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Original Article

The prevention of coronary arterial abnormalities in Kawasaki disease: A meta-analysis of the corticosteroid effectiveness

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Acquired heart disease in children

Abstract *Objective:* The use of corticosteroid in Kawasaki disease (KD) remains controversial among current guidelines. The objective of this study is to summarize the effectiveness and safety of corticosteroid to prevent coronary arterial lesions in Kawasaki disease, both as initial and rescue therapy.

Methods: The Medline, EMBASE, Google scholar, Cochrane Central Register of Controlled Trials databases, ClinicalTrials.gov, and Japanese Institutional Repositories Online were searched for studies up to 31 March 2017. Studies that compared incidence of coronary artery lesions between regimens with corticosteroid and regimen without it in a well-defined controlled group were included. The incidence of coronary artery lesion was analyzed by meta-analysis.

Results: Nineteen studies published between 1999 and 2016 fulfilled eligibility criteria. There were 3591 patients included for analysis. There was a significant reduction in incidence of coronary artery lesions with usage of corticosteroid with a pooled odds ratio of 0.72 (95% CI 0.57–0.92; $p = 0.01$) than that without usage of corticosteroid. In general, a greater effect was seen in the patient received corticosteroid as initial and adjuvant therapy with intravenous immune globulin (pooled odds ratio 0.39, 95% CI 0.21–0.73, $p = 0.007$) than those who received corticosteroid as rescue therapy. The risk reduction was statistically significant in

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Japanese groups (OR 0.56, 95% CI 0.42–0.75 in fixed effects model) but not significant in non-Japanese groups (OR 1.45, 95% CI 0.91–2.30 in fixed effects model).

Conclusions: We demonstrated an overall reduction in incidence of coronary artery lesions with the use of corticosteroid as initial and adjuvant treatment for Kawasaki disease.

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Introduction

Kawasaki disease is an acute inflammatory disease, associated with vasculitis, affecting predominantly medium-sized arteries, particularly the coronary arteries. Kawasaki disease is most common cause of acquired heart disease in the children in the developed world.^{1–3} Coronary artery lesions (CAL) occur in 15–25% of untreated patients.⁴ Because randomized controlled studies and meta-analysis^{5,6} have confirmed that Intravenous immune globulin (IVIG) plus aspirin compared with aspirin alone reduces the risk of CAL, IVIG has been taken as standard treatment. The role of corticosteroid, on the other hand, is controversial. Reluctance to employ corticosteroid regimens in acute Kawasaki disease derived from an early study,⁷ but the selection bias in that study was obvious, that is, only sickest patients received corticosteroid. In the light of Japanese RAISE study,⁸ Japanese Society of Pediatric suggested that corticosteroid may be used as initial therapy if patients' risk score indicates severe Kawasaki disease in their revised guideline. They also endorsed corticosteroid as rescue therapy for IVIG resistant patients.⁹ The 2004 American Heart Association guideline withheld recommendation of primary corticosteroid as the American Pediatric Heart Network study had not been completed then.^{4,10} Therefore, given the controversy of corticosteroid therapy, we performed this study to measure the overall effectiveness of corticosteroid on preventing coronary artery abnormalities.

Methods

This meta-analysis was performed under the framework of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).¹¹

Eligibility criteria

Studies were considered eligible if the available data contained sufficient information to allow assessment of validity and incidence. To be eligible the study must meet the following criteria

- 1) The study followed the established diagnostic criteria of Kawasaki disease for all patients.
- 2) The study included corticosteroid as treatment within one month from diagnosis.
- 3) There was an explicit treatment process.
- 4) The study had stated definition of coronary artery lesions and echocardiography or cardiac catheterization was adopted to detect them.

Information source

The MEDLINE (through PubMed), EMBASE, Google scholar, Cochrane Central Register of Controlled Trials databases, ClinicalTrials.gov, and Japanese Institutional Repositories Online were searched up to 31 March 2017.

Search and study selection

The topic search terms were used in combination with the Cochrane highly sensitive search strategy for identifying randomized controlled trials. We used the following free text and MeSH terms to search all trials registers and databases: mucocutaneous lymph node syndrome, Kawasaki disease, adrenal cortex hormones, corticosteroid, methylprednisolone, dexamethasone.

Data collection process

The quality of the included studies was appraised by assessing allocation concealment, generation of the allocation sequence, and inclusion of all randomized participants. The risk of bias assessment was according to the Cochrane Handbook for Systematic Reviews of Interventions.

Data items

The primary outcome was the incidence of CAL. The secondary outcome was the duration of fever after intervention. Reported adverse events were also collected for meta-analysis.

Risk of bias across studies

The potential of publication bias was assessed using funnel plots and two statistical tests as Harbord's modified test and Peters' test.^{12–14} Statistical heterogeneity was assessed using the I^2 statistics.¹⁵ We assigned adjectives of low, moderate, and high I^2 values of 25%, 50%, and 75%. The 95% confidence interval (CI) of I^2 was also calculated to avoid false negative result of heterogeneity.

Synthesis of results and summary measures

The risk of CAL was measured as odds ratio as it gave symmetric results for events and free risk. The duration of fever was measured in days. The adverse event was measured in risk difference. The effect sizes were pooled

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