Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose

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Authors' objectives
To determine the effect of various doses of intravenous gamma globulin (IVGG) with aspirin administered within the first 7 to 10 days of illness, on the prevalence of coronary abnormalities (CAA) in Kawasaki disease.

Searching
The authors do not provide details of the sources searched. The only details of the search strategy were that articles published in English or Japanese since 1984 were considered.

Study selection
Study designs of evaluations included in the review
Multicentre, randomised controlled trials using intact gamma globulin and including the blinded, independent assessment of echocardiographic findings.

Specific interventions included in the review
Moderate-dose aspirin (30 to 50 mg/kg per day with or without IVGG, and high-dose aspirin (80 to 120 mg/kg per day) with or without IVGG.

Participants included in the review
Patients in Japan and the USA undergoing IVGG treatment for acute Kawasaki disease.

Outcomes assessed in the review
The prevalence of CAA was measured at the subacute and convalescent stages. The subacute stage was 30 days after onset of illness in Japanese studies, and 2 to 3 weeks after enrolment in US studies. The convalescent stage was 60 days after onset of illness in Japan studies, and 6 to 8 weeks after enrolment in the US studies) stages.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not report the criteria used to assess quality, or how the quality assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The relationship of the total dose of IVGG to the prevalence of CAA was assessed by regression analysis, using the method of Fleiss (see Other Publications of Related Interest), which weights the various sample sizes.

How were differences between studies investigated?
The chi-squared test was used to compare the prevalence of CAA among various treatment groups.
Results of the review
Seven studies were included since 1984. These were divided into two groups: 868 Japanese participants (5 trials) who were treated with moderate-dose aspirin with IVGG, and 761 US participants (2 trials) who were treated with high-dose aspirin with IVGG.

In 868 Japanese patients receiving moderate-dose aspirin (30 to 50 mg/kg per day), the prevalence of CAA at the subacute stage was 26.8% with aspirin alone, 18.1% with a total IVGG dose of less than 1 g/kg, 17.3% with a total IVGG dose of 1.0 to 1.2 g/kg, and 5.3% with a total IVGG dose of 2 g/kg. The corresponding figures at the convalescent stage were 17.5, 13.5, 9.8 and 3.5%, respectively.

In 761 US patients receiving high-dose aspirin (80 to 120 mg/kg per day), the prevalence of CAA at the subacute stage was 23.0% with aspirin alone, 9.0% with a total IVGG dose of 1 g/kg, 8.6% with a total IVGG dose of 1.6 g/kg, and 4.6% with a total IVGG dose of 2 g/kg. The corresponding figures at the convalescent stage were 17.7, 9.0, 6.3 and 3.8%, respectively.

For the combined group results, the prevalence of CAA at the subacute stage was 25.8% with aspirin alone, 18.1% with a total IVGG dose of less than 1 g/kg (mean: 0.4), 15.7% with a total IVGG dose of 1.0 to 1.2 g/kg (mean: 1.1), 8.6% with a total IVGG dose of 1.6 g/kg, and 4.8% with a total IVGG dose of 2 g/kg (correlation, adjusted $R^2=0.966$, p=0.0017). The corresponding figures at the convalescent stage were 17.6, 13.5, 9.7, 6.3 and 3.8%, respectively, (correlation, adjusted $R^2=0.993$, p=0.0602).

The chi-squared analysis between the moderate- and high-dose aspirin groups at any IVGG dose during the subacute stage showed no significant differences. The convalescent stage curves were virtually superimposable, demonstrating that the IVGG effect on CAA is independent of salicylate dose.

Authors' conclusions
Two g/kg IVGG combined with aspirin, at least 30 to 50 mg/kg per day, provides maximum protection against the development of CAA after Kawasaki disease.

CRD commentary
The authors did not state how they searched the literature, or whether they searched for unpublished trial data; however, they have searched both Japanese and English databases.

The authors did not present any criteria for quality or relevance other than the justification that there would be least bias if the included trials were large, multicentre randomised trials, which included blinding in evaluation and standard definitions. There was no discussion of the quality issues relating to participant inclusion, whether the study design was intention-to-treat, or whether there were any drop-outs from the trials. In addition, any side-effects of the treatments were not discussed.

The authors used p-values rather than confidence intervals, which were not calculated. The p-value showed the result was highly significant, but not the degree of certainty that can be claimed for that significance. Calculation of the confidence intervals would have provided an indication of the width of the confidence intervals for the various drug interventions used in this review, and how close those intervals were to the line of no effect by treatment.

The review presented results in the form of prevalence. The regression analysis showed a very close correlation between the use of IVGG and the reduction of CAA.

A chi-squared analysis was conducted, but the results were not reported.

The authors’ conclusions of a dose response for IVGG do follow from the prevalence results, which showed that there was an inverse relationship between progressively higher IVGG doses and lower CAA rates, regardless of the aspirin dosage. However, their recommendation that the IVGG treatment should be combined with at least 30 to 50 mg/kg per day aspirin was not supported in their review.
Implications of the review for practice and research
The authors state that their findings should be confirmed by prospective controlled studies. No other recommendations for research were stated.

Bibliographic details

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9427895

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.