Mending a broken heart: management options for preventing cardiac sequelae in Kawasaki disease

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Background: Kawasaki disease (KD) is one of the commonest causes of acquired heart disease in children worldwide. [1] Coronary artery abnormalities (CAAs) develop in 15-25% of untreated children with Kawasaki disease. [2] Intravenous immunoglobulins (IVIG) and aspirin have been widely used for the treatment of Kawasaki disease, with proven benefits. Novel drugs may also prove to have beneficial effects in reducing disease progression. [1,3,4] **Objective:** This descriptive review was conducted in order to investigate the efficacy of current and emerging treatment options in preventing disease progression in Kawasaki disease in children. **Methods:** The electronic databases PubMed, MEDLINE via Ovid, Science Direct and The Cochrane Library were reviewed. English language publications from the last 25 years were included. The primary outcome of efficacy was the reduction of CAAs and rate of improvement in febrile illness in children. **Results:** A total of 30 articles were identified. IVIG in conjunction with aspirin were the most useful in reducing the incidence of CAAs. Use of IVIG versus placebo showed a significant decrease in the incidence of CAAs after IVIG at thirty days. [5] Corticosteroids were found to be effective for refractory KD treatment. Etanercept did not appear to worsen the likelihood of CAAs. **Conclusion:** There is strong evidence for the use of IVIG. Combination of IVIG with aspirin was more effective in reducing the incidence of CAAs compared to IVIG alone. Emerging medications such as etanercept, infliximab and ulinastatin seem effective; however, trials are limited and underpowered.

Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a systemic vasculitis which presents mainly as a self-limiting acute illness of infants and children under the age of five years. It has also become an important disease to exclude upon the presentation of a febrile child. [1,2,6] Worldwide it is one of the commonest causes of acquired heart disease in children. [1,2] While KD has high prevalence in Asians, cases are also being increasingly reported in other racial groups. [1,3] In Asian countries the incidence has increased from 69 to 218 cases per 100,000, in children less than five years of age. This incidence is 10-15 times greater than in the Caucasian population. [2,7] Results of a national scheme conducted in 1994 in Australia revealed the annual incidence of KD was 3.7/100 000 children < five years old. [8]

KD particularly affects the small and medium sized elastic arteries, causing a multisystem inflammatory vasculitis that has a specific tendency to cause coronary artery abnormalities (CAAs) in 15-25% of untreated patients. [1,7,9]. These CAAs can either be coronary artery aneurysms, which are focal dilations of a vessel, or coronary artery ectasia, which is diffuse dilation of the coronary artery. Children presenting with KD are diagnosed mainly by clinical criteria. These have been summarised by the American Heart Association in early 1993 and outlined in Table 1. [1]

Laboratory investigations provide minimal diagnostic utility, but may be useful in excluding other causes of febrile illness in children. [1]

The cause of the development of KD is largely unknown. [4] It is thought that an undefined infectious trigger in a genetically predisposed individual results in the disease. [7] This has been supported by

Table 1. *Criteria for the diagnosis of Kawasaki Disease. [10]*

Criterion	Description
Fever Duration of five or more days plus four of the following:	
Conjunctivitis	Bilateral, bulbar, non-suppurative
Lymphadenopathy	Cervical, >1.5cm
Changes to lips or oral mucosa	Red cracked lips, strawberry tongue, or diffuse erythema of the oropharynx
Rash	Polymorphous, no vesicles or crusts
Changes of extremities	Initial stage: erythema and oedema of palms and soles. Convalescent stage: peeling of skin from fingertips
KD may be diagnosed with fewer than four features if coronary artery aneurysms are detected. [1,4,6]	

observations of a seasonal peak in disease incidence in the winter and spring months, epidemics with a clear epicentre, and a peak incidence in the toddler age group compared to children who are less than three months old and to adults. [4] A provisional hypothesis is that a bacterial toxin, acting as a super antigen, in turn acting as a trigger; this is based on the existing clinical similarities between KD and staphylococcal or streptococcal toxin mediated illnesses, specifically desquamation and strawberry tongue. [3,4,11] Drug treatments target specific steps of a disease pathway in order to prevent progression of disease. [3] Cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6) have been noted to increase during the acute phase of Kawasaki disease. [3] It has also been noted that there are higher TNF-α levels in KD patients with coronary involvement than in patients without coronary involvement. [12] Targeting different aspects of disease progression allows the development of new therapeutic interventions. Such developments will be discussed later. [7]

Timely diagnosis and treatment of KD is vital in order to reduce

potentially dangerous or debilitating cardiac sequelae. Cardiac complications of treatment delay and treatment failure include development of coronary artery aneurysms or ectasia in approximately 15-25% of affected children. Other complications that may follow are myocardial infarction or thrombosis. Treatment with intravenous immunoglobulin (IVIG) in the acute phase of Kawasaki disease reduces the risk to 5%. [1,3,4] Early detection and timely treatment therefore has a huge impact on disease progression and treatment of refractory KD. [3,6]

Methodology

A number of databases including Google Scholar, PubMed, Science Direct and The Cochrane Library were searched for papers regarding the treatment options for KD, and from these key terms were identified. The following search terms were used either alone or in combination: Kawasaki disease, Kawasaki disease treatment, Kawasaki disease diagnosis, management of Kawasaki disease, treatments, IL-1, TNF-alpha, pharmacological treatment of Kawasaki disease.

Studies were chosen based on relevance to the literature review focus: the treatment options available for KD, cardiac sequalae, particularly, coronary artery abnormalities. Articles included were published in the last 25 years in the English language. A total of 30 articles were found to be relevant.

Current guidelines for treatment of Kawasaki Disease

There are a number of different guidelines worldwide for the treatment of KD, but there is general consensus that prompt treatment of KD significantly reduces disease progression (Table 2). [1]

As seen in Table 2, the use of aspirin and 2.0 g/kg/per day of IVIG is the recommended treatment for KD. IVIG is given as early as possible with variation in the dosages of aspirin required, especially in the acute phase of the disease.

Table 2. *Comparisons of guidelines for treatment of Kawasaki disease.*

Country Guidelines	IVIG	Aspirin
Australian Royal Children's Hospital Melbourne	Immediate hospital management and commencement of 2 grams/kg of IVIG over 10 hours within 10 days of illness. [13]	3-5 mg/kg of aspirin given once a day for 6-8 weeks. [13] An echocardiogram done at initial presentation and, if negative, again at 6-8 weeks. [13]
American Heart Organisation	Single dose of 2 g/kg IVIG. [1]	High dose aspirin of 80-100 mg/kg divided into four doses. [1]
United Kingdom (National Institute of Health and Excellence)	IVIG 2 g/kg as a single infusion over 12 hours.	30-50 mg/kg/day of aspirin divided into four doses. [14] Ongoing aspirin 2-5 mg/kg/day when fever settles, minimal duration of 6 weeks depending on echocardiogram and ECG investigations.

Treatment options for Kawasaki Disease

Salicylate

The acute phase of KD causes marked inflammation and, as a result, there is a conformational change in coronary artery endothelium. [3,4,13,14] Aspirin is widely used for a number of medical conditions, and its anti-inflammatory effects are of great benefit to those diagnosed with KD. [3] Aspirin has anti-inflammatory, antipyretic and antiplatelet effects, which make it ideal in this acute phase and for long term management of the disease. [1,6,14] In low doses, aspirin inhibits platelet generation of thromboxane A2, resulting in an antithrombotic effect. The main concern with long term use of aspirin in children is the risk of toxicity. [6,15]

It has been shown that there is no difference in the incidence of CAAs in patients who are treated with high dose (> 80 mg/kg/dose) versus a low dose (< 80 mg/kg/day) of aspirin in the acute phase of KD. [14] In North America, use of high doses is accepted during the initial phase, while in Japan, concern about toxicity has led to moderate use (30-50 mg/kg/day) in the acute phase. [1]

A Cochrane review analysed randomised controlled trials of the use of salicylate in treatment of KD. Only one relevant study was identified, which compared aspirin alone to aspirin plus IVIG. [6] There was no difference in the incidence of CAAs up to 30 days following disease onset between patients treated with IVIG 200 mg/kg daily for five days and patients treated with IVIG 200 mg/kg plus 35-50 mg/kg/day of aspirin. [6] The data collection period was limited to 60 days, therefore the study was unable to identify any deleterious effects of either regime over a longer period. [6] The use of aspirin did not appear to add a benefit when used with IVIG, but not using aspirin altogether was not effective in reducing CAAs. There is a lack of randomised controlled trials focusing on this issue, and currently there is not enough evidence to recommend the omission of aspirin in treatment of children with KD.

There is also evidence that in the acute phase of KD there is reduced absorption and increased clearance of aspirin. When higher doses are used, therapeutic levels are usually not reached. [16,17] However, hepatotoxicity, gastritis and gastrointestinal bleeding are common concerns with using high dose and long term aspirin regimens, with the possibility of developing Reye's syndrome in the children treated. [13-15,17] Although adverse effects from the use of aspirin were not identified in randomised controlled trials, this lack of evidence could be attributed to the short duration of follow-up in these trials.

Intravenous immunoglobulins (IVIG)

Studies from Japan have shown that administration of IVIG during the initial acute episode of KD has a considerable impact on reducing coronary artery abnormalities. [5,18] IVIG is a blood-based product which contains pooled, polyvalent IgG extracted from the plasma of human donors. [18] It has generalised anti-inflammatory effects which help reduce fever and the acute markers of inflammation associated with KD. It is understood that once IVIG is injected, it forms an immune complex which interacts with Fc receptors on dendritic cells and as a result mediates anti-inflammatory effects. [7,19] This in turn reduces the severity of the inflammatory state and reduces the conformational changes of the coronary arteries, therefore reducing coronary ectasia; however, the complete mechanism of action is unknown. [5,20,21]

A meta-analysis of existing randomised controlled trials compared the effectiveness of IVIG with a number of different interventions. [5] Results showed that IVIG was significantly better than placebo in reducing new CAAs, at 30 days (RR = 0.74, 95% CI 0.61-0.90).[5] There was no difference between the groups at 60 days. The meta-analysis showed that when 400 mg/kg/day of IVIG was used for five days versus 2 gm/kg in a single dose there was a reduction in CAAs at thirty days after using the higher single dose (RR = 4.47, 95% CI 1.55 - 12.86). [5] There was also a significant reduction in duration of fever with the higher doses. [5] IVIG did not seem to be associated with an increase in adverse events, although IVIG can have important adverse effects, including headache, dermatitis, pulmonary oedema, anaphylactic reaction, acute renal failure, venous thrombosis and aseptic meningitis. [5,14]

Overall, it was found that using higher doses of IVIG per kg was more beneficial than using lower doses. There was no difference between different types of preparations of IVIG and the incidence of adverse effects. [1,5] Randomised controlled trials and meta-analyses have

confirmed that IVIG plus aspirin is more helpful in reducing risk of CAAs compared to aspirin alone. [1,5,6] Although aspirin does not appear to effect aneurysm formation, all trials of IVIG treatments have included the use of aspirin with IVIG, as it was the treatment of choice prior to IVIG development. Further, as there is insufficient evidence about the use of IVIG alone, use of aspirin in conjunction with IVIG continues. [6]

Corticosteroids

Interest in the use of corticosteroids developed when children continued to develop CAAs despite effective IVIG and aspirin treatment. [1,14,22] Glucocorticoids have a number of mechanisms of action. The most important for the treatment of KD are the potent anti-inflammatory effects. [23]

A multicentre, randomised, double blind, placebo-controlled trial in 2007 determined the effect of adding methylprednisolone to conventional primary therapy in reducing CAAs. [19] All patients received the conventional therapy of IVIG of 2 g/kg and aspirin 80-100 mg/kg per day until children were afebrile for 48 hours, then 3-5 mg/kg per day of aspirin from that day on. Methylprednisolone 30 mg/kg was given as a single intravenous dose to half of the participants. It did not improve coronary artery outcomes at week one or five. [1,19] Its use shortened the duration of the initial period of hospitalisation and accelerated the recovery of laboratory biomarkers such as estimated sedimentation rate (ESR) at week 1 ($p = 0.02$) and tendency for lower c-reactive protein (CRP) ($p = 0.07$). [19] The total number of days of fever and of hospitalisation did not differ between the intervention and control group. [19,24-26]

Children who had a persistent fever and who then received retreatment with IVIG and IV methylprednisolone showed improved that coronary outcomes when compared to the placebo group, indicating that children with higher risk for CAAs may benefit from glucocorticoid treatment. [19] Limitations of this study included that only a single dose of IV methylprednisolone was used as the intervention, and the study focused on a relatively low risk population. There are limited data available on possible adverse effects from its use due to short duration of follow-up. [19]

Similarly, a Cochrane review focusing on steroid use in KD found that steroids did not reduce the incidence of coronary artery aneurysm. Several of the studies identified were limited by the quality of the study design and by sample size. [3,25,27] A meta-analysis published in 2012 showed a significant reduction in the rates of initial treatment failure among those who received corticosteroid therapy in combination with IVIG compared to IVIG alone (Odds Ratio: 0.05; 95% CI: 0.32-0.79; $p = 0.003$). [25] This supported the study by Newburger and colleagues (2007), which showed that the use of corticosteroids reduced the time required for CRP to return to normal. Although corticosteroid therapy combined with IVIG in primary treatment or as treatment for IVIG-resistant patients improved the clinical course without increasing coronary artery abnormalities in children with acute KD, it did not cause any reduction of already existing CAAs. [25]

Future treatments and research

According to current American Heart Association guidelines, further IVIG is required to reduce cardiac sequelae if patients have a recurrent fever beyond 36 hours after completion of the IVIG infusion. [1] This highlights the importance of developing further treatments to prevent treatment failure.

As previously mentioned, serum levels of inflammatory cytokines such as TNF-α, IL-1 and IL-6 are increased during acute KD. [3,4] A higher percentage of patients with coronary artery involvement were also TNF-α positive. It is postulated that TNF-α activity plays an important role in the pathogenesis of Kawasaki disease. [3,4,28] This cytokine promotes conformational changes to the arterial endothelium and offers a potential mechanism for development of vascular diffuse dilatation and coronary artery aneurysms. TNF-α inhibitors fall into two classes, monoclonal antibodies and soluble receptors. [1,3] Both etanercept and infliximab (a monoclonal antibody against TNF-α) have beneficial effects on the treatment of KD. [12,28]

A prospective open-label trial of etanercept in patients with KD in conjunction with IVIG and aspirin was inconclusive in determining the benefit of adding etanercept to IVIG. [12] Patients received a 0.8 mg/kg/dose of etanercept immediately after IVIG infusion, and then received a weekly dose. [12] Fifteen patients completed the study, and they did not require retreatment with IVIG for persistent or recurrent fever, nor did they have worsening coronary artery involvement/cardiac dysfunction. [12] This study was underpowered due to the small sample size and therefore could not determine if adding etanercept to IVIG and aspirin was beneficial. A randomised controlled trial of this combination would be effective for both acute phase and refractory phases of the disease.

Similarly, infliximab controls disease progression and improves outcomes in IVIG-resistant KD. [29] A retrospective chart review in 2007 compared the duration of fever and coronary artery dimensions of patients with KD. [29] Patients who had their first retreatment with infliximab defervesced earlier and had a shorter hospital stay than those retreated with IVIG. However, coronary artery outcomes and adverse events were similar in both groups. [29] This was a retrospective chart review in one hospital, so the general applicability of the results is limited. Further large scale randomised studies are needed to guide practice.

In a retrospective study published in 2011, 369 patients were treated with a combination of Ulinastatin, aspirin and IVIG for initial therapy in the acute phase, compared to 1179 patients treated with conventional initial treatment of IVIG and aspirin. [30] Ulinastatin reduces neutrophil counts, and causes high plasma levels of neutrophil elastase, improving IVIG's effectiveness, and as a result reduces the occurrence of CAAs. [30] CAAs were reduced in the group receiving Ulinastatin in comparison to the control group; 3% versus 7%, respectively ($p = 0.01$). [30] Many of the CAAs occurred in patients who had refractory KD, but the occurrence of CAAs was less likely in the Ulinastatin group compared to the control group; 13% versus 22%, respectively ($p = 0.001$). [30] Due to the retrospective nature of this study, despite being adequately powered, more evidence is required before changing practice.

Conclusion

It is important to exclude Kawasaki disease in the commonly presenting febrile child. It is the leading cause of acquired heart disease in children under the age of five. Coronary artery abnormalities are an important complication of a failure of KD treatment, affecting 15-25% of untreated children. Timely diagnosis and treatment with high dose IVIG and aspirin is supported with the best level of evidence and appears to be the most effective way of treating KD. In patients with recurrent KD, or failure of the initial therapy, use of adjunctive treatments such as corticosteroids, TNF-α inhibitors and Ulinastatin have some benefit. However, large scale randomised controlled trials are required to support future evidence based practices.

Conflict of interest

None declared.

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