attempts were made to contact authors of all open and/ or unpublished trials identified.

5) The citation lists of relevant publications, review articles, abstracts of scientific meetings and included studies were also searched for both published and unpublished works.

Data collection and analysis

Selection of trials

Study selection was undertaken by two reviewers (RMO and HB), after employing the search strategy outlined above. Both reviewers independently assessed whether the studies met the inclusion criteria; any discrepancies were to be resolved by a third reviewer (KR), but this proved unnecessary. Further information was sought from the authors where papers contained insufficient information to make a decision about eligibility.

Quality assessment

Assessment of methodological quality

The quality of all studies which were deemed eligible for the review was then assessed independently by at least two reviewers; discrepancies were to be resolved by discussion, but again this proved unnecessary. The quality of allocation concealment was graded as either adequate (A), unclear (B), or inadequate (C).

Assessment of methodological quality

Rate each item as follows:
Clearly yes- rate A
Not sure - rate B (seek details from authors)
Clearly no - rate C

Section (i): Internal Validity

Was the assigned treatment adequately concealed prior to allocation?
Were the outcomes of patients who withdrew or were excluded after allocation described and included in an "intention to treat" analysis?
Were the outcome assessors blind to assignment status?
Were the treatment and control groups comparable at entry?
Were the subjects blind to assignment status following allocation?
Were the treatment providers blind to assignment status?
Were the care programmes, other than the trial options, identical?
Were the withdrawals <10% of the study population?

Section (ii): External Validity

Were the inclusion and exclusion criteria for entry clearly defined?
Were the outcome measures used clearly defined?
Were the accuracy, precision, and observer variation of the outcome measures adequate?
Was the timing of the outcome measures appropriate?
Were the outcome measures clearly reported?

Data collection

For each included trial, information was collected regarding location of the study, methods of the study (as per quality assessment checklist), participants characteristics (age range, eligibility criteria), types of interventions and outcomes. Where possible, missing data were sought from the authors. Data extraction was performed independently by at least two reviewers. No discrepancies were experienced.

Analysis

Each dichotomous outcome was measured for effect in terms of relative risk, with 95% confidence intervals and combined for meta-analysis with RevMan software using the Peto-modified Mantel-Haenszel method. Where there were sufficient data, a summary statistic for each outcome was calculated using a random effects model. The results in the "Comparison and data table" section of this review are presented using a random effects model. The heterogeneity of the studies was analysed by inspecting the scatter in the data points and the overlap in the confidence intervals and more formally by checking the results of the chi-squared test.

A *priori*, sensitivity analysis using only trials with documented diagnostic criteria was conducted. The trials that did document this all used the same criteria.

Continuous outcomes between groups in the meta-analysis are shown as a weighted mean difference (WMD) and 95% confidence interval. A random approach has been used as heterogeneity was detected.

Some papers reported multiple trials. When this was the case, the separate trials were entered into the "Comparison and data table" by author, followed by date, followed by either A, B or C (where A is the earliest of the trials documented) i.e. Smith 1990A, Smith 1990B, Smith 1990C. Because it is only possible to analyse two comparisons in RevMan at one time, where there were three arms in the comparison being made (e.g. 100 mg/kg/day IVIG versus 200 mg/kg/day IVIG versus 400 mg/kg/day IVIG, this is indicated by a number following either the date or the indication of multiple studies in one paper (e.g. Smith 1990(1),

Smith 1990(2), Smith 1990(3) OR Smith 1990A(1), Smith 1990A(2), Smith 1990A(3)). When there were multiple treatment arms in a study with a common control the control numbers were divided equally between the arms. If the control group contained an uneven number of participants so that numbers could not be equally divided, then the analysis was done in both ways to detect possible differences in the results caused by an unequal division of the numerator and denominator.

The main analyses were based on 19 trials although not all trials assessed all of the outcomes. Subgroup analyses were performed on:
1) comparisons of dose
2) comparisons of type of IVIG

It is the intention of the reviewers that a new search for RCTs will be performed yearly and the review updated accordingly.

RESULTS

Description of studies

Fifty-nine abstracts identified in the search initially appeared possibly to fit the criteria for the review. After obtaining the full papers, thirty-eight of these were excluded, leaving twenty-one papers eligible for inclusion. However, on further investigation, and in some cases translation, it was clear that some trials were reported in multiple papers, while other papers reported multiple trials. For two papers we could not contact authors to clarify whether randomisation method was adequate. A total of sixteen different trials were finally included.

Trials excluded from the review

On obtaining the full papers, 36 papers were found not to report RCTs (Brogan 2002; Burns 1995; Dunning 2002; Engle 1989; Fasth 1990; Fournier 1985; Fukunishi 2000; Fukushige 1995; Furusho 1983; Harada 1991; Hsu 1993; Hwang 1989; Hwang 1996; Kondo 1983; Lux 1991; Marasini 1991; Mori 2000; Newburger 1989; Newburger 1996; Nigrovic 2002; Pallotto 1995; Plotkin 1988; Rowley 1992; Saalouke 1991; Sargraves 1993; Shimei 1996; Shinohara 1996; Siegel 1988; Silverman 1995; Suez 1995; Suzuki 1989; Terai 1997; Tse 2002; Wu 1993; Yangawa 1999; Yavez 1996), one study compared IVIG with prednisolone rather than placebo or no treatment (Nonaka 1995), and one study used quasi-randomisation only by way of alternation (Matsushima 1986). A further two papers (five comparisons) did not report method of randomisation and the authors failed to reply to our requests for clarification (Furusho 1991A; Furusho 1991B(1); Furusho 1991B(2); Furusho 1991B(3); Furusho 1991C). A post protocol decision was made to exclude trials where the method of randomisation was not explicit. These latter trials will be reassessed for inclusion if we receive clarification of the randomisation method used.

Trials included in the review

Trial design characteristics

Interventions

Comparisons
There were eleven comparisons of IVIG and placebo (Harada 1991A(2); Harada 1991A(3); Harada 1991B(2); Harada 1991B(3); Nagashima 1987; Newburger 1986; Ogino 1987A; Ogino 1987B; Ogino 1990; Onouchi 1995A(2); Onouchi 1995A(3)). Two of these used 100 mg/kg in a single dose (Harada 1991A(2); Harada 1991A(3)), two used 100 mg/kg/day over five days (Harada 1991B(2); Harada 1991B(3)), two used comparisons of 200 mg/kg/day for three days (Ogino 1987A; Onouchi 1995A(2)), three used 400 mg/kg/day for three days (Nagashima 1987; Ogino 1987B; Onouchi 1995A(3)), one used 400 mg/kg/day for five days (Newburger 1986), and one used 1 gm/kg stat (immediately) (Ogino 1990).

Treatment dose
There were thirteen dose comparisons (Barron 1990; Harada 1991C; Morikawa 1994(1); Newburger 1991; Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3); Onouchi 1995A(1); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3); Sato 1995; Sato 1999). One of these compared 50-100 mg/kg/day versus 200 mg/kg/day for five days (Nishihara 1988(1)), one compared 50-100 mg/kg/day versus 400 mg/kg/day for five days (Nishihara 1988(2)), three compared 100 mg/kg/day versus 400 mg/kg/day for five days (Harada 1991C; Nishihara 1988(2); Onouchi 1995B(2)) four compared 200 mg/kg/day versus 400 mg/kg/day for five days (Morikawa 1994(1); Morikawa 1994(3); Nishihara 1988(3); Onouchi 1995B(3)), one study compared 400 mg/kg/day for five days versus 1 gm/kg/stat (Barron 1990), one study compared 400 mg/kg for four days versus 2 mg/kg/stat (Newburger 1991), and two studies compared 400 mg/kg/day versus 2 gm/kg stat (Sato 1995; Sato 1999).

Type of IVIG
There were four comparisons of different types of IVIG (Harada 1991A(1); Harada 1991B(1); Morikawa 1994(2); Morikawa 1994(3)). Three of these were direct comparisons. One compared 100 mg/kg/day of pepsin-treated IVIG versus 100 mg/kg/day of intact-type IVIG over five days (Harada 1991B(1)), one compared 100 mg/kg of pepsin-treated IVIG versus 100 mg/kg of intact-type IVIG in a single dose (Harada 1991A(1)), one compared 200 mg/kg/day of polyethylene glycol-treated human IVIG versus 200 mg/kg/day of freeze-dried sulphonated human IVIG (Morikawa 1994(2)). However, the remaining comparison compared different types of IVIG and different doses; 200 mg/kg/day of freeze-dried sulphonated human immunoglobulin versus 400 mg/kg/day of polyethylene glycol-treated human IVIG (Morikawa 1994(3)).

In addition, the types of IVIG given in the other comparisons are as follows: three studies (three comparisons) used S-sulphonated intact-type IVIG (Ogino 1987A; Ogino 1987B; Ogino 1990), five studies (six comparisons) used intact-type IVIG (Harada 1991A(2); Harada 1991A(3); Harada 1991B(2); Harada 1991B(3); Harada 1991C; Newburger 1986; Newburger 1991); one study (one comparison) used purified human IVIG (Barron 1990), two studies used polyethylene-glycol-treated IVIG (Morikawa 1994(1); Nagashima 1987), one study (three comparisons) used alkylated human IVIG (Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3)), one study (three comparisons) used pH 4 stabilised acid human IVIG (Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3)), two studies (three comparisons) used either S-sulphonated human IVIG or polyethylene-glycol-treated IVIG but did not report the results for the patients separately (Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3)), and two studies (two comparisons) did not state the type of IVIG used (Sato 1995; Sato 1999).

Control
All studies using a no treatment group used aspirin.

Baseline characteristics of participants Age

Four studies (ten comparisons) only enrolled children under four years of age (Harada 1991A(1); Harada 1991A(2); Harada 1991A(3); Harada 1991B(1); Harada 1991B(2); Harada 1991B(3)Harada 1991C; Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3)), two studies (six comparisons) enrolled children under five years old (Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3)), one study (three comparisons) enrolled children under six years old (Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3)), and three studies (three comparisons) enrolled children to at least six years of age (no cut off given) (Ogino 1987A; Ogino 1987B; Ogino 1990). Four studies (four comparisons) gave mean ages Barron 1990; Nagashima 1987; Newburger 1986; Newburger 1991. All of these were between two and three years of age. In two studies it was unclear what age the children enrolled were (Sato 1995; Sato 1999).

Duration of symptoms at randomisation
No study enrolled children more than ten days from the onset of symptoms with the majority of children were randomised within seven days. Ten trials (twenty comparisons) required children to be within seven days from the onset of symptoms (Barron 1990; Harada 1991A(1); Harada 1991A(2); Harada 1991A(3); Harada 1991B(1); Harada 1991B(2); Harada 1991B(3); Harada 1991C; Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3); Ogino 1987A; Ogino 1987B; Ogino 1990; Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3)), three studies (five comparisons) enrolled children within nine days from onset of symptoms (Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3); Sato 1995; Sato 1999), and three trials (three comparisons) enrolled children within ten days from the onset of symptoms (Nagashima 1987; Newburger 1986; Newburger 1991).

Diagnostic criteria
Eight studies (fourteen comparisons) did not stipulate the criteria on which a diagnosis of Kawasaki disease was made (Harada 1991A(1); Harada 1991A(2); Harada 1991A(3); Harada 1991B(1); Harada 1991B(2); Harada 1991B(3); Harada 1991C; Nagashima 1987; Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3); Ogino 1987A; Ogino 1987B; Ogino 1990).

Criteria for a diagnosis of Kawasaki disease as set out by the Centers for Disease Control, New York (CDC 1980) and the Ministry of Health and Welfare, Tokyo (RCKD 1984) were used by eight trials (fourteen comparisons) (Barron 1990; Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3); Newburger 1986; Newburger 1991; Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3); Sato 1995; Sato 1999). These include a fever (>38.5 rectally) present for at least five days without other explanation and in the presence of four of the five following criteria to form a diagnosis of Kawasaki disease:

1) Bilateral congestion of the ocular conjunctivae, 2) Changes of the lips and oral cavity (at least one of the following: dryness, erythema (redness of the skin), fissuring of lips, strawberry tongue, diffuse erythema of oral and pharyngeal mucosa without discrete lesions), 3) Changes of the extremities (at least one of the following: erythema of palms and soles, indurative edema, periungual (surrounding the nail) desquamation (peeling of the skin) of fingers and toes), 4) Polymorphous exanthem (a rash of indefinite or variable appearance), 5) Non-suppurative cervical adenopathy (>1.5 cm).

Coronary artery abnormalities at randomisation
Five trials (nine comparisons) excluded children from the study who had coronary artery aneurysms at randomisation (Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3); Sato 1999). It is unclear whether Sato 1995 also excluded these children. However, the rest of the trial closely mirrors Sato 1999.

Harada's score Harada's score has been used to try to identify those children at highest risk of acquiring coronary artery abnormalities when suffering from Kawasaki disease, Children are scored on the following:
1) white blood count ≥ 12,000 cu mm;
2) platelet count < 350,000 cu mm;
3) C reactive protein ≥ 3+;
4) hematocrit <35%;
5) albumin < 3.5g/dl;
6) age 12 months;
7) male.
A score of four or more is felt to indicate that a child is at high risk of developing CAAs.

Two trials (two comparisons) applied this score prior to randomisation to ascertain which children should be randomised to receive one of two treatment regimens (Sato 1995; Sato 1999). Children who scored four or more within nine days from the onset of symptoms were randomised in both trials.

Studied outcomes
Death: one study reported an incidence of death (Newburger 1991).

Coronary artery dilation and coronary artery aneurysms (diagnosed by echocardiography, coronary angiography or autopsy): fifteen studies reported coronary artery abnormalities diagnosed by echocardiography. In the remaining study it was not stated how coronary artery abnormalities were detected (Sato 1995). One trial (Nagashima 1987) has been excluded from the meta-analysis examining coronary artery abnormalities as it reported total number of coronary artery abnormalities rather than coronary artery abnormalities per child. However, it has been included in the analysis of fever duration.

Myocardial function abnormalities (diagnosed by echocardiography, coronary angiography or autopsy): one study reported mitral insufficiency (Barron 1990).

Duration of fever: nine trials (fifteen comparisons) reported duration of fever as an outcome (Barron 1990, Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3); Nagashima 1987, Newburger 1986; Newburger 1991; Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3); Sato 1995; Sato 1999).

Adverse effects: nine trials (fifteen comparisons) reported adverse effects as an outcome (Barron 1990; Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3); Nagashima 1987; Newburger 1986; Newburger 1991; Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3); Sato 1995; Sato 1999).

Duration of hospital stay: two studies reported duration of hospital stay as an outcome (Sato 1995; Sato 1999).

Longterm cardiac sequelae: no study followed up beyond a year.

Support/sponsorship
Three studies documented source of funding (Barron 1990; Newburger 1986; Newburger 1991). Two of these (Newburger 1986; Newburger 1991), received funding from the National Institute of Health (U.S.) The remaining study (Barron 1990), was partially funded by Baxter Healthcare Corporation.

Risk of bias in included studies

Randomisation

Of sixteen studies that met the inclusion criteria, ten studies (twenty-two comparisons) used central randomisation (Harada 1991A(1); Harada 1991A(2); Harada 1991A(3); Harada 1991B(1); Harada 1991B(2); Harada 1991B(3); Harada 1991C; Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3); Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3); Ogino 1987A; Ogino 1987B; Ogino 1990; Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3)), four studies (four comparisons) used a random tables (Barron 1990; Nagashima 1987; Sato 1995; Sato 1999), and two studies (two comparisons) used sealed, opaque, sequentially numbered envelopes (Newburger 1986; Newburger 1991).

Concealment of allocation

Twelve studies (twenty-four comparisons) displayed adequate allocation concealment (Harada 1991A(1); Harada 1991A(2); Harada 1991A(3); Harada 1991B(1); Harada 1991B(2); Harada 1991B(3); Harada 1991C; Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3); Newburger 1986; Newburger 1991; Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3); Ogino 1987A; Ogino 1987B; Ogino 1990; Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3)), while the allocation in the remaining four studies was unclear (Barron 1990; Nagashima 1987; Sato 1995; Sato 1999).

Blinding

One study (three comparison) used triple blinding (Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3)). Four studies (six comparisons) used single blinding (Barron 1990; Newburger 1986; Newburger 1991; Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3)). It was unclear whether any blinding was used in the eleven remaining included studies (nineteen comparisons) (Harada 1991A(1); Harada 1991A(2); Harada 1991A(3); Harada 1991B(1); Harada 1991B(2); Harada 1991B(3); Harada 1991C; Nagashima 1987; Ogino 1987A; Ogino 1987B; Ogino 1990; Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3); Sato 1995; Sato 1999).

Power calculations

Two studies documented power calculations. One study (three comparisons) (Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3)) calculated that to have 80% power with a 2.5% level of significance to show that a lower dose of IVIG was at least equivalent to the control drug, 300 children had to be randomised to each group. The trialists successfully enrolled three hundred and thirteen children but suffered fourteen dropouts in some analyses. The second study (one comparison) (Newburger 1991) calculated that to have 80% power with a 1% level of significance to detect a "meaningful" difference (meaningful was not defined), three hundred children needed to be enrolled. Five hundred and forty-nine children were enrolled. At the minimum, five hundred and twenty children were analysed.

Number of centres

One study (three comparisons) had ninety-five participating centres (Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3)), one study (three comparisons) had thirty-nine participating centres (Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3)), three studies (three comparisons) (Ogino 1987A; Ogino 1987B; Ogino 1990) had thirty-two participating centres, one study (three comparisons) (Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3)) had twenty-eight participating centres, one study (six comparisons) had sixteen participating centres (Nagashima 1987), one study (three comparisons) had thirteen participating centres (Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3)), two studies (two comparisons) (Barron 1990; Newburger 1991), had seven participating centres, one study (one comparison) (Newburger 1986), had six participating centres, two studies (two comparisons) were single centre (Sato 1995; Sato 1999), and in three studies (seven comparisons) (Harada 1991A(1); Harada 1991A(2); Harada 1991A(3); Harada 1991B(1); Harada 1991B(2); Harada 1991B(3); Harada 1991C), the number of participating centres was not stated, although it was stated that they were "multicentre".

Thirteen studies (twenty-five comparisons) were based in Japan (Harada 1991A(1); Harada 1991A(2); Harada 1991A(3); Harada 1991B(1); Harada 1991B(2); Harada 1991B(3); Harada 1991C; Morikawa 1994(1); Morikawa 1994(2); Morikawa 1994(3); Nagashima 1987; Nishihara 1988(1); Nishihara 1988(2); Nishihara 1988(3); Ogino 1987A; Ogino 1987B; Ogino 1990; Onouchi 1995A(1); Onouchi 1995A(2); Onouchi 1995A(3); Onouchi 1995B(1); Onouchi 1995B(2); Onouchi 1995B(3) ; Sato 1995; Sato 1999), two studies (two comparisons) were based in the USA (Newburger 1986; Newburger 1991), and one study (one comparison) was based in the USA and Canada (Barron 1990).

Intention to treat analysis

No study reported performing an intention to treat analysis.

Effects of interventions

All coronary abnormalities

IVIG versus Placebo

The meta-analysis of seven studies (ten comparisons) (Harada 1991A(2); Harada 1991A(3); Harada 1991B(2); Harada 1991B(3); Newburger 1986; Ogino 1987B; Ogino 1990; Onouchi 1995A(2); Onouchi 1995A(3); Ogino 1987A), showed a significant difference in the number of new coronary artery abnormalities in favour of the IVIG group at thirty days relative risk (RR) (95% confidence intervals (CI)) = 0.74 (0.61 to 0.90). There was no significant difference between IVIG and placebo groups at sixty days RR (95% CI) = 0.75 (0.51 to 1.10) and at one-hundred and eight days plus RR (95% CI) =0.58 (0.28 to 1.17).

Significant heterogeneity was detected in these comparisons. When a priori, sensitivity analysis was conducted using only those studies documenting recognised diagnostic criteria (all trials that did document this documented the same criteria) (Newburger 1986; Onouchi 1995A(2); Onouchi 1995A(3)), no significant heterogeneity remained but the results remained similar to the above. At both thirty days and sixty days there was a

significant decrease of new coronary artery abnormalities in favour of the IVIG group; thirty days RR (95% CI) = 0.36 (0.18 to 0.71), sixty days RR (95% CI) = 0.38 (0.16 to 0.89). None of the studies in this sensitivity analysis followed up beyond 60 days.

Heterogeneity may also have been introduced by the combining of different doses of IVIG. Thus, subgroup analyses were performed considering total dose received:
100 mg/kg: There was no statistically significant difference between treatment and placebo at thirty days RR (95% CI) = 1.04 (0.83 to 1.31), sixty days RR (95% CI) = 1.15 (0.59 to 2.22) or one hundred and eighty plus days RR (95% CI) = 1.31 (0.35 to 4.92) (Harada 1991A(2); Harada 1991A(3)).
500 mg/kg: There was a statistically significant effect in favour of treatment at thirty days RR (95% CI) = 0.72 (0.63 to 0.84) and sixty days RR (95% CI) = 0.56 (0.32 to 1.01). There was a trend towards a reduction in new coronary artery abnormalities (p=0.07) at one hundred and eighty plus days RR (95% CI) = 0.44 (0.18 to 1.07) (Harada 1991B(2); Harada 1991B(3)).
600 mg/kg: There was no statistically significant difference between treatment and control groups at either thirty days RR (95% CI) = 0.90 (0.67 to 120) or sixty days RR (95% CI) = 1.38 (0.59 to 3.18) (Ogino 1987A; Onouchi 1995A(2)).
1000 mg/kg: There was no statistically significant difference between treatment and control groups at either thirty days RR (95% CI) = 0.81 (0.43 to 1.50), sixty days RR (95% CI) = 1.50 (0.14 to 15.91) or one hundred and eighty plus days RR (95% CI) = 0.18 (0.01 to 3.64) (Ogino 1990).
1200 mg/kg: There was a statistically significant difference between treatment and control groups, in favour of treatment at thirty days RR (95% CI) = 0.51 (0.29 to 0.92). There was no significant difference between the two groups at sixty days RR (95% CI) = 0.65 (0.25 to 1.71) (Ogino 1987B; Onouchi 1995A(3)).
1600 mg/kg: There was a statistically significant difference between treatment and control groups, in favour of treatment, at both thirty days RR (95% CI) = 0.35 (0.15 to 0.83) and sixty days RR (95% CI) = 0.21 (0.06 to 0.72) (Newburger 1986).

IVIG versus Placebo (excluding children with coronary artery abnormalities)
A subgroup analysis was performed on those trials excluding children with coronary abnormalities on enrolment or data from trials that reported these children separately (Newburger 1986; Ogino 1987A; Ogino 1987B; Ogino 1990; Onouchi 1995A(2); Onouchi 1995A(3)). There was a statistically significant reduction in the children receiving IVIG RR (95% CI) = 0.67 (0.46 to 1.00) at thirty days. There was a trend towards a reduction in coronary artery abnormalities at sixty days (p=0.06) RR (95% CI) = 0.57 (0.29 to 1.12), but no statistically significant difference at one-hundred and eighty plus days RR (95% CI) = 0.18 (0.01 to 3.64).

Significant heterogeneity was detected in these comparisons. Again, a priori, sensitivity analysis was conducted using only those studies documenting recognised diagnostic criteria (all trials that did document this documented the same criteria) (Newburger 1986; Onouchi 1995A(2); Onouchi 1995A(3)). No significant heterogeneity remained and again the results remained similar to the above in all trials. At thirty days, there was a significant decrease of new coronary artery abnormalities in favour of the IVIG group RR (95% CI) = 0.63 (0.43 to 0.93). At sixty days there was no significant difference between the IVIG and placebo groups RR (95% CI) = 0.60 (0.14 to 1.94). None of the studies in this sensitivity analysis followed up beyond 60 days.

IVIG versus Placebo (only children with coronary artery abnormalities at diagnosis)
A subgroup analysis, of the effect of treatment versus placebo on coronary artery abnormalities that were present at diagnosis, showed no statistically significant difference between the two groups at either thirty days RR (95% CI) = 0.75 (0.43 to 1.28), sixty days RR (95% CI) = 1.16 (0.68 to 1.97) or one hundred and eighty plus days RR (95% CI) = 0.84 (0.12 to 5.71) (Newburger 1986; Ogino 1987A; Ogino 1987B; Ogino 1990).

When further subgroups were performed on the total dose received, there was no statistically significant difference between treatment and control groups in any of the available data; 600 mg/kg total dose at up to thirty days RR (95% CI) = 0.54 (0.21 to 1.40) (Ogino 1987A), 600 mg/kg between thirty-one and sixty days RR (95% CI) = 0.84 (0.18 to 3.92) (Ogino 1987A), 1000 mg/kg up to thirty days RR (95% CI) = 0.75 (0.37 to 1.53) (Ogino 1990), 1000 mg/kg between thirty-one and sixty days RR (95% CI) = 0.75 (0.05 to 11.58) (Ogino 1990), 1000 mg/kg at one hundred and eighty days plus RR (95% CI) = 0.84 (0.12 to 5.71) (Ogino 1990), 1200 mg/kg up to thirty days RR (95% CI) = 2.43 (0.51 to 11.52) (Ogino 1987B), 1200 mg/kg between thirty and sixty days RR (95% CI) = 0.28 (0.01 to 6.74) (Ogino 1987B), 1600 mg/kg up to thirty days RR (95% CI) = 0.33 (0.04 to 3.14) (Newburger 1986), and 1600 mg/kg between thirty and sixty days RR (95% CI) = 0.33 (0.04 to 3.14) (Newburger 1986).

Duration of fever

Two studies (three comparisons) (Nagashima 1987; Onouchi 1995A(2); Onouchi 1995A(3)), reported duration of fever (in days) after IVIG administration as a mean and standard deviation. This was a statistically significant difference in the duration of fever between the IVIG and placebo groups in favour of IVIG weighted mean difference (WMD) (95% CI) = 0.66 (-4.99 to 6.31) days.

Dose comparisons

Only comparisons that had two or more studies are displayed as Forest Plots in the meta-analysis.

100 mg/kg/day for five days versus 200 mg/kg/day for five days
There were two comparisons of 100 mg/kg/day for five days versus 200 mg/kg/day for five days (Nishihara 1988(1); Onouchi 1995B(1)). There was a statistically significant reduction of coronary artery abnormalities in favour of 200 mg/kg/day at thirty days RR (95% CI) = 1.76 (1.07 to 2.89).

100 mg/kg/day for five days versus 400 mg/kg/day for five days
There were three comparisons of 100 mg/kg/day for five days versus 400 mg/kg/day for five days (Harada 1991C; Nishihara 1988(2); Onouchi 1995B(2)). There was a statistically significant reduction of coronary artery abnormalities in favour of 400 mg/kg/day at both thirty days RR (95% CI) = 2.79 (1.59 to 4.91) and at sixty days RR (95% CI) = 3.14 (1.38 to 7.15).

200 mg/kg/day for three days versus 400 mg/kg/day for three days
There was one comparison of 200 mg/kg/day for three days versus 400 mg/kg/day for three days (Onouchi 1995A(1)). There was no statistically significant difference in the number of coronary artery abnormalities at either thirty days RR (95% CI) = 1.27 (0.44 to 3.61) or sixty days RR (95% CI) = 1.16 (0.28 to 4.86). There was also

no statistically significant difference in the duration of fever after administration of treatment WMD (95% CI) = -0.9 (-2.50 to 0.7).

200 mg/kg/day for five days versus 400 mg/kg/day for five days

There were five comparisons of 200 mg/kg/day for five days versus 400 mg/kg/day for five days (Morikawa 1994(1); Morikawa 1994(3); Nishihara 1988(3); Onouchi 1995A(1); Onouchi 1995B(3)). The meta-analysis showed a statistically significant difference in favour of the 400 mg/kg for five days group. RR (95% CI) = 2.44 (1.49 to 4.00).

Fractionation comparisons

400 mg/kg/day for five days versus 2 gm/kg single dose

There were two comparisons of 400 mg/kg/day for five days versus 2 gm/kg in a single dose (Sato 1995; Sato 1999). There was a statistically significant reduction in coronary artery aneurysms in favour of the 2 gm/kg single dose at thirty days RR (95% CI) = 4.47 (1.55 to 12.86).

There was also a statistically significant reduction in duration of fever after administration of IVIG in favour of the 2 gm/kg single dose WMD (95% CI) = 2.0 (0.77 to 3.23) and duration of hospital stay WMD (95% CI) = 2.80 days (0.64 to 4.96).

Dose and fractionation comparisons

400 mg/kg/day for five days versus 1 gm/kg single dose

There was one comparison of 400 mg/kg/day x five days versus 1 gm/kg in a single dose (Barron 1990). There was no statistically significant difference between the groups at seven weeks RR (95% CI) = 2.94 (0.50 to 17.14). The study also found no statistically difference in the number of adverse events RR (95% CI) = 0.86 (0.19 to 3.93). However the study did find a statistically significant decrease in temperature within the first two days of receiving IVIG in favour of the 1 gm/kg single dose.

The study reported the incidence of patients with mitral insufficiency. All six patients reported had mitral insufficiency on enrolment (three in each group). There was no significant difference in duration.

The duration of hospitalisation was also found to be significantly less in the 1 gm/kg single dose group than in the 400 mg/kg/day group, but this at least in part, was due to children in the 400 mg/kg/day group being required to be in hospital for at least five days.

400 mg/kg/day for four days versus 2 gm/kg single dose

There was one comparison of 400 mg/kg/day for four days versus 2 gm/kg in a single dose (Newburger 1991). There was a statistically significant reduction in the number of coronary artery abnormalities in favour of the 2 gm/kg single dose at both two weeks RR (95% CI) = 2.31 (1.28 to 4.17) and at seven weeks RR (95% CI) = 1.91 (1.01 to 3.61).

When children with coronary artery abnormalities were excluded from the analysis there was a statistically significant reduction of coronary artery abnormalities at two weeks RR (95% CI) = 2.43 (0.92 to 6.43), but no statistically significant difference at seven weeks RR (95% CI) = 1.69 (0.60 to 4.71).

There was no statistically significant difference in the number of adverse events between the two groups WMD (95% CI) = 0.65 (0.23 to 1.86) but there was a significant reduction in the number of hours of fever in favour of the 2 gm/kg single dose WMD (95% CI) = 0.41(0.05 to 0.77).

Death

One death was reported in the 400 mg/kg group, of a child in the sub-acute phase who had suffered from a giant aneurysm.

Comparisons of IVIG preparation

100 mg/kg/day of intact IVIG versus 100 mg/kg/day of pepsin-treated IVIG

There were two comparisons of intact versus pepsin-treated IVIG (Harada 1991A(1); Harada 1991B(1)). There was a near statistically significant difference (P=0.06) in the number of new coronary artery aneurysms in the two groups at thirty days RR (95% CI) = 0.84 (0.71 to 1.01). There was no statistically significant difference at sixty days RR (95% CI) = 0.84 (0.49 to 1.45).

200 mg/kg/day of freeze-dried, sulfonated IVIG versus 200 mg/kg/day of polyethylene glycol treated IVIG

There was one comparison of 200 mg/kg/day of freeze-dried, sulfonated IVIG versus 200 mg/kg/day of polyethylene glycol treated IVIG (Morikawa 1994(2). There was no statistically significant difference between the two groups at thirty days RR (95% CI) = 0.81 (0.43 to 1.53). There was also no statistical difference in the reduction of temperature at twenty-four hours RR (95% CI) = 0.84 (0.52 to 1.35).

DISCUSSION

The aim of this review was to assess the effectiveness of intravenous immunoglobulin in treating Kawasaki disease in children. The results of the meta-analysis showed a statistically significant decrease in new CAAs at thirty days in favour of IVIG plus salicylate over salicylate alone, and also in favour of a single high dose regime over four or five day low dose regime. There was also a significant decrease in duration of fever and duration of hospitalisation, with no statistically significant increase in adverse events. The results did not differ when children with coronary artery abnormalities at presentation were excluded from the analysis.

The included trials comparing IVIG and salicylate with salicylate alone compared markedly different doses and dose regimes. This is likely to have accounted for some of the observed heterogeneity between studies. Sensitivity analysis of the six studies including documentation of the diagnostic criteria for Kawasaki Disease suggested this may also have accounted for some of the heterogeneity.

Two studies (Sato 1995; Sato 1999), used a "Harada Score" to identify those at very low risk of acquiring a CAA when suffering from Kawasaki disease, who did not receive IVIG therapy. Both of these two studies reported an untreated group of forty-six children and fifty-eight children respectively, with low Harada scores, in whom none had any coronary artery abnormality on follow up. A much larger cohort study of untreated children with low scores would be required in order to confirm the safety of this approach.

Atypical or incomplete Kawasaki Disease has been described in children not fulfilling the diagnostic criteria but still having coronary artery changes (Rowley 1987; Schuh 1988; Levy 1990). None of the included studies provides any direct evidence of the benefit of IVIG in such circumstances.

No studies enrolled patients who were more than ten days beyond the onset of symptoms.

IVIG does not appear to be associated with an increase in adverse events. Few studies explicitly stated that they were reporting deaths. Only one death was reported in all the included studies.

AUTHORS' CONCLUSIONS

Implications for practice

Children fulfilling the diagnostic criteria for Kawasaki disease should be treated with high dose intravenous immunoglobulin (2 gm/kg single dose) within 10 days of onset of symptoms.

Implications for research

Research is needed to determine the benefit from immunoglobulin therapy in children with atypical and late presentation.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barron 1990

Study characteristics	
Methods	Unit of randomisation: child Method of randomisation: randomised schedule in blocks of 4 and assigned in sequential order Timing of randomisation: at diagnosis Blinding: yes (single - outcome assessors) Power calculation: nil Number of centres: 7 51 patients randomised 7 exclusions 44 patients analysed Source of funding: partly funded by Baxter Healthcare Corporation
Participants	Children with fever for at least 3 consecutive days and meeting the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see Description of Studies in the main body of the review). Chldren who were not within the first 7 days of onset of symptoms were excluded from the study Age: 30.1 +/- 19.1 in the 400 mg/kg/day group, 38.2 +/- 22.2 in the 1gm/kg group Location: US and Canada Timing and duration: 1987-1988
Interventions	400mg/kg/day of purified human IVIG + 80 to 100 mg/kg/day oral aspirin until 25 hours after resolution of fever, than 3 to 5 mg/kg for a minimum of 2 months VS 1 gm/kg of purified human IVIG + 80 to100 mg/kg/day oral aspirin until 25 hours after resolution of fever, than 3 to 5 mg/kg for a minimum of 2 months Duration: 4 days (400mg/kg/day), single dose (1 gm/kg)
Outcomes	Coronary artery aneurysms Adverse effects Duration of fever
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Barron 1990 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Harada 1991A(1)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: centralised randomisation Timing of randomisation: at diagnosis Blinding: unclear Power calculation: nil Number of centres: not stated. However the paper states "multicentre" 214 patients randomised in all 3 comparisons 1 exclusion 213 patients analysed Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Diagnostic criteria not stated Age: under 4 years Location: Japan Timing and duration: 1983-1985
Interventions	100 mg/kg/day pepsin-treated IVIG + 50 mg/kg/day oral aspirin VS 100 mg/kg/day intact-type IVIG + 50 mg/kg/day oral aspirin Duration: Single dose
Outcomes	Coronary artery abnormalities
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Harada 1991A(2)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: centralised randomisation Timing of randomisation: at diagnosis Blinding: unclear Power calculation: nil Number of centres: not stated. However the paper states "multicentre"

Harada 1991A(2) *(Continued)*

	214 patients randomised in all 3 comparisons 1 exclusion 213 patients analysed Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Diagnostic criteria not stated Age: under 4 years Location: Japan Timing and duration: 1983-1985
Interventions	100 mg/kg/day pepsin-treated IVIG + 50 mg/kg/day oral aspirin Control: 50 mg/kg/day oral aspirin Duration: Single dose (IVIG), aspirin duration not stated
Outcomes	Coronary artery abnormalities
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Harada 1991A(3)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: centralised randomisation Timing of randomisation: at diagnosis Blinding: unclear Power calculation: nil Number of centres: not stated. However the paper states "multicentre" 214 patients randomised in all 3 comparisons 1 exclusion 213 patients analysed Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Diagnostic criteria not stated Age: under 4 years Location: Japan Timing and duration: 1983-1985
Interventions	100 mg/kg/day intact-type IVIG + 50 mg/kg/day oral aspirin Control: 50 mg/kg/day oral aspirin Duration: Single dose (IVIG), aspirin duration not stated

Harada 1991A(3) *(Continued)*

Outcomes	Coronay artery abnormalities
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Harada 1991B(1)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: centralised randomisation Timing of randomisation: at diagnosis Blinding: unclear Power calculation: nil Number of centres: not stated. However the paper states "multicentre" 295 patients randomised in all 3 comparisons 6 exclusions at 30 days, 17 at 60 days and 18 at 1 year 289 patients analysed at 30 days, 278 at 60 days and 277 at one year Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Diagnostic criteria not stated Age: under 4 years Location: Japan Timing and duration: 1985-1986
Interventions	100 mg/kg/day pepsin-treated IVIG + 50 mg/kg/day oral aspirin VS 100 mg/kg/day intact-type IVIG + 50 mg/kg/day oral aspirin Duration: 5 days
Outcomes	Coronary artery abnormalities
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Harada 1991B(2)

Study characteristics	
Methods	Unit of randomisation: child Method of randomisation: centralised randomisation Timing of randomisation: at diagnosis Blinding: unclear Power calculation: nil Number of centres: not stated. However the paper states "multicentre" 295 patients randomised in all 3 comparisons 6 exclusions at 30 days, 17 at 60 days and 18 at 1 year 289 patients analysed at 30 days, 278 at 60 days and 277 at a year Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Diagnostic criteria not stated Age: under 4 years Location: Japan Timing and duration: 1985-1986
Interventions	100 mg/kg/day pepsin-treated IVIG + 50 mg/kg/day oral aspirin Control: 50 mg/kg/day oral aspirin Duration: 5 days (IVIG), aspirin duration not stated
Outcomes	Coronay artery abnormalities
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Harada 1991B(3)

Study characteristics	
Methods	Unit of randomisation: child Method of randomisation: centralised randomisation Timing of randomisation: at diagnosis Blinding: unclear Power calculation: nil Number of centres: not stated. However the paper states "multicentre" 295 patients randomised in all 3 comparisons 6 exclusions at 30 days, 17 at 60 days and 18 at 1 year 289 patients analysed at 30 days, 278 at 60 days and 277 at a year Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Diagnostic criteria not stated

Harada 1991B(3) *(Continued)*

	Age: under 4 years Location: Japan Timing and duration: 1985-1986
Interventions	100 mg/kg/day intact-type IVIG + 50 mg/kg/day oral aspirin Control: 50 mg/kg/day oral aspirin Duration: 5 days (IVIG), aspirin duration not stated
Outcomes	Coronary artery abnormalities
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Harada 1991C

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: centralised randomisation Timing of randomisation: at diagnosis Blinding: unclear Power calculation: nil Number of centres: not stated. However the paper states "multicentre" 242 patients randomised 8 exclusions 234 patients analysed Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Diagnostic criteria not stated Age: under 4 years Location: Japan Timing and duration: 1987-1988
Interventions	100 mg/kg/day intact-type IVIG + 50 mg/kg/day oral aspirin VS 400 mg/kg/day intact-type IVIG + 50 mg/kg/day oral aspirin Duration: 5 days
Outcomes	Coronary artery abnormalities
Notes	

Risk of bias

Harada 1991C *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Morikawa 1994(1)

Study characteristics	
Methods	Unit of randomisation: child Method of randomisation: centralised Timing of randomisation: time of diagnosis Blinding: yes (triple) Power calculation: yes (80% with 150 in each group) Number of centres: 95 313 patients randomised 2 exclusions from the adverse effects analysis, 11 from the CAA analysis and 11 from the duration of fever analysis 311 patients analysed for the adverse effects outcome, 299 patients analysed for the CAA outcome and 299 patients were analysed for the fever duration outcome Source of funding: not stated
Participants	Children within 9 days from the onset of symptoms and meeting the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review) Age: less than 6 years old Location: Japan Timing and duration: 1991-1993
Interventions	200 mg/kg/day of polyethyleneglycol-treated human immunoglobulin VS 400 mg/kg/day of IV polyethyleneglycol-treated human immunoglobulin Duration: 5 days
Outcomes	Coronary artery abnormalities Adverse effects Duration of fever
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Morikawa 1994(2)

Study characteristics	
Methods	Unit of randomisation: child

Morikawa 1994(2) *(Continued)*

	Method of randomisation: centralised Timing of randomisation: time of diagnosis Blinding: yes (triple) Power calculation: yes (80% with 150 in each group) Number of centres: 95 311 patients randomised 1 exclusion from the adverse effects analysis, 11 from the CAA analysis and 10 from the duration of fever analysis 310 patients analysed for the adverse effects outcome, 299 patients analysed for the CAA outcome and 300 patients were analysed for the fever duration outcome Source of funding: not stated
Participants	Children within 9 days from the onset of symptoms and meeting the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review) Age: less than 6 years old Location: Japan Timing and duration: 1991-1993
Interventions	200 mg/kg/day of polyethyleneglycol-treated human immunoglobulin VS 200 mg/kg per day of freeze-dried, sulfonated human immunoglobulin Duration: 5 days
Outcomes	Coronary artery abnormalities Adverse effects Duration of fever
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Morikawa 1994(3)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: centralised Timing of randomisation: time of diagnosis Blinding: yes (triple) Power calculation: yes (80% with 150 in each group) Number of centres: 95 312 patients randomised 1 exclusion from the adverse effects analysis, 7 from the CAA analysis and 6 from the duration of fever analysis 311 patients analysed for the adverse effects outcome, 304 patients analysed for the CAA outcome and 305 patients analysed for the fever duration outcome Source of funding: not stated

Morikawa 1994(3) *(Continued)*

Participants	Children within 9 days from the onset of symptoms and meeting the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review) Age: less than 6 years old Location: Japan Timing and duration: 1991-1993
Interventions	400 mg/kg/day of IV polyethyleneglycol-treated human immunoglobulin VS 200 mg/kg per day of freeze-dried, sulfonated human immunoglobulin Duration: 5 days
Outcomes	Coronary artery abnormalities Adverse effects Duration of fever
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Nagashima 1987

Study characteristics

Methods	Unit of randomisation: coronary artery abnormalities Method of randomisation: Random number table Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 16 136 patients randomised 0 exclusions 136 patients analysed Source of funding:
Participants	Chidren within 10 days from onset of symptoms. Diagnostic criteria not stated. Children with coronary artery abnormalities on presentation were excluded Age: 25.6 +/- 20.1 months in the IVIG group; 22.7 +/- 14.4 months in the aspirin group Location: Japan Timing and duration: 1984-1986
Interventions	400 mg/kg/day of polyethyleneglycol-treated IVIG immunoglobulin + 30/mg/kg aspirin Placebo: yes (aspirin only)

Nagashima 1987 *(Continued)*

	Duration: 3 days (IVIG), aspirin duration not stated
Outcomes	Coronary artery abnormalities Adverse effects Length of febrile period
Notes	This study has been excluded from the meta-analysis as it reports total number of coronary artery abnormalities, rather than coronary artery abnormalities per child.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Newburger 1986

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: opaque, sealed, consecutively numbered envelopes Timing of randomisation: at diagnosis Blinding: yes (single - outcome assessors) Power calculation: nil Number of centres: 6 168 patients randomised 4 exclusions 153 patients analysed at 2 weeks, 158 at 7 weeks Source of funding: National Institute of Health
Participants	Children within 10 days from the onset of symptoms and meeting the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review) Age: 2.7 +/- 0.2 in the IVIG group, 2.3 +/- 0.2 in the aspirin only group Location: USA Timing and duration: 1984-1985
Interventions	400 mg/kg/day intact-type IVIG + 100mg/kg/day of oral aspirin for 14 days and 3 to 5 mg/kg/day there after Control: 100 mg/kg/day of oral aspirin for 14 days and 3 to 5 mg/kg/day there after Duration: 4 days (IVIG), aspirin duration not given
Outcomes	Coronary atery abnomalities Duration of fever Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Newburger 1986 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Newburger 1991

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: opaque, sealed, consecutively numbered envelopes Timing of randomisation: at diagnosis Blinding: yes (single, outcome assessors) Power calculation: yes (80% power with 350 patients enrolled) Number of centres: 7 549 patients randomised 26 exclusions at 2 weeks, 29 at 7 weeks 523 patients analysed at 2 weeks, 520 at 7 weeks Source of funding: National Institute of Health
Participants	Children within 10 days from the onset of symptoms and meeting the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review) Age: 2.9 +/- 0.1 in the 400 mg/kg/day group and 2.9 +/- 0.1 in the 2 gm/kg single infusion group Location: USA Timing and duration: 1986 to 1989
Interventions	400 mg/kg/day intact-type IVIG VS 2 gm/kg intact-type IVIG Duration: 4 days (400 mg/kg/day), single dose (2 gm/kg)
Outcomes	Coronary artery abnormalities Duration of fever Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Nishihara 1988(1)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: central randomisation Timing of randomisation: at diagnosis Blinding: yes (single - outcome assessors)

Nishihara 1988(1) *(Continued)*

	Power calculation: nil Number of centres: 13 128 patients randomised 18 exclusions 110 patients analysed Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. diagnostc criteria was not stated. Children were excluded if they had received IVIG prior to randomisation Age: Under 4 years Location: Japan Timing and duration: 1984-1988
Interventions	50 to100 mg/kg/day of either S-sulphonated human IVIG or polyethylene-glycol-treated IVIG + 30 mg/kg/day oral aspirin VS 200 mg/kg/day of either S-sulphonated human IVIG or polyethylene-glycol-treated IVIG + 30 mg/kg/day oral aspirin Duration: 5 days (IVIG), aspirin duration not stated
Outcomes	Coronary artery dilation
Notes	This trial used historical controls so this group are not included in the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Nishihara 1988(2)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: central randomisation Timing of randomisation: at diagnosis Blinding: yes (single - outcome assessors) Power calculation: nil Number of centres: 13 128 patients randomised 18 exclusions 110 patients analysed Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. diagnostc criteria were not stated. Children were excluded if they had received IVIG prior to randomisation Age: Under 4 years Location: Japan

Nishihara 1988(2) *(Continued)*

	Timing and duration: 1984-1988
Interventions	50 to 100 mg/kg/day of either S-sulphonated human IVIG or polyethylene-glycol-treated IVIG + 30 mg/kg/day oral aspirin VS 400 mg/kg/day of either S-sulphonated human IVIG or polyethylene-glycol-treated IVIG + 30 mg/kg/day oral aspirin Duration: 5 days (IVIG), aspirin duration not stated
Outcomes	Coronary artery dilation
Notes	This trial used historical controls so this group are not included in the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Nishihara 1988(3)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: central randomisation Timing of randomisation: at diagnosis Blinding: yes (single - outcome assessors) Power calculation: nil Number of centres: 13 128 patients randomised 18 exclusions 110 patients analysed Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. diagnostc criteria was not stated. Children were excluded if they had received IVIG prior to randomisation Age: Under 4 years Location: Japan Timing and duration: 1984-1988
Interventions	200 mg/kg/day of either S-sulphonated human IVIG or polyethylene-glycol-treated IVIG + 30 mg/kg/day oral aspirin VS 400 mg/kg/day of either S-sulphonated human IVIG or polyethylene-glycol-treated IVIG + 30 mg/kg/day oral aspirin Duration: 5 days (IVIG), aspirin duration not stated
Outcomes	Coronary artery dilation
Notes	This trial used historical controls so this group are not included in the review

Nishihara 1988(3) *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Ogino 1987A

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: centrally randomised Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 32 115 patients randomised 15 exclusions 96 patients analysed Source of funding: not stated
Participants	Children within 7 days of onset of illness. Diagnostic criteria were not defined. Children who had received any IVIG prior to randomisation were excluded Age: not stated. Until at least 72 months Location: Japan Timing and duration: 1984-1985
Interventions	200mg/kg/day of S-Sulphonated IVIG + 30/mg/kg/day of aspirin until serum CPR became negative and then 10/mg/kg/day Control: yes (aspirin only) Duration: 3 days (IVIG), aspirin duration not stated
Outcomes	Coronary artery aneurysms Coronary artery dilations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Ogino 1987B

Study characteristics

Ogino 1987B *(Continued)*

Methods	Unit of randomisation: child Method of randomisation: centrally randomised Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 32 142 patients randomised 25 exclusions 117 patients analysed Source of funding: not stated
Participants	Children within 7 days of onset of illness. Diagnostic criteria were not defined. Children who had received any IVIG prior to randomisation were excluded Age: not stated. Untl at least 72 months Location: Japan Timing and duration: 1985-1986
Interventions	400mg/kg/day of S-Sulphonated IVIG + 30/mg/kg/day of aspirin until serum CPR became negative and then 10/mg/kg/day Control: yes (aspirin only) Duration: 3 days (IVIG), aspirin duration not stated
Outcomes	Coronary artery aneurysms Coronary artery dilations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Ogino 1990

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: centrally randomised Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 32 84 patients randomised 0 exclusions 84 patients analysed Source of funding: not stated

Ogino 1990 *(Continued)*

Participants	Children within 7 days of onset of illness. Diagnostic criteria were not defined. Children who had received any IVIG prior to randomisation were excluded Age: not stated. Until at least 72 months Location: Japan Timing and duration: 1986-1988
Interventions	1000mg/kg/day of S-Sulphonated IVIG + 30/mg/kg/day of aspirin until serum CPR became negative and then 10/mg/kg/day Control: yes (aspirin only) Duration: single dose (IVIG), aspirin duration not stated
Outcomes	Coronary artery aneurysms Coronary artery dilations
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Onouchi 1995A(1)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: central radomisation Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 28 148 patients randomised to all 3 comparisons 22 exclusions from all 3 comparisons 126 patients analysed in all comparisons. Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Kawasaki disease diagnosed by the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review). Children who had received steroids, indomethacin or IVIG prior to randomisation were excluded from the study Age: under 5 years Location: Japan Timing and duration: 1986 to 1987
Interventions	200 mg/kg/day of reduced alkylated human IVIG + 50mg/kg/day of aspirin until the patient became afebrile and then 30/mg/kg/day VS

Onouchi 1995A(1) *(Continued)*

	400 mg/kg/day of reduced alkylated human IVIG + 50mg/kg/day of aspirin until the patient became afebrile and then 30/mg/kg/day Duration: 3 days (IVIG), duration of aspirin unclear
Outcomes	Coronary artery anormalities Duration of fever Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Onouchi 1995A(2)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: central radomisation Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 28 148 patients randomised to all 3 comparisons 22 exclusions from all 3 comparisons 126 patients analysed in all comparisons. Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Kawasaki disease diagnosed by the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review). Children who had received steroids, indomethacin or IVIG prior to randomisation were excluded from the study Age: under 5 years Location: Japan Timing and duration: 1986 to 1987
Interventions	200 mg/kg/day of reduced alkylated human IVIG + 50mg/kg/day of aspirin until the patient became afebrile and then 30/mg/kg/day Control: yes (aspirin alone) Duration: 3 days (IVIG), duration of aspirin unclear
Outcomes	Coronary artery anormalities Duration of fever Adverse effects
Notes	

Onouchi 1995A(2) *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Onouchi 1995A(3)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: central radomisation Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 28 148 patients randomised to all 3 comparisons 22 exclusions from all 3 comparisons 126 patients analysed in all comparisons. Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Kawasaki disease diagnosed by the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review). Children who had received steroids, indomethacin or IVIG prior to randomisation were excluded from the study Age: under 5 years Location: Japan Timing and duration: 1986 to 1987
Interventions	400 mg/kg/day of reduced alkylated human IVIG + 50mg/kg/day of aspirin until the patient became afebrile and then 30/mg/kg/day Control: yes (aspirin alone) Duration: 3 days (IVIG), duration of aspirin unclear
Outcomes	Coronary artery anormalities Duration of fever Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Onouchi 1995B(1)

Study characteristics	
Methods	Unit of randomisation: child Method of randomisation: central radomisation Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 39 169 patients randomised to all 3 comparisons 9 exclusions from all 3 comparisons 160 patients analysed for a coronary artery abnormalities in all 3 comparisons. Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Kawasaki disease diagnosed by the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review) Children who had received steroids, indomethacin or IVIG prior to randomisation were excluded from the study Age: under 5 years Location: Japan Timing and duration: 1990 to 1991
Interventions	100 mg/kg/day pH4 stabilised acid human immmunoglobulin + 30 mg/kg/day of oral aspirin VS 200 mg/kg/day pH4 stabilised acid human immmunoglobulin + 30 mg/kg/day of oral aspirin Duration: 5 days
Outcomes	Coronary artery anormalities Duration of fever Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Onouchi 1995B(2)

Study characteristics	
Methods	Unit of randomisation: child Method of randomisation: central radomisation Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 39 169 patients randomised to all 3 comparisons

Onouchi 1995B(2) *(Continued)*

	9 exclusions from all 3 comparisons 160 patients analysed in all comparisons for coronary artery otcomes. Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Kawasaki disease diagnosed by criteria stipulated by the JKDRC (see the description of studies in the body of the review). Children who had received steroids, indomethacin or IVIG prior to randomisation were excluded from the study Age: under 5 years Location: Japan Timing and duration: 1990 to 1991
Interventions	100 mg/kg/day pH4 stabilised acid human immmunoglobulin + 30 mg/kg/day of oral aspirin VS 400 mg/kg/day pH4 stabilised acid human immmunoglobulin + 30 mg/kg/day of oral aspirin Duration: 5 days
Outcomes	Coronary artery anormalities Duration of fever Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Onouchi 1995B(3)

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: central radomisation Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 39 169 patients randomised to all 3 comparisons 9 exclusions from all 3 comparisons 160 patients analysed in all comparisons for coronary atery outcomes. Source of funding: not stated
Participants	Children within 7 days of the onset of symptoms. Kawasaki disease diagnosed by the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see the description of studies in the body of the review). Children who had received steroids, indomethacin or IVIG prior to randomisation were excluded from the study Age: under 5 years Location: Japan

Onouchi 1995B(3) *(Continued)*

	Timing and duration: 1990 to 1991
Interventions	200 mg/kg/day pH4 stabilised acid human immmunoglobulin + 30 mg/kg/day of oral aspirin VS 400 mg/kg/day pH4 stabilised acid human immmunoglobulin + 30 mg/kg/day of oral aspirin Duration: 5 days
Outcomes	Coronary artery anormalities Duration of fever Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Sato 1995

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: random number table Timing of randomisation: at diagnosis Blinding: unclear Power calculation: nil Number of centres: not stated 108 patients randomised 0 exclusions 108 patients analysed Source of funding: not stated
Participants	Children diagnosed with Kawasaki disease (diagnostic criteria not given) and scoring at least four on the Harada scale within the first 9 days of illness (see Description of Studies in the main body of the review). Age: not stated Location: Japan Timing and duration: not stated
Interventions	400 mg/kg/day of IVIG (type not stated) + 30 mg/kg/day of oral aspirin during the febrile period and 5 mg/kg/day there after VS 2 gm/kg IVIG (type not stated) + 30 mg/kg/day of oral aspirin during the febrile period and 5 mg/kg/day there after Duration: 5 days - 400 mg/kg/day, 2 gm/kg - single dose
Outcomes	Coronary artery abnormalities Duration of fever Duration of hospital stay

Sato 1995 *(Continued)*

	Adverse effects
Notes	Controls in this study were not randomised so are not included in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sato 1999

Study characteristics

Methods	Unit of randomisation: child Method of randomisation: random number table Timing of randomisation: at diagnosis Blinding: not stated. Clearly the patients and the treatment providers were not blinded. It is not stated if outcome assessors had any blinding Power calculation: nil Number of centres: 1 145 patients randomised 0 exclusions 145 patients analysed Source of funding: not stated
Participants	Children with fever for at least 5 consecutive days and meeting the diagnostic criteria for Kawasaki disease as set by the CDC, New York (see Description of Studies in the main body of the review). Children also had to score at least four on the Harada scale within the first 9 days of illness (see Description of Studies in the ain body of the review). Children with coronary artery abnormalities at diagnosis were excluded from the study Age: not stated Location: Japan Timing and duration: 1991-1995
Interventions	400 mg/kg/day IVIG (type not stated) + 30 mg/kg/day of oral aspirin during the febrile period and 5 mg/kg/day there after VS 2gm/kg IVIG (type not stated) + 30 mg/kg/day of oral aspirin during the febrile period and 5 mg/kg/day there after Duration: 400 mg/kg - 5 days, 2gm/kg -single dose
Outcomes	Coronary artery abnormalities Fever duration Duration of hospital stay Adverse effects
Notes	

Risk of bias

Sato 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Brogan 2002	Not an RCT
Burns 1995	Not an RCT
Dunning 2002	Not an RCT
Engle 1989	Not an RCT
Fasth 1990	Not an RCT
Fournier 1985	Not an RCT
Fukunishi 2000	Not an RCT
Fukushige 1995	Not an RCT
Furusho 1983	Not an RCT.
Furusho 1991A	Every effort has been made to contact the authors of this study to confirm randomisation. We have had no reply. If we receive a reply in the future we will reassess the trials eligibility for inclusion
Furusho 1991B(1)	Every effort has been made to contact the authors of this study to confirm randomisation. We have had no reply. If we receive a reply in the future we will reassess the trial's eligibility for inclusion
Furusho 1991B(2)	Every effort has been made to contact the authors of this study to confirm randomisation. We have had no reply. If we receive a reply in the future we will reassess the trial's eligibility for inclusion
Furusho 1991B(3)	Every effort has been made to contact the authors of this study to confirm randomisation. We have had no reply. If we receive a reply in the future we will reassess the trial's eligibility for inclusion
Furusho 1991C	Every effort has been made to contact the authors of this study to confirm randomisation. We have had no reply. If we receive a reply in the future we will reassess the trial's eligibility for inclusion
Harada 1991	Not an RCT
Hsu 1993	Not an RCT
Hwang 1989	Not an RCT
Hwang 1996	Not an RCT
Kondo 1983	Not an RCT
Lux 1991	Not an RCT

Study	Reason for exclusion
Marasini 1991	Not an RCT
Matsushima 1986	Only quasi-randomisation was used (alternation)
Mori 2000	Not an RCT
Newburger 1989	Not an RCT
Newburger 1996	Not an RCT
Nigrovic 2002	Not an RCT
Nonaka 1995	Drug comparison was IV prednisilone versus IVIG reather IVIG versus placebo or no treatment
Pallotto 1995	Not an RCT
Plotkin 1988	Not an RCT
Rowley 1992	Not an RCT
Saalouke 1991	Not an RCT
Sargraves 1993	Not an RCT
Shimei 1996	Not an RCT
Shinohara 1996	Not an RCT
Siegel 1988	Not an RCT
Silverman 1995	Not an RCT
Suez 1995	Not an RCT
Suzuki 1989	Not an RCT
Terai 1997	Not an RCT
Tse 2002	Not an RCT
Wu 1993	Not an RCT
Yangawa 1999	Not an RCT
Yavez 1996	Not an RCT

DATA AND ANALYSES

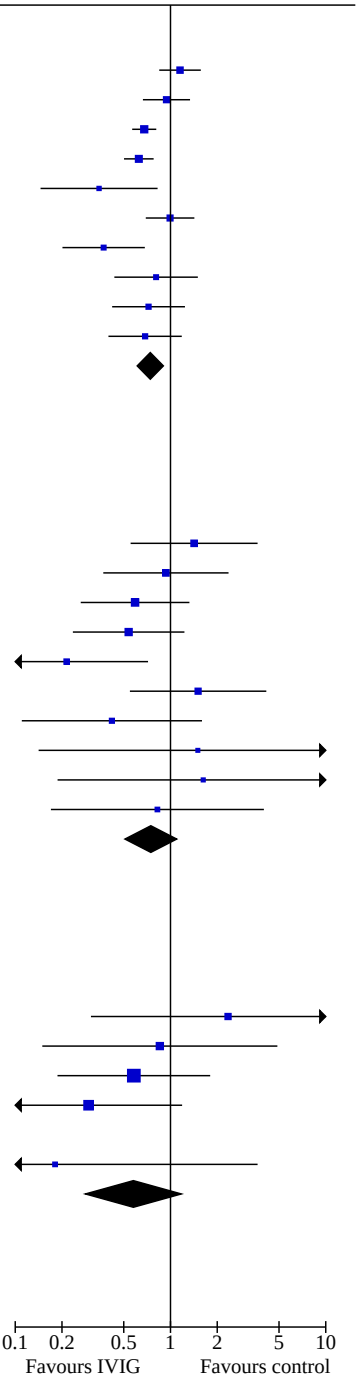
Comparison 1. IVIG vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 CAAs. All total doses. All Children.	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 0 to 30 days	10	970	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.61, 0.90]
1.1.2 31 to 60 days	10	1020	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.51, 1.10]
1.1.3 180+ days	6	721	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.28, 1.17]
1.2 CAAs. All total doses. Excluding children with CAAs at diagnosis	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 0-30 days	6	521	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 1.00]
1.2.2 31-60 days	7	527	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.24, 1.04]
1.3 CAAs. All total doses. Only children with CAAs at diagnosis.	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 0-30 days	4	445	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.43, 1.28]
1.3.2 31-60 days	4	446	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.20, 1.73]
1.4 CAAs. All total doses. All children. Studies using recognised diagnostic criteria.	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 0-30 days	3	238	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.41, 0.93]
1.4.2 31-60 days	3	263	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.16, 4.03]
1.5 CAAs. All total doses. No CAAs at enrollment. Studies using recognised diagnostic criteria.	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 0-30 days	3	233	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.43, 0.93]
1.5.2 31-60 days	3	237	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.14, 1.98]
1.6 CAAs. 100 mg/kg total dose. All children	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 0-30 days	2	213	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.83, 1.31]
1.6.2 31-60 days	2	213	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.59, 2.22]
1.6.3 180 days+	2	276	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.35, 4.92]
1.7 CAAs. 500 mg/kg total dose. All children	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.7.1 0-30 days	2	283	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.63, 0.84]
1.7.2 31-60 days	2	276	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.32, 1.01]
1.7.3 180+ days	2	277	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.18, 1.07]
1.8 CAAs. 600 mg/kg total dose. All children	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.8.1 0-30 days	2	140	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.67, 1.20]
1.8.2 31-60 days	2	141	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.59, 3.18]
1.9 CAAs. 1200 mg/kg total dose. All children	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.9.1 0-30 days	2	175	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.29, 0.92]
1.9.2 31-60 days	2	175	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.25, 1.71]
1.10 Duration of fever	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.10.1 Duration of fever after initiation of treatment	3	262	Mean Difference (IV, Random, 95% CI)	0.66 [-4.99, 6.31]

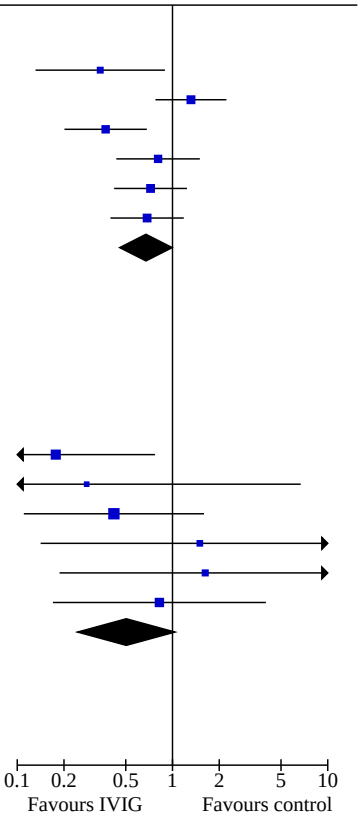
Analysis 1.1. Comparison 1: IVIG vs control, Outcome 1: CAAs. All total doses. All Children.

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 0 to 30 days						
Harada 1991A(2)	50	73	22	37	12.8%	1.15 [0.85 , 1.57]
Harada 1991A(3)	36	66	22	38	11.7%	0.94 [0.66 , 1.34]
Harada 1991B(2)	60	93	20	21	16.4%	0.68 [0.57 , 0.81]
Harada 1991B(3)	54	95	20	22	15.3%	0.63 [0.50 , 0.78]
Newburger 1986	6	75	18	78	4.0%	0.35 [0.15 , 0.83]
Ogino 1987A	28	49	23	40	11.5%	0.99 [0.69 , 1.42]
Ogino 1987B	11	63	24	51	6.6%	0.37 [0.20 , 0.68]
Ogino 1990	14	48	13	36	6.5%	0.81 [0.43 , 1.50]
Onouchi 1995A(2)	12	24	9	13	7.7%	0.72 [0.42 , 1.24]
Onouchi 1995A(3)	15	34	9	14	7.6%	0.69 [0.40 , 1.18]
Subtotal (95% CI)		**620**		**350**	**100.0%**	**0.74 [0.61 , 0.90]**
Total events:	286		180			
Heterogeneity: Tau² = 0.05; Chi² = 23.60, df = 9 (P = 0.005); I² = 62%						
Test for overall effect: Z = 3.03 (P = 0.002)						
1.1.2 31 to 60 days						
Harada 1991A(2)	14	73	5	37	13.4%	1.42 [0.55 , 3.64]
Harada 1991A(3)	10	66	6	37	13.7%	0.93 [0.37 , 2.36]
Harada 1991B(2)	11	93	9	45	17.2%	0.59 [0.26 , 1.32]
Harada 1991B(3)	10	93	9	45	16.5%	0.54 [0.24 , 1.23]
Newburger 1986	3	79	14	79	8.8%	0.21 [0.06 , 0.72]
Ogino 1987A	9	49	5	41	11.9%	1.51 [0.55 , 4.14]
Ogino 1987B	3	62	6	52	7.4%	0.42 [0.11 , 1.60]
Ogino 1990	2	48	1	36	2.5%	1.50 [0.14 , 15.91]
Onouchi 1995A(2)	3	24	1	13	3.0%	1.63 [0.19 , 14.09]
Onouchi 1995A(3)	4	34	2	14	5.4%	0.82 [0.17 , 3.99]
Subtotal (95% CI)		**621**		**399**	**100.0%**	**0.75 [0.51 , 1.10]**
Total events:	69		58			
Heterogeneity: Tau² = 0.05; Chi² = 10.49, df = 9 (P = 0.31); I² = 14%						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.1.3 180+ days						
Harada 1991A(2)	9	138	1	36	12.2%	2.35 [0.31 , 17.93]
Harada 1991A(3)	3	65	2	37	16.6%	0.85 [0.15 , 4.88]
Harada 1991B(2)	6	93	5	45	39.4%	0.58 [0.19 , 1.80]
Harada 1991B(3)	3	93	5	46	26.2%	0.30 [0.07 , 1.19]
Ogino 1987A	0	50	0	42		Not estimable
Ogino 1990	0	40	2	36	5.6%	0.18 [0.01 , 3.64]
Subtotal (95% CI)		**479**		**242**	**100.0%**	**0.58 [0.28 , 1.17]**
Total events:	21		15			
Heterogeneity: Tau² = 0.00; Chi² = 3.50, df = 4 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.52 (P = 0.13)						

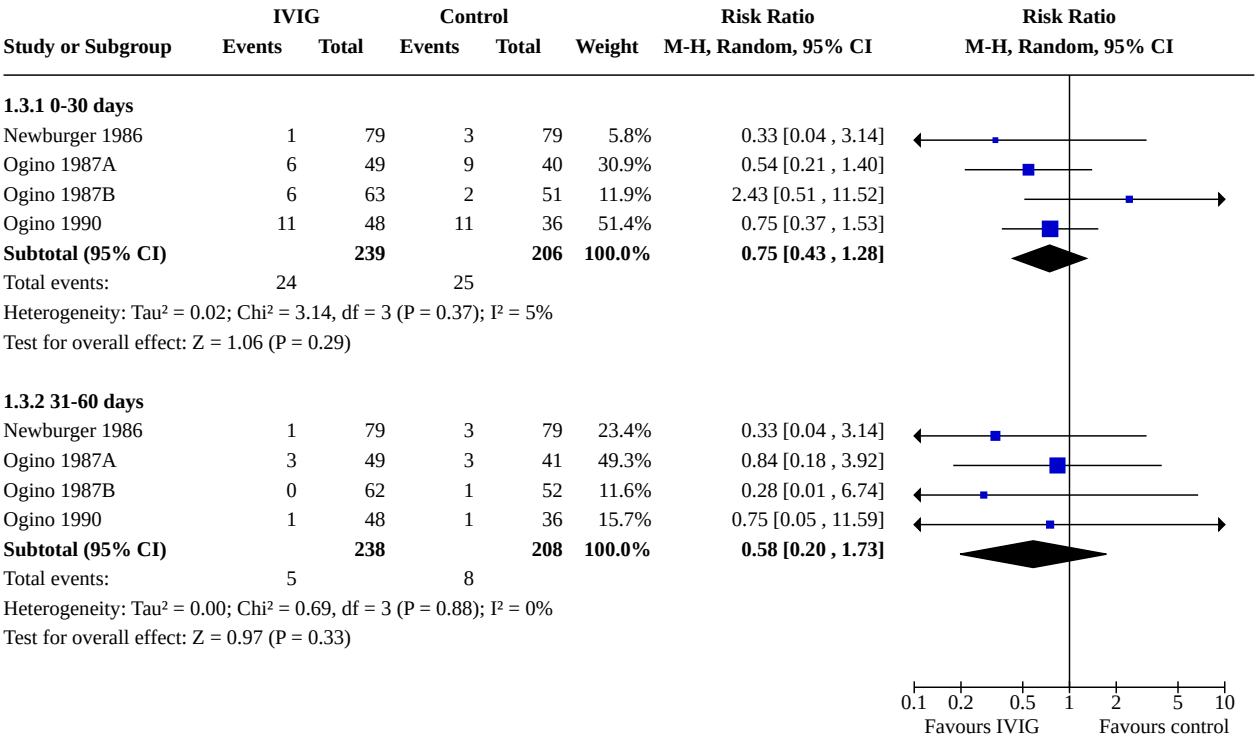


Analysis 1.2. Comparison 1: IVIG vs control, Outcome 2: CAAs. All total doses. Excluding children with CAAs at diagnosis

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 0-30 days						
Newburger 1986	5	73	15	75	10.5%	0.34 [0.13 , 0.89]
Ogino 1987A	22	49	14	41	18.9%	1.31 [0.78 , 2.23]
Ogino 1987B	11	63	24	51	16.9%	0.37 [0.20 , 0.68]
Ogino 1990	14	48	13	36	16.7%	0.81 [0.43 , 1.50]
Onouchi 1995A(2)	12	24	9	13	18.6%	0.72 [0.42 , 1.24]
Onouchi 1995A(3)	15	34	9	14	18.5%	0.69 [0.40 , 1.18]
Subtotal (95% CI)		**291**		**230**	**100.0%**	**0.67 [0.46 , 1.00]**
Total events:	79		84			
Heterogeneity: Tau² = 0.14; Chi² = 12.22, df = 5 (P = 0.03); I² = 59%						
Test for overall effect: Z = 1.98 (P = 0.05)						
1.2.2 31-60 days						
Harada 1991A(2)	0	1	0	1		Not estimable
Newburger 1986	2	77	11	75	24.1%	0.18 [0.04 , 0.77]
Ogino 1987A	0	49	1	41	5.2%	0.28 [0.01 , 6.69]
Ogino 1987B	3	62	6	52	29.3%	0.42 [0.11 , 1.60]
Ogino 1990	2	48	1	36	9.4%	1.50 [0.14 , 15.91]
Onouchi 1995A(2)	3	24	1	13	11.2%	1.63 [0.19 , 14.09]
Onouchi 1995A(3)	4	34	2	14	20.9%	0.82 [0.17 , 3.99]
Subtotal (95% CI)		**295**		**232**	**100.0%**	**0.50 [0.24 , 1.04]**
Total events:	14		22			
Heterogeneity: Tau² = 0.00; Chi² = 4.52, df = 5 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.86 (P = 0.06)						

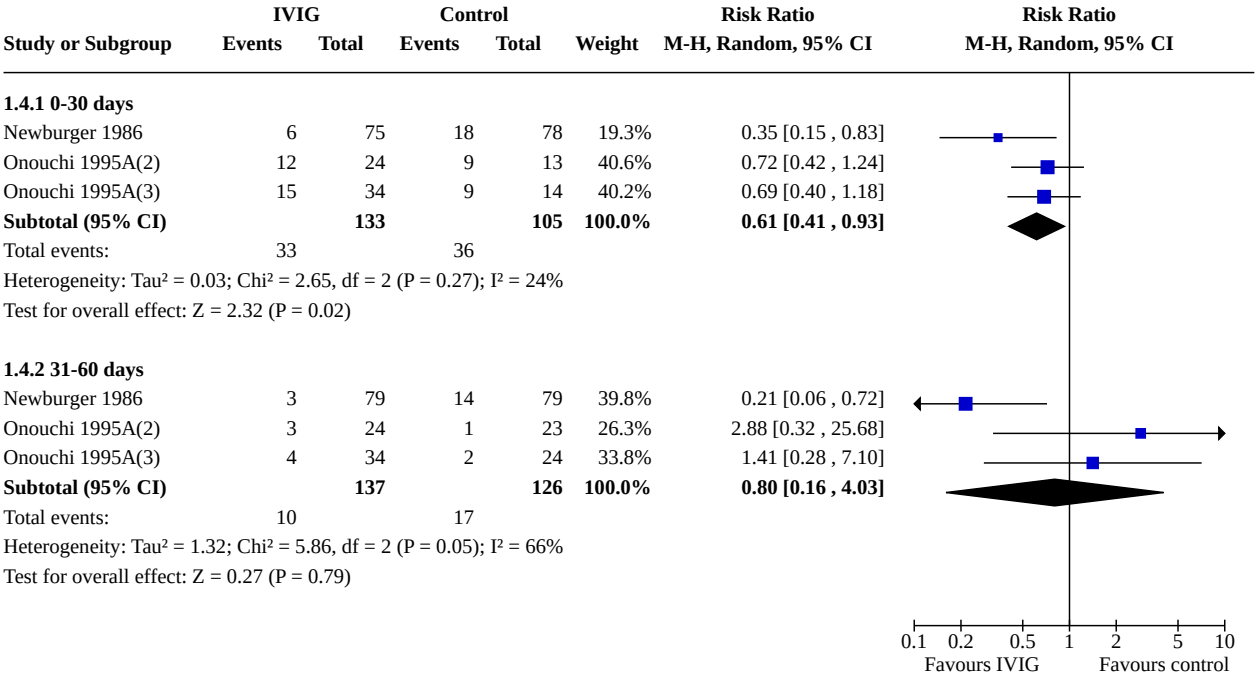


Analysis 1.3. Comparison 1: IVIG vs control, Outcome 3: CAAs. All total doses. Only children with CAAs at diagnosis.



Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 0-30 days						
Newburger 1986	1	79	3	79	5.8%	0.33 [0.04 , 3.14]
Ogino 1987A	6	49	9	40	30.9%	0.54 [0.21 , 1.40]
Ogino 1987B	6	63	2	51	11.9%	2.43 [0.51 , 11.52]
Ogino 1990	11	48	11	36	51.4%	0.75 [0.37 , 1.53]
Subtotal (95% CI)		**239**		**206**	**100.0%**	**0.75 [0.43 , 1.28]**
Total events:	24		25			
Heterogeneity: Tau² = 0.02; Chi² = 3.14, df = 3 (P = 0.37); I² = 5%						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.3.2 31-60 days						
Newburger 1986	1	79	3	79	23.4%	0.33 [0.04 , 3.14]
Ogino 1987A	3	49	3	41	49.3%	0.84 [0.18 , 3.92]
Ogino 1987B	0	62	1	52	11.6%	0.28 [0.01 , 6.74]
Ogino 1990	1	48	1	36	15.7%	0.75 [0.05 , 11.59]
Subtotal (95% CI)		**238**		**208**	**100.0%**	**0.58 [0.20 , 1.73]**
Total events:	5		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						

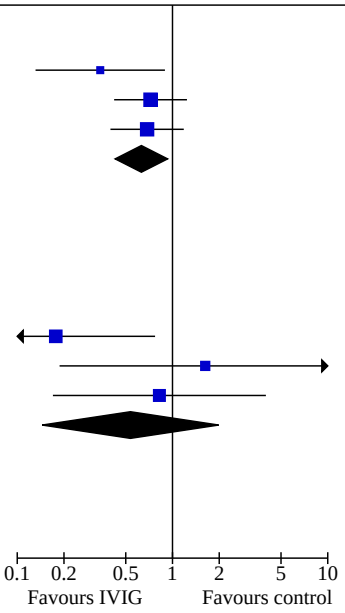
Analysis 1.4. Comparison 1: IVIG vs control, Outcome 4: CAAs. All total doses. All children. Studies using recognised diagnostic criteria.



Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 0-30 days						
Newburger 1986	6	75	18	78	19.3%	0.35 [0.15 , 0.83]
Onouchi 1995A(2)	12	24	9	13	40.6%	0.72 [0.42 , 1.24]
Onouchi 1995A(3)	15	34	9	14	40.2%	0.69 [0.40 , 1.18]
Subtotal (95% CI)		**133**		**105**	**100.0%**	**0.61 [0.41 , 0.93]**
Total events:	33		36			
Heterogeneity: Tau² = 0.03; Chi² = 2.65, df = 2 (P = 0.27); I² = 24%						
Test for overall effect: Z = 2.32 (P = 0.02)						
1.4.2 31-60 days						
Newburger 1986	3	79	14	79	39.8%	0.21 [0.06 , 0.72]
Onouchi 1995A(2)	3	24	1	23	26.3%	2.88 [0.32 , 25.68]
Onouchi 1995A(3)	4	34	2	24	33.8%	1.41 [0.28 , 7.10]
Subtotal (95% CI)		**137**		**126**	**100.0%**	**0.80 [0.16 , 4.03]**
Total events:	10		17			
Heterogeneity: Tau² = 1.32; Chi² = 5.86, df = 2 (P = 0.05); I² = 66%						
Test for overall effect: Z = 0.27 (P = 0.79)						

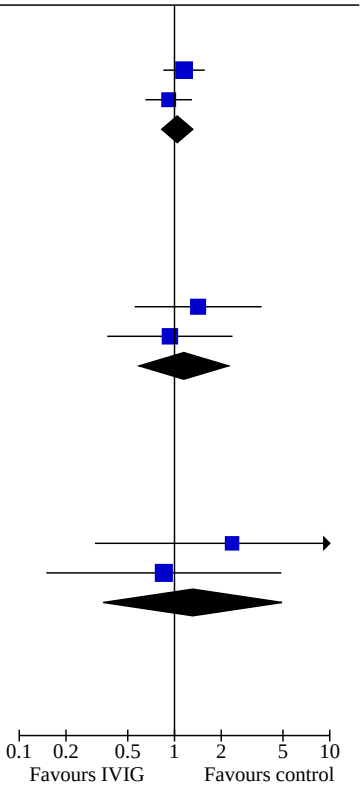
Analysis 1.5. Comparison 1: IVIG vs control, Outcome 5: CAAs. All total doses. No CAAs at enrollment. Studies using recognised diagnostic criteria.

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 0-30 days						
Newburger 1986	5	73	15	75	15.3%	0.34 [0.13 , 0.89]
Onouchi 1995A(2)	12	24	9	13	42.6%	0.72 [0.42 , 1.24]
Onouchi 1995A(3)	15	34	9	14	42.1%	0.69 [0.40 , 1.18]
Subtotal (95% CI)		**131**		**102**	**100.0%**	**0.63 [0.43 , 0.93]**
Total events:	32		33			
Heterogeneity: Tau² = 0.02; Chi² = 2.30, df = 2 (P = 0.32); I² = 13%						
Test for overall effect: Z = 2.33 (P = 0.02)						
1.5.2 31-60 days						
Newburger 1986	2	77	11	75	38.9%	0.18 [0.04 , 0.77]
Onouchi 1995A(2)	3	24	1	13	24.8%	1.63 [0.19 , 14.09]
Onouchi 1995A(3)	4	34	2	14	36.3%	0.82 [0.17 , 3.99]
Subtotal (95% CI)		**135**		**102**	**100.0%**	**0.54 [0.14 , 1.98]**
Total events:	9		14			
Heterogeneity: Tau² = 0.58; Chi² = 3.53, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 0.94 (P = 0.35)						



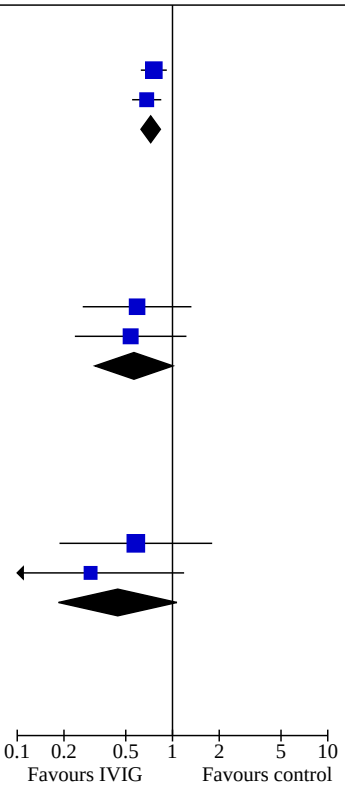
Analysis 1.6. Comparison 1: IVIG vs control, Outcome 6: CAAs. 100 mg/kg total dose. All children

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 0-30 days						
Harada 1991A(2)	50	73	22	37	55.7%	1.15 [0.85 , 1.57]
Harada 1991A(3)	36	66	22	37	44.3%	0.92 [0.65 , 1.30]
Subtotal (95% CI)		**139**		**74**	**100.0%**	**1.04 [0.83 , 1.31]**
Total events:	86		44			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
1.6.2 31-60 days						
Harada 1991A(2)	14	73	5	37	49.3%	1.42 [0.55 , 3.64]
Harada 1991A(3)	10	66	6	37	50.7%	0.93 [0.37 , 2.36]
Subtotal (95% CI)		**139**		**74**	**100.0%**	**1.15 [0.59 , 2.22]**
Total events:	24		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
1.6.3 180 days+						
Harada 1991A(2)	9	138	1	36	42.4%	2.35 [0.31 , 17.93]
Harada 1991A(3)	3	65	2	37	57.6%	0.85 [0.15 , 4.88]
Subtotal (95% CI)		**203**		**73**	**100.0%**	**1.31 [0.35 , 4.92]**
Total events:	12		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.40 (P = 0.69)						



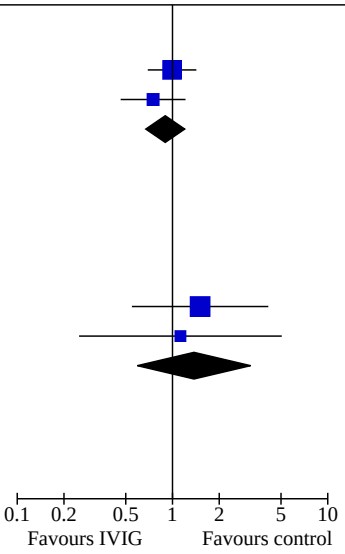
Analysis 1.7. Comparison 1: IVIG vs control, Outcome 7: CAAs. 500 mg/kg total dose. All children

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 0-30 days						
Harada 1991B(2)	60	93	40	47	55.8%	0.76 [0.63 , 0.92]
Harada 1991B(3)	54	95	40	48	44.2%	0.68 [0.55 , 0.85]
Subtotal (95% CI)		**188**		**95**	**100.0%**	**0.72 [0.63 , 0.84]**
Total events:	114		80			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 4.41 (P < 0.0001)						
1.7.2 31-60 days						
Harada 1991B(2)	11	93	9	45	51.3%	0.59 [0.26 , 1.32]
Harada 1991B(3)	10	93	9	45	48.7%	0.54 [0.24 , 1.23]
Subtotal (95% CI)		**186**		**90**	**100.0%**	**0.56 [0.32 , 1.01]**
Total events:	21		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.94 (P = 0.05)						
1.7.3 180+ days						
Harada 1991B(2)	6	93	5	45	60.0%	0.58 [0.19 , 1.80]
Harada 1991B(3)	3	93	5	46	40.0%	0.30 [0.07 , 1.19]
Subtotal (95% CI)		**186**		**91**	**100.0%**	**0.44 [0.18 , 1.07]**
Total events:	9		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 1.81 (P = 0.07)						



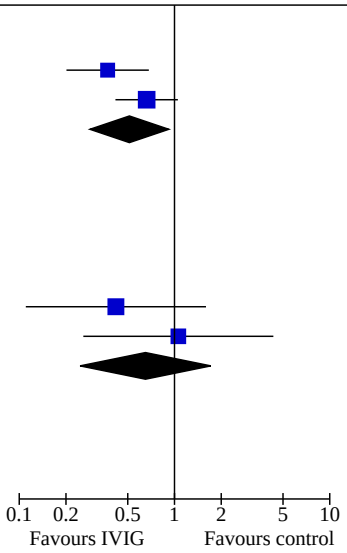
Analysis 1.8. Comparison 1: IVIG vs control, Outcome 8: CAAs. 600 mg/kg total dose. All children

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 0-30 days						
Ogino 1987A	28	49	23	40	64.0%	0.99 [0.69 , 1.42]
Onouchi 1995A(2)	12	24	18	27	36.0%	0.75 [0.46 , 1.21]
Subtotal (95% CI)		**73**		**67**	**100.0%**	**0.90 [0.67 , 1.20]**
Total events:	40		41			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
1.8.2 31-60 days						
Ogino 1987A	9	49	5	41	68.8%	1.51 [0.55 , 4.14]
Onouchi 1995A(2)	3	24	3	27	31.2%	1.13 [0.25 , 5.06]
Subtotal (95% CI)		**73**		**68**	**100.0%**	**1.38 [0.59 , 3.18]**
Total events:	12		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						



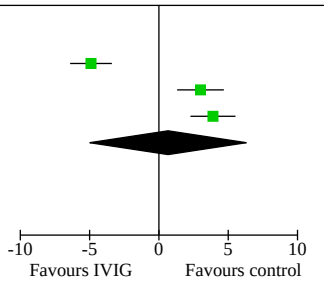
Analysis 1.9. Comparison 1: IVIG vs control, Outcome 9: CAAs. 1200 mg/kg total dose. All children

Study or Subgroup	IVIG Events	IVIG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 0-30 days						
Ogino 1987B	11	63	24	51	44.3%	0.37 [0.20 , 0.68]
Onouchi 1995A(3)	15	34	18	27	55.7%	0.66 [0.42 , 1.05]
Subtotal (95% CI)		**97**		**78**	**100.0%**	**0.51 [0.29 , 0.92]**
Total events:	26		42			
Heterogeneity: Tau² = 0.10; Chi² = 2.36, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 2.24 (P = 0.02)						
1.9.2 31-60 days						
Ogino 1987B	3	62	6	52	52.7%	0.42 [0.11 , 1.60]
Onouchi 1995A(3)	4	34	3	27	47.3%	1.06 [0.26 , 4.33]
Subtotal (95% CI)		**96**		**79**	**100.0%**	**0.65 [0.25 , 1.71]**
Total events:	7		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.38)						



Analysis 1.10. Comparison 1: IVIG vs control, Outcome 10: Duration of fever

Study or Subgroup	IVIG Mean	IVIG SD	IVIG Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 Duration of fever after initiation of treatment								
Nagashima 1987	3	3.1	69	7.9	5.5	67	33.4%	-4.90 [-6.41 , -3.39]
Onouchi 1995A(2)	8.6	3.7	38	5.6	2.95	23	33.2%	3.00 [1.32 , 4.68]
Onouchi 1995A(3)	9.5	3.6	42	5.6	2.95	23	33.3%	3.90 [2.28 , 5.52]
Subtotal (95% CI)			**149**			**113**	**100.0%**	**0.66 [-4.99 , 6.31]**
Heterogeneity: Tau² = 24.26; Chi² = 74.50, df = 2 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 0.23 (P = 0.82)								



Comparison 2. Comparison of dose regimens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 100 mg/kg x 5 days vs 200 mg/kg x 5 days	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1.1 All coronary artery abnormalities - 0-30 days	2	162	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.07, 2.89]
2.2 100 mg/kg x 5 days vs 400 mg/kg x 5 days	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 All coronary artery abnormalities - 0-30 days	3	401	Risk Ratio (M-H, Random, 95% CI)	2.79 [1.59, 4.91]

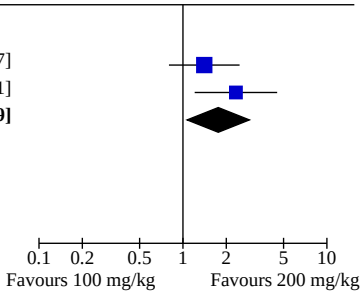
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.2 All coronary artery abnormalities - 31-60 days	2	333	Risk Ratio (M-H, Random, 95% CI)	3.14 [1.38, 7.15]
2.3 200 mg/kg x 5 days vs 400 mg/kg x 5 days	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3.1 All coronary artery abnormalities - 0-30 days	4	623	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.49, 4.00]
2.4 400 mg/kg x 5 days vs 2 gm/kg single dose	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.4.1 All coronary artery abnormalities - 0-30 days	2	253	Risk Ratio (M-H, Random, 95% CI)	4.47 [1.55, 12.86]
2.5 Fever 200 mg/kg x 3 days vs 400 mg/kg/day x 3 days	2		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2: Comparison of dose regimens, Outcome 1: 100 mg/kg x 5 days vs 200 mg/kg x 5 days

Study or Subgroup	100 mg/kg x 5 days Events	Total	200 mg/kg x 5 days Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 All coronary artery abnormalities - 0-30 days						
Nishihara 1988(1)	15	32	14	42	55.8%	1.41 [0.80 , 2.47]
Onouchi 1995B(1)	21	44	9	44	44.2%	2.33 [1.21 , 4.51]
Subtotal (95% CI)		**76**		**86**	**100.0%**	**1.76 [1.07 , 2.89]**
Total events:	36		23			

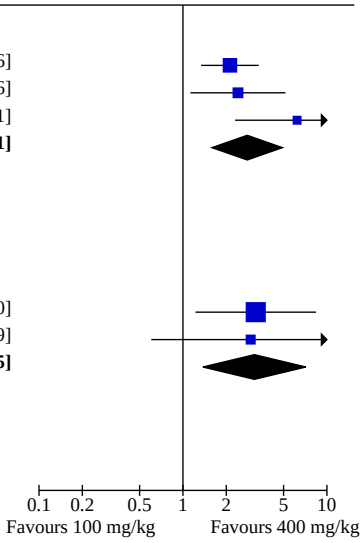
Heterogeneity: Tau² = 0.03; Chi² = 1.33, df = 1 (P = 0.25); I² = 25%

Test for overall effect: Z = 2.23 (P = 0.03)



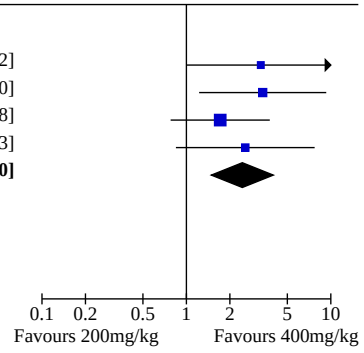
Analysis 2.2. Comparison 2: Comparison of dose regimens, Outcome 2: 100 mg/kg x 5 days vs 400 mg/kg x 5 days

Study or Subgroup	100 mg/kg x 5 days Events	Total	400 mg/kg x 5 days Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 All coronary artery abnormalities - 0-30 days						
Harada 1991C	45	122	20	115	47.3%	2.12 [1.34 , 3.36]
Nishihara 1988(2)	15	32	7	36	30.6%	2.41 [1.13 , 5.16]
Onouchi 1995B(2)	21	44	4	52	22.0%	6.20 [2.30 , 16.71]
Subtotal (95% CI)		**198**		**203**	**100.0%**	**2.79 [1.59 , 4.91]**
Total events:	81		31			
Heterogeneity: Tau² = 0.12; Chi² = 3.81, df = 2 (P = 0.15); I² = 47%						
Test for overall effect: Z = 3.57 (P = 0.0004)						
2.2.2 All coronary artery abnormalities - 31-60 days						
Harada 1991C	17	122	5	115	73.1%	3.20 [1.22 , 8.40]
Onouchi 1995B(2)	5	44	2	52	26.9%	2.95 [0.60 , 14.49]
Subtotal (95% CI)		**166**		**167**	**100.0%**	**3.14 [1.38 , 7.15]**
Total events:	22		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 2.72 (P = 0.007)						



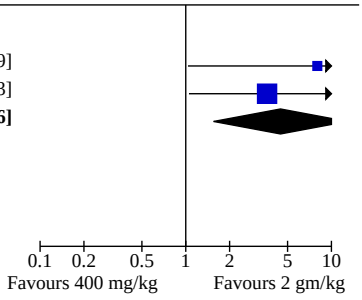
Analysis 2.3. Comparison 2: Comparison of dose regimens, Outcome 3: 200 mg/kg x 5 days vs 400 mg/kg x 5 days

Study or Subgroup	200 mg/kg x 5 days Events	Total	400 mg/kg x 5 days Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 All coronary artery abnormalities - 0-30 days						
Morikawa 1994(1)	19	147	3	76	17.3%	3.27 [1.00 , 10.72]
Morikawa 1994(3)	27	152	4	76	23.7%	3.38 [1.23 , 9.30]
Nishihara 1988(3)	14	42	7	36	39.0%	1.71 [0.78 , 3.78]
Onouchi 1995B(3)	9	44	4	50	19.9%	2.56 [0.85 , 7.73]
Subtotal (95% CI)		**385**		**238**	**100.0%**	**2.44 [1.49 , 4.00]**
Total events:	69		18			
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 3 (P = 0.69); I² = 0%						
Test for overall effect: Z = 3.54 (P = 0.0004)						



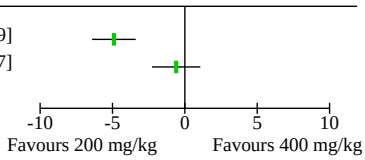
Analysis 2.4. Comparison 2: Comparison of dose regimens, Outcome 4: 400 mg/kg x 5 days vs 2 gm/kg single dose

Study or Subgroup	400 mg/kg x 5 days Events	Total	2 gm/kg single dose Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 All coronary artery abnormalities - 0-30 days						
Sato 1995	8	54	1	54	26.7%	8.00 [1.04 , 61.79]
Sato 1999	11	73	3	72	73.3%	3.62 [1.05 , 12.43]
Subtotal (95% CI)		**127**		**126**	**100.0%**	**4.47 [1.55 , 12.86]**
Total events:	19		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.78 (P = 0.005)						



Analysis 2.5. Comparison 2: Comparison of dose regimens, Outcome 5: Fever 200 mg/kg x 3 days vs 400 mg/kg/day x 3 days

Study or Subgroup	200kg/kg x3 Mean	SD	Total	400mg/kg x 3 Mean	SD	Total	Mean Difference IV, Random, 95% CI
Nagashima 1987	3	3.1	69	7.9	5.5	67	-4.90 [-6.41 , -3.39]
Onouchi 1995A(1)	3.1	3.8	38	3.7	3.8	42	-0.60 [-2.27 , 1.07]



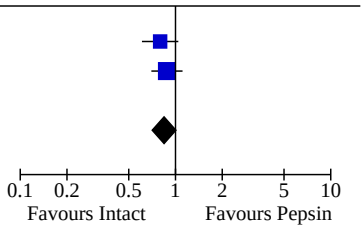
Comparison 3. Type of IVGG comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Intact vs pepsin treated IVIG - Coronary artery abnormalities 0-30 days	2	327	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.71, 1.01]
3.2 Intact vs pepsin treated IVIG - Coronary artery abnormalities 31-60 days	2	325	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.49, 1.45]
3.3 Intact vs pepsin treated IVIG - Coronary artery abnormalities - 180+ days	2	324	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.20, 1.38]

Analysis 3.1. Comparison 3: Type of IVGG comparisons, Outcome 1: Intact vs pepsin treated IVIG - Coronary artery abnormalities 0-30 days

Study or Subgroup	Intact Events	Total	Pepsin treated Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Harada 1991A(1)	36	66	50	73	42.4%	0.80 [0.61 , 1.04]
Harada 1991B(1)	54	95	60	93	57.6%	0.88 [0.70 , 1.11]
Total (95% CI)		**161**		**166**	**100.0%**	**0.84 [0.71 , 1.01]**
Total events:	90		110			

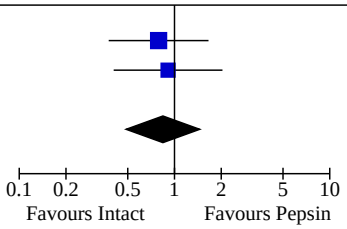
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Type of IVGG comparisons, Outcome 2: Intact vs pepsin treated IVIG - Coronary artery abnormalities 31-60 days

Study or Subgroup	Intact Events	Intact Total	Pepsin treated Events	Pepsin treated Total	Weight	Risk Ratio M-H, Random, 95% CI
Harada 1991A(1)	10	66	14	73	54.3%	0.79 [0.38 , 1.66]
Harada 1991B(1)	10	93	11	93	45.7%	0.91 [0.41 , 2.04]
Total (95% CI)		**159**		**166**	**100.0%**	**0.84 [0.49 , 1.45]**
Total events:	20		25			

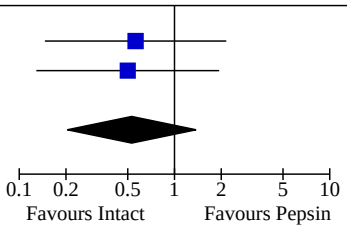
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Type of IVGG comparisons, Outcome 3: Intact vs pepsin treated IVIG - Coronary artery abnormalities - 180+ days

Study or Subgroup	Intact Events	Intact Total	Pepsin treated Events	Pepsin treated Total	Weight	Risk Ratio M-H, Random, 95% CI
Harada 1991A(1)	3	65	6	73	50.4%	0.56 [0.15 , 2.16]
Harada 1991B(1)	3	93	6	93	49.6%	0.50 [0.13 , 1.94]
Total (95% CI)		**158**		**166**	**100.0%**	**0.53 [0.20 , 1.38]**
Total events:	6		12			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategy for MEDLINE, EMBASE and CINAHL

Search strategy
1. Kawasaki Disease/
2. Mucocutaneous Lymph Node Syndrome/
3. 1 or 2
4. intravenous immunoglobulin/
5. immunoglobulin$
6. gammaglobulin$
7. IVIG
8. IVGG
9. 4 or 5 or 6 or 7 or 8
10. coronary aneurysm/
11. coronary aneurysm$
12. heart aneurysm/
13. heart aneurysm$
14. coronary vessel anomalies/
15. 10 or 11 or 12 or 13 or 14
16. 3 and 9
17. 15 and 16

Appendix 2. Search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL)

Search strategy
#1 MUCOCUTANEOUS LYMPH NODE SYNDROME
#2 (mucocutaneous and (lymph and (node and system)))
#3 (kawasaki next disease*)
#4 (#1 or #2 or #3)
#5 IMMUNOGLOBULINS INTRAVENOUS
#6 (intravenous next immunoglobulin*)
#7 ANTI-INFLAMMATORY AGENTS ANTIRHEUMATIC AGENTS AND
#8 INFLAMMATION MEDIATORS
#9 aspirin
#10 salicylate*
#11 (acetylsalicylic next acid)
#12 asa #13 (#5 or #6 or #7 or #8 or #9 or#10 or #11)
#14 (#4 and #12)

WHAT'S NEW

Date	Event	Description
14 December 2021	Review declared as stable	This review has been superseded by Cochrane Review: 'Intravenous immunoglobulin for the treatment of Kawasaki disease' (https://doi.org/10.1002/14651858.CD014884) and will no longer be updated.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 4, 2003

Date	Event	Description
25 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Richmal Oates-Whitehead: Jointly (with HB) conceptualised the review, took the lead in writing the protocol and overall review, performed initial searches of databases for trials, was involved in selecting trials for inclusion, and performed independent data extraction and quality assessment of the included trials.

Harry Baumer: Jointly (with ROW) conceptualised the review. Commented on drafts of the protocol. Performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the review.

Linda Haines: Commented on drafts of the protocol. Performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the review.

Samantha Love: Commented on drafts of the protocol. Performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the review.

Ian Maconochie: Performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the review.

Amit Gupta: Commented on drafts of the protocol. Performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the review.

Kevin Roman: Commented on drafts of the protocol. Performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the review.

Jaspal Dua: Commented on and edited all sections of the protocol.

Ichiko Flynn: Translated Japanese studies when required.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Royal College of Paediatrics and Child Health, UK

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK

INDEX TERMS

Medical Subject Headings (MeSH)

Immunoglobulins, Intravenous [*therapeutic use]; Mucocutaneous Lymph Node Syndrome [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans