

High-dose aspirin for Kawasaki disease: outdated myth or effective aid?

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ABSTRACT

Objective. To compare the efficacy and safety of intravenous immunoglobulin (IVIG) plus high-dose aspirin (HDA) vs. IVIG plus low-dose aspirin (LDA) for the treatment of Kawasaki disease, with an emphasis on coronary artery outcomes.

Methods. This study was a retrospective, medical record review of paediatric patients with Kawasaki disease comparing 6 centres that routinely used HDA for initial treatment and 2 that used LDA in 2004-2013. Treatment response and adverse events were compared. The primary outcome measure was the occurrence of coronary aneurysm at the subacute or convalescent stage.

Results. The cohort included 358 patients, of whom 315 were initially treated with adjunctive HDA and 43 with LDA. There were no demographic differences between the groups. Coronary aneurysms occurred in 10% (20/196) of the HDA group and 4% (1/24) of the LDA group ($p=0.34$). Equivalence tests indicate it is unlikely that the risk of coronary aneurysm in LDA exceeds HDA by more than 3.5%. There were no significant between-group differences in the need for glucocorticoid pulse therapy or disease recurrence. Coronary ectasia rate and hospitalisation time were significantly greater in the HDA group. Adverse events were similar in the two groups.

Conclusion. We found no significant clinical benefit in using IVIG+HDA in Kawasaki disease compared to IVIG+LDA. The use of adjunctive HDA in this setting should be reconsidered.

Introduction

Kawasaki disease is an acute febrile vasculitic syndrome of early childhood that

can lead to morbidity or even mortality due to the development of coronary artery aneurysms (1-5). Acetylsalicylic acid (aspirin) is a non-steroidal anti-inflammatory drug. In high doses (1 g/day, adults), it exerts an anti-inflammatory effect by inhibiting the cyclooxygenase pathway of arachidonic acid metabolism. In lower doses (75-150 mg/day, adults), it exerts an anti-thrombotic effect by inhibiting platelet-derived thromboxane A2 (4, 5). Kawasaki disease is generally treated initially with intravenous immunoglobulin (IVIG) together with high anti-inflammatory doses of aspirin: 80-100 mg/kg/day according to the American Academy of Pediatrics/American Heart Association (AAP/AHA) guidelines or 30-50 mg/kg according to the Japanese Ministry of Health guidelines. After fever resolves, patients are switched to low anti-thrombotic doses of aspirin: 3-5 mg/kg/day by both guidelines (1, 6, 7).

Historically, the treatment of Kawasaki consisted of high-dose aspirin (HDA) only (8, 9). After the introduction of IVIG, several randomised controlled trials showed that IVIG was efficacious in ameliorating clinical signs and preventing inflammation and the subsequent development of coronary aneurysms (10-12). However, HDA (at least 30 mg/kg/day) was consistently used as an adjunct in all these studies (10-12) and it continues to be widely used in the acute phase of the disease (1, 6, 7).

The present study was prompted by our discovery that 2 Israeli medical centres do not routinely administer HDA during the acute phase of Kawasaki disease, but initiate treatment with low-dose aspirin (LDA) together with IVIG. The aim of the study was to compare their experience with that of 6 other

Israeli medical centres that follow the AAP/AHA guidelines (6).

Methods

The medical records of all children with Kawasaki disease attending 8 paediatric tertiary medical centres in Israel from January 2004 to December 2013 were reviewed. Inclusion criteria for the study were clinical diagnosis of Kawasaki disease, either complete (fever >5 days+4-5/5 criteria) or incomplete (fever >5 days+2-3/5 criteria); admission during the acute phase of the disease; and treatment with at least one course of IVIG (2 g/kg) plus HDA or LDA. Patients admitted in the subacute phase of the disease were excluded

Data were collected on demographics, clinical manifestations, adverse events, and coronary involvement defined according to the AHA guidelines (4). They were assessed by a paediatric cardiologist, who was blinded to the treatment. The primary efficacy outcome was the occurrence of a coronary aneurysm at the subacute or convalescent stage. Secondary outcomes were occurrence of ectasia, disease recurrence (defined as recurrence of fever after >72 hours), and total hospitalisation time. Aneurysm was defined as an isolated and distinct outpouching of a coronary artery segment. Ectasia was defined as a qualitatively dilated or abnormally tapered (distally or proximally) artery. A concomitant finding of aneurysm and ectasia was classified as an aneurysm. Of note, echocardiographic data were not always available when the procedure was done in an outpatient clinic. Safety was defined by severity of adverse events, which were graded according to the Rheumatology Common Toxicity Criteria, v. 2.0, as follows: 1 – mild, 2 – moderate, 3 – severe, 4 – life threatening (13). The study was approved by the Institutional Review Board of each participating hospital.

Student *t*-test was used to evaluate differences in continuous variables between patients treated with HDA and LDA. Pearson chi-square test was used for categorical variables. The Westlake-Schuirmann equivalence test was used to assess the likelihood of LDA exceeding HDA in risk of outcome events.

Fig. 1.

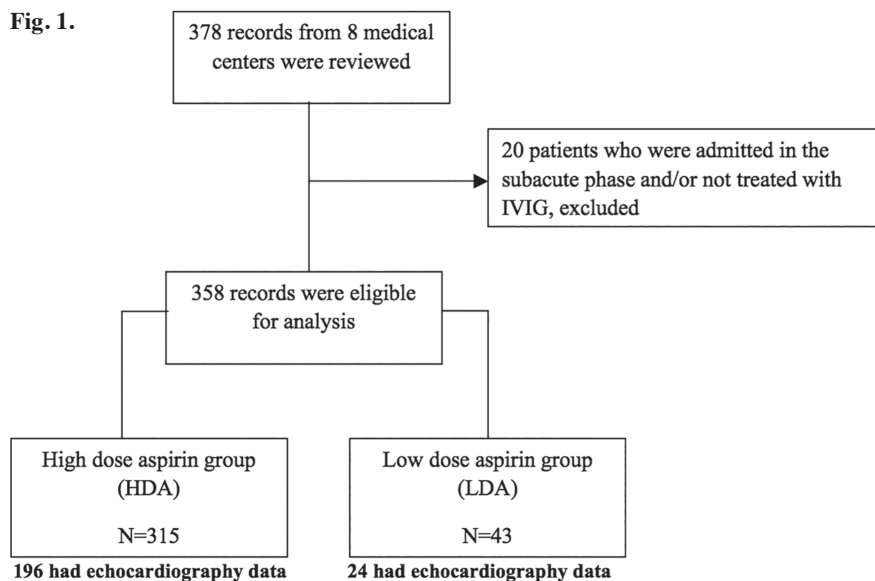


Table I. Demographic and clinical data of patients with Kawasaki disease who received intravenous immunoglobulin plus high or low dose aspirin.

Variable	HD Aspirin (n=315)	LD Aspirin (n=43)	p-value
Age (years), mean±SD	2.4 ± 1.9	2.9 ± 3.1	0.38
Gender (males), %	63.5%	65.1%	0.87
Weight (kg), mean±SD	13.1 ± 6.0	14.7 ± 9.0	0.26
Fever duration to start of therapy (days), mean±SD	8.1 ± 3.0	9.1 ± 4.0	0.04
Complete Kawasaki, %	61.9%	53.5%	0.32

HD: high dose; LD: low dose.

Table II. Efficacy outcome measures.

Outcome	HD Aspirin (n=315)	LD Aspirin (n=43)	p-value
Coronary aneurysms in the sub -acute or convalescent stage, %	10.2% (20/196)	4.2% (1/24)	0.34
Coronary ectasia in the sub -acute or convalescent stage, %	24.5% (48/196)	4.2% (1/24)	0.024
Fever ≥ 72 hrs after therapy start, %	9.3%	7%	0.62
Glucocorticoid pulse therapy, %	8.2%	10%	0.84
Admission time (d)	7.3±4.6	5.7±2.8	0.03

HD: high dose; LD: low dose.

Results

The records of 378 patients were reviewed (Fig. 1). Twenty patients were excluded because they were admitted in the subacute disease phase of the disease and/or were not treated with IVIG. Of the remaining 358 patients, 315 were treated with IVIG+HDA 80-100 mg/kg/day, according to the AAP/AHA guidelines and 43 started treatment directly with IVIG+LDA (3-5 mg/kg).

About 60% of patients had complete Kawasaki and about 40% incomplete. Subanalyses of the efficacy and safety measures yielded similar results for both types (data not shown).

The clinical data are summarised in Table I. There were no significant differences in demographic parameters between the HDA and LDA groups. The hospitals are located in close proximity (*i.e.* up to 100 km from each oth-

er) and serve similar populations. The LDA group had a significantly longer duration until initiation of treatment ($p < 0.04$).

Findings for the efficacy outcome measures are shown in Table II. Echocardiography performed at the subacute or convalescence stage (our primary outcome measure) revealed the presence of coronary aneurysms in 10.2% of the HDA group (20/196 patients) and 4.2% of the LDA group (1/24 patients), and of coronary ectasia in 24.5% (48/196) and 4.2% (1/24) of patients, respectively. The between-group difference in the rate of coronary aneurysms was not significant ($p = 0.34$) and equivalence tests indicated it is unlikely ($p < 0.05$) that the risk of coronary aneurysm in LDA exceeds HDA by more than 3.5%. The difference in the rate of coronary ectasia and in total hospitalisation time was statistically significant – less in the LDA group ($p = 0.024$ and $p = 0.03$ respectively). No significant differences were found for other secondary outcome measures (Table II).

There were no significant differences between the HDA and LDA groups in adverse events, overall or by disease severity ($p = 0.26$). No adverse events occurred in 95.1% of the HDA group and 89.5% of the LDA group. Almost all adverse events were intermittent and categorised as mild. Most occurred during IVIG infusion. However, in the HDA group, 3 patients had adverse events that may be attributable directly to the drug. These included abdominal pain in 1 patient and epistaxis in 2; 1 of the patients with epistaxis also had rectal bleeding. Elevations in liver enzyme levels occurred in 74 patients overall, but they were documented before onset of therapy and therefore, attributed to the disease.

Discussion

The present study shows that the treatment of the acute phase of Kawasaki disease with IVIG and LDA is at least as good as IVIG and HDA, and might be even better. There was no significant difference between the LDA and HDA groups in the rate of occurrence of coronary aneurysms at the subacute or convalescence stages. This was defined as

our primary outcome measure because coronary aneurysms usually do not develop in the acute phase of the disease. They are considered its most serious complication, leading to long-term morbidity and in rare cases mortality (1). Interestingly, a study conducted before the introduction of IVIG comparing patients treated with aspirin only to those treated with antibiotics only found that the incidence of coronary lesions was not significantly lower in the aspirin group compared to the antibiotics group (8).

No randomised controlled trials that evaluated administration of LDA in addition to IVIG have been published. One randomised controlled study comparing high (80–100 mg/kg) and moderate (30–50 mg/kg) doses of aspirin with IVIG yielded no between-group differences (14). However, the moderate dose also known to have an anti-inflammatory effect, which could explain the results. Saulsbury (15) was the first to evaluate the use of a low, anti-thrombotic dose of aspirin for the treatment of Kawasaki disease. In a small retrospective study, he found no differences in time to fever reduction between the IVIG+HDA and IVIG+LDA groups. However, none of the patients acquired coronary abnormalities. Later, Hsieh *et al.* (16) retrospectively evaluated 162 patients treated with IVIG alone during the acute phase. Ten percent had had coronary artery aneurysms before IVIG therapy was initiated, and another 4% acquired aneurysms after IVIG therapy was completed. This study did not include a control group, but the results were comparable with previous studies of patients treated initially with IVIG and aspirin. A 2006 Cochrane review concluded that there is insufficient evidence to indicate whether children with Kawasaki disease should continue to receive salicylate as part of their treatment regimen (17). Finally, Lee *et al.*, in a retrospective study showed that although HDA shortened the duration of fever, treatment without aspirin in the acute phase had no effect on the response to IVIG, resolution of the inflammation, or development of coronary artery aneurysms (18).

The effectiveness of HDA in the treatment of Kawasaki disease was also

questioned in experimental studies. In an *in vitro* study, Lau *et al.* (19) examined splenocytes from a murine model of Kawasaki disease to which IVIG or salicylate was added at concentrations corresponding to therapeutic serum levels in patients. They found that IVIG reduced the immune response leading to decreased expression of the proinflammatory cytokine tumour necrosis factor (TNF)-alpha, whereas pharmacologic doses of salicylate enhanced TNF-alpha production. Indeed, anti-TNF-alpha medication is one of the treatment options for patients with Kawasaki disease who fail to respond to conventional treatment (20).

There were no between-group differences in demographic characteristics. The 2 centres that use LDA are located in the centre of Israel close to other participating centres. About 40% of patients in both groups had incomplete Kawasaki. This rate is close to that reported by a single Turkish centre (21), but higher than that found in Asian centres (10–18%) (22, 23). Nevertheless, although the groups differed in duration of fever to onset of therapy, the difference was not clinically significant (9.1 ± 4 days in the LDA group, 8.1 ± 3 days in the HDA group). Additionally, the LDA group included some patients with longer fever duration, which made them preemptively more prone to complications, although their total admission time was significantly lower.

Adverse events were relatively mild and transient. The laboratory abnormalities identified were generally related to the disease itself, not to its treatment. Moreover, most of the adverse events occurred during IVIG infusion and were directly related to its use. Three cases of epistaxis, rectal bleeding, and abdominal pain may have been attributable to aspirin, but they occurred in less than 2% of the HDA group. Indeed, even at the high doses used in Kawasaki disease, aspirin is considered relatively safe. Toxicity (salicylism) occurs with much higher doses and serum aspirin levels need to be measured after the fifth day of administration (24, 25). Serum aspirin levels were not measured in our patients, but no signs of salicylism were found in any of the participating medical centres.

In addition, Reye's syndrome, a complication of aspirin use, is extremely rare in Kawasaki disease (26).

This study was limited by its retrospective design. There were differences in data collection and echocardiography protocols (timing and performance) among the centres, but all were done after the acute phase, in the convalescent stage. Moreover, the LDA group was relatively small as it was derived from only 2 of the 8 centres. In addition, not all echocardiography data were available because we could not access outpatient electronic medical records. Finally, the study population was of Jewish and Arabic ethnicity, possibly limiting the generalisability of the results to other populations. This factor is particularly pertinent for Asian populations, which have more severe disease, although the Japanese guidelines recommend a lower aspirin dose than do the American guidelines (1, 6, 7).

A randomised prospective controlled study comparing the efficacy of IVIG combined with HDA or LDA in the treatment of Kawasaki disease is needed to reach a definitive conclusion. However, a well-powered study (0.8) with a 7% limit showing that LDA is not inferior to HDA in preventing coronary artery aneurysms would require a sample size of 4,087 in each arm, which is highly impractical.

In conclusion, this study takes a stand in the ongoing debate regarding the necessity of using HDA in the treatment of the acute phase of Kawasaki disease. It shows that the use of LDA together with IVIG is at least as effective and as safe as HDA and IVIG. Since IVIG itself has strong anti-inflammatory effects, adding ASA might not be necessary. We believe that based on this and previous studies, modification of the current treatment guidelines for Kawasaki disease should be considered.

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