Treatment of Acute Kawasaki Disease: Aspirin’s Role in the Febrile Stage Revisited

Kai-Sheng Hsieh, MD*‡; Ken-Pen Weng, MD§; Chu-Chuan Lin, MD*; Ta-Cheng Huang, MD*; Cheng-Liang Lee, MD*; and Shih-Ming Huang, MD*|

ABSTRACT. Objective. To evaluate the effect of treatment without aspirin in the acute phase of Kawasaki disease (KD) and to determine whether it is necessary to expose children to high- or medium-dose aspirin.

Methods. A total of 162 patients who fulfilled the established criteria of acute KD between 1993 and 2003 were included in this retrospective study. All patients were treated with high-dose intravenous immunoglobulin (IVIG; 2 g/kg) as a single infusion without concomitant aspirin treatment. Low-dose aspirin (3–5 mg/kg per day) was subsequently prescribed when fever subsided. Patients who had defervescence within 3 days after the completion of IVIG treatment were classified as the IVIG-responsive group, and those whose fever persisted for >3 days were classified as the IVIG-nonresponsive group. The 162 patients were divided further into 2 groups: those who were treated with IVIG before illness day 5, and those who were treated after illness day 5. We compared the response rate of IVIG therapy, duration of fever, and incidence of coronary artery abnormalities (CAAs) between these groups.

Results. A total of 153 patients were classified into the IVIG-responsive group, and 128 (83.66%) of them had defervescence within 24 hours after completion of IVIG therapy. Nine (5.56%) patients were classified into the IVIG nonresponsive group, and all received additional IVIG (2 g/kg) without aspirin. Six (66.67%) had defervescence within 3 days after additional therapy. Patients in the IVIG-nonresponsive group had a significantly higher incidence of CAAs than those in the IVIG-responsive group (25% vs 2.92%). In the group that was treated before illness day 5 (n = 16), all patients had defervescence within 3 days after IVIG therapy and 13 (81.25%) had defervescence within 24 hours. In the group that was treated after illness day 5 (n = 146), 137 (93.84%) patients had defervescence within 3 days and 115 (78.77%) had defervescence within 24 hours. One (6.67%) patient in the group that was treated before illness day 5 got a new onset of CAAs, as did 3 (3.85%) in the group that was treated after illness day 5. There was no statistically significant difference in the response rate of IVIG therapy, duration of fever, and incidence of CAAs between these 2 groups.

Conclusion. The results of our study indicate that the treatment without aspirin in acute stage of KD had no effect on the response rate of IVIG therapy, duration of fever, or incidence of CAAs when children were treated with high-dose (2 g/kg) IVIG as a single infusion, despite treatment before or after day 5 of illness. We conclude that it seems unnecessary to expose children to high- or medium-dose aspirin therapy in acute KD when the available data show no appreciable benefit in preventing the failure of IVIG therapy, formation of CAAs, or shortening the duration of fever. Pediatrics 2004; 114:e689–e693. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1037; Kawasaki disease, immunoglobulin, coronary aneurysm, aspirin.

ABBREVIATIONS. KD, Kawasaki disease; IVIG, intravenous immunoglobulin; CAA, coronary artery abnormality.

Kawasaki disease (KD) is an acute systemic vasculitis of unknown origin that occurs predominantly in children who are <5 years old. The most significant complication is coronary arteritis, and aneurysm formation occurs in 20% to 25% of untreated children. Although intravenous immunoglobulin (IVIG) has been shown to reduce both the duration of fever and the incidence of coronary artery abnormalities (CAAs) with the use of 2 g/kg in a single dose, the role and appropriate dose of aspirin during the acute phase is still unclear. In North America, high-dose (80–100 mg/kg per day) aspirin is most widely used during the acute phase. In Japan, concern about hepatic toxicity has led to the use of moderate-dose (30–50 mg/kg per day) aspirin as a recommended standard therapy in the acute phase. The purpose of this study was to evaluate the effect of treatment without aspirin in acute KD from 10 years’ experience in a single medical center, and we discuss the need for adding aspirin to the initial treatment of acute KD.

METHODS

We performed a retrospective study at the Veterans General Hospital, Kaohsiung, a tertiary referral center with 1200 beds. Medical records of all children who received a diagnosis of KD in our hospital between 1993 and 2003 were reviewed. A total of 162 children who fulfilled the established criteria of acute KD were included in the study group. All patients were treated with high-dose IVIG (2 g/kg) as a single infusion for 10 to 12 hours without concomitant aspirin therapy. We excluded patients who were treated with a regimen other than 2 g/kg of IVIG in a single dose or patients who were referred to us after being in the acute phase of the disease. Fever was defined as an oral or rectal temperature...
of 38°C or greater, and antipyrretic medication such as acetaminophen was used to control fever. After the fever subsided, low-dose aspirin (3-5 mg/kg per day) was prescribed. The inclusion criteria also consisted of patients who were treated before day 5 of onset of fever. Patients who had defervescence within 3 days after the completion of IVIG treatment were defined as the IVIG-responsive group, and those whose fever persisted for >3 days after IVIG treatment were defined as the IVIG-nonresponsive group. The 162 patients were divided further into 2 groups: those who were treated with IVIG before illness day 5, and those who were treated with IVIG after illness day 5. We compared the response rate, duration of fever, and incidence of CAAs between these groups. Patients for whom IVIG therapy failed received an additional dose (2 g/kg) of IVIG therapy immediately when fever persisted for >3 days. All patients had 2-dimensional echocardiography performed at the time of diagnosis and again at weeks 2, 4, and 8 after treatment and annually in follow-up. CAAs were defined as follows: (1) the internal lumen diameter >3 mm in children <5 years old, (2) the internal lumen diameter >4 mm in children >5 years old, (3) the internal lumen diameter 1.5 times greater than that of an adjacent segment, or (4) clearly irregular coronary artery lumen.8,9

Statistical Analysis

The descriptions of basic data, such as age and gender, are expressed as the mean ± standard deviation and percentage. The t-test was used for comparison of continuous variable data. For investigating the difference for the incidence of CAAs and efficacy of IVIG treatment without aspirin between groups, χ² test and Fisher exact test were undertaken. The advantage of Fisher exact test was applicable to the rare data set. Values were considered significantly different at P < .05. Statistical analyses were performed using the SPSS statistical software package (version 10.0.7C for Windows).

RESULTS

A total of 162 patients who fulfilled the inclusion criteria were reviewed. There were 100 boys and 62 girls with ages ranging from 2 months to 7.8 years. Baseline patient demographics are summarized in Table 1.

Response of Fever Without Aspirin

There were 153 cases (94.44%) with defervescence within 3 days after completion of IVIG therapy, and 128 (83.66%) of these became afebrile within 24 hours (Fig 1). The febrile days before therapy in IVIG-responsive and -nonresponsive groups were 6.11 ± 2.17 and 5.56 ± 0.73 days (P = .228), respectively. There were no significant differences in the duration of fever before IVIG therapy, age, or gender between these 2 groups. Nine (5.56%) patients who failed initial IVIG therapy received additional IVIG (2 g/kg) therapy without aspirin immediately when fever persisted for >3 days, and 6 (66.67%) of these had defervescence within 3 days after the additional therapy (Table 1).

Incidence of CAAs Without Aspirin

Seventeen (10.49%) patients had CAAs at the time of diagnosis. Six (4.14%) patients got new CAA formation after IVIG therapy, 4 (2.92%) patients in the IVIG-responsive group and 2 (25%) patients in the nonresponsive group. There was a significant difference in the incidence of CAAs between the 2 groups (P = .033). Patients in the IVIG-nonresponsive group had a significantly higher incidence of CAAs than those in the IVIG-responsive group (Table 2).

Treatment Without Aspirin Before and After Illness Day 5

Sixteen patients were treated before day 5 of fever (range: day 2 to day 4), and 146 patients were treated on day 5 or after (range: day 5 to day 17). There were no significant differences in age or gender between these 2 groups. A total of 137 (93.84%) patients who were treated after illness day 5 had defervescence within 3 days after IVIG therapy. No patient who was treated before illness day 5 had persistent fever for >3 days. There was no significant difference in the responsive rate of IVIG therapy between these 2 groups (P = .655). In addition, most patients had defervescence within 24 hours (81.25% in those who were treated before illness day 5 and 78.77% in those

TABLE 1. Patient Characteristics and Demographics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>IVIG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>162</td>
<td>153 (94.44%)</td>
</tr>
<tr>
<td>Age, mean; y</td>
<td>1.79 ± 1.58</td>
<td>1.73 ± 1.53</td>
<td>2.76 ± 2.17</td>
</tr>
<tr>
<td>Maximum</td>
<td>7.83</td>
<td>7.83</td>
<td>0.25</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.25</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>1.6:1</td>
<td>1.6:1</td>
<td>1.6:1</td>
</tr>
<tr>
<td>Febrile days before therapy</td>
<td>6.08 ± 2.12</td>
<td>6.11 ± 2.17</td>
<td>5.56 ± 0.73</td>
</tr>
<tr>
<td>Maximum</td>
<td>17</td>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>
who were treated after illness day 5). There was no difference between these 2 groups in the proportion of patients who were defervescent at 24, 48, or 72 hours after treatment. One (6.67%) patient who was treated before illness day 5 got a new onset of CAAs in the follow-up, and 5 (3.85%) patients who were treated after illness day 5 did so. There was also no significant difference in the incidence of new-onset CAAs between these 2 groups (*P = .91; Table 3).

**DISCUSSION**

In our study, 94.44% of patients had defervescence within 3 days after completion of IVIG therapy. The overall resistance to the first dose of IVIG was 5.56%, similar to those of other studies, in which 5% to 30% of patients experienced a persistent fever despite initial IVIG and aspirin treatment.3,10–14 All patients who failed initial IVIG therapy received additional IVIG 2 g/kg therapy without aspirin, and 66.67% of these had defervescence within 3 days after the additional IVIG, similar to results of other studies with approximately two thirds of initial nonresponders responding to a second dose of IVIG plus aspirin.12,15,16 The result of our study indicates that the use of aspirin in acute KD has no significant effect on preventing the failure of IVIG therapy. In addition, when patients are not responsive to initial IVIG therapy, early re-treatment with other anti-inflammatory measures (additional IVIG or corticosteroid therapy), rather than high-dose aspirin, should be considered.

In previous studies, >85% of children with KD responded to IVIG and aspirin therapy with cessation of fever within 48 hours of the infusion.2,3 Saulsbury et al5 first published a report in 2002 to compare the high-dose (80–100 mg/kg per day) with low-dose (3–5 mg/kg per day) aspirin plus high-dose IVIG (2 g/kg) in the treatment of acute KD. The mean duration of fever was 47 ± 8 hours in patients who were treated with high-dose aspirin and 34 ± 5 hours in patients who were treated with low-dose aspirin. They found that there was no difference in the duration of fever as a function of aspirin dose.5 In our study, 83.66% patients became afebrile within 24 hours after IVIG therapy, and a total of 96.73% patients had defervescence within 48 hours. The results are compatible with the previous findings. We speculate that there is equal effect on the resolution of fever without regard to the use of aspirin, and the major determinant of defervescence in acute KD depends on the IVIG, not aspirin.

Although aspirin is part of standard therapy in KD because of its anti-inflammatory, antipyretic, and antiplatelet effects, no prospective study has shown that aspirin at any dose reduces the incidence of CAAs.17 A US clinical trial by Melish18 compared IVIG 2 g/kg plus high-dose (100 mg/kg per day) aspirin with IVIG plus low-dose (3–8 mg/kg per day) aspirin and found that there was no significant difference between the two groups in the incidence of CAAs. A meta-analysis by Durongpisitkul et al19 demonstrated that high-dose (2 g/kg) IVIG therapy plus high-dose (>80 mg/kg) or lower-dose (<80 mg/kg) aspirin regimen was associated with a similar incidence of CAAs after disease onset (4.8% vs 4.0%). In our present study, the incidence of CAAs was 4.14%, and this was not higher than those reported in previous studies. These findings show that IVIG is remarkably effective in preventing CAAs whether aspirin is given in anti-inflammatory, antipyretic, or antiplatelet doses. In addition, we demonstrated that there was a high ratio of CAA development when fever was unresponsive to IVIG treatment, similar to the result of the retrospective

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**TABLE 2. Summary of CAAs After IVIG Therapy Without Aspirin**

<table>
<thead>
<tr>
<th>Incidence of CAAs</th>
<th>Total</th>
<th>IVIG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before IVIG therapy</td>
<td>23/162 (14.20%)</td>
<td>20/153 (13.07%)</td>
<td>3/9 (33.33%)</td>
</tr>
<tr>
<td>After IVIG therapy</td>
<td>6/145 (4.14%)</td>
<td>4/137 (2.92%)</td>
<td>2/8 (25%)</td>
</tr>
</tbody>
</table>

**TABLE 3. Comparison of Efficacy of IVIG Treatment Without Aspirin Between Treatment Before Illness Day 5 and Treatment After Illness Day 5**

<table>
<thead>
<tr>
<th>Before Illness Day 5</th>
<th>After Illness Day 5</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16 (9.88%)</td>
<td>146 (90.12%)</td>
</tr>
<tr>
<td>Age, mean; y</td>
<td>1.27 ± 0.96</td>
<td>1.85 ± 1.63</td>
</tr>
<tr>
<td>Maximum</td>
<td>4.00</td>
<td>7.83</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>1.3:1</td>
<td>1.7:1</td>
</tr>
<tr>
<td>IVIG-responsive</td>
<td>16 (100%)</td>
<td>137 (93.84%)</td>
</tr>
<tr>
<td>&lt;1 d</td>
<td>13 (81.25%)</td>
<td>115 (78.77%)</td>
</tr>
<tr>
<td>1–2 d</td>
<td>2 (12.50%)</td>
<td>18 (12.33%)</td>
</tr>
<tr>
<td>2–3 d</td>
<td>1 (6.25%)</td>
<td>4 (2.74%)</td>
</tr>
<tr>
<td>IVIG-nonresponsive</td>
<td>0</td>
<td>9 (6.16%)</td>
</tr>
<tr>
<td>Incidence of CAAs</td>
<td>2/16 (12.5%)</td>
<td>21/146 (14.38%)</td>
</tr>
<tr>
<td>Before IVIG therapy</td>
<td>1/16 (6.25%)</td>
<td>16/146 (10.96%)</td>
</tr>
<tr>
<td>After IVIG therapy</td>
<td>1/15 (6.67%)</td>
<td>5/130 (3.85%)</td>
</tr>
</tbody>
</table>

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*www.pediatrics.org/cgi/doi/10.1542/peds.2004-1037*
study by Burns et al\textsuperscript{10} in 9 clinical centers with the use of aspirin. As the pediatrician and the parent become more familiar and alert to KD, there is a tendency to diagnose and treat it sooner. However, whether early IVIG treatment results in early recovery from fever or fewer CAAs is not well documented. In addition, the role and the effect of aspirin in the early treatment still have not been well evaluated. More recently, a nationwide KD survey in Japan by Muta et al\textsuperscript{20} compared the rate of additional IVIG and prevalence of CAAs between an early group (treated on days 1–4; 4,731 cases) and a conventional group (days 5–9; 4,020 cases). They found that there was no evidence that IVIG treatment on day 4 or earlier has greater efficacy in preventing CAAs than that on days 5 to 9. In addition, early treatment was likely to result in a greater requirement for additional IVIG. In our study without the use of aspirin, we found that there was no significant difference in the response rate of IVIG therapy, duration of fever, or incidence of CAAs when children were treated with high-dose (2 g/kg) IVIG as a single infusion, regardless of treatment before or after day 5 of illness. We conclude that it seems unnecessary to expose children to high- or medium-dose aspirin therapy in acute KD when the available data show no appreciable benefit in preventing the failure of IVIG therapy, formation of CAAs, or shortening the duration of fever.

**ACKNOWLEDGMENTS**
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**REFERENCES**


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