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Glucocorticoid combined with ulinastatin therapy: Another choice for Kawasaki Disease

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Abstract

Objective: To investigate the clinical efficacy of corticosteroid combined with ulinastatin in the treatment of Kawasaki disease.

Method: A prospective non-randomized study method was used to treat children diagnosed with typical Kawasaki disease. Patients were admitted to hospital between January 1, 2011, and December 31, 2013. Patients were allocated to treatment (Group A) or control (Group B) groups according to the wishes and financial situation of their parents. Both groups were taking oral aspirin as basic treatment. Group A (46 patients) were treated with intravenous methylprednisolone, 15 mg/kg/d, combined with intravenous ulinastatin, and Group B (58 patients) received the standard treatment of intravenous immunoglobulin (IVIG), 2 g/kg/d. The main factors observed were differences in the internal diameter of the coronary artery before treatment and at 1 week, 3,6,12 months,2 years and 3 years after treatment; efficacy of supplementary treatment; differences in white blood cell (WBC), blood platelets (PLT), hemoglobin (HB), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) before treatment, at the end of treatment and at week 3; number of days in hospital; fee in hospital. All data were statistically analyzed.

Results: There was no statistical difference between the two groups in respect of the internal diameter of the coronary artery before treatment or at 1 week, 6 months ,12 months,2 years or 3 years after treatment ($P > 0.05$). All patients in Group A had normal body temperatures within 48 h and 43 patients (93.47%) had normal temperatures within 24 h. In Group B, 42 patients (72.41%) had normal body temperatures within 24 h, and 48 (82.75%) within 24 h. Comparing the two groups, the time taken to normalize body temperature was statistically different ($P < 0.01$). Two patients in Group A (4.35%) and ten patients in Group B (17.24%) received additional treatment ($P < 0.01$). There was no statistically significant difference between the groups in CRP levels before treatment and 1 week or 3 weeks after treatment ($P = 0.9476$). The restoration of ESR values was faster in Group A than in Group B ($P < 0.01$). HB values increased faster in Group A than in Group B ($P < 0.01$), while WBC counts fell faster in Group B than in Group A ($P < 0.001$). There was no statistical difference between the groups in PLT counts before treatment or 1 week and 3 weeks after treatment ($P = 0.5344$). The average number of days in hospital was the same for both groups ($P = 0.5811$), while fees in the treatment group were much lower than in the control group ($P < 0.001$).

Conclusion: Methylprednisolone and ulinastatin treatment of Kawasaki disease in the acute phase, compared with IVIG, provides better control of body temperature, shortens the duration of fever and reduces inflammation. 3 years follow ups of Coronary ultrasound after the treatment showed that there was no difference in coronary artery outcomes between the two groups. For the same number of days hospitalized, methylprednisolone–ulinastatin treatment can greatly reduce hospital costs, providing an economical, safe and effective option.

Introduction

Kawasaki disease (KD), a mucocutaneous lymph node syndrome, is an acute, febrile, self-limiting disease commonly occurring in children, with systemic vasculitis as the main pathological change. Currently, high dose intravenous immunoglobulin (IVIG) combined with aspirin is the standard, effective treatment of KD. It has been reported that approximately 10%–20% of patients experience persistent fever or return of fever after the first IVIG treatment [1,2], known as IVIG no response or drug resistant KD [3], and 3%–5% of patients develop coronary artery aneurysm. For the treatment of these patients, most Chinese and international clinicians agree with the use of a second or even third IVIG treatment [4,5] and, if these fail, subsequent combination use of hormone, ulinastatin, biological agents, immune inhibitors or other methods [4,6–8], increasing the treatment cost to patients. However, there is still some disagreement between Chinese and international clinicians regarding the use of hormone therapy in the early stage of KD [9]. In this study, with full consent of patients, the efficacy and safety of intravenous methylprednisolone combined with ulinastatin were evaluated in the treatment of KD in patients who could not afford IVIG treatment according to admission conditions.

Material and methods

General information

The study recruited 104 patients (98 Han ethnics, six Uygur ethnics; 71 male and 33 females, male: female = 2.15) admitted to the Department of Rheumatology in Urumqi Children's Hospital between January 1, 2011, and December 31, 2014, who were diagnosed with KD according to the diagnostic criteria revised at the Fifth International Conference on KD [10]. Exclusion criteria included atypical KD, fever lasting more than 10 days, primary or secondary bacterial infection and failure to follow up. Patients were provided with treatment plans by attending physicians according to their condition upon admission:

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IVIG + Aspirin treatment was proposed first (Group B); intravenous injection of methylprednisolone combined with ulinastatin was proposed to those denied IVIG treatment for financial reasons (Group A). Group A was composed of 22 patients younger than 3 years of age (47.83%), 21 patients aged between 3 and 9 years (45.65%) and three patients older than 9 years (6.52%). Group B was composed of 36 patients younger than 3 years of age (62.07%) and 22 patients aged between 3 and 9 years (37.93%). All patients were fully informed and signed the informed consent before treatment.

Dosage and administration methods

Group A: Intravenous injection of 15 mg/kg/d methylprednisolone (Pfizer Manufacturing Belgium NV) for 3 days, followed by oral prednisone (1–2 mg/kg/d initially then continuous dose reduction until stopped within 4 weeks), combined with intravenous ulinastatin (Guangdong Tianpu Biochemical Pharmaceutical Company, Ltd.), 15,000 U/kg/day for 5 days (divided into three doses). If body temperature did not fall within 48 h or a moderate/large coronary artery aneurysm occurred, 2 g/kg IVIG was administered as supplementary treatment.

Group B: IVIG (produced by Shandong Taibang Biological Products Co., Ltd) was administered within 5–10 days of disease onset at a dose of 2 g/kg, followed by a shock therapy 8–12 h afterward. A further two 2 g/kg IVIG shock therapies or intravenous methylprednisolone/ulinastatin were administered if body temperature did not drop or the fever returned, according to the disease condition and the financial situation of the parents. An additional dose of ulinastatin was given to patients with normal body temperature and moderate/mild coronary artery aneurysm.

All patients received basic treatment of oral 50 mg/kg/d aspirin, 5 mg/kg/d persantin and 20 mg/kg/d vitamin E for 2 weeks. The dose of aspirin was reduced to 5 mg/kg/d 72 h after body temperature returned to normal, stopped if the coronary artery appeared to be normal by color ultrasonic cardiogram (US VOLUSON E8) conducted at week 8, otherwise the dose was continued until the coronary artery returned to a normal state.

Observational indicators and follow-up

Main indicator: diagnostic criteria according to ultrasonic echocardiography of coronary artery ectasia [11]. A coronary artery diameter of ≤ 2.5 mm (< 3 years old), ≤ 3 mm (3–9 years old), ≤ 3.5 mm (> 9 years old) was considered normal (Grade 0). Mild dilation (Grade I): obvious but limited aneurismal dilation with a diameter ≤ 4 mm. Moderate coronary artery aneurysm (Grade II): single, multiple or widespread dilation with a diameter of 4–7 mm. Severe large coronary artery aneurysm (Grade III): giant tumor with a diameter ≥ 8 mm, mostly extensive and involving more than one branch of the coronary artery. The coronary artery status of each patient was monitored before treatment and at 1 week, 3,6,12 months,2 years and 3 years after treatment by certified physicians using cardiac ultrasound inspection.

Secondary indicators: (1) Number of cases with abated fever 24 and 48 h after treatment (body temperature below 37 °C maintained for more than 48 h). (2) Number of cases not responding to treatment and the outcome of supplementary treatment. (3) Counts of peripheral white blood cells and platelets; hemoglobin levels. (4) C-reactive protein levels and erythrocyte sedimentation rate. (5) Average days of hospital stay and cost.

The 104 patients were monitored through follow-up for 3 years by coronary artery ultrasound.

Statistical analysis

The statistical analysis was performed using SAS JMP Pro software. All quantitative data were analyzed using Student's t-test and analysis of the count data, presented as case number and percentage, was performed using the Wilcoxon test. A difference with $P < 0.05$ was considered statistically significant.

Results

Changes in coronary artery diameter before and after treatment (Tables 1 and Table 2)

Of the 46 patients in Group A, 40 (86.96%) had normal coronary artery diameter before treatment and six had mild dilation (Grade I). Examination 1 week after treatment showed nine cases of Grade I coronary artery and one case of moderate coronary artery aneurysm. The number of cases with normal coronary artery increased to 43 and the number of cases with mild coronary artery dilation fell from nine to one in the follow-up examinations at 3 and 6 months after treatment. Normal coronary artery diameter was observed in 45 patients (75.86%) in Group B. Over time, the number of patients with normal coronary artery increased consistently while the number with mild dilation declined. However, moderate coronary artery aneurysm occurred

Table 1. Change of the diameter of coronary artery

	Before treatment			1 week after treatment			3 months after treatment			6 months after treatment		
	0	I	II	0	I	II	0	I	II	0	I	II
Group A (*n*=46)	40(86.96%)	6(13.04%)	0(0.00%)	36(78.26%)	9(19.57%)	1(2.17%)	43(93.48%)	1(2.17%)	2(4.35%)	43(93.48%)	1(2.17%)	2(4.35%)
Group B (*n*=58)	45(77.59%)	12(20.69%)	1(1.72%)	46(79.31%)	9(15.52%)	3(5.17%)	51(87.96%)	6(10.34%)	1(1.75%)	53(91.38)	4(6.90%)	1(1.75%)
Z	-1.2455			0.0415			-0.36228			0.068109		
P	0.213			0.9669			0.7171			0.9457		

Table 2. Change of the diameter of coronary artery

	Before treatment			12 months after treatment			2 years after treatment			3 years after treatment		
	0	I	II	0	I	II	0	I	II	0	I	II
Group A(*n*=46)	40(86.96%)	6(13.04%)	0(0.00%)	43(93.48%)	2(4.35%)	1(2.17%)	44(95.65%)	1(2.17%)	1(2.17%)	44(95.65%)	1(2.17%)	1(2.17%)
Group B (*n*=58)	45(77.59%)	12(20.69%)	1(1.72%)	54(93.10%)	3(5.17%)	1(1.75%)	56(96.55%)	1(1.75%)	1(1.75%)	56(96.55%)	1(1.75%)	1(1.75%)
Z	-1.2455			0.0312			-0.0687			-0.0687		
P	0.213			0.9884			0.9965			0.9965		

in two patients after treatment, both of whom had normal coronary arteries before treatment. The coronary arteries of both patients returned to normal during the 1-year follow-up. As shown in Table 3, no statistical difference in coronary artery diameters was observed in the patients of Group A compared to Group B before treatment and 1 week, 3,6,12 months,2 years and 3 years after treatment ($P > 0.05$).

Time needed to reduce fever

The time required to reduce fever was significantly shorter in Group A than in Group B ($P < 0.005$), as shown in Table 3.

Outcomes of supplementary treatment

Normal body temperature was achieved within 48 h for all 46 patients in Group A, but two cases later required supplementary treatment. One case, a 10-month-old male patient, experienced recurrence of fever 2 weeks after treatment with a left coronary artery diameter of 3.0 mm and aneurismal dilation of 4.6 mm in the right coronary artery. Normal body temperature was restored with supplementary administration of 2.0 g/kg IVIG. At the 1-year follow-up a left coronary artery diameter of 3.0 mm and a right coronary artery diameter of 3.7 mm with ball-like dilation were observed. The other case, a 4-year-old child, suffered recurrence of the disease 15 months after the first onset with a left coronary artery diameter of 4.4–5.5 mm and a right coronary artery diameter of 3.9–5.6 mm observed 8 days after treatment. Supplementary treatment with IVIG 2 g/kg was employed. A left coronary artery diameter of 3.1 mm and a right coronary artery diameter of 2.9 mm were observed at follow-up examination 30 months later, with no abnormality seen in an exercise electrocardiogram.

Supplementary treatment was given to ten (17.24%) of 58 patients in Group B. Normal body temperature was restored in two patients following intravenous methylprednisolone treatment, while the remaining eight patients were given a second treatment of 2 g/kg IVIG. A further two patients regained normal body temperature, while the body temperature of one case returned to normal after combined treatment with ulinastatin. Among the remaining five cases with persistent fever, two were treated with ulinastatin and two received methylprednisolone combined with ulinastatin to restore normal body temperature. The fever in the other case remained after three IVIG (2 g/kg) treatments but was finally brought to normal with intravenous 2 mg/kg/d methylprednisolone.

Changes in C-reactive protein and erythrocyte sedimentation rate

As shown in Table 4, there was no significant difference observed in C-reactive protein levels between the two groups at different time points ($P_{group} = 0.9476$). However, the erythrocyte sedimentation rates of patients in the two groups were significantly different at various time points. The reduction in ESR in Group A was significantly faster than in Group B ($P_{group} = 0.0008$).

Changes in peripheral white blood cell counts, hemoglobin levels and platelet counts (Table 5)

As shown in Table 5, the peripheral white blood cell counts of patients in Group A were significantly higher than those of Group B at different time points ($P_{group} < 0.0001$). The white blood cell counts of patients in Group B returned to normal faster than those in Group A ($P < 0.05$).

The effect of treatment on hemoglobin levels was greater in Group A compared with that in Group B ($P_{group} = 0.0013$). The hemoglobin levels in Group A gradually increased over time, while the levels in Group B fell briefly 1 week after treatment then gradually increased by week 3. The increase in hemoglobin levels was significantly faster in Group A ($P < 0.05$).

There was no significant difference in the change of platelet counts between the two groups ($P_{group} = 0.5344$); the platelet counts in both groups increased at week 1 then gradually decreased by week 3 at different rates. The fall in platelet counts in Group A was significantly faster than in Group B ($P < 0.05$).

Table 3. Cases with normal body temperature at different time points (%)

	n	~24h	~48h	>48h	Z	*P*
Group A	58	42(72.41)	6(10.34)	10(17.51%)	5.206	<0.05
Group B	46	43(93.47)	3(6.52)	0		

Table 4. Changes of C-reactive protein and blood sediment in the two treatment groups

	CRP (mg/L)		ESR (mm/h)	
	Group A(n=46)	Group B(n=58)	Group A (n=46)	Group B (n=58)
Before treatment	68.29±69.92	66.51±53.31	53.85±28.36	50.98±30.90
1 week after treatment	12.21±9.93	16.22±23.87	24.96±20.35	53.74±30.41
3 weeks after treatment	7.91±2.11	7.91±1.48	9.38±6.98	23.16±24.01
Statistics/P	F_{group}=0.00004	P_{group}=0.9476	F_{group}=0.117	P_{group}=0.0008
	F_{time}=0.9830	P_{time}<0.0001	F_{time}=1.3981	P_{time}<0.0001
	$F_{time*group}$=0.0130	$P_{time*group}$=0.5231	$F_{time*group}$=0.3147	$P_{time*group}$=<0.0001

Table 5. Changes of white blood cell, hemoglobin and platelet counts of the two different treatment plans at different time points

	WBC($\times10^9$)		HB($\times10^{12}$)		PLT($\times10^9$)	
	Group A(n=46)	Group B(n=58)	Group A	Group B(n=58)	Group A(n=46)	Group B(n=58)
Before treatment	15.2±6.112	13.60±5.92	112.26±14.90	108.69±13.69	375.72±168.68	351.41±127.23
1 week after treatment	14.27±4.52	9.12±3.72	115.26±10.12	106.34±12.36	562.33±202.62	491.43±175.94
3 weeks after treatment	11.77±4.63	8.00±2.41	121.76±12.03	112.72±11.72	413.50±141.21	448.33±148.56
	F_{group}=0.2892	P_{group}<0.0001	F_{group}=0.1077	P_{group}=0.0013	F_{group}=0.0039	P_{group}=0.5344
Statistics/P	F_{time}=0.4875	P_{time}<0.0001	F_{time}=0.5353	P_{time}<0.0001	F_{time}=1.0709	P_{time}<0.0001
	$F_{time*group}$=0.0934	$P_{time*group}$=0.0110	$F_{time*group}$=0.0726	$P_{time*group}$=0.0290	$F_{time*group}$=0.0701	$P_{time*group}$=0.0360

Comparison of the average days of hospital stay, total cost of hospitalization and cost of medicine (Table 6).

As shown in Table 5, there was no significant difference in the average hospital stay between the two groups ($P > 0.05$). Although the average number of days spent in hospital was comparable, the total cost of hospitalization for patients in Group A was significantly lower than for those in Group B ($P < 0.0001$).

Discussion

Many studies have suggested that the mechanism of pathogenesis and the pathological changes in KD is systemic vasculitis caused by abnormal activation of the immune system [12–14]. Some cytokines and, especially, anti-centromere antibodies activate neutrophils and cause vasculitis damage at an early stage in KD [7]. Glucocorticoids might act directly on the glucocorticoid receptor leading to stabilization of the cell membrane and inhibition of receptor activation, inhibition of multiple cytokines and Cox-2, and play a role in reducing inflammation [15]. Multiple studies by both Chinese and international scientists indicate that combined use of methylprednisolone and aspirin, either as a primary treatment of KD or an initial treatment used before IVIG, can effectively control body temperature, promote the recovery of dilated coronary arteries and reduce the incidence of coronary artery disease [16-18]. Ulinastatin, a trypsin inhibitor, also inhibits the activity of polymorphonuclear leukocytes (PMN) and is a free radical scavenger with an inhibitory effect on endogenous shock. Application of ulinastatin at the early stage of KD could block the pathogenic pathways of PMN, inhibit the destructive effect of PMN on fibrin and elastin, and prevent the formation of coronary artery aneurysm and its complications. Sundel et al. effectively controlled body temperature by giving intravenous ulinastatin to IVIG patients for 5–9 days [16].

The current study combined methylprednisolone with ulinastatin in KD treatment. In terms of the time needed to reduce fever, the percentage of patients with normal body temperature was significantly higher in Group A compared to Group B. Assessment of coronary artery diameter showed no significant difference between the two groups before treatment or at 1 week, 3,6,12 months,2 years and 3 years after treatment; Moderate coronary artery aneurysm occurred in two patients in Group A and two patients in Group B after restoration of body temperature. However, recovery of the patients in Group B was much faster, which could be due to the aggressive supplementary treatment used in the acute stage after failure of initial treatment in Group B. In addition, one patient in Group A suffered a second onset of KD, with severe hypoproteinemia, ascites and intestinal obstruction, which might have affected the study result. Jingying Pan [19] has suggested that there is a high risk of coronary artery damage in recurrent KD cases, with incidence of giant coronary artery aneurysm 1.5–2-fold higher than in first onset disease. Therefore, in order to reduce the incidence of coronary artery aneurysm, IVIG or combined hormone therapy should be preferred for the treatment of recurrent KD. In this study, ten patients in Group B (17.24%) did not respond to the first treatment, which is consistent with the literature [20,21]. One patient still suffered fever after three courses of IVIG (2.0 g/kg), whose body temperature was finally controlled by additional treatment with intravenous methylprednisolone (2 mg/kg/d). Eight patients were given a second course of IVIG (2.0 g/kg) treatment, while two patients regained normal body temperature. Newburger [22] has suggested reevaluation of the effect of additional treatment after failure of initial IVIG therapy.

According to the assessment of inflammatory indicators after treatment, no significant difference in C-reactive protein levels was observed for the two groups at different time points. The reduction of erythrocyte sedimentation rate in Group A was faster than in Group B, which could be due to the inhibitory effect of the combination treatment on the activity of the proinflammatory factor, NF-κB, with consequent reduction in the release of proinflammatory factors and alleviation of the inflammatory reaction [23]. The slower erythrocyte sedimentation rate in Group B could be related to the decreased negative charge on the erythrocyte surface caused by introduction of the large immunoglobulin, which promotes erythrocyte aggregation and rouleaux, resulting in increased blood viscosity. However, glucocorticoid could also promote an increase in erythrocyte count, hemoglobin content, platelet count and fibrinogen concentration, leading to increased blood viscosity. Therefore, glucocorticoid is superior to IVIG in terms of controlling erythrocyte sedimentation rate.

Changes in peripheral white blood cell counts differed between the two groups at different time points. The rate of decrease was faster in Group B, which could be due to the promotion of neutrophil release in bone marrow and inhibited migration of neutrophils from the circulation to the periphery caused by hormone usage in Group A. As for the effect on hemoglobin, the levels in Group A were higher than in Group B at different time points. The hemoglobin levels in Group A gradually increased, while the levels in Group B temporarily dropped 1 week after treatment but increased again after 3 weeks for unknown reasons. Furthermore, no significant difference in platelet counts was observed between the two groups, suggesting that use of glucocorticoid in KD treatment was not the reason for elevated platelet counts. The platelet counts in both groups increased by various degrees 1 week after treatment. This could be a consequence of the saturation of the reticuloendothelial system with immune complex in KD patients, resulting in reduced elimination of platelet aggregates, stimulated formation and activated metabolism of platelets. It could also be related to damage of vascular endothelial cells, exposure of the collagen fiber of the vascular wall, and platelet adhesion and activation during the acute phase of KD.

As indicated in the basic information on patients, the average age and weight of patients in Group A were higher than those in Group B. The lack of patients older than 9 years in Group B was a flaw of the current study. Since its dosage was calculated based on body weight, IVIG therapy would definitely increase the financial burden of the family with older or heavier patients. There was no significant difference

Table 6. Average days of hospital stay, total cost of hospitalization and cost of medicine between the two groups of patients

	average days of hospital stay (days)	total cost of hospitalization (Yuan)	cost of medicine (Yuan)
Group A(n=46)	9.326±3.795	6969.8±2615.23	3036.48±2028.17
Group B(n=58)	8.966±2.847	11792.7±3142.51	7979.40±2668.75
t	-0.554	8.371	10.4
P	0.5811	0.0001	0.0001

in the number of hospitalized days between the two groups. However, the total cost of hospitalization for patients in Group A was much lower than for those in Group B. In other words, the short-term hormone impact treatment did not increase the incidence of hospital infection or other adverse reactions.

Conclusion

As demonstrated in the current study, use of glucocorticoid in the early phase of KD effectively controlled inflammation. Ulinastatin could inhibit the destruction of blood vessel fibrin and elastin. With the additive anti-coagulation effect of aspirin, combined use of these three drugs did not increase the risk of coronary artery disease. China is a nation with a vast territory, unbalanced regional economic development and a huge gap in financial conditions among different populations. There should be multiple treatment options for KD to meet the needs of different populations with assured safety. Combined use of methylprednisolone and ulinastatin could be an effective and affordable option for treatment of KD.

References

1. Fury W, Tremoulet AH, Watson VE, Best BM, Shimizu C, et al. (2010) Transcript abundance patterns in Kawasaki disease patients with intravenous immunoglobulin resistance. *Hum Immunol* 71: 865-873. [Crossref]
2. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Tsuboi S, et al. (2012) Epidemiologic features of Kawasaki disease in japan: Resuits of the 2009-2010 nationwide survey. *J Epidemiol* 22: 216-221. [Crossref]
3. Prieto Tato LM, Cuesta Rubio MT, Guillén Martín S, Ruiz Jiménez M, Cortés Coto MT, et al. (2010) Kawasaki disease: Diagnosis and treatment. *An Pediatr(Barc)* 73: 25-30. [Crossref]
4. Min Zhang, Xiu-fen Hu (2013) Research of immunoglobulin-resistant Kawasaki disease. *J Appl Clin Pediatr* 28: 1672-1676.
5. Freemman AF,Shulman ST (2004) Refractory Kawasaki disease. *Pediatr Infect Dis J* 23: 463-464. [Crossref]
6. Jibiki T, Kato I, Shiohama T, Abe K, Anzai S, et al. (2011) Intravenous immune globulin plus corticosteroids in refractory Kawasaki disease. *Pediatr Int* 53: 729-735 [Crossref]
7. Suzuki H1, Terai M, Hamada H, Honda T, Suenaga T, et al. (2011) Closporin A treatment for Kawasaki disease refractory to initialand additional intravenous immunoglobulin. *Pediatr Infect Dis* 30: 871-876 [Crossref]
8. Ravelli A, Magni-Manzoni S, Pistorio A (2005) Preliminary diagnosis guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *J Pediatr* 146: 598-604.
9. Athappan G, Gale S, Ponniah T (2009) Corticosteroid therapy for primary treatment of Kawasaki disease-weight of evidence:A meta-analysis and systematic review of the literature. *Cardiovasc J Afr* 20: 233-236 [Crossref]
10. Ayusawa M1, Sonobe T, Uemura S, Ogawa S, Nakamura Y, et al. (2005) Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int* 47: 232-234. [Crossref]
11. Ya-mei Hu, Zai-fang Jiang (2002) Applied Pediatrics, 7th Edition. Beijing: People's medical publishing House, 689-705.
12. Fang Liu (2011) Study Progress of Etiology and Pathogenesis of Kawasaki Disease. *J Appl Clin Pediatr* 26: 1671-1618.
13. Rowley AH, Shulman ST (2010) Pathogenesis and management of Kawasaki disease. *Expert Rev Anti Infect Ther* 8: 197-203. [Crossref]
14. Yun Wang, Guan-fu Ma, Qin Fu (2010) Changes of Serum Interleukin-6, Interleukin-8 Levels and Their Associations with Coronary Artery Lesions in Children with Kawasaki Disease. *J Appl Clin Pediatr* 25: 632-633.
15. Yin Liu, Shi-mei Ji (2002) Methylhydroprednisone treatment of Kawasaki Disease. *Chin J Pediatr* 40: 753-754.
16. Sundel RP, Baker AL, Fulton DR, Newburger JW (2003) Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 142: 611-616. [Crossref]
17. Mao-rong Chen, Yun-gang Yang (2006) Effect of Methylprednisolone on treatment of Kawasaki disease and dynamic changes of the internal diameter of coronary artery. *J Clin Pediatr (Chinese)* 24: 520-522.
18. Xiao-hui Li (2013) New development in the diagnosis and treatment of Kawasaki Disease. *J Appl Clin Pediatr* 28: 9-13.
19. Jing-yin Pan, Yu-xin Bai, Hua Zhu (2013) Epidemiological features of Kawasaki disease in China. *Int J Pediatr (Chinese)* 40: 466-469.
20. Ashouri N, Takahashi M, Dorey F, Mason W (2008) Risk Factors for nonresponse to therapy in kawasaki disease. *J Pediatr* 153: 365-368. [Crossref]
21. Zhang W, Li Q, Zhao XD, Tang XM, Wang XG, et al. (2006) Clinical analysis of 942 cases of Kawasaki disease. *Zhonghua Er Ke Za Zhi* 44: 324-328. [Crossref]
22. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, et al. (2004) Diagnosis, treatment,and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 110: 2747-2771. [Crossref]
23. Liakopoulos OJ, Schmitto JD, Kazmaier S, Bräuer A, Quintel M, et al. (2007) Cardiopulmonary and systemic effects of methylperdniisolone in patients undergoing cardiac surgery. *Arm Thorac Surg* 84: 110-119. [Crossref]