Corticosteroids for the Treatment of Kawasaki Disease in Children

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Introduction

Kawasaki disease (KD) is a multisystemic vasculitis of medium vessels, with a poorly understood etiopathogenesis, which may depend on a genetic predisposition and/or an abnormal host response to infectious triggers.[1] The peak onset is between 18 and 24 months and its geographical distribution varies widely, with a higher incidence reported in Japan.[2,3] The development of coronary arteries aneurysms, which may occur in up to 25% of untreated patients, is the most important complication of KD. It may lead to stenosis and thrombosis of coronary arteries, with KD being the leading cause of childhood-acquired heart disease in developed countries.[4,5] There are two overlapping but distinct diagnostic criteria, from Japan's KD Research Committee and from the American Heart Association.[6,7]

Well-accepted first line treatment of KD involves a single infusion of high-dose intravenous immunoglobulin (IV Ig) alongside a high dose of acetylsalicylic acid (ASA).[3] However, approximately 20% of KD patients have clinical refractory symptoms to the first-line regimen and are at high-risk for complications. Other high-risk factors include age < 12 months, severe increase in inflammatory markers, clinical features of shock, existing arterial aneurysms and Kobayashi score ≥ 5 (score to predict non-responsiveness to IV Ig, based on laboratory variables and demographic data).[8] Treatment options for high-risk patients include a second dose of IV Ig and the use of corticosteroids, with or without infliximab.[7,9] Corticosteroids have long been used in other vasculitis similar to KD; however, their use in KD remains controversial because earlier studies showed a deleterious effect.[10] More recently, there have been studies exploring their early use in high-risk patients, but the most safe and effective type, frequency, dose and duration of treatment remains unclear as well as whether corticosteroids should be administered alongside IV Ig, ASA or infliximab. Identifying patients that may benefit most from corticosteroids, based on parameters such as severity, ethnicity and pre-steroid treatment status, also needs to be clarified.

Aim

This Cochrane Corner presents and discusses the results of the systematic review of the Cochrane Database of Systematic Reviews published in 2017 that aimed to assess the impact of corticosteroid use in KD in children, as either first-line or second-line treatment, on the incidence of coronary artery abnormalities, and on mortality, time to normalisation of laboratory parameters, duration of acute symptoms and long-term impact on coronary morbidity.[11]

Methods

A systematic review was conducted by searching databases and clinical trial registration platforms up to 25 November 2016. Trials with published full-text or abstract reports or ongoing were identified from a variety of sources, including the following databases Cochrane Vascular Specialized Register, CENTRAL, MEDLINE, EMBASE, CINAHL, AMED as well as the trials registries World Health Organization International Clinical

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Trials Registry Platform, ClinicalTrials.gov and ISRCTN Register. The authors included all randomised controlled trials or *quasi*-experimental studies of children and adolescents, with a diagnosis of KD, who fulfilled the five criteria for one of the two diagnostic guidelines or with only four criteria plus evidence of cardiac complications at echocardiography or angiography. The interventions of interest were corticosteroids, alone or as a co-adjuvant treatment, either as first or second-line regimen. All forms of corticosteroid therapy in any combination or with immunoglobulin, ASA or infliximab were considered. The comparator groups could include placebo, immunoglobulin, ASA or infliximab. Only parallel trials were included, cross-over trials were not eligible.

The primary outcomes were the incidence of coronary artery abnormalities (measured via diameter or *z*-scores and defined by the Zorzi criteria or the Japanese Ministry of Health criteria) and the incidence of any serious adverse effects attributable to corticosteroids.[12,13] The secondary outcomes were mortality (all-cause), duration of clinical symptoms (for example, fever and rash), time to normalisation of laboratory parameters (C-reactive protein and erythrocyte sedimentation rate), length of hospital stay and long-term (> one year after onset) coronary morbidity (non-aneurysmal).

The risk of bias in the included trials was assessed using the Cochrane Risk of Bias Tool, and the quality of the evidence was evaluated using GRADE. Statistical heterogeneity was assessed using the I^2 statistic. Several measures of the treatment effect were used according to the type of outcomes: odds ratio (OR) for dichotomous variables, mean difference (MD), or standardised mean differences (SMD) when needed, for continuous variables. Measures of effect were presented with 95% confidence intervals (CI). Subgroup analyses were planned according to:

- Type of corticosteroid used;
- Corticosteroid dosing;
- Corticosteroid treatment frequency;
- Corticosteroid treatment duration;
- Corticosteroid route of administration;
- Corticosteroid as first versus second-line use;
- Geographical distribution of trial participants/ethnicity;
- KD severity (non-high risk *versus* high risk);
- Concomitant treatments.

Results

Seven randomised controlled trials were included, with a total of 922 participants. Fourteen studies were excluded due to data inaccessibility (four studies), assessment of different outcomes (six studies), additional differential treatments besides corticosteroids (two studies), ongoing trial (one study) and delayed use of corticosteroids only if patients did not respond to two treatments with IV Ig (one study). Of the seven studies included, both intervention and control groups received IV Ig in all of them, while five also received ASA, two also received diphenhydramine and one dipyridamole. Risk of bias for random sequence generation, allocation concealment, blinding of the participants and personnel and blinding of the outcome assessment were only considered low, in three (43%), four (43%), one (14%) and four (57%) studies, respectively. Overall, the quality of evidence was considered moderate.

Table 1 summarises the main results for the primary outcome and of the subgroup analyses. Corticosteroids reduced the incidence of coronary artery abnormalities. There were also reductions in duration of clinical symptoms (MD -1.65 days, 95% CI -3.31 to 0.00, 210 participants, I^2 = 88%) and length of hospital stay (MD -1.41 days, 95% CI -2.36 to -0.46, 39 participants). The quality of evidence for these two outcomes was considered moderate. Time to normalisation of the laboratory parameters was shorter in the corticosteroid group (MD -2.80 days, 95% CI -4.38 to -1.22, 178 participants) and the quality of evidence was considered high for this outcome. Due to short follow-up periods and missing data, the authors considered that there was insufficient information available to draw conclusions on the incidence of adverse effects attributable to corticosteroids, mortality and long-term coronary morbidity.

Subgroup analyses did not show a statistically significant effect on the incidence of coronary artery abnormalities with a single intravenous corticosteroid dose (one-off steroid IV) (OR 0.56, 95% CI 0.29 to 1.08, 277 participants, I^2 = 36%), while there were fewer abnormalities when the intravenous scheme was followed by an oral course of corticosteroid (OR 0.13, 95% CI 0.05 to 0.32, 452 participants, I^2 = 0%); the test for subgroup differences was statistically significant. Therapeutic regimens were globally reported as a single dose of methylprednisolone IV or longer courses of prednisolone, with no further detailed information. Consequently, subgroup analyses for corticosteroid dosing, treatment frequency, total treatment duration, route of administration and corticosteroid first *versus* second-line use, were not performed due to insufficient data.

Regarding the geographical distribution of trial participants/ethnicity, the use of corticosteroids showed a protective effect on the incidence of coronary artery abnormalities in studies conducted in Japan compared to those conducted in North America. Most of North

American studies were single-dose trials. On KD severity, studies with high-risk participants found large magnitude of treatment effect (OR 0.13, 95% CI 0.06 to 0.29, 377 participants, I^2 = 0%), while in studies with low risk participants the benefit was lower (OR 0.53, 95% CI 0.29 to 1.00, 530 participants, I^2 = 6%).

The subgroup analysis for concomitant recognised treatments was not performed, as insufficient information was available.

Conclusion

The use of corticosteroids in the treatment of children with KD reduced the incidence of coronary artery abnormalities, the duration of clinical symptoms, the time for laboratory parameters to normalise and the length of the hospital stay.

Regarding subgroup analysis, the decrease in incidence of coronary artery abnormalities potentially disappeared when only low-risk participants were analysed; fewer coronary artery abnormalities were found with a single intravenous dose of corticosteroids followed by an oral course and a protective effect of corticosteroids may be positively associated with ethnicity. There was insufficient data available regarding the incidence of adverse effects attributable to corticosteroids, mortality and long-term coronary morbidity.

The authors concluded that the evidence suggests that treatment with long courses of corticosteroids should be considered for all children diagnosed with KD, until further research is available, namely in countries other than Japan and using different therapeutic regimens.

Comments

The current and accepted guidelines for KD treatment advocate the use of a single dose of IV Ig (administered as soon as possible and ideally until the tenth day of disease) alongside ASA.[8,14]

Despite this, the co-adjuvant use of corticosteroids has often been adopted in clinical practice, especially in patients with KD at high risk of IV Ig resistance, but the benefits vary in different sets of patients and according to the corticosteroid regimens used.[15] The present meta-analysis provided evidence supporting this benefit, but the data available remain insufficient to help establish clear indications for corticosteroids use and type of therapeutic regimens in KD. These data reinforce the fact that several aspects of KD diagnosis and management are still unclear. It would be of utmost importance to establish well-defined criteria to identify high-risk patients, applicable to patients of all ethnicities.[15,16] In addition, children with atypical (incomplete) KD, in who the diagnosis might be more challenging, are usually younger, but paradoxically present a higher probability of developing coronary artery abnormalities. In these cases, it would also be particularly important to determine the criteria for standard treatment initiation, when KD diagnosis is plausible.[17] More studies are also needed on the potential risk for severe adverse effects of corticosteroid use in KD, such as extremely high white blood cell counts, acute hepatomegaly and bradycardia, and their impact on mortality and long-term coronary morbidity on these patients.[18]

In Portugal, a recent epidemiological study reported a mean annual incidence of KD of 6.5 per 100,000 children < 5 years.[19] The majority of Portuguese paediatric centres follow the American Heart Association recommendations and use corticosteroids as a backup

Table 1. Summary of results

Comparison and outcomes	Participants (studies)	Relative effect OR (95% CI)
Corticosteroids *versus* no corticosteroids		
Incidence of coronary artery abnormalities	907 (7)	0.29 (0.18 to 0.46)
Steroid course	729 (6)	0.30 (0.18 to 0.50)
- One-off steroid IV methylprednisolone	277 (3)	0.56 (0.28 to 1.08)
- Longer tapering course of prednisolone	452 (3)	0.13 (0.05 to 0.32)
Geographical distribution	907 (7)	0.29 (0.18 to 0.46)
- Centres in Japan	678 (5)	0.14 (0.07 to 0.29)
- Centres in North America	229 (2)	0.77 (0.37 to 1.59)
KD severity	907 (7)	0.29 (0.18 to 0.46)
- High risk score	377 (3*)	0.13 (0.06 to 0.29)
- Low risk score	530 (5)	0.53 (0.29 to 1.00)

CI - confidence interval; IV - intravenous; KD - Kawasaki disease; OR - odds ratio.
* Ikeda 2006 study was considered both on the high and low-risk groups.

in IV Ig resistant KD.[19] Current evidence supports that corticosteroids should be considered in KD treatment but more studies in European populations are needed in order to clarify the best approach on their use in KD.

Keywords: Adolescent; Adrenal Cortex Hormones/therapeutic use; Child; Coronary Artery Disease/prevention & control; Mucocutaneous Lymph Node Syndrome/drug therapy; Randomized Controlled Trials as Topic

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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