Clinical Pediatrics: Open Access

OPEN ACCESS Freely available online

Research Article

Effectivity of Pretreatment in Kawasaki Disease

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ABSTRACT

Background: This study aimed to determine the effect of glycerin enema as a pretreatment before starting treatment of Kawasaki disease (KD). We investigated differences in the duration of fever and the coronary arterial maximum Z score in patients with KD.

Methods: This single-center, cohort study had a target population including 181 consecutive patients who were diagnosed with KD between 2017 and 2019 in our institution. The control group (n=86) was treated with the usual treatment (intravenous immunoglobulin) for KD from January 2017 to October 2018. Eighty-six patients with KD in the pretreatment group were also treated with the usual treatment from November 2018 to November 2019. Pretreatment was also performed by glycerin enema (2 ml/kg/dose) before initiation of intravenous immunoglobulin therapy.

Results: The median duration of fever (95% confidence interval [CI]) in the control and pretreatment groups was 43.5 (30–53) and 22.0 (19–38) hours, respectively. The difference in duration of fever between the groups was largest within the first 100 hours (Peto–Peto Wilcoxon test, p=0.008 After 4 weeks of treatment, the mean maximum Z score in the pretreatment group (−0.35 ± 0.65) was significantly lower than that in the control group (−0.04 ± 0.95; 95% CI 0.061–0.553, p=0.015).

Conclusions: An enema is an effective treatment method in the acute phase of KD. We recommend this pretreatment by enema because this treatment also has a low cost.

Keywords: Pediatrics; Clinical pediatrics; Kawasaki disease; Enema; Pretreatment

INTRODUCTION

Kawasaki disease (KD) is an acute vasculitis in young children and causes coronary artery abnormalities, such as coronary artery aneurysm or ectasia. KD is the leading cause of acquired heart disease in children in developed countries [1,2]. Intravenous immunoglobulin (IVIG) administered in the acute phase can reduce the incidence of coronary artery abnormalities [3,4].

However, approximately 20% of patients with KD develop persistent or recrudescent fever after standard therapy with IVIG and aspirin [5]. Randomized, clinical trials of prednisolone, infliximab, and cyclosporin have suggested the efficacy of combined treatment with IVIG for KD [6-8]. Although various treatment options have been available in the past 50 years [6-10], development of coronary artery abnormalities, which are serious and sometimes life-threatening complications, has not been completely eradicated [11,12].

The etiology and pathogenesis of KD remain unknown. In the early and acute stages of KD, an antigen-driven immune response might occur owing to an etiological agent with a respiratory or gastrointestinal portal of entry and it is integral to pathogenesis of this illness [13]. In the early stage of KD, if the KD-causative antigen remains at the entrance of the intestinal tract, such as the colon, removing the antigen contained in the feces before entering the body might result in a weakened immune response.

To examine the effect of pretreatment, we investigated differences in the duration of fever and the coronary arterial maximum Z score between control and pretreatment groups in patients with KD.

PATIENTS AND METHODS

Study design and population

This single-center, cohort study had a target population including

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Received: July 14, 2019; **Accepted:** January 12, 2021; **Published:** January 19, 2021

Citation: Fuse S, Mori T, Hirakawa S, Sakurai N, Iwasa M, Itoh T, et al. (2021) Effectivity of Pretreatment in Kawasaki Disease. Clin Pediatr OA 6:170 doi: 10.35248/2572-0775.21.6.170

181 consecutive patients who were diagnosed with KD between 2017 and 2019 in our institution. Between January 2017 and October 2018, patients were treated with the usual treatment for KD (control group). Between November 2018 to November 2019, patients were treated with the usual treatment of KD, as well as by pretreatment (pretreatment group).

Inclusion criteria were children with a diagnosis of KD who were treated with IVIG and aspirin. Exclusion criteria were patients who had the symptom of diarrhea, those who received surgery because of severe complications of KD, and those who received plasma exchange therapy because of unresponsive medical treatment of KD. A total of 86 patients in the control group and 86 patients in the pretreatment group were enrolled (Figure 1).

This study was approved by the NTT EAST Medical Center Sapporo Ethics Committee (Reference no. 18-01260). The parents provided written informed consent for retrospective use of the patients' clinical data from November 2018. Anonymous retrospective clinical data before October 2018 were obtained by opting out on the homepage of NTT EAST Medical Center Sapporo.

Treatment of KD and pretreatment

All patients received aspirin 30 mg/kg/day and IVIG 2 g/kg for 24 hours. An additional dose of IVIG 2 g/kg or infliximab (IFX) 5 mg/kg for 2 hours was administered to patients who were non-responders (defined as a body temperature ≥ 37.5°C at 48 hours after initiation of primary therapy). We administered a third or more doses of IVIG and/or cyclosporin 5 mg/kg to patients who did not respond to the second or further therapies.

Pretreatment was performed by glycerin enema with a 2 ml/kg/dose before initiation of IVIG therapy to patients in the pretreatment group from November 2018 to November 2019. These patients had defecation in response to the enema.

Outcome

The primary endpoint was the duration of fever until defervescence after initiation of treatment with and without pretreatment. Fever was defined as a body temperature of ≥ 37.5°C and defervescence was defined as a lowering of body temperature to <37.5°C for ≥ 48 hours from starting IVIG administration. Axillary body temperature was measured every 3 hours until defervescence, and then once a day until day 10.

The secondary endpoint was the maximum Z score of the coronary artery as measured by echocardiography at 4 weeks after onset of KD. The maximum Z score was defined by the largest Z score in the following four segments of the coronary artery: proximal right coronary artery, left main coronary artery, proximal left anterior descending artery, and left circumflex artery. The Z score of the coronary artery was normalized toy the body surface area and calculated using an LMS4 calculator [14,15].

Statistical analysis

Parametric and non-parametric variables are shown as the mean ± SD and the median and interquartile range, respectively. Significant differences in the patients' profile between the groups with and without pretreatment were assessed using Student's t-test or the Mann–Whitney U test. Categorical variables are shown as n (%) and were assessed using Fisher's exact test. The duration of fever from initiating IVIG is shown using the Kaplan–Meier method, and significance between the two groups was assessed using the Peto–Peto Wilcoxon test. The differences in the maximum Z score of the coronary artery at baseline and 4 weeks were assessed using Student's t-test. A two-tailed $p<0.05$ was considered significant. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16].

RESULTS

Patients' characteristics

The patients' characteristics, including age, sex, maximum C-reactive protein value, Kobayashi score, Kobayashi score ≥ 5, baseline maximum Z score, number of baseline coronary artery dilatations (maximum Z score ≥ 2.0), and IVIG initiation day were not different between the control and pretreatment groups. There was also no difference in the total number of treatment methods between the two groups (Table 1). In the control group, 68 (79%) patients received IVIG treatment once, 10 (12%) patients received IVIG treatment twice, 7 (8%) patients received IVIG three times or IVIG and IFX twice, and 1 (1%) patient received IVIG and cyclosporin four times. In the pretreatment group, 78 (85%) patients received IVIG treatment once, 11 (13%) patients received IVIG twice or IVIG and IFX, and 2 (2%) patients received IVIG and IFX twice (Table 2).

No side effects or adverse events due to enema as pretreatment were observed.

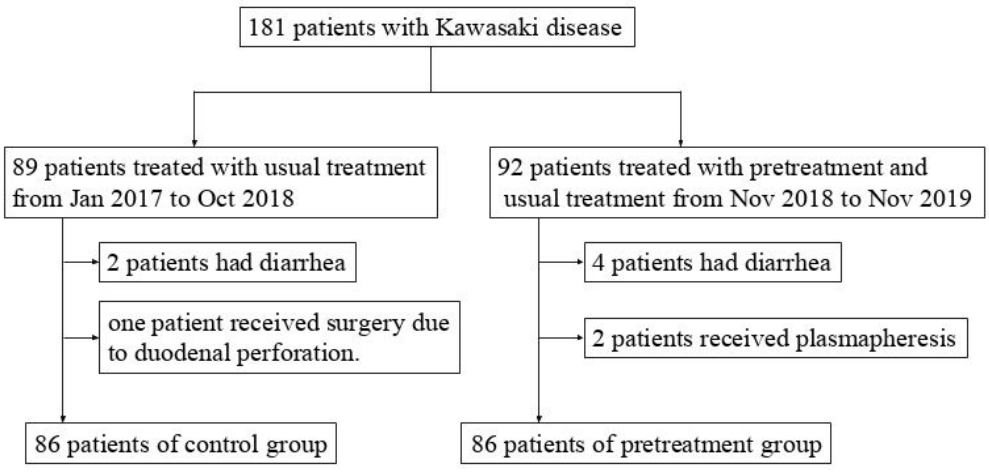

Figure 1: Flow chart of patient enrollment.

Table 1: Patient profile.

	Control n=86	Pretreatment n=86	p value
Age, years	2.4 ± 1.7	2.8 ± 2.4	0.291
Male:female	55:31	45:41	0.164
Maximum CRP, mg/L	77.7 ± 46.3	73.0 ± 51.0	0.523
Kobayashi score	2 (1 – 4)	2 (1 – 4)	0.706
Patients of Kobayashi score ≧ 4	15 (17%)	16 (19%)	1
Baseline maximum Z score	1.40 ± 1.53	1.67 ± 1.32	0.214
Baseline coronary artery dilatation	29 (34%)	40 (47%)	0.119
IVIG initiated day	4.7 ± 1.3	4.8 ± 1.8	0.605
Total number of treatments		0.253	
1	68	73	
2	10	11	
3	7	2	
4	0	0	
5	1	0	

Note: Parametric and non-parametric variables are given as the mean ± SD and the median and interquartile range (IQR), respectively. Note: CRP, C-reactive protein, IVIG, intravenous immunoglobulin

Table 2: Varieties of treatment methods.

Treatment methods	Control n=86	Pretreatment n=86
IVIG	68	73
IVIG x 2	10	11
IVIG +IFX	0	1
IVIG x 3	3	0
IVIG x 2 + IFX	5	2
IVIG x 4 + CsA	1	0

Note: IVIG, Intravenous immunoglobulin; IFX, Infliximab; CsA, Cyclosporin.

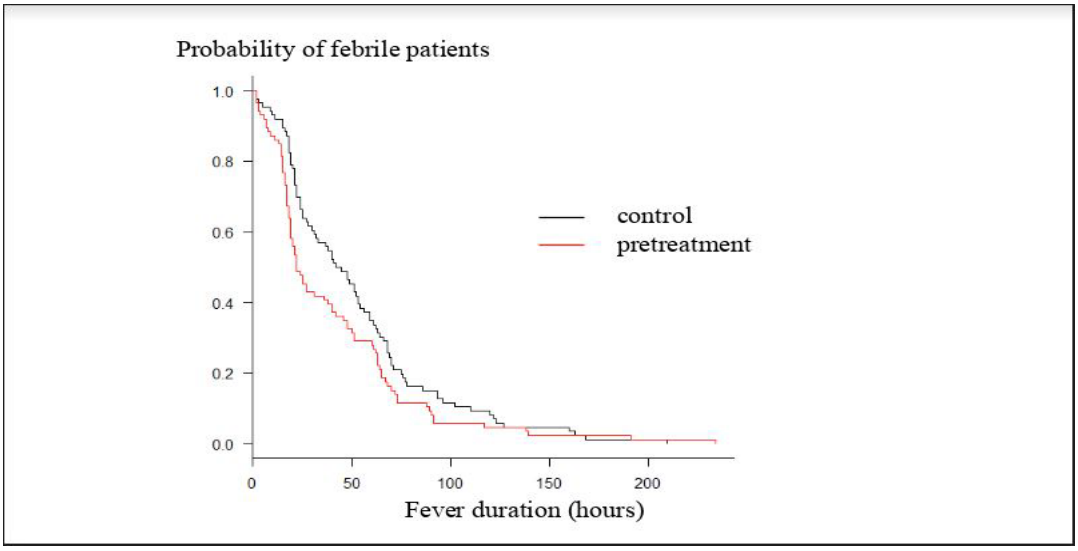

Figure 2: Duration of fever in the control and pretreatment groups.

A Kaplan–Meier plot of the duration of fever after initiating IVIG therapy showed that defervescence was achieved earlier in the pretreatment group than in the control group (Peto-Peto Wilcoxon test, p=0.008).

Duration of fever

The Kaplan–Meier plot of the duration of fever after initiating IVIG therapy showed that defervescence was achieved earlier with the pretreatment group than in the control group. The median duration of fever (95% confidence interval [CI]) in the control and pretreatment groups was 43.5 (30–53) and 22.0 (19–38) hours, respectively. The difference in duration of fever between the two groups was largest within the first 100 hours (Peto–Peto Wilcoxon test, p=0.008) (Figure 2). The effect of shortening the duration of fever was clearly recognized in the early stage (within 100 hours),

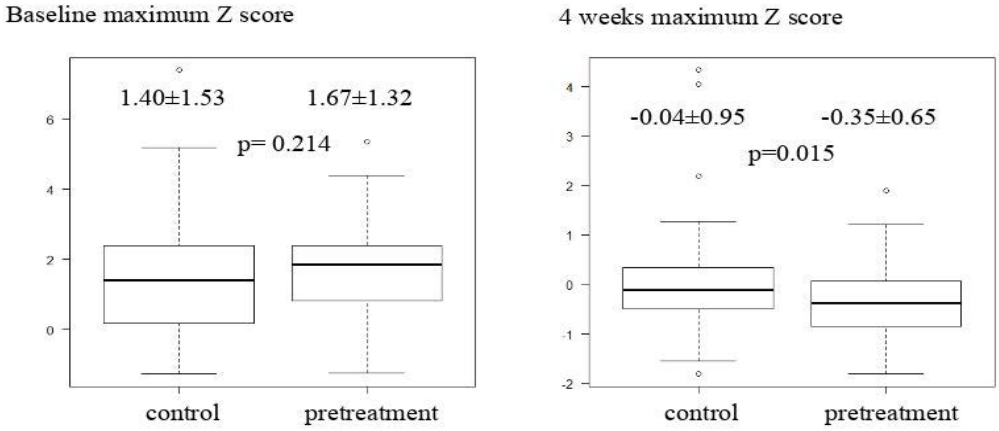

Figure 3: Maximum Z score at baseline and 4 weeks in the control and pretreatment groups.

The baseline maximum Z score in the control and pretreatment groups was not significantly different between the two groups. The maximum Z score in the pretreatment group was significantly lower than that in the control 4 weeks after the onset of KD (p=0.015).

especially after the start of IVIG therapy. After 150 hours from the start of the treatment, pretreatment had no effect on shortening the duration of fever.

Coronary artery outcome

There was no significant difference in the baseline maximum Z score between the control and pretreatment groups. After 4 weeks of treatment, the maximum Z score was significantly lower in the pretreatment group than in the control group (95% CI 0.061–0.553, p=0.015) (Figure 3). Therefore, a coronary artery protective effect was observed in the pretreatment group.

DISCUSSION

We found that the duration of fever was shorter in the pretreatment group than in the control group. This finding suggested that the immune response due to KD-specific antigen invasion in the intestinal tract occurred in the early phase of KD. Invasion of the immune-reactive antigen may have already been completed in patients after 150 hours from the start of treatment. We also found a coronary artery protective effect in the pretreatment group. This finding suggested that the enema decreased the antigen invasion into blood vessels owing to defecation and weakened the immune reaction in the intestinal tract.

Microbiota theory

Many studies [17] have shown that the composition of the gut microbiota in patients with KD differs from healthy subjects. The immune system might lose tolerance toward part of the resident intestinal flora and environmental factors (i.e., a Western lifestyle or improved public hygiene systems) could transform commensal flora into pathogenic flora, as observed in different gastrointestinal disorders. In the throat flora, there is no difference between patients with KD and febrile controls, even in the mean mitogenic activity of isolated bacteria [18]. However, the range of bacterial species that are isolated from jejunal biopsies are characterized by a wider variety of Gram-positive cocci in the acute phase of KD. Notably, five types of streptococci (*Streptococcus salivarius, Streptococcus mitis, Streptococcus oralis, Streptococcus sangius, and Gemella haemolysans*) and two types of staphylococci (*Staphylococcus capitis and Staphylococcus hyicus*) have been isolated only from patients with KD [19].

The presence of *Eubacterium* and *Peptostreptococcus* species is significantly higher in patients with KD than in those with other febrile diseases, but no significant differences in these species have been observed between patients with KD and healthy children [20]. Using metagenomic analysis with non-culture-based methods on feces, a high presence of Streptococcus species, including *Streptococcus pneumoniae, pseudopneumoniae, mitis, oralis, gordonii*, and *sanguinis*, was detected in the fecal samples of patients with KD on admission [21]. Temporary removal of abnormal gut microbiota or intestinal flora by enema may indirectly mitigate exacerbation of KD.

Intestinal barrier dysfunction and abnormal permeability theory

A murine model of KD provided a mechanistic link [22] with acute KD vasculitis and intestinal barrier dysfunction and abnormal permeability. KD vasculitis is characterized by increased gut permeability with leakage of secretory IgA and IgA-C3 immune complex deposition in cardiovascular lesions, which promotes further vascular inflammation. An enema appears to remove some secretory IgA and IgA-C3 immune complexes.

Innate immune disorder theory

Hara [23,24] suggested that KD is not an infectious disease, but an innate immune disorder. He proposes that KD results from exposure of a genetically predisposed individual to innate immune pathogen-associated molecular patterns from microbes growing under biofilm-like conditions, as well as microbe-associated molecular patterns.

Elevated serum transaminase and total bilirubin levels are often found in KD, and these correlate with the severity of KD or IVIG non-responses [25-27]. Blood flow from the intestine reaches the liver via the portal vein. Toxins that enter the intestine are detoxified in the liver. Elevated transaminase and bilirubin levels in patients with KD may reflect detoxification in the liver from intestinal, invasive, KD-specific toxins. Blood flow from the rectum directly enters the systemic circulation without going through the portal vein. If a KD-specific antigen invades the rectum, it enters the systemic circulation directly without detoxification in the liver. Early elimination of feces containing KD-specific antigens may be useful in reducing the condition of KD.

The usefulness of an enema could be explained by the three theories of KD mentioned above. An enema has no adverse events, is low cost, and is a simple procedure. We consider that an enema is an excellent pretreatment for treatment of KD.

CONCLUSION

An enema appears to be an effective treatment method in the acute phase of KD. Because this treatment is low cost, enema pretreatment for KD should be universally performed.

ACKNOWLEDGEMENTS

We thank Ellen Knapp, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

CONTRIBUTORS' STATEMENT

Dr. Shigeto Fuse conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

SOURCES OF FUNDING

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

DECLARATION OF CONFLICTING INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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