Kawasaki disease (KD) is an acute febrile illness characterized by mucosal inflammation, skin rash, and cervical lymphadenopathy, and is observed most often in children younger than 5 years of age [1–3]. KD is an acute vasculitis syndrome of unknown etiology that primarily affects small and medium-sized arteries, particularly the coronary artery [4–9].

Standard treatment for KD is intravenous immunoglobulin (IVIG) and aspirin [10,11]. Administration of high-dose IVIG reduces both the duration of fever and the incidence of coronary artery aneurysms when given within a few days after the onset of the disease [3]. Nonetheless, approximately 10% of patients have persistent fever despite treatment [3]. The aims of the present study were to determine the rate of treatment failure of the first dose of IVIG in our patients with KD and to determine the possible predisposing factors, such as age and gender.

The purpose of this study was to determine the initial rates of intravenous γ-globulin treatment (IVIG) failure in Kawasaki disease (KD) and their predisposing factors. This study was a retrospective analysis of the initial response to IVIG (2 g/kg), assessed from the medical reports of all patients admitted to Namazee Hospital pediatric ward, from March 1998 to March 2002, and who fulfilled the criteria for KD. Data were available for 64 patients, 58 of whom (90.6%) became afebrile 48 hours after completion of the initial dose of IVIG (Group I) and six (9.4%) who remained febrile (Group II). Two patients had a prompt response to a second dose of IVIG. In Group I, five patients (8.6%) developed coronary artery disease, seen on echocardiography. In Group II, two patients (33.3%) developed coronary artery disease. No significant difference was found in the prevalence of coronary artery disease between the two groups (p = 0.12), or in age or gender. The rate of initial treatment failure was 9.4% in this cohort of patients, which is comparable with previous reports. No predictive factors such as coronary artery disease, age or gender were found for initial treatment failure in KD.

**Key Words:** Kawasaki disease, intravenous immunoglobulin, coronary artery disease


**Patients and Methods**

We reviewed the records of all patients who fulfilled the criteria for diagnosis of KD [10]. They were treated with IVIG (2 g/kg) and aspirin (80–100 mg/kg/day) at Namazee Hospital, which is affiliated with Shiraz University of Medical Sciences, during a 4-year period, from 1998 to 2002. Information obtained from the medical records included patient age, gender, and duration of illness at first treatment. The first day of fever was assumed to be the first day of illness. We routinely obtain an echocardiogram on the first day of hospital admission, and echocardiography results were used to assess clinical outcome. Treatment failure was defined as persistent fever for at least 48 hours after completion of the IVIG infusion. Patients were divided into two groups according to the response 48 hours after completion of IVIG administration: Group I included patients who became afebrile by 48 hours, while Group II patients remained febrile.

**Statistical analysis**

Data compared between the two groups were gender, age, duration of fever prior to IVIG treatment, and coronary
artery disease. Data analysis was performed with Epi Info 2002 (Centers for Disease Control and Prevention, Atlanta, GA, USA), Fisher’s exact test and SPSS version 11.5 (SPSS Inc, Chicago, IL, USA).

RESULTS

The medical records of 64 patients were reviewed. All patients received IVIG 2 g/kg in a single dose or two doses on two consecutive days. Clinical data are shown in Table 1. The male to female ratio was 1.8:1 and ages ranged from 5 months to 12 years with a mean of 4 years (3.8 years in males, 4.4 years in females).

Most patients (58, 90.6%) were afebrile 48 hours after completion of the initial dose of IVIG infusion (Group I), but six (9.4%) remained febrile (Group II) (Figure). Two patients with initial treatment failure (33.3%) responded to a second dose of IVIG. Gender distribution was similar in the two groups (64% of Group I and 67% of Group II were male). Patients in Group I were slightly older than those in Group II (Table 1). Significantly more patients in Group II than Group I were treated within 5 days of the start of fever ($p = 0.02$) (Table 2).

In Group I, two patients (3.4%) had mild mitral regurgitation at first echocardiography, one patient (1.7%) showed mild mitral regurgitation, mild tricuspid regurgitation, and minimal pericardial effusion, and five patients (8.6%) showed coronary abnormalities (3 developed dilatation of coronary arteries and 2 developed coronary artery aneurysm) (Table 3). In Group II, first echocardiography was normal in four patients, one of whom developed coronary artery aneurysm after 2 weeks. Of the other two patients, one (16.7%) showed mild tricuspid regurgitation and mitral regurgitation, and one (16.7%) showed dilated coronary arteries. Therefore, two patients in Group II had coronary lesions.

DISCUSSION

Namazee Hospital is a referral center for Fars Province (population, 3 million) in South Iran, where hospital pediatricians are familiar with the diagnosis and treatment of KD. In 2001, Sadeghi et al reported the demographic features and clinical manifestations of KD in Iran [12].

<table>
<thead>
<tr>
<th></th>
<th>Group I ($n = 58$)</th>
<th>Group II ($n = 6$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mo)</td>
<td>50.7 ± 34.8</td>
<td>28.8 ± 27.9</td>
<td>0.142</td>
</tr>
<tr>
<td>&lt; 1 yr</td>
<td>2 (3.4%)</td>
<td>1 (16.7%)</td>
<td>0.142</td>
</tr>
<tr>
<td>1–5 yr</td>
<td>41 (70.7%)</td>
<td>4 (66.7%)</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt; 5 yr</td>
<td>15 (25.9%)</td>
<td>1 (16.7%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean body weight (kg)</td>
<td>16.1 ± 6.1</td>
<td>11.9 ± 4.1</td>
<td>0.105</td>
</tr>
<tr>
<td>Mean duration of fever after first dose of IVIG (d)</td>
<td>1.3 ± 0.48</td>
<td>5.6 ± 1.86</td>
<td>0.002*</td>
</tr>
<tr>
<td>Number of coronary lesions</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Group I: responsive to initial intravenous immunoglobulin treatment; Group II: not responsive to initial intravenous immunoglobulin treatment; IVIG = intravenous γ-globulin treatment. *$p < 0.05$. 
Treatment failure in the present study was 9.4%, comparable to results from other studies, which range from 13.2% to 23% [3,13,14]. Among patients who failed initial treatment (Group II), two (33.3%) received a second dose of IVIG. The US/Canadian Kawasaki Syndrome Study Group found that the rate of retreatment for persistent or recurrent fever varied among participating centers (25–100%) [13]. Retreatment with a third or further dose (2 g/kg) has also been reported [15].

There was no significant difference between the groups in the prevalence of coronary artery disease (5/58 vs 2/6; p = 0.12). Hashino et al found an overall prevalence of coronary artery lesions of 6.5%, which rose to 48.6% in the treatment failure group [3], while Burns et al reported prevalences of 11% and 24%, respectively [13]. Our results are similar to those of Durongpisitkul et al [16].

The severity of clinical manifestations of KD that lead to retreatment with IVIG or using a second line of treatment such as steroid, cyclophosphamide or infliximab varies [15–17]. This may reflect different genetic susceptibility.

Gender, age and weight were not predictors of treatment failure in KD (Table 1), which supports previous findings [14,16].

Two recent reports of the efficacy of early treatment of KD (< 5 days after fever onset) found that early treatment resulted in persistent fever [18,19] and more frequent retreatment with IVIG [19]. This is in agreement with our results, where three of the six patients in the treatment failure group received their initial IVIG on or before day 5, significantly more so than in Group I (5/58; p = 0.02) (Table 2). It is recommended that, to prevent coronary artery disease, KD be treated before day 10 of illness [11]. This treatment strategy tends towards treating as soon as possible, but it is not documented if early treatment (before day 5) is associated with fewer complications and lower morbidity.

We conclude that initial treatment failure is not uncommon in KD, although it is not associated with early coronary artery disease. The long-term prognosis after initial treatment failure should be evaluated in future studies.

**REFERENCES**


