Treatment of Kawasaki Disease using Locally Product Intravenous Immunoglobulin†

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Abstract

Background : Kawasaki disease (KD) is an acute febrile illness of unknown origin. Several kinds of IVIG have been shown to be effective in the decrease of the incidence of coronary artery abnormalities (CAA) which is the most serious complication. Nowadays, the National Blood Centre, Thai Red Cross Society can manufacture IVIG from the plasma of Thai blood donors which is much cheaper than the imported intravenous immunoglobulin (IVIG's). The effectiveness of this Thai Red-Cross IVIG in Kawasaki disease has never been documented.

Objective : To determine the initial treatment response and prevalence of CAA in KD treated with a high dose (2 g/kg) of Thai Red-Cross IVIG.

Patients and Method : All patients with a diagnosis of KD who had initial treatment with 2 g/kg of Thai Red-Cross IVIG at Queen Sirikit National Institute of Child Health from December 2001 to February 2003 were reviewed retrospectively.

Results : All 22 cases (100%) had good response to a single treatment with a high dose of IVIG. The only patient who did not complete the IVIG treatment had a severe reaction following the administration of the drug and needed discontinuation and intervention. During the convalescent phase, there were only 2 cases (9.09%) with CAA in the first month and 1 case (4.55%) at the 3-month follow-up. This only case with CAA at 3 months had multiple aneurysms at the left main and left anterior descending coronary arteries. No giant aneurysms were found in the present study.

Conclusion : The efficacy of a high dose (2 g/kg) of Thai Red-Cross IVIG in Kawasaki disease is excellent. However, the severe reaction in one patient needs further surveillance.

Key word : Kawasaki, Using Locally Product

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Kawasaki disease (KD) is an acute febrile illness of unknown origin[1]. Although all IVIG are not the same, several kinds of IVIG have been shown to be effective in the decrease of the incidence of coronary artery abnormalities (CAA) which is the most serious complication if administered early in the course of the disease[2,3]. Nowadays, the National Blood Centre, Thai Red Cross Society can manufacture IVIG from the plasma of Thai blood donors which is much cheaper than the imported IVIG's. This Thai Red-Cross IVIG has been shown to be effective in cases of idiopathic thrombocytic purpura[4] but its effectiveness in Kawasaki disease has never been documented.

Objective

To determine the initial treatment response and prevalence of CAA in KD treated with a high dose (2 g/kg) of Thai Red-Cross IVIG.

PATIENTS AND METHOD

All patients with a diagnosis of KD who had initial treatment with 2 g/kg of Thai Red-Cross IVIG at Queen Sirikit National Institute of Child Health from December 2001 to February 2003 were included in this retrospective study. Medical records were reviewed retrospectively for demographic data, laboratory results, clinical courses and echocardiographic findings until 3 months after the onset of fever. The diagnosis was based on the criteria of the American Heart Association[5]. IVIG was given as a single bolus dose, continuous drip in 12 hours. Aspirin was given in all at the dosage of 80-100 mg/Kg/day during the febrile stage and reduced to 3-5 mg/kg/day after that.

Response to IVIG was considered at 48 hours after the completion of the IVIG treatment. If the body temperature was under 37.5°C for at least 2 episodes 4 hours apart, the response was considered to be good and vice versa.

An echocardiogram was performed as soon as possible after the diagnosis was made. The second echocardiogram was performed in the subacute period about 1 month later and the third one about 3 months after the onset of fever.

The definition of CAA was based on published criteria[6] as follows:

1. Lumen diameter at least 3 mm in a child < 5 years old or at least 4 mm in a child ≥ 5 years old,

2. Internal diameter of a segment at least 1.5 times as large as that of an adjacent segment or

3. Clearly irregular lumen.

A giant aneurysm was defined as an aneurysm > 8 mm in diameter.

RESULTS

Twenty three cases were enrolled in the present study with an age range from 4-38 (19.47 ± 14.01) months and weight 6.7-12.0 (10.61 ± 3.10) kg. Eleven cases (41.83%) were male. The duration of fever before the diagnosis was made and ranged from 5-12 (6.85 ± 2.50) days. The clinical manifestation is shown in Table 1. The laboratory data are shown in Table 2.

IVIG was started at day 5-12 (6.89 ± 2.05) after the onset of fever. A 33-month-old patient had a higher fever up to 40.0°C with chill and cyanosis just a few minutes after the administration of the IVIG on day 5 of the disease. The authors stopped the medication, gave supportive treatment with intravenous fluid, tepid sponge, oxygen and oral paracetamol. He looked well after a few minutes. The authors tried another brand of IVIG one day after that and the patient responded well without any reaction.

The other 22 cases (100%) had a good response to a single treatment with a high dose of IVIG. No reactions were observed in these patients. During the convalescent phase, there were only 2 cases (9.09%) with CAA in the first month and 1 case (4.55%) at the 3-month follow-up. This only case with CAA had multiple aneurysms at the left main and left anterior descending coronary artreries. No giant aneurysms were found.

DISCUSSION

A single intravenous infusion of high dose gamma globulin together with aspirin therapy have

Table 1. Clinical characteristics.

	No.	Per cent
Total	23	100
Conjunctival injection	22	95.65
Oral changes	22	95.65
Skin rash	21	91.30
Extremity changes	18	78.26
Lymphadenopathy	17	73.91

Table 2 The laboratory findings.

	Range	Mean ± SD
Hematocrit (%)	26.0-39.8	31.27 ± 3.04
White cell counts (cells/mm^3)	10,800-26,800	17,755.56 ± 4,567.947
Platelet counts (cells/mm^3)	168,000- 620,000	373,375 ± 127,232
Erythrocyte sedimentation rate (mm/hour)	37-113	71.58 ± 19.83

been accepted to be effective in the treatment of Kawasaki disease[7,8]. However, this drug is very expensive. Experts tried to select patients who needed IVIG[9] or decreased the dose of IVIG[10] but without appreciable results.

Although there are differences among available immunoglobulin preparations for intravenous use[11], the National Blood Centre, Thai Red Cross Society has manufactured IVIG from the plasma of Thai blood donors with good efficacy against idiopathic thrombocytopenic purpura[4] and is much cheaper than the imported IVIG's. The price of 10 grams of Thai Red Cross IVIG was 8,144 Baht while those of other two products commonly used in our Institute were 15,191 and 16,290 Baht. This Thai Red Cross IVIG is a sterile, lyophilized preparation of immune globulin. The manufacturing process isolates immunoglobulin G without chemical or enzymatic modification using polyethyleneglycol thus producing intact molecules of immunoglobulin G. This reassures the authors that it will be as effective as other native IVIGs[12].

Burns JC, et al performed a multicenter, retrospective survey of all children with KD evaluated at nine clinical centers across North America during a 15-month period and found that at 48 hours after completion of the initial IVIG infusion, 50/378 patients (13.2%) still had fever [13]. In the present study, all of the patients who received a complete dose of IVIG had no fever at 48 hours.

Without treatment, the prevalence of CAA was as high as 30 per cent[3]. High dose IVIG can decrease this complication to less than 5 per cent[8]. In the present study, the prevalence of CAA was similar to the data from a meta-analysis on the efficacy of immunoglobulin treatment in Kawasaki disease in which CAA were found in 9.1 per cent (95% confidence interval 6.9-11.4%) and 4 per cent (95% confidence interval 2-6.1%) at 60 days[14]. Although the efficacy of this high dose (2 g/kg) of Thai Red-Cross IVIG in Kawasaki disease is quite impressive, the exact efficacy may be somewhat different because of the retrospective and uncontrolled nature of the study. There were several patients in this same period who received other brands of IVIG or did not receive any IVIG's. The adverse reaction to IVIG is not uncommon, however, severe reactions are rare[15]. In the presented patient, the authors cannot be sure whether the reactions were from the IVIG itself or other contamination. Further close surveillance is needed.

Although the American Heart Association recommends a repeat echocardiogram at 1 year after the onset of Kawasaki disease[16], the authors agree with Scott JS, et al[17] that in the current environment of cost-containment, additional echocardiographic studies are justified only if abnormalities are present at 4 to 6 weeks and the result of echocardiogram at 3 months should be used to consider whether another echocardiogram is needed.

SUMMARY

The efficacy of a high dose (2 g/kg) of Thai Red-Cross IVIG in Kawasaki disease was excellent. However, the severe reaction of one of the presented patients needs further close surveillance.

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ผลการรักษาโรคคาวาซากิด้วยอิมมูโนโกลบุลินชนิดฉีดเข้าหลอดเลือดที่ผลิตในประเทศ

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บทนำ : โรคคาวาซากิเป็นโรคที่ยังไม่ทราบสาเหตุ มีภาวะแทรกซ้อนที่สำคัญ คือ การเกิดความผิดปกติของหลอดเลือดหัวใจ การรักษาในปัจจุบันแนะนำให้ใช้ Intravenous immunoglobulin (IVIG) ในขนาดสูงเข้าหลอดเลือดดำใน 10 วันแรกของโรค ปัญหาคือยานี้ยังมีราคาแพง สภากาชาดไทยเพิ่งเริ่มผลิต IVIG ใช้เองในประเทศมาไม่นานนี้ แต่ยังไม่เคยมีรายงานผลการใช้ยาดังกล่าวในโรคนี้มาก่อน

วัตถุประสงค์ : ศึกษาผลการรักษาโรคคาวาซากิด้วยยา IVIG ของสภากาชาดไทย โดยดูจากไข้ที่ลดภายใน 48 ชั่วโมง และการเกิดความผิดปกติของหลอดเลือดหัวใจในช่วง 1 เดือนแรก และเมื่อ 3 เดือนนับจากวันเริ่มมีไข้

ผู้ป่วยและวิธีการ : ศึกษาย้อนหลังจากเวชระเบียนของผู้ป่วยทุกรายที่เป็นโรคคาวาซากิในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี และได้ยา IVIG ของสภากาชาดไทย ตั้งแต่เดือน ธันวาคม 2544 ถึงเดือนกุมภาพันธ์ 2546

ผลการศึกษา : ศึกษาผู้ป่วยที่เข้าในการศึกษานี้มีทั้งสิ้น 23 ราย ศึกษาผลการรักษาได้เพียง 22 ราย เนื่องจาก 1 รายมีปฏิกิริยารุนแรงหลังการให้ยา ไข้ลดภายใน 48 ชั่วโมงทุกราย พบความผิดปกติของหลอดเลือดหัวใจในช่วง 1 เดือนแรก 2 ราย (ร้อยละ 9.09) และลดลงเหลือรายเดียว (ร้อยละ 4.55) เมื่อ 3 เดือนหลังจากเริ่มมีไข้ รายที่ยังมีความผิดปกติหลงเหลือนี้ เป็นที่หลอดเลือด left main และ left anterior descending coronary artrery

สรุป : ผลการรักษาโรคคาวาซากิด้วยยา IVIG ของสภากาชาดไทยได้ผลดีมาก จำเป็นต้องติดตามดูปฏิกิริยารุนแรงที่เกิดหลังการให้ยาในผู้ป่วยรายหนึ่งในการศึกษานี้ ต่อไปอย่างใกล้ชิดว่าเป็นผลโดยตรงจากยาหรือไม่ต่อไป

คำสำคัญ : คาวาซากิ, ผลการรักษา, อิมมูโนโกลบุลินผลิตในประเทศ

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