Effect of initial corticosteroid therapy on coronary artery aneurysm formation in Kawasaki disease: a meta-analysis of 862 children

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CRD summary
This review assessed the effects of initial corticosteroid therapy for preventing coronary artery aneurysms in children with Kawasaki disease. The authors concluded that corticosteroids, used in addition to conventional therapy, were beneficial. However, since most of the included studies were non-randomised trials, this might have resulted in an overestimation of treatment effects.

Authors' objectives
To assess the effects of initial corticosteroid therapy for treating Kawasaki disease and preventing the formation of coronary aneurysms.

Searching
MEDLINE and the Cochrane CENTRAL Register were searched from 1966 to February 2005; the search terms were reported. The bibliographies of relevant articles were checked.

Study selection
Study designs of evaluations included in the review
Studies needed to include a control group for the entire study, or subsets of patients whose treatment differed only by the inclusion of a corticosteroid.

Specific interventions included in the review
Studies where a corticosteroid was part of the initial management of disease were eligible for inclusion. The comparator was either control or a drug regimen identical to the treatment group but without a corticosteroid (standard therapy). Additional drugs were allowed so long as both groups received them. Prednisolone or methylprednisolone were assessed in the included studies. Standard therapy was aspirin or intravenous immunoglobulin (IVIG), alone or in combination. Additional therapies included cephalaxin, dipyridamole and propranolol, or combinations of these. Where stated, the length of treatment ranged from one dose to 48 days. Further details of drug doses were given.

Participants included in the review
Studies on children, where all participants had a diagnosis of Kawasaki disease, were eligible for inclusion. Diagnosis of Kawasaki disease was defined as meeting the American Heart Association's or the Japanese Ministry of Health's diagnostic criteria, or fever for 5 days plus any four of the following: conjunctivitis, mucositis of the oral pharynx, peripheral oedema, unilateral lymphadenopathy and rash. Where stated, the mean ages in the included studies ranged from 1.5 to 4.4 years and the maximum period of symptoms before enrolment were 7 to 10 days.

Outcomes assessed in the review
The primary outcome was the development of coronary aneurysms. Only studies where a 2-dimensional echocardiograph or coronary artery catheterisation were performed at least 2 weeks after treatment were eligible for inclusion. Where stated, coronary imaging follow-up was performed at between 3 weeks and 3 months.

How were decisions on the relevance of primary studies made?
One author assessed studies for inclusion, blinded to author or location of study. A second author made the selection unblinded. Any conflicts were resolved by discussion.

Assessment of study quality
Articles were scored for quality according to the following items: diagnostic criteria, experimental study design, time of follow-up coronary imaging, and blinding of imaging interpretation.

The authors scored each article and any conflicts were resolved by consensus.

Data extraction
The data were extracted onto a standardised form. Studies that had more than one treatment group were treated as separate studies if a suitable control group could be identified. The proportion of people developing aneurysms in each group was calculated and used to estimate the odds ratio (OR) and 95% confidence intervals (CIs). Where no events occurred, 0.5 was used in the calculations.

Methods of synthesis
How were the studies combined?
Pooled ORs and 95% CIs were estimated using a fixed-effect meta-analysis. Funnel plots were used to assess publication bias.

How were differences between studies investigated?
Heterogeneity was assessed by calculating Cochran's Q statistic. To determine the percentage of heterogeneity across studies, the I-squared statistic was calculated. Outlying studies were identified through linear regression and Galbraith plots. Suspected sources of heterogeneity were investigated using subgroup analyses.

Results of the review
Eight studies (1,208 participants) were included. Of these, two (70 participants) were randomised controlled trials, one (294 participants) was a retrospective study, and the designs of the remaining five studies (844 participants) were unclear.

Only two studies stated that the participants were randomised to treatments; none of the other studies mentioned how the participants were assigned to treatments. Funnel plots suggested an absence of publication bias.

When data from all studies were combined there was significant statistical heterogeneity. The Galbraith plot identified two studies that appeared to be the sources of this heterogeneity. When these were removed from the analysis, statistical heterogeneity was eliminated.

Significantly fewer participants experienced coronary artery aneurysms with corticosteroids as compared with control (OR 0.546, 95% CI: 0.371, 0.803, P=0.002; 8 studies).

In a subgroup analysis, participants receiving corticosteroids experienced fewer aneurysms than those on aspirin alone (OR 0.601, 95% CI: 0.392, 0.921, P=0.019; 5 studies). Participants receiving corticosteroids plus aspirin and IVIG had fewer aneurysms than those receiving aspirin plus IVIG alone (OR 0.352, 95% CI: 0.136, 0.909, P=0.031; 3 studies).

Authors' conclusions
When combined with aspirin-containing regimens, corticosteroids significantly reduced the incidence of coronary artery aneurysms when used as initial treatment for Kawasaki disease.

CRD commentary
The inclusion criteria for this review were clearly stated. Two relevant databases were searched and studies in any language appear to have been included. The methods of the review were described. Although the quality of the included studies was assessed, this assessment did not appear to have been used to inform the review: the studies that were excluded from the analysis were done so on the basis of heterogeneity rather than quality. The details of some of the study designs were unclear, but all except two were non-randomised trials. This type of study is open to a greater degree of bias, which may result in an overestimation of treatment effects.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors referred to an ongoing multicentre trial which should provide further evidence of the role of corticosteroids in Kawasaki disease.

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