Low-Dose Methylprednisolone Therapy for Intravenous Immunoglobulin-Resistant Kawasaki Disease

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Research article

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Abstract

Background

The dose of methylprednisolone therapy for intravenous immunoglobulin-resistant Kawasaki disease (IVIG-resistant KD) remains controversial. The study aims to investigate the effect of low-dose intravenous methylprednisolone (IVMP) therapy on children with IVIG-resistant KD.

Methods

36 IVIG-resistant KD children were recruited. Coronary artery lesions (CAL) were recorded before these children were first treated with IVIG. 15 patients were treated with a second course of IVIG (2 g/kg/dose) after unsuccessful treatment with IVIG (2 g/kg/dose), named IVIG group. 21 patients with IVIG-resistant KD were treated with a second course of IVIG and low-dose IVMP (2 mg/kg/day) for 3-5 days after unsuccessful treatment with IVIG, named IVIG+IVMP group, including 8 patients with CAL and 13 patients without CAL. The level of brain natriuretic peptide (BNP) in serum was detected by electrochemiluminescence immunoassay.

Results

The treatment was successful in 21 (100%) of the patients who received additional IVIG along with IVMP and 10 (66.7%) who received additional IVIG. In IVIG+IVMP group, BNP decreased significantly after patients received additional IVIG along with IVMP. 72h After treated with additional IVIG and IVMP, there was no difference of BNP levels between patients with CAL and without CAL in IVIG+IVMP group. None of the patients was with CAL followed up for 1 year in IVIG+IVMP group.

Conclusion

This study suggest that low-dose IVMP along with additional IVIG is an effective treatment for IVIG-resistant KD, and low-dose IVMP increases no risk of CAL.

Background

Kawasaki disease (KD), first reported by a doctor in Kawasaki Japan in 1967, also known as mucocutaneouslymph syndrome, is considered to be an acute systemic vasculitis. Most prognosis of KD is good and self-limiting, but KD can cause severe cardiovascular disease, especially coronary arteries[1]. Intravenous immunoglobulin (IVIG) is an effective treatment for KD. But 10%-20% of such patients are resistant to IVIG therapy, who have a high risk for coronary artery lesions (CAL) [2]. The patients were considered IVIG-resistant KD when fever persisted or recurred 48 h after treatment with high-dose IVIG and aspirin. Several investigators have recommended the use of steroid pulse therapy for these patients with IVIG-resistant KD [3–5]. While some studys have showed high-dose steroid in pulse therapy may be associated with the risk of coronary aneurysms [6, 7]. In this study, we use low-dose intravenous methylprednisolone (IVMP) along with a second course of IVIG in patients with IVIG-resistant KD.

Studies have showed that brain natriuretic peptide (BNP) play a significant role in the pathogenesis of KD [8], and predicts the risk of CAL in Kawasaki disease [9, 10]. In this study, we detected the level of BNP in IVIG + IVMP group with CAL and without CAL. IVIG + IVMP group was followed up for one year. Thus, we can find the influence of low-dose IVIG on coronary artery.

Materials And Methods

General information

36 IVIG-resistant KD children were hospitalized in The First People's Hospital of Changzhou from June 2014 to May 2019, aged from 11 months to 8 years. Informed consent was obtained for all research individuals. We recorded CAL before these children were first treated with IVIG. 15 patients with IVIG-resistant KD were treated with a second course of IVIG (2 g/kg/dose) after unsuccessful treatment with IVIG (2 g/kg/dose), which we named IVIG group, including 6 patients with CAL and 9 patients without CAL. 21 patients with IVIG-resistant KD were treated with a second course of IVIG (2 g/kg/dose) and low-dose IVMP (2 mg/kg/day) for 3–5 days after unsuccessful treatment with IVIG (2 g/kg/dose), which we named IVIG + IVMP group, including 8 patients with CAL (named CAL group) and 13 patients without CAL (named Non-CAL group).

Methods

The venous blood was taken 2mL, centrifuged at 3000 r/min for 10 minutes to separate the serum. Store the serum at -70 °C. We use electrochemiluminescence labeling immunoassay technology to detect the level of serum BNP. The analytical instrument is ROCHE E170 automatic electrochemiluminescence analyzer. All the cases signed an informed consent form and were approved by the Ethics Committee of The First People's Hospital of Changzhou, China.

Statistical analysis

The data was analyzed with SPSS 20.0 software. Age were expressed as the median $\pm$ standard deviation (mean $\pm$ s). The comparison of the mean of non-normal distribution measurement data is done by mann-whitney test, and the comparison of the mean of normal distribution data is by t test. The comparison of data between groups was performed by K-S test, expressed as $\pm$ s. $P < 0.05$ was significant.

Results

Treatment results

36 IVIG-resistant KD children were divided into IVIG group and IVIG + IVMP group. Treatment results were showed in Fig. 1. There was no significant difference in gender, age and rate of CAL between IVIG group and IVIG + IVMP group ($P > 0.05$, Table 1). Also there was no significant difference in gender and age

between CAL and Non-CAL in IVIG + IVMP group ($P > 0.05$, Table 2). 10 (66.7%) were responders in IVIG group and 21 (100%) were responders in IVIG + IVMP group. The number of responders between IVIG group and IVIG + IVMP group was statistically significant ($P < 0.05$, Table 3).

Table 1
Characteristics of patients in IVIG group and IVIG + IVMP group

Group	IVIG group (n = 15)	IVIG + IVMP group (n = 21)	^a p
Gender (male/female)	8/7	12/9	0.821
Age (months)	34.5(23.78)	29.7(21.19)	0.905
Rate of CAL (%)	40.0%	38.1%	0.908
^a IVIG + IVMP group is compared with IVIG group.			

Table 2
Characteristics of patients in IVIG + IVMP group

IVIG + IVMP group	CAL group (n = 8)	Non-CAL group (n = 13)	^a p
Gender (male/female)	5/3	7/6	0.697
Age (months)	29.4(27.19)	32.9(29.76)	0.921
^a Non-CAL group is compared with CAL group.			

Table 3
Comparison between the IVIG group and IVIG + IVMP group

	Effective (n)	Ineffective (n)	Total (n)	Efficiency (%)
IVIG group	10	5	15	66.7%
IVIG + IVMP group	21	0	21	100%
^a p	0.004			
χ^2	8.129			
^a The efficiency of IVIG + IVMP group is compared with IVIG group.				

Influence Of Ivmp On Bnp

In IVIG + IVMP group, before treated with low-dose IVMP and additional IVIG, the level of BNP in CAL group was significantly higher than Non-CAL group ($P < 0.05$, Table 4). The level of BNP was significantly

decreased after IVIG-resistant KD children was treated with low-dose IVMP and additional IVIG both in CAL group and Non-CAL group. 72h After the treatment, there was no significant difference in BNP levels between CAL group and Non-CAL group ($P > 0.05$, Table 4).

Table 4
Changes of BNP levels

IVIG + IVMP group	CAL group(n = 8)	Non-CAL group (n = 13)	cdep
Before	339.71 ± 66.36pg/ml	269.53 ± 43.81pg/ml	^c P = 0.001
24h	215.24 ± 47.43pg/ml	149.08 ± 36.72pg/ml	^d P = 0.000
72h	69.08 ± 32.14pg/ml	59.13 ± 26.58pg/ml	^e P = 0.935
^a p	0.000	0.000	
^b p	0.000	0.000	
Before means: before IVIG-resistant KD children were treated with low-dose IVMP and additional IVIG. 24h means: 24h after IVIG-resistant KD children were treated with low-dose IVMP and additional IVIG. 72h means: 72h after IVIG-resistant KD children were treated with low-dose IVMP and additional IVIG.			
^a Before is compared with 24h in CAL group or Non-CAL group; ^b 24h is compared with 72h in CAL group or Non-CAL group; ^c before IVIG-resistant KD children were treated with low-dose IVMP and additional IVIG, Non-CAL is compared with CAL group; ^d 24h after IVIG-resistant KD children were treated with low-dose IVMP and additional IVIG, Non-CAL is compared with CAL group; ^e 72h after IVIG-resistant KD children were treated with low-dose IVMP and additional IVIG, Non-CAL is compared with CAL group.			

Follow-up Changes Of Ca In Ivig + ivmp Group

We followed up changes of CA in IVIG + IVMP group for 1 year, and found all the children finally were without CAL (Table 5&6). This result suggest that low-dose IVMP did not increase the risk of CAL.

Table 5
Follow-up changes of CA in CAL group of IVIG + IVMP group

CAL	Without CAL	CAL smaller	No change in CAL	CAL larger
1W	3	3	2	0
1M	6	2	0	0
3M	8	0	0	0
6M	8	0	0	0
12M	8	0	0	0
W means week; M means months.				

Table 6
Follow-up changes of CA in Non-CAL group of IVIG + IVMP group

Non-CAL	Without CAL	With CAL
1W	13	0
1M	13	0
3M	13	0
6M	13	0
12M	13	0
W means week; M means months.		

Discussion

The literature showed glucocorticoids may promote coagulation and aggravate the formation of coronary aneurysms [11]. Some scholars demonstrated that KD patients treated with steroids alone had a higher incidence of CAL than other groups [6, 7]. Corticosteroid therapy may delay the reconstruction of the coronary arterial wall in KD patients with CAL. The reports suggest that prednisolone (2 mg/kg/day) may have an additional benefit when used with IVIG [12, 13]. In 2014, Japanese Circulation Society recommends IVIG-resistant KD patients could be treated with steroid [14]. In 2017, American Heart Association recommends IVIG-resistant KD patients could be treated with steroid instead of additional IVIG (2 g/kg/dose) [15]. In 2018, the report in Rheumatology recommends low-dose IVMP for 5–7 days or steroid plus for 3 days, then instead of low-dose oral steroid, and the doctor decides whether to use additional IVIG [16]. So far, there was no uniform approach to how to treat IVIG-resistant KD patients. We think that until the pathophysiology of KD vasculitis is completely elucidated, the steroid dose should be held to a minimum. In this study, low-dose intravenous methylprednisolone (2 mg/kg/day) along with additional IVIG (2 g/kg/dose) therapy for 3–5 days was successful in the treatment of IVIG-resistant KD.

We found that low-dose IVMP along with additional IVIG in IVIG-resistant KD children is effective. Thus the results suggest that many IVIG-resistant KD patients may not require steroid pulse therapy.

The report has showed that increased BNP predicts the risk of CAL in KD [9, 10]. In our study, we found the level of BNP was significantly increased in CAL group of IVIG + IVMP group. After treated with low-dose IVMP and additional IVIG, there was no significant difference in BNP levels between CAL group and Non-CAL group. We followed up children of IVIG + IVMP group for 1 year and finally found all children without CAL. These results suggest low-dose IVMP along with additional IVIG is effective for IVIG-resistant KD, and do not increase the risk of CAL.

For the small sample size in this study, the results may be limited. In this study, CAL group are with mild to moderate CAL, and without severe CAL, so may low-dose IVMP along with additional IVIG is ineffective for those IVIG-resistant KD patients with severe CAL. In the future, we will collect more IVIG-resistant KD patients to further explore the therapeutic effect of low-dose IVMP.

Conclusions

The results of this study suggest that low-dose IVMP along with additional IVIG is an effective treatment for IVIG-resistant KD, and low-dose IVMP increases no risk of CAL. Our study provides favorable evidence for methylprednisolone therapy for IVIG-resistant KD.

Abbreviations

IVIG

Intravenous immunoglobulin

KD

Kawasaki disease

IVIG-resistant KD

Intravenous immunoglobulin-resistant Kawasaki disease

IVMP

Intravenous methylprednisolone

CAL

Coronary artery lesions

BNP

Brain natriuretic peptide

Declarations

Availability of data and materials

The data supporting the conclusions of this article are included within the article.

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Contributions

Yibo Zhuang and Hongxue Zheng designed the study. Hongxue Zheng and Lingtao Zhu collected the data of patients and analysed the data. All authors interpreted and discussed the data. All authors drafted and revised the manuscript. All authors read and approved the final manuscript.

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Statement of ethics

This study was approved by the Ethics Committee of The First People's Hospital of Changzhou, China and was followed with the Helsinki Declaration. Informed consent was obtained for all research individuals.

Consent for publication

The authors hereby declare that the article is original and that its contents have not been published in full or in part. We also would like to declare that the manuscript has been read and approved by all authors.

Conflict of Interests

There is no conflict of interests to disclose. No conflicts of interest, financial or otherwise, are declared by the authors.

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Figures

Figure 1

Treatment results.