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가와사키병 환자에서 보조 일차치료로서 정맥내 dexamethasone 일회 투여가 염증표지자 농도에 미치는 영향

권정은

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The impact of single dose intravenous dexamethasone as an adjunctive therapy for primary treatment on concentrations of inflammatory biomarkers in children with Kawasaki disease

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Purpose: This study was performed to investigate the impact of single dose dexamethasone as an adjunctive therapy for primary treatment on values of inflammatory markers in children with Kawasaki disease (KD).

Methods: We investigated inflammatory markers, including white blood cells, erythrocyte sedimentation rate, C-reactive protein (CRP), interleukin (IL)-6, and IL-10 in 42 children with complete KD who were hospitalized in the Kyungpook National University Children's Hospital from March 2016 through April 2017. The children underwent primary treatment for KD with intravenous immunoglobulin (IVIG) and/or dexamethasone. They were divided into 2 groups according to the use of dexamethasone. To assess the change in values of inflammatory markers, the blood was drawn twice from each child; before and 24 hours after the administration of IVIG.

Results: Of the 42 study children, 18 and 24 were classified as the dexamethasone and control groups, respectively. No significant differences were found between the 2 groups in terms of the length of hospital stay, duration of fever, and time required for IVIG administration. In both groups, white blood cells, CRP, IL-6, and IL-10 significantly decreased after the primary therapy. The delta scores of CRP, IL-6, and IL-10 were higher in the dexamethasone group (P = 0.015, P = 0.001, and P = 0.002, respectively). No coronary artery abnormalities were found in both groups.

Conclusion: This study suggests an anti-inflammatory effect of single dose dexamethasone as an adjunctive therapy for primary treatment in children with KD without shortening the duration of fever and the length of hospital stay.

Key words: Biomarkers; Coronary Vessels; Dexamethasone; Fever; Interleukins; Mucocutaneous Lymph Node Syndrome

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Introduction

Kawasaki disease (KD) is an acute, idiopathic febrile vasculitis that usually occurs in young children with 15%–25% incidence of coronary artery abnormalities (CAAs)[1-4]. Intravenous immunoglobulin (IVIG), a current standard treatment for KD[5], is thought to

reduce systemic inflammation via controlling the production of cytokine or neutralizing toxins and preventing the occurrence of CAAs[5-7]. Among the adverse effects of IVIG, fever is the most common cause of stopping administration of IVIG, which is vital in controlling the inflammation. Therefore, fever control is important for initial treatment for KD.

Dexamethasone is a long-acting fluoridated glucocorticoid with a long half-life, and has anti-inflammatory and immunosuppressive effects without mineralocorticoid effects[8,9]. Anti-inflammatory potency of dexamethasone is 6.7 times higher than the equivalent dose of methylprednisolone[8], which is used primarily in clinical trials to control inflammation.

We hypothesized that primary treatment for KD combined with single dose dexamethasone can have anti-inflammatory effects with relief from fever, proper IVIG administration, and early disease control. The purpose of this study was to investigate the impact of single dose dexamethasone as an adjunctive therapy for primary treatment on inflammation control of KD with a focus on the changes in values of inflammatory markers.

Methods

1. Study design and setting

From March 2016 through April 2017, 143 children were hospitalized for complete KD in the Kyungpook National University Children's Hospital. Inclusion criteria were complete KD as a final diagnosis, a blood test before and 24 hours after the administration of IVIG, and agreement of the children's guardians for the analysis of inflammatory markers using a serum left after the conventional tests. This study protocol was approved by the institutional review board (IRB no. KNUCH 2016-06-013). Written informed consents were obtained from the guardians of participating children.

IVIG was the primary treatment for all children. At the start of IVIG infusion, children without fever were immediately treated with IVIG whereas children with fever (> 38.8°C) received acetaminophen and/or ibuprofen for fever control before the infusion. If the fever control failed, single dose intravenous dexamethasone (0.1 mg/kg) was administered. IVIG-resistant KD was diagnosed when fever recurred or persisted for at least initial 36 hours after the initial infusion of IVIG. Children with IVIG-resistant KD received secondary treatment of additional IVIG and intravenous methylprednisolone (30 mg/kg). Acetylsalicylic acid was not being used as a primary treatment during the study period because the medication was not in use in the hospital due to an incident of acetylsalicylic acid-related Reye's syndrome.

2. Variables of interest and inflammatory markers

As baseline characteristics, we obtained information regarding age (months), sex, the Kobayashi score (≥ 4; high-risk for IVIG resistance)[10], length of hospital stay (day), duration of fever (total [day] and from administration of IVIG to defervescence [hour]), time required to IVIG administration (hour), use of the antipyretics, and implementation of the secondary treatment. Groups were designated as per the use of dexamethasone. Outcomes included CAAs, inotropic support, hospitalization to the intensive care units, and in-hospital mortality.

We have routinely performed blood tests on the day of hospitalization and 24 hours after IVIG administration. Inflammatory markers of interest included white blood cells, erythrocyte sedimentation rate, C-reactive protein (CRP), and interleukin (IL)-6, and IL-10. The other laboratory tests were counts of neutrophils and platelets, and concentrations of hemoglobin and aminotransferases. The ILs were analyzed using the remaining serum from the above-mentioned tests which was stored at -80°C. According to the manufacturer's instruction, a multiplex assay on the Luminex 200 Total System (Luminex Corp., Austin, TX) was used for measuring the ILs. The changes in laboratory data and cytokine concentrations before and after primary

treatment were presented as delta (Δ) scores.

3. Echocardiography

CAAs were evaluated by performing echocardiography twice during the hospitalization. We used the Z-score of size of the coronary artery based on aortic valve annular diameter for confirmation of CAAs[11]. The aortic valve annular diameters were measured with magnification in parasternal long-axis views from the inner edge of the proximal valve insertion hinge point within the arterial root to the inner edge of the opposite hinge point. Dilatation and aneurysm were defined as Z-scores of 2 to < 2.5 and ≥ 2.5, respectively[5].

4. Statistical analysis

All statistical analyses were performed with IBM SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY). Statistics were presented as medians (interquartile ranges) or numbers (%). The Mann-Whitney U-tests were used to compare the changes in values of the inflammatory markers as per the use of dexamethasone, and before and after the primary treatment. For this purpose, paired t-test and Wilcoxon signed-rank test were used. A $P < 0.05$ was considered statistically significant.

Results

1. Baseline characteristics

A total of 42 children were enrolled and divided into the 2 groups according to the use of dexamethasone as an adjunctive therapy for primary treatment: 18 children in the dexamethasone group and 24 in the control group. No differences were found between the groups in the baseline characteristics (Table 1). There were no children with CAAs, inotropic support, hospitalization to the intensive care units or in-hospital mortality.

2. Inflammatory markers

Table 2 lists the changes in values of the inflammatory markers and the other laboratory tests. In both groups, all tests but platelet counts showed significant changes before and after the primary therapy. Among the markers with the significant changes in both groups, white blood cells, CRP, and the ILs decreased. The delta scores of CRP, IL-6, and IL-10 were significantly higher in the dexamethasone group than the control group (Table 3). The scores of the other laboratory findings showed no significant differences between the 2 groups.

Table 1. Baseline characteristics according to the use of dexamethasone as an adjunctive therapy for primary treatment

Characteristic	Total (N = 42)	Dexamethason (N = 18)	Control (N = 24)	P value
Age, mo	26.5 (18.1-55.2)	24.8 (21.4-50.8)	27.9 (16.4-56.1)	0.633
Boys	27 (64.2)	12 (66.7)	15 (62.5)	0.291
Kobayashi score	2.0 (1.0-3.0)	2.0 (1.0-3.0)	1.0 (0.8-2.0)	0.597
Length of hospital stay, d	5.0 (4.0-7.0)	5.0 (4.0-5.0)	4.5 (3.0-7.3)	0.620
Total duration of fever, d	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (5.8-8.0)	0.907
IVIG-to-defervescence, h*	34.5 (12.3-62.0)	39.5 (12.8-68.0)	34.0 (12.8-56.3)	0.800
Time for IVIG infusion, h	13.0 (11.1-17.0)	14.0 (12.1-17)	12.2 (10.0-16.3)	0.580
Antipyretics administration	2.0 (2.0-3.0)	2.0 (1.3-2.8)	2.0 (2.0-3.0)	0.865
Secondary treatment	23 (54.8)	12 (66.7)	11 (45.8)	0.188

Values are presented as medians (interquartile ranges) or numbers (%).
* Duration of fever from administration of IVIG to defervescence.
IVIG: intravenous immunoglobulin.

Table 2. Laboratory data before and after the primary treatment

Variable	Dexamethasone (N = 18)			Control (N = 24)		
	Before	After	P value	Before	After	P value
WBCs, 10^3/mm^3	11.9 (9.0-16.2)	7.3 (6.5-8.9)	< 0.001	14.1 (11.9-16.5)	7.8 (5.4-9.6)	< 0.001
Neutrophils, %	68.3 (58.9-75.6)	34.6 (24.0-55.0)	< 0.001	65.6 (58.6-76.8)	32.2 (24.1-42.3)	< 0.001
Hb, g/dL	11.9 (11.2-12.6)	11.2 (10.6-11.7)	< 0.001	11.8 (10.9-12.5)	10.9 (10.6-11.5)	0.005
PLTs, 10^3/mm^3	312.0 (285.0-364.5)	313.0 (297.5-377.8)	0.392	338.0 (288.0-402.0)	365.0 (312.0-432.0)	0.984
ESR, mm/h	40 (30-65)	72 (53-81)	0.001	48 (42-62)	67 (61.0-86.5)	< 0.001
CRP, mg/dL	8.9 (4.0-12.4)	4.1 (3.0-5.2)	0.003	5.7 (4.1-10.4)	3.7 (1.3-6.7)	< 0.001
AST, U/L	41.5 (33.3-90.3)	38.0 (30.3-59.0)	0.030	41.5 (36.0-60.5)	34.0 (28.3-39.5)	0.046
ALT, U/L	29.0 (13.0-183.3)	22.0 (12.5-135.3)	0.026	24.5 (17.0-87.3)	26.0 (14.3-42.5)	0.017
IL-6, pg/mL	63.1 (41.8-126.4)	4.0 (1.9-15.5)	0.001	38.9 (25.5-125.3)	9.5 (1.9-15.2)	0.002
IL-10, pg/mL	121.9 (30.5-181.6)	18.4 (5.8-31.5)	0.026	41.9 (17.8-128.7)	14.6 (8.7-41.7)	0.026

Values are presented as medians (interquartile ranges).
WBC: white blood cell, Hb: hemoglobin, PLT: platelet, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, IL: interleukin.

Table 3. Comparison of laboratory findings

Variable	Dexamethasone (N = 18)	Control (N = 24)	P value
Δ WBCs, 10^3/mm^3	–4.6 (–7.4 to –2.0)	–7.3 (–8.9 to –2.8)	0.157
Δ Neutrophils, %	–34.7 (–44.3 to –18.6)	–29.4 (–45.7 to –19.5)	0.612
Δ CRP, mg/dL	–5.1 (–7.7 to –0.1)	–2.8 (–4.8 to –0.8)	0.015
Δ AST, U/L	–19 (–186 to –9)	–10 (–17 to –6)	0.191
Δ ALT, U/L	–10 (–90 to –1)	–5 (–46 to –3)	0.761
Δ IL-6, pg/mL	–58.6 (–112.8 to –33.4)	–26.8 (–120.0 to –10.3)	0.001
Δ IL-10, pg/mL	–69.4 (–168.4 to –9.9)	–27.7 (–110.6 to –6.5)	0.002

Values are presented as medians (interquartile ranges).
WBC: white blood cell, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, IL: interleukin.

Discussion

The present study suggests single dose dexamethasone as an adjunctive therapy for primary treatment for KD may lead to (1) significant reduction of values of inflammatory markers, such as CRP, IL-6, and IL-10, but (2) no direct effect of reducing fever duration and shortening the length of hospital stay.

Corticosteroids have been used during the acute phase of KD as an adjunctive therapy for primary treatment combined with IVIG for selected cases, such as KD shock syndrome, clinical myocarditis, or high-risk for IVIG resistance or CAAs[5]. For these cases, intravenous methylprednisolone has been considered the major corticosteroid. Intravenous methylprednisolone combined with IVIG as the primary treatment is associated with a shorter fever duration and length of hospital stay, and faster reduction in concentrations of inflammatory markers and conventional clinical markers, in comparison with IVIG alone[12-14]. Dexamethasone is 25-30 times more potent than hydrocortisone in anti-inflammatory effect, and has a 36-72 hours duration of action[15]. This strength of dexamethasone makes its indications for acute and serious diseases, such as croup, acute exacerbations of asthma, and anaphylaxis[15]. Dexamethasone in KD may attenuate the cytokine reactions in vivo[13], and inhibit the activation of monocytes, macrophages, coronary arterial endothelial cells, and T cells in vitro[16].

A combination of dexamethasone (0.3 mg/kg/day for 3 days) and IVIG as the primary treatment in

KD shows more favorable disease course compared to IVIG alone as demonstrated by: (1) shorter duration of fever and length of hospital stay, (2) refractoriness to primary treatment, and (3) lower concentration of CRP after IVIG treatment[17,18]. The present study using the 0.1 mg/kg single dose dexamethasone did not show benefits of febrile duration, length of hospital stay or refractoriness to primary treatment. This disparity might be related to the lower dose of dexamethasone in this present study. The larger decreases in the concentrations of CRP, IL-6, and IL-8 in the dexamethasone group suggest an anti-inflammatory effect of the single dose dexamethasone.

The use of dexamethasone as an adjunctive therapy for primary treatment for KD may prevent the adverse effects of IVIG via anti-inflammatory effect, reduce the number of additional uses of antipyretics, and stabilize administration of IVIG without a fever-related delay in infusion. In this study, the time required for IVIG infusion was about 13 hours in both groups without a difference in the use of antipyretics. The time interval included the time required for fever control before and during IVIG administration. Single dose of dexamethasone was helpful in the dexamethasone group, which had fever at the start of IVIG infusion even after the initial antipyretic therapy.

This study had limitations, including the small size of the study population and absence of comparison among various doses of dexamethasone.

In conclusion, single dose dexamethasone as an adjunctive therapy for primary treatment may have an anti-inflammatory effect in children with KD without effects in shortening the duration of fever and the length of hospital stay.

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Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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