Acetylsalicylic acid for children with Kawasaki disease

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Abstract

Question A 7-year-old child in my office was recently discharged from the hospital after receiving intravenous immunoglobulin for Kawasaki disease. Should I continue treatment with acetylsalicylic acid (ASA), and if so, what is the appropriate dose?

Answer The role of ASA for Kawasaki disease during the acute febrile phase has recently been called into question. According to several studies, ASA might reduce the duration of fever but it does not appear to directly reduce the incidence of coronary artery complications. However, with no high-quality randomized controlled trials, the evidence is scarce and more studies with good methodology are needed to determine the value of ASA in the treatment of Kawasaki disease. Currently, guidelines recommending the use of ASA should be followed.

Kawasaki disease (also known as *mucocutaneous lymph node syndrome*) is an acute, systemic inflammatory disease with associated vasculitis of unknown cause.[1] It was first described by the Japanese pediatrician Tomisaku Kawasaki in 1967.[2] It is believed that the condition might result from an exaggerated immune response to an infection in patients with genetic susceptibility and thus lead to vascular endothelial irritation and injury.[3,4] Kawasaki disease is the leading cause of acquired heart disease among children in North America and Japan.[5,6] It usually affects children younger than 5 years of age.[6,7] In the province of Ontario, the annual incidence of Kawasaki disease in 2004 to 2006 was 26.2 per 100 000 children younger than age 5.[8] More patients were seen in late fall to winter with a male-to-female ratio of 1.6:1.[8]

Diagnosis of Kawasaki disease is made clinically. The American Heart Association suggests that the diagnostic criteria for classic (typical) Kawasaki disease are the presence of fever for at least 5 days and 4 out of 5 of the following clinical features: bilateral conjunctival injection; oral changes such as cracked and erythematous lips and strawberry tongue; cervical lymphadenopathy; extremity changes such as erythema of the palms and soles or desquamation of the fingers and toes; and polymorphous rash. Incomplete (atypical) Kawasaki disease occurs in children with fever for at least 5 days with 2 or 3 of these findings.[1] Other less-frequent symptoms of Kawasaki disease include gastrointestinal (diarrhea, vomiting, and abdominal pain), respiratory (cough and rhinorrhea), and rheumatologic (joint pain and swelling) symptoms.[1]

Complications of Kawasaki disease mainly involve the cardiovascular system such as coronary artery aneurysms, myocarditis, pericarditis, pericardial effusion, valvular dysfunction, left ventricular dysfunction, and arrhythmias.[1]

Treatment of Kawasaki disease aims to reduce inflammation and prevent cardiac complications. The American Heart Association guidelines recommend administration of intravenous immunoglobulin (IVIG) (2 g/kg over 12 hours) in combination with high-dose acetylsalicylic acid (ASA) (80 to 100 mg/kg per day divided into 4 doses). After fever subsides for 48 to 72 hours, the guidelines recommend reducing the dose of ASA to 3 to 5 mg/kg once daily for 6 to 8 weeks. If coronary abnormalities such as stenosis or aneurysms develop and persist, low-dose ASA might be required for life.[1] Intravenous immunoglobulin modulates cytokine production and influences T cell activity, while different doses of ASA might reduce inflammation and reduce the risk of thrombosis.[1]

The role and efficacy of high-dose ASA for Kawasaki disease during the acute febrile phase has been called into question recently owing to the lack of clear evidence for preventing coronary artery complications and the risk of Reye syndrome.[9]

Using ASA for Kawasaki disease

A systematic review and meta-analysis from a decade ago reported that 1 randomized controlled study examining the incidence of coronary artery lesions at 30 days after onset of symptoms in 102 children was not

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powered sufficiently to show a statistical difference between children who received a combination of IVIG and ASA (30 to 50 mg/kg per day until fever subsided then 10 to 30 mg/kg per day until acute reaction disappeared) and those who received IVIG alone (relative risk of 1.30, 95% CI 0.37 to 4.56).[9] The second study in the meta-analysis showed that although high-dose ASA shortened fever duration, no effect on coronary artery abnormalities at follow-up was noted. Among children with Kawasaki disease who received 2 g/kg of IVIG, prevalence of fever on day 3 was 40% in those who received low-dose ASA (3 to 8 mg/kg per day for 3 months) compared with 18% in children receiving high-dose ASA (100 mg/kg per day for 14 days then 3 to 5 mg/kg per day). Prevalence of fever on day 6 was 9% in the low-dose ASA group and 3% in the high-dose ASA group. Coronary artery abnormalities on admission were reported in none of the 45 children in the low-dose ASA group and in 2 of the 40 children in the high-dose ASA group; and at follow-up in 1 of 45 patients in the low-dose ASA group and in 1 of 40 patients in the high-dose ASA group. Because the study had too small a sample size to detect a significant effect on an uncommon outcome, the meta-analysis concluded that there was insufficient evidence regarding whether or not to recommend the use of ASA.

Coronary artery abnormalities and ASA

A retrospective study compared coronary artery abnormalities between 568 American and 514 Japanese children with Kawasaki disease using echocardiography to measure *z*-max scores (ie, maximum internal diameter of the left anterior descending or right coronary artery reported as SD units from the mean *z* score, normalized for body surface area) within 12 weeks after onset and calculated using 2 different regression equations (Dallaire from Canada and Fuse from Japan).[10] Normal *z*-max scores were defined as less than 2.5 SD units. Median *z*-max scores using the Dallaire equation for the American and Japanese subjects were 1.9 and 2.3 SD units, respectively ($P<.001$). Even when using the Fuse *z*-score equation, the American children still had a higher percentage of normal coronary arteries (*z*-max score of <2.5; $P<.001$) and a higher percentage of Japanese children had *z*-max scores between 2.5 and 5.0 ($P<.001$). There was no significant difference reported in rates of patients with a *z*-max score of at least 5.0 between the 2 countries. In a multivariable model adjusting for age, sex, and treatment response, being Japanese was still associated with a higher *z*-max score. This study supported the notion that a *z* score could be used as a standard measurement of coronary artery diameter in children with Kawasaki disease.

Five retrospective and prospective observational studies suggested that high-dose ASA does not reduce coronary artery lesions, with a surprising possibility that ASA might be associated with a higher incidence of coronary artery abnormalities; however, results might have been confounded by the indication to treat those children with ASA.[11-15]

Lee and colleagues reported that there was no significant difference noted in the incidence of coronary artery lesions between 180 Korean children who received IVIG with or without ASA in the acute phase (7.8% vs 3.9%, respectively; $P=.514$).[11] Two studies[12,13] compared high-dose ASA with low-dose ASA. A retrospective study from Taiwan reported that the incidence of coronary artery lesions was similar between children who received IVIG with high-dose ASA (>30 mg/kg per day) and those receiving IVIG with low-dose ASA (3 to 5 mg/kg per day) (52 of 305 children vs 84 of 546 children, respectively; $P=.67$).[12] Another recent retrospective study from Israel reported coronary aneurysms in 10% of 196 children receiving IVIG with high-dose ASA compared with only 4% of 24 children who received IVIG with low-dose ASA ($P=.34$), suggesting that there was no significant difference between the groups but that there might be a higher rate of adverse outcomes for the disease with high-dose ASA.[13] High-dose ASA was further shown to be associated with a higher prevalence of coronary artery lesions. In a retrospective study of 182 Japanese children, 111 received IVIG with delayed administration of anti-inflammatory drugs and 71 received IVIG with anti-inflammatory drugs (ASA or flurbiprofen) in the acute phase; the study revealed that the prevalence of coronary artery lesions was 1 out of 111 children in the delayed anti-inflammatory drug group compared with 11 out of 71 children in the second group ($P<.001$), and after 30 days of illness the prevalence was 0 out of 111 children compared with 4 out of 71 children, respectively ($P=.022$).[14] Similar results were reported in a nationwide questionnaire from South Korea.[15] The prevalence of coronary artery aneurysms based on *z* score (24.8% vs 18.3%; $P=.001$) and Japanese criteria (19.0% vs 10.4%; $P<.001$) was higher in 7947 patients who received IVIG with medium- to high-dose ASA (≥30 mg/kg per day) compared with 509 patients who received IVIG with low-dose ASA (3 to 5 mg/kg per day) during the acute febrile phase. Based on both univariate analyses and multivariate logistic regression analyses, children who received medium- to high-dose ASA had approximately 1.5 and 2 times higher likelihood of having coronary artery aneurysms than those who received low-dose ASA based on *z* score and Japanese criteria, respectively.

However, the higher prevalence of coronary artery abnormalities in children who received ASA might have been confounded by indication, as health care providers were more likely to prescribe ASA to children with coronary artery abnormalities compared with those without coronary artery complications.

Duration of fever and ASA

Lee and colleagues suggested that mean (SD) duration of fever after IVIG completion was 13.3 (13.5) hours in the group receiving IVIG without ASA, compared with 6.2 (8.3) hours in the IVIG with the high-dose ASA group ($P<.001$).[11] Kim and colleagues[15] also reported that the mean duration of fever was shorter (5.7 vs 6.1 days; $P=.001$) in the medium- to high-dose ASA group compared with the low-dose ASA group. Results from both studies suggested that high-dose ASA might shorten the duration of fever; however, its benefit for the treatment outcome remains unclear.

Adverse effects of ASA

Kuo and colleagues[12] reported that after IVIG treatment, children receiving high-dose ASA had significantly lower hemoglobin levels compared with those taking low-dose ASA (mean [SD] of 10.42 [0.08] vs 10.70 [0.07] g/dL, respectively; $P=.006$). Furthermore, because hepcidin is involved in iron metabolism, an increase in serum hepcidin levels in children with Kawasaki disease results in lower serum iron levels available for erythropoiesis and thus leads to anemia. Higher serum hepcidin levels and delayed decrease in hepcidin levels were observed in those receiving high-dose ASA compared with those receiving low-dose ASA (mean [SD] of 163.98 [52.94] vs 81.48 [13.56] ng/mL [$P=.04$], and 56.90 [46.42] vs 162.04 [22.66] ng/mL [$P=.02$], respectively).

Another concern related to ASA use is the development of Reye syndrome, as reported in a few children with Kawasaki disease who received high-dose ASA. Children developed acute onset of altered mental status with hepatomegaly and abnormal elevation of hepatic aminotransferase levels. Reye syndrome was diagnosed after liver biopsy.[16,17]

Duration of low-dose ASA therapy

According to the American Heart Association guidelines, the ASA dose should be reduced after the child has been afebrile for 48 to 72 hours.[1] Low-dose ASA (3 to 5 mg/kg per day) should be maintained for 6 to 8 weeks after the onset of disease. A recent retrospective study in 84 Korean children with Kawasaki disease reported that most of the inflammatory (white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level) and thrombotic markers (D-dimer assay) normalized within approximately 3 to 4 weeks.[18] If no coronary artery lesions were detected by echocardiography, low-dose ASA was discontinued. Follow-up at 6 to 8 weeks indicated no new coronary artery lesions despite short-term low-dose ASA treatment. While intriguing evidence, this single retrospective study is unlikely to change practice.

Conclusion

Intravenous immunoglobulin with high-dose ASA should be the treatment of choice for children with Kawasaki disease until fever subsides, and low-dose ASA should be given for 6 to 8 weeks thereafter. The role and effectiveness of ASA in children with Kawasaki disease during the acute phase has been called into question recently, especially in regards to anticipated reduction in the incidence of coronary artery abnormalities. More research is expected in order to guide potential changes in practice.

Competing interests
None declared

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Child Health Update is produced by the Pediatric Research in Emergency Therapeutics (PRETx) program (**www.pretx.org**) at the BC Children's Hospital in Vancouver, BC. **Drs Sakulchit** and **Benseler** are members and **Dr Goldman** is Director of the PRETx program. The mission of the PRETx program is to promote child health through evidence-based research in therapeutics in pediatric emergency medicine.

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