Sulfamethoxazole / Trimethoprim confer no change on the clinical course of Kawasaki disease

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ABSTRACT Kawasaki disease (KD) is one of the most common vasculitis in childhood, but its etiology is still unknown. We hypothesized that Sulfamethoxazole / Trimethoprim (S/T) would inhibit overproduction of cytokine due to heat shock protein produced by intestinal bacteria in patients with KD and improve the clinical course of KD indirectly. We have conducted a prospective study to assess the usefulness of S/T for KD. For patients with KD (S/T group, N=23), we use S/T in addition to the standard treatment in the guidelines such as intravenous immunoglobulin (IVIG) and moderate dose aspirin. The control group (non S/T group, N=32) is patients with KD treated with the standard treatment in the guidelines. The baseline characteristics did not demonstrate notable differences between the two groups. We compare duration of fever, rate of initial IVIG failure, the day of illness membranous desquamation appeared, and the occurrence of coronary artery lesion (CAL) between two groups. Membranous desquamation appeared rather earlier in S/T group than in non S/T group (11.4±3.0 day of illness vs 12.9±3.5 day of illness, P=0.078), but there was no statistically significant difference. Duration of fever (39±59 hours vs 42±57 hours, P=0.41), rate of initial IVIG failure (26% vs 31%, P=0.30), and number of CAL (8.6% vs 9.3%, P=0.87) were found no significant difference between two groups. These data indicated that the use of S/T in acute phase of KD didn't improve any clinical course of KD.

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INTRODUCTION

Kawasaki disease (KD) is one of the most common vasculitis in childhood[1,2]. Its etiology and pathophysiology have remained unknown over 45 years from the first report in 1969. A number of epidemiological and clinical observations suggest that KD is caused by an infectious agent, with suggestions ranging from Staphylococci, Streptococci, Yersinia, Mycoplasma or Chlamydia, to viruses such as adenovirus, parvovirus or

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Epstein-Barr virus[3-6]. But so far, all theories are still controversial, because no single causative pathogen has been consistently demonstrated from patient with KD[3-6].

In 2008, one group showed that serum heat shock protein (HSP) level is significantly higher in patients with KD than healthy children, because HSP is overproduced by intestinal bacteria in patients with KD[7]. And this report suggested that HSP act with superantigens to induce cytokine storm, is the cause and/or a factor of worsening KD.

We hypothesized that oral antibiotics inhibit the production of HSP, and prevent to deteriorate KD. Although all bacteria to produce HSP and superantigen are sensitive to Sulfamethoxazole / Trimethoprim (S/T)[7], little has been reported on the effectiveness of S/T to KD[8]. This is the first report evaluated the effect of oral S/T for KD.

METHOD

From January 2010 to December 2012, children diagnosed with KD or suspected incomplete KD in Kawasaki Medical School Hospital were eligible for the enrolment of this study. After the consent of our study, S/T was orally administered 2 times per day at a dose of 0.05 g/kg/time for 7 consecutive days[9,10]. After the diagnosis of KD, we started intravenous immunoglobulin (IVIG) therapy at a dose of 2 g/kg and moderate dose of aspirin that conforms to the Clinical Guideline for Medical Treatment of Acute Stage Kawasaki Disease published by Japanese Society of Pediatric Cardiology and Cardiac Surgery (JSPCCS)[11]. After afebrile for 48 hours, the dose of aspirin was reduced to 3 to 5 mg/kg once daily, and continued to 90 days after onset. If they were unresponsive to first IVIG therapy, we added the treatment for initial IVIG poor responder in accordance with the guidelines[11].

Patient we didn't consent from and patients whose AST and/or ALT was more than 300 IU/L on admission were excluded, because S/T might exacerbate hepatopathy[9,10].

Patients who presented with coronary artery legion (CAL) before the initial treatment began were also excluded from the study.

The control group (non S/T group) was patients with KD treated in accordance with the guidelines in Kawasaki Medical School Hospital between January, 2006 and December, 2012. We compared these two groups for using or non-using S/T in patients with KD. We compared duration of fever, rate of initial IVIG failure, the day of illness membranous desquamation appeared, and the occurrence of CAL of these two groups.

The trial was also adapted after agreement from the funders and ethics committee at Kawasaki Medical School.

Diagnosis

Our criteria for a diagnosis of KD included fever (temperature ≧38°C) accompanied by the presence of at least 4 of the following 5 findings: bilateral conjunctival injection, changes in the lips and the oral cavity, nonpurulent cervical lymphadenopathy, polymorphous exanthema, and changes in the extremities.

These diagnostic criteria are based on the Diagnostic Guidelines for Kawasaki Disease (5th revision)[12]. The first day of illness was defined as the first day fever was present. Patients were excluded if the clinical or laboratory evidence suggested atypical KD[13] or any other disease known to mimic KD, such as adenovirus infection, Epstein-Barr virus infection, scarlet fever, or bacterial cervical lymphadenitis.

Requirements for Additional Treatment after initial IVIG

Additional treatment was provided when patients had persistent fever lasting 24 hours after the completion of the initial IVIG treatment or in the presence of recrudescent fever associated with

KD symptoms after an afebrile period[11]. We use ulinastatin in addition to 2nd IVIG therapy as additional treatment[14].

Assessment of Coronary Artery Lesions (CAL)

A pediatric cardiologist had recurrently assessed the coronary arteries using 2-dimensional echography, and we reviewed their records at least 1 month after the onset of KD. In accordance with the Japanese Ministry of Health criteria, CAL was diagnosed when any of the examinations resulted in the following findings[14]: an internal lumen diameter >3.0 mm in a child <5 years of age or >4.0 mm in a child $\geqq 5$ years of age, an internal segment diameter at least 1.5 times larger than that of an adjacent segment, or an irregular lumen.

Assessment of Adverse Events

Adverse events associated with S/T, such as the elevation of transaminase, neutropenia, rash, and hyperkalemia were reported[9,10]. In the present study, neutropenia was diagnosed when the neutrophil count decreased to 1500 cells/mm³. Every 2-4 days, we performe blood tests to find occurrence of adverse events after admission of S/T until their discharge.

Analyses

Statistical analysis was performed by using ystat 2008. Means, medians, and ranges were calculated for descriptive data. Analyses of clinical features were performed by using the Fisher exact or x^2 tests for categorical variables and Wilcoxon test for numerical variables. Univariate analyses of features predicting an adverse outcome were performed by using logistic regression. A P value <0.05 was accepted as statistically significant.

RESULT

S/T group

From January 2010 to December 2012, there are 50 hospitalizations for patients diagnosed with KD or suspected KD in Kawasaki medical school hospital. 1 mimic KD and 7 atypical KD were excluded from this study, because they didn't meet our KD criteria. 42 KD patients were enrolled to this study. 1 case was excluded because of CAL before the initial treatment began, and 4 cases were excluded because of elevated transaminase, and 3 cases were excluded because they didn't need IVIG

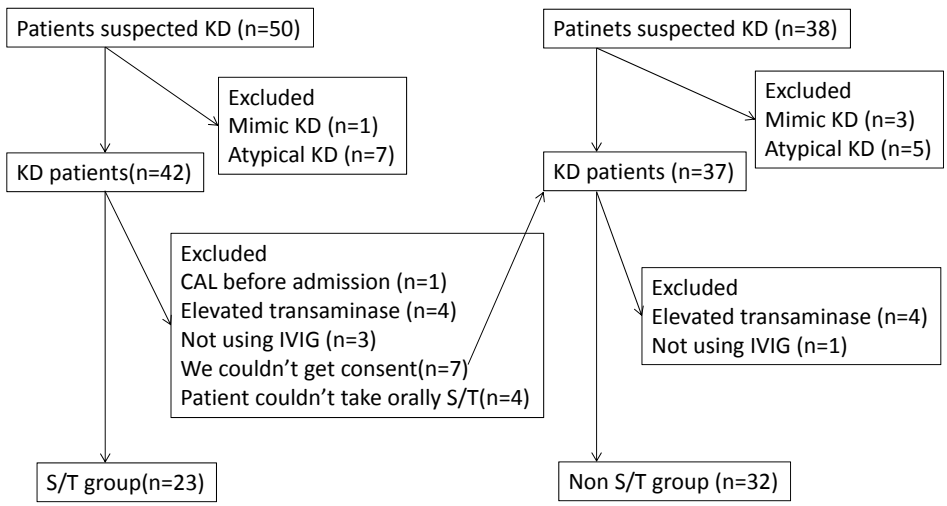

Fig. 1. Flowchart of the patients enrolled in this study.

therapy. We tried to get consents from 34 cases, and 7 patients we couldn't get consent from their family were excluded from S/T group. (7 patients we couldn't get consent were enrolled as non S/T group.) We tried to administer S/T for 27 patients, but 4 patients couldn't take orally S/T because of bitter taste of KD. Finally, we register 23 patients were eligible to the S/T group in our study (Fig. 1).

Non S/T group

From January 2006 to December 2009, there are 38 hospitalizations for patients diagnosed with KD or suspected KD in Kawasaki medical school hospital. 1 mimic KD and 5 atypical KD were excluded from this study, because they didn't meet our KD criteria. Further, 7 patients we couldn't get consent to participate in S/T group were enrolled as candidates of non S/T group.

4 cases were excluded because of elevated transaminase, and 1 case was excluded because the patient didn't take IVIG therapy. Finally, we enrolled 32 patients as non S/T group. There was no patient CAL before the initial treatment began in non S/T group (Fig. 1).

Characteristics and Laboratory Findings of the Patients

Twenty three patients in the S/T group and 32 patients in the control group (non S/T group) were included in the present study. Table 1 describes the baseline characteristics and laboratory findings for the S/T group and the control group. No significant differences were found between the S/T group and the control group.

Duration of fever

Average time to become antipyretic from starting first IVIG is 39 ± 59 hours in S/T group, and 42 ± 57 hours in non S/T group. (P=0.41) These are no significant difference (Table 2).

Requirements for Additional Rescue Treatment

Six cases (26%) in S/T group and 10 cases (31%) in non S/T group needed to use additional treatment because of poor response to initial IVIG. (P=0.30) The percentages of initial IVIG failure are no significant difference between two groups (Table 2).

The day of illness membranous desquamation appeared

Membranous desquamation, an indication of convalescence, appeared rather earlier in S/T group than in non S/T group (11.4 ± 3.0 day of illness vs 12.9 ± 3.5 day of illness, P=0.078), but these were no statistically significant difference between two groups (Table 2).

Comparison of the Coronary Artery Outcomes

We found two cases (8.6%) of coronary artery aneurysms in ST group, and three cases (9.3%) in

Table 1. Characteristics of study patients

	S/T group	Non S/T gruop	P value
n	23	32	
Age（months, mean ± SD）	25.1 ± 19.3	30.4 ± 22.5	0.18
WBC（/μL, mean ± SD）	13,300 ± 3,550	12,300 ± 4,170	0.17
CRP（mg/dL, mean ± SD）	8.0 ± 3.6	6.8 ± 5.5	0.15
AST（IU/L, mean ± SD）	69 ± 10	46 ± 20	0.10
ALT（IU/L, mean ± SD）	72 ± 87	49 ± 53	0.10
Alb（mg/dL, mean ± SD）	3.6 ± 0.4	3.8 ± 0.4	0.06
T-bil（mg/dL, mean ± SD）	0.7 ± 0.7	1.0 ± 1.0	0.15
Gunma score（mean ± SD）	3 ± 1.7	2.9 ± 2.1	0.39
The day we used first IVIG（Days ± SD）	5.0 ± 1.3	4.6 ± 1.2	0.17

Table 2. Clinical outcome of the two groups

	S/T group	Non S/T group	P value
n	23	32	
The refractory rate of Initial IVIG therapy n（%）	6（26%）	10（31%）	0.30
The antipyretic day (Days ± SD)	7.5 ± 2.2	7.1 ± 2.8	0.30
Duration from initial IVIG to antipyretic (Hours ± SD)	39 ± 59	42 ± 57	0.41
The day of membranous desquamation (Days ± SD)	11.4 ± 3.0	12.9 ± 3.5	0.078
CAL n（%）	2（8.6%）	3（9.3%）	0.87

non S/T group. (P=0.87) These all 5 cases of CAL were evanescent small aneurythms. And it was confirmed that all CAL has disappeared in follow up echocardiogram three months after from onset of KD (Table 2).

Assessment of Adverse Events

In S/T group, two cases of evanescent neutropenia that were believed to have been caused by S/T were observed during their admissions. These two cases of neutropenia were improved with no treatment a few days after from onset of their neutropenia. And no infectious disease due to neutropenia was observed.

DISCUSSION

Although we hypothesized that early admission of oral S/T improve the prognosis of KD, our study has disclosed that S/T don't result in any effects on the clinical course of KD in acute phase. These results are consistent with the common knowledge, it is well known, that antimicrobial agents are ineffective for KD.

Our study has several limitations to evaluate the effectiveness of S/T for KD. First, we didn't measure serum HSP level and serum cytokine level at any time. It was reported all bacteria to produce HSP are sensitive to S/T[7]. We assume that S/T inhibit to produce HSP and cytokine in patient with KD. In our study, membranous desquamation, a feature in recovery period for KD[12], has appeared more early in S/T group than in control group, but there were no significant differences. This result suggests that S/T bring early recovery phase because of suppressing the production of HSP in acute phase of KD. But we couldn't prove it because of racking the data of serum HSP level.

Secondly, we might have excluded severe KD from our study. In severe KD, many values such as serum albumin, transaminase and bilirubin tend to be abnormal values[15,16]. Because we couldn't use S/T for the cases with high transaminase (≧300 IU/L) for fear of exacerbation of liver failure, we might exclude severe KD from this study. We guess S/T is effective to suppress cytokine storm for severe KD more than not severe KD, but we can't use S/T for severe KD for fear of side effects of S/T[15,16]. We believe it is a reason we can't show any significant difference between two groups in our study.

Thirdly, there are few cases which needed additional IVIG therapy, because our study population is small. Nagata *et al*. reported S/T is effective to KD which is unresponsive to IVIG. In this report, Nagata *et al*. administered S/

T for 7 cases of KD that were unresponsive to second IVIG therapy and studied the antipyretic potency of the treatment[8]. In 6 out of the 7 cases, they demonstrated that antipyretic potency was observed without side effects within 2 days of the initial administration. In spite of most severe cases, the coronary lesions didn't deteriorate with the exception of the 1 case that had formed giant aneurysms. And no side effects believed to have been caused by S/T were observed during the course of treatment or follow-up in this report. We couldn't compare the effectiveness of S/T for IVIG resistant KD because our study hasn't enough number of patients with KD.

Nagata *et al.* suggests S/T is safe and effective for patient with severe KD in acute phase[8]. In contrast, we provide evidence that S/T is not effective for patient with mild KD. And we can't compare the effectiveness of S/T for severe KD. Therefore the usefulness of S/T for patient with KD is still controversial. We try to increase the number of cases and plan a new randomized control trial to assess the usefulness of S/T for patient with severe KD in acute phase. Further evidence will be needed.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no competing financial interests.

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