Corticosteroid pulse therapy or additional intravenous immunoglobulin for patients with IVIG-resistant Kawasaki disease

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Abstract

There have been no robust data from clinical trials to guide the clinician in the choice of therapeutic agents for the child with IVIG resistance, the treatment regimen for IVIG resistant patients varies between institutions, and the best option has not yet been established therefore. In this trial, a total of 955 patients with KD were selected and were initially treated with IVIG. (2g/kg), of whom 80 (8.38%) assessed as IVIG resistant were randomly divided into two groups: group A received second IVIG treatment (n = 40), group B received methylprednisolone pulse therapy (MPT, n = 40). The whole fever time, duration of fever after retreatment, hospital days, medical cost, readmission rate, and laboratory examination difference ()$werecalculated.CALsoutcomeswerefollowedupovertwoyears.PatientsinMPTgrouphadshorterfeverafterretreatmentandlowermedicalcosts,n$
$termfollow-up.theMPTusedtotreatIVIG-resistantKDstillneedtobeconsideredcarefully.$

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Conflicts of interest

The authors declare no competing financial interests.

Introduction

Kawasaki Disease (KD) is an acute, self-limited febrile illness of unknown cause that predominantly affects children <5 years of age.[1] Ithas been reported worldwide and is the leading cause of acquired heartdisease in children in developed countries.[2]The efficacy of intravenous immunoglobulin(IVIG)administered in the acute phase of KD is well established to reduce the prevalence of coronary artery abnormalities(CALs).[3]However, the approximately 10% to 20% of patients with KDwho do not respond to the initialtreatment with IVIGat least 36 hours after the end of their IVIG infusion are termed IVIG resistant.[4]It is wellknown that those with IVIG-resistant KD have a higher riskfor the development of CALs.[5–6]The treatment regimenfor IVIG resistant patients varies between institutions, and the best option has not yet beenestablished.[7]IVIG-resistant patients are usuallytreated with additional IVIG, the retrospective trials have tested efficacy, but IVIG retreatment has never been tested in an adequately randomized trial.[8–9]Thus, IVIG retreatment for IVIG-resistant KD is farfrom an established therapy.Corticosteroids have also been used to treat patients who have failed to respond to initial IVIG therapy for KD.[10]Several retrospective study results suggest thatcorticosteroid pulse therapy for IVIG-resistant KD may reduce the riskfor CALs.[11–12]There have been no prospective randomized controlled clinical trials(RCTs)comparing corticosteroid pulse therapy(CPT) with a second dose of IVIG for IVIG-resistant KD patients, and there are no robust data from clinical trials to guide the clinician in the choice of therapeutic agents for the child with IVIG resistance.[13]Therefore, we

conducted a prospectiveRCT to determine whether patients with initial IVIG-resistant KD may benefit from CPT compared with additionalIVIG.

Methods

Trial design

This was a prospective, single-center, RCT. A total of 955 patients with KD at the Department of Cardiology of Guangzhou Women and Children's Medical Center fromJanuary 2018 toJune 2019 were selected and were initially treated with IVIG. 80 patientswho were assessed as IVIGresistant were randomly divided into two groupsusing a random number table. TheResearch Ethics Committee of Guangzhou Women and Children's Medical Centerapprovedthis study (NO. GZR2015-099), and the children and their families provided their written informed consent.The registration number of this randomized controlled clinical trial is: ChiCTR-EOC-17013266.

Trial completion location

The trial was completed in the Department of Cardiology of Guangzhou Women and Children's Medical Center fromJanuary 2018 toJune 2019,Guangdong Province, China.

Sample size

Refer to the formula[14] n = (μα + μβ) 2σd2 / δd2, where μα and μβ can be found in the μ value table, σd is the standard deviation of the difference, and δd is the difference. After looking up the table, μα = 1.960, μβ = 1.280, and σd = 0.038 and δd = 0.028 were pre-tested by the research group, and 45 samples of each group were calculated. Considering the 10% test exit rate, the overall calculation was finally obtained.We

Use random number table method to group.

Grouping method

Non-participating nurses use a computer to generate random tables. Patientswho were assessed as IVIGresistant by doctors were randomly divided into two groups.When eligible subjects enter the trial, the nurses assign groups to trial researchers for clinical trial intervention.

Blind method

The trials did not use blind grouping.

Patient involvement statement

We collectedIVIG-resistant KD patients from the Department ofCardiology of Guangzhou Women and Children's Medical Center fromJanuary 2018 toJune 2019, patients who meet the inclusion criteriacarried out a research project description for the family, obtain consent and sign informed.Patients were involved in the research and actively contributed to identifying the issue of inconsistent reporting, the need for guidance, and the research question.Patients were involved as research partners in all aspects of the study including identifying the design of this study,identifyingthe original research question, identifying the need for therapy and identifying the need for consensus.The research reports and results will be disseminated to all study participants via email.

Diagnosis criteria of KD

The diagnosis of KD was made according to the guideline by the AHA in 2017.[13]

Diagnosis criteria of IVIG-resistant KD

KD patients who developrecrudescent or persistent fever at least 36 hours afterthe end of their first IVIG infusion are termed IVIG resistant.[13]

Diagnosis criteria of coronary artery lesions

We use themaximal Z scores from echocardiographicfor evaluationof the severity of CALs. [13]

Z -Score Classification:

1. No involvement: Z scores always <2.

2.Dilation only:Z score [?]2 but <2.5.

3.Small aneurysm (Z score [?]2.5 to <5).

4.Medium aneurysm (Z score [?]5 to <10, andabsolute dimension <8 mm).

5.Giant aneurysm (Z score [?]10, orabsolute dimension [?]8 mm).

Inclusion criteria of KD patients

1.KD patients diagnosed and hospitalized in our hospitalwho met the diagnostic criteria for KD and IVIG-resistant KD by AHA in 2017.[13]

2.All patients were initially treated with high-dose IVIG (2g/kg given as a single intravenous infusion) and were administeredof aspirin orally (30–50mg.kg^{-1}.d^{-1}) within the first 10 days of the onset of fever.

Exclusion criteria of KD patients

1.There are other diseases that affect the temperature change in the course of the KD,such as sepsis, influenza,and juvenile idiopathic arthritis.

2.KD patients who do not have detailed information about the initial treatment outside the hospital.

3.With a history of KD.

4.Receive hormone or immunosuppressant treatment within 30 days.

5.Severe immune disease,such as immunodeficiency or chromosomal abnormality.

6.Refusal to sign informed consent.

7. Unable to follow up for at least 6 months.

Trail withdrawal and termination criteria

1. If participants voluntarily withdraw informed consent at any time during the study, they will withdraw from the trial and be excluded from data analysis Initial treatment 2.If the following conditions occur, the test will be terminated:Patient gives up treatment;Fever more than 36 hours after re-treatment.

Initial treatment

All patients meeting the diagnostic criteria for KDwere initially treated with high-dose IVIG (2g/kg given as a single intravenousinfusion) together withaspirin orally (30–50mg.kg^{-1}.d^{-1}) within the first10 days of the onset of fever. We defined a responder as a patient who showed resolution of fever(<38) within 36h after initialIVIG treatment.[15]

Additional IVIG treatment and corticosteroid pulse therapy

IVIG-resistant patientswere randomly divided into two groups by random number table: group A receivedadditional IVIG (2g/kg given as a single intravenousinfusion); group B receivedmethylprednisolone15 mg.kg^{-1}.d^{-1}intravenously for 3 days, without asubsequent course and taper of oral prednisone. Both groups tookaspirin orally (30–50mg.kg^{-1}.d^{-1}).During corticosteroid pulse infusion and IVIG treatment, patients underwentcontinuous cardiac monitoring. Frequentevaluations were made after the infusion untilvital signs were stable.

Observation indicators

Thelaboratory values of white blood cells(WBC), neutrophils (%), C-reactive protein(CRP), hemoglobin (HGB), platelets(PLT), albumin, and sodium1 day before and one week afterretreatment,andcalculated difference before and after treatment(). $The whole fever time(Total days from the onset of fever to temperature stable for 48h after treatment), duration of f$

Coronary arterylesions(CALs)

The incidence ofCALs was assessedat 7 days after diagnosis andfollowedup at 1, 3, 6,12, and 24 months after hospital dischargeusing Z scores from ultrasound echocardiography according to the diagnosis criteria of CALs.[13]

Data management

Relevant quality control is carried out throughout the trial process to ensure the authenticity, accuracy and objectivity of the paper data; Two people enter electronic data and lock the data for storage.

Quality control of clinical trials

Participants must participate in relevant training and be qualified; regular follow-up monitoring to ensure that the test process and results are objective, true, and accurate.

Statistical analysis

Data analysis using SPSS19.0 software.Measurement data consistent with a normal distribution are expressed as $x \pm s$, and comparison between groups is made with t -tests. For statistical analysis, the Kruskal-Wallis test wasused for paired numeric data, the Mann-WhitneyUtest forunpaired numeric data, and the chi-squared test for categorical variables.A P -value lower than 0.05 by two-tailedanalysis was accepted as statistically significant.

Results

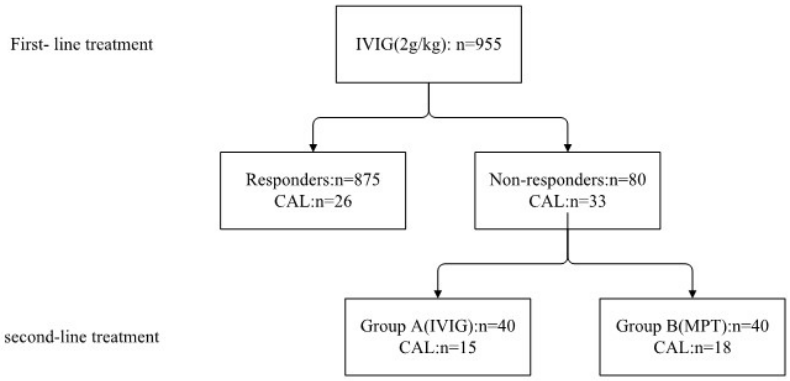

Figure1. **Protocol and results of the treatment in this study** .IVIG,intravenous immunoglobulin;CAL, coronary arterial lesion; MPT,methylprednisolone pulse therapy

As shown (figure1), 955 patientswith KD were treated with IVIG (2g/kg) immediatelyafter being diagnosed with KD. 875 of these patients (91.62%) were clinical responders to the initial treatment, and 26 of these patients(2.97%) showed coronary artery lesion. However, the remaining 80 patients(8.38%) were assessed as IVIG resistant,and 33 of these patients(41.25%) showed coronary artery lesion. 80 IVIG-resistant patientswere randomly divided into two groups:Group A receiving additional IVIG (n =40, 2g/kg), Group B receivingmethylprednisolone pulse therapy(MPT,n =40,methylprednisolone 15mg/kgintravenously for 3 days,

without asubsequent course and taper of oral prednisone)within 36h after initial IVIG treatment.Although 5 patients developed bradycardia in thesteroid pulse group, these cases improved spontaneously.

Table 1: **Age, gender, inpatient day, whole fever time, duration of fever after re-treatment, and medical cost in both groups**

	Group A(n=40)	Group B(n=40)	95% CI	P-V
Age/m	21.0±14.4	25.6±21.1	0.48-1.67	0.1
Gender (male:female) Weigh/kg	28:11 10.7±3.2	28:13 11.7±4.7	0.63-1.37 0.13-0.57	0.9
Hospital day/d	6.7±2.6	6.2±2.3	0.27-0.83	0.2
Whole fever time/d	11.2±2.3	10.3±2.0	0.21-2.60	0.1
Duration of fever after retreatment/h	18±4.4	11±6.3	0.11-0.70	**0.0**
Medical cost/yuan Readmission rate	¥11261±3564 10.0%(4/40)	¥8218±2145 27.5%(11/40)	0.19-0.81 0.23-0.76	**0.0**

Data are expressed as mean±SD . Group A: IVIG retreatment group; group B:methylprednisolonepulsetherapy

As shown in Table 1, no significant difference was found between thetwogroups with regard to age, gender, weight, hospital days and whole fever time. The duration of fever(>38) after additional treatment in patientstreated with MPT (11+-6.3 hours)was significantly shorter than that in patientstreated with additional IVIG treatment (18+-4.4 hours;P <0.05). A significant difference was foundin medical cost between the twogroups(Y=11261+-3564 in Group A versus Y=8218+-2145in Group B;P <0.05), but the readmission rate in patientstreated with MPT(27.5%,11/40)was significantly higher than that in patientstreated with additional IVIG treatment (10.0%, 4/40;P <0.05).

Table 2: Laboratory data on additional treatment

		Group A (n=40)	Group B (n=40)	95% CI	P-Value
WBC/10^9.L^{-1}	before therapy	16.1±6.9	18.7±6.9	0.50-3.98	0.292 0.087 0.247
	after therapy	10.7±4.2 5.2±7.2	11.6±5.3 7.0±5.9	0.71-1.57	
	^{W}BC			0.50-3.94	
Neutrophils/%	before therapy	54.4±11.9	56.5±14.7	0.06-3.58	0.053 0.127
	after therapy	40.4±15.0	44.2±14.1	0.06-3.99	**0.048**
	$^{N}eutrophils$	12.5±15.0	14.6±14.0	0.27-0.84	
CRP/mg.L^{-1}	before therapy	100.4±56.3	123.1±69.8	0.19-7.25	0.652 0.725
	after therapy	16.0±25.2	21.9±31.5	0.28-6.99	**0.039**
	^{C}RP	80.5±46.8	101.5±64.7	0.10-0.52	
HGB/g/l	before therapy	92.8±11.3	94.9±13.3	0.27-1.57	0.125 0.265 0.114
	after therapy	102.2±13.5	101.0±13.5	0.28-1.57	
	^{H}GB	9.1±15.0	6.1±12.4	0.25-1.32	
PLT/×10^9.L^{-1}	before therapy	447±210.5	408±176.8	0.6-3.72	0.458 0.850
	after therapy	599.9±204.7	647.2±229.7	0.52-1.20	**0.027**
	^{P}LT	149.0±254.8	238.6±291.5	0.13-0.57	
albumin/g/L	before therapy	92.8±11.3	94.9±13.3	0.51-1.19	0.232 0.335 0.110
	after therapy	102.2±13.5	101.0±13.5	0.52-1.20	
	$^{a}lbumin$	3.8±5.4	5.4±6.7	0.19-0.80	
sodium/mmol/l	before therapy	130.8±19.5	134.1±2.9	0.30-7.25	0.630 0.095
	after therapy	137.3±1.9	138.7±2.1	0.28-6.99	**0.043**
	$^{s}odium$	3.3±2.6	4.8±2.8	0.27-0.83	

Data are expressed asmean±SD . WBC, white blood cells; HGB, hemoglobin; CRP, C-reactive protein; PLT,platelets. Group A:IVIG retreatment group; Group B:MPT group.**before therapy**

:values1 day before the 2nd treatment.**after therapy** : values 7 days after the 2nd treatment.

:$difference in laboratory data were calculated using following equation$: $(values 7 days after the 2nd treatment) - (values 1 day before the 2nd treatment)$.

The differences in laboratory data between1 day before and 7 days after additional treatment are shown inTable2.No significant difference was foundbetween the twogroupsin$^{W}BC, ^{H}GBand^{a}lbumin, but^{N}eutrophils\%, ^{C}RP, ^{P}LT, and^{s}odiumafteradditionaltreatmentinpatientstreated$ $0.048, \boldsymbol{P} = 0.039, \boldsymbol{P} = 0.027, \boldsymbol{P} = 0.043, \boldsymbol{P}$<0.05).

***Table 3*: Coronary arterial lesions in the two groups**

Follow-up time	Group A (n = 40)	Group A (n = 40)	Group A (n = 40)	Group A (n = 40)	Group B (n = 40)	Group B (n = 40)	Group B (n = 40)	Group B (n = 40)	X^2	P
	dilation	SA	MA	GA	dilation	SA	MA	GA	CALs	CALs
7 days (n = 80)	5/40	8/40	2/40	0/40	6/40	9/40	3/40	0/40	0.464	0.650
1 month (n = 79)	2/39	5/39	1/39	0/39	2/40	4 /40	3/40	1/40	1.939	0.202
3 months (n = 78)	3/39	0/39	1/39	0/39	0/39	0/39	2/39	1/39	0.157	1.000
6 months (n = 71)	2/35	0/35	0/35	0/35	0/36	2/36	1/36	1/36	0.668	0.674
12months (n = 53)	0/28	0/28	0/28	0/28	0/25	2/25	1/25	1/25	4.846	0.043
24months (n = 33)	0/18	0/18	0/18	0/18	0/14	2/15	2/15	0/15	5.462	0.033

SA: small aneurysm.MA: medium aneurysm.GA: giant aneurysm. CALs= dilation +SA+MA+GA

As shown in Table 3, there was nostatistically significant difference in the incidenceof CALs between the twogroups at 7days (P =0.650,P >0.05), and no statistically significant difference at 1 month, 3 months and 6 months after hospital discharge(P =0.202,P >0.05;P =1.000,P >0.05; P = 0.674,P>0.05).But at 12 months and 24 months of follow up, the MPT group had a higher incidence of CALs compared with the second IVIG treatment group (P = 0.043,P ¡0.05; P = 0.033¡0.05).

Harms or unintended effects

Five patients developed bradycardia in theMPT group, but these cases improved spontaneously. In theadditionalIVIG treatment group, there were no adverse reactions occurred.

Discussion

In the current prospective RCT with 955 KD patients and 80 IVIG-resistant KD patients, we verified thatthe medical costs of patients treated with MPT were significantly lower and the duration of fever after retreatment wassignificantly shorter than those ofpatients treated with additional IVIG treatment. In addition, the WBC, PLT, Na, and N% of patients treated with MPT returned to normal faster than those ofpatients treated with additional IVIG treatment. MPThad a higher incidence of treatment failure and CALs compared with the second IVIG treatmentgroupin long-term follow-up.To the best of our knowledge, this is the first prospective RCT to study MPTandadditionalIVIGfor patients withIVIG-resistant KD in China.

The incidence of patients with KD who do not respond to the initialtreatment with IVIGis approximately 10% to 20%.[4]Our research shows thatthe incidence of IVIG resistant is about 8.38%. A large amount of research suggests that the incidence of CALsin IVIG-resistant KD is as high as22%-45.8%[16,17],our study shows that 33 of 80IVIG resistant patients had coronary artery lesion,the incidence of CALs is about 41.25%.Because the incidence of CALsis so high, it is important to find a more beneficial treatmentforthese children. The current retreatment options mainly include additionalIVIG,corticosteroids, infliximab, etc.[18–21]Several retrospective study results suggest that CPT for IVIG-resistant KD may reduce the riskfor CALs,[22]but there are no robust data from clinical trials to guide the clinician in the choice of therapeutic agents for the child with IVIG resistance.[13]

Corticosteroids were used as the initial therapy for KD long before the first report by Furusho et al in 1984.[23]In the past, some studies reported that steroid treatment for KD is unsafe and is contraindicated due to the high incidence of CALs.[24]Recently, becauseof its cost-effectiveness, corticosteroid pulse therapy in IVIG-resistant KD has increasingly attracted clinicians' attention.[25]Shinohara et al.[26] found that prednisolone could significantly shorten fever duration and led to a lower prevalence of coronary artery aneurysms. A recentmeta-analysis by Chen et al.[27]found that a combination of corticosteroids with standard-dose IVIG as an initial treatment in high-risk patients could reduce the rate of CALs.There is still no convincing research on the clinical efficacy of steroid pulse therapy on KD. In particular, the long-term effect of steroid pulse therapy onthe coronary arterieshas not been clarified.[28]

In ourtrial, through comparison between an IVIG retreatment group and MPT group, we found that patients in the MPT group had a shorter duration of fever after retreatment and lower medical costs, more rapid decline in CRP, N%, and PLT levels, and more rapid rise in Na, and they were not significantly different in terms of preventing the development CALs in short-term follow-up([?]6 months). But our research found that the MPT group had a higher incidence CALs compared with the second IVIG treatmentgroupin long-term follow-up(¿6months).

The optimal steroid regimen is therefore not known, and both pulsed and longer-term steroid therapy remain options. Furukawa et al.[27]found that the incidence of CALs was similar between the intravenous methylprednisolone followed by oral methylprednisolone tapered over 7 days and a second infusion of IVIG. Kobayashi et al.[19]foundthat patients treated with IVIG plus prednisolonehad significantly lower rates of persistent or recrudescent fever and CALs than those whoreceived IVIG mono-therapy.In our study,we gaveintravenous methylprednisolone 15mg.kg^{-1}.d^{-1} for 3 consecutive days, without asubsequent course and taper of oral prednisone.This study suggeststhat patients in the MPTgroup had a shorter duration of fever after retreatment and lower medical costs, more rapid decline in CRP, N%, and PLT levels, and more rapid rise in Na,buthad a higher incidence CALs compared with the second

IVIG treatmentgroupin long-term follow-up(¿6months). However,we discovered that the readmission rate in patientstreated with MPTwas significantly higher than that in patientstreated with additional IVIG treatment.We think the high readmission rate may be related to the sudden withdrawal of intravenous methylprednisolone andlack ofa subsequent course and taper of oral prednisone.

The guideline[13] suggests that administration of high-dose pulse steroidsfor retreatment of patients with KD who have had recurrent or recrudescent fever after additional IVIG,butone study suggests that high-dose MPT may cause bradycardia and elevated blood pressure and blood sugar.[29]Therefore, clinicians are more cautious about the application of MPT to IVIG-resistant KD, and more ordinary doses are used.The dose of methylprednisolone used in ourstudy was 15mg.kg^{-1}.d^{-1}, and although five patients developed bradycardia, these cases improved spontaneously.

Immunoglobulin is expensive, and as a blood product posesrisks related to blood transfusion. The anti-inflammatory effect of corticosteroids is certain and their medical cost is relatively low. Acomprehensive analysis of cost-effectiveness shows that there is a bright future for IVIG-resistant KD.[30]Our studyshows that the MPTgroup had a shorter duration of fever after retreatment and lower medical costs, more rapid decline in CRP, N%, and PLT levels, and more rapid rise in Nain the treatment of IVIG-resistant KD.But our study shows that the readmission rate inMPT groupwas significantly higher, and had a higherincidence CALs in long-term follow-up, So the MPT used to treat IVIG-resistant KD still need to be considered carefully.

Though this study is the largest to be performed in Chinese children and the firstprospective RCT for patients with IVIG-resistant KD in China,certain limitations should be acknowledged. First, the sample size in the current study is still small, Therefore, multi-center prospective RCTs with larger sample sizesare needed to confirm whether MPTor additionalIVIGis better for patients with IVIG-resistant KD. Second, we only compared the efficacy and safety of re-treatment of IVIG therapy with MPT (15mg.kg^{-1}.d^{-1} for 3 consecutive days, without a subsequent course and taper of oral prednisone)in patients with IVIG-resistant KD.Many other therapies have not been compared,such as steroid pulse therapy(20-30mg.kg^{-1}.d^{-1} for 3 consecutive days, with a subsequent course and taper of oral prednisone).

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Authors' contributions

YF Wang andW Li performed the research study and collected the data; X F Xie and X Zhanganalyzed the data; P Huang designed the research study; ZP Wang and F Y Chenwrote the paper; L Zhang and P Y Liu prepared all the tables. All the authors reviewed the manuscript and approved the final draft. All authors contributed significantly to this work.

Availability of data and material

The data used to support the findings of this study are included within the article.The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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