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Clinical Guideline on the Use of Intravenous Gammaglobulin in Children with Kawasaki Disease: Prevention of Coronary Artery Lesions

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Foreword

This Guideline had been developed by the Quality Assurance Sub-committee, COC in Paediatrics and the expert authors for the Hospital Authority according to the state of medical knowledge at the time of publication. It has been established that doctors can act in accordance with a practice accepted as proper by a responsible body of medical opinion even though others may adopt a different practice. As such, this guideline is for general guidance only; the management of individual cases must be the clinical judgment and decision of the medical practitioners after considering all relevant circumstances, information and up-to-date medical knowledge. In view of the general nature of this guideline and the changes in medical science, the Hospital Authority, the Paediatric COC and the expert authors do not assume or accept any responsibility for this guideline.

Explanatory Notes on Level of Evidence and Grading System on Recommendation

The definition of types of evidence and grading recommendations originate from the US Agency for Health Care Policy and Research (AHCPR) and are also recommended and used by the Royal College of Paediatrics and Child Health.

Levels of evidence

Level	*Type of evidence (based on AHCPR 1992)*
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of recommendations

Grade	*Type of recommendation (based on AHCPR 1994)*
A (Levels Ia, Ib)	Requires at least one randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (Level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Evidence is graded upon the methodological qualities. Guidelines normally contain many different recommendation based upon different levels of evidence. It is important that users are aware of the level of evidence on which each guideline recommendation is based. The link between guideline recommendation and the supporting evidence should be made explicit. Separating the strength of the recommendation from the level of evidence helps in situations where extrapolation is required to take the evidence of a methodologically strong study and apply it to the target population. Gradings of recommendation in addition to level of evidence allow more flexibility for future revision. However, it is important to emphasis that the grading does not relate to the importance of the recommendation. Currently, there are discussions on taking account of relevant high quality non-RCTs and qualitative research and to incorporate them into an appropriate grading system.

The Use of Intravenous Gammaglobulin in Children with Kawasaki Disease: Prevention of Coronary Artery Lesions

Summary of recommendation

Recommendation

There is sufficient evidence to recommend IVIG treatment in the acute phase of KD. IVIG plus aspirin is more effective than aspirin alone to prevent development of coronary artery abnormalities.

(Level I Evidence, Grade A Recommendation)

Treatment with IVIG 2.0 gm/kg plus aspirin is more effective than lower IVIG dose plus aspirin in preventing development of coronary artery aneurysm.

(Level I Evidence, Grade A Recommendation)

There is not enough evidence to exclude low risk patient from IVIG treatment

In children predicted to be at high risk of coronary artery disease the single infusion method is more effective than multiple small infusions to prevent coronary artery lesions at the acute stage (first two weeks). Also the single infusion method results in shorter duration of fever and has a potential to shorten hospital stay.

The evidence is in support of giving IVIG as a single bolus infusion.

(The IVIG infusion is normally given in 12 hours but the infusion rate may require adjustment in the presence of cardiac and renal insufficiency)

(Level I Evidence, Grade A Recommendation)

IVIG is generally safe but not without risk.

Overall Recommendations

IVIG should be given to all children with acute Kawasaki disease. **(Grade A)**
A single dose infusion of 2.0 gm/kg over 12 hours is preferred. **(Grade A)**

The Use of Intravenous Gammaglobulin in Children with Kawasaki Disease: Prevention of Coronary Artery Lesions

Introduction

KD is an acute febrile disease occurring mainly in infancy and children. The incidence of KD in Hong Kong is about 30/100,000 in children less than five years of age.[1]

The pathologic basis of KD is an acute systemic vasculitis of unknown etiology. At the acute stage of the disease, coronary arteries are frequently involved in the inflammatory process. More than 50% of the patients may have mild coronary dilatations.[2] Majority of these dilatations are transient. However about 10% to 20% patients develop coronary artery aneurysms.[3] Follow up studies show that only 50% of the aneurysms regress. Persistent aneurysms may progress to coronary artery stenosis and become a risk factor of ischaemic heart disease.[4]

Aspirin and corticosteroid were used for the treatment of acute KD long before IVIG was found to be effective. Aspirin is the first medication used in KD. However the prevalence of coronary artery lesion was not significantly affected by aspirin alone.[5] The use of corticosteroid remains controversial. A previous study showed high incidence of coronary artery lesions after treatment by steroid.[6] Recently a retrospective study from Japan suggested that steroid did not make coronary lesion worse and showed significant reduction of coronary artery aneurysms.[7]

In 1984 Furusho reported that IVIG at 400 mg/kg per day for five days could reduce the incidence of coronary artery abnormalities.[8] Since then many trials with a variety of treatment regimens had been carried out. In 1993 the American Heart Association published a statement recommending single dose 2.0 gm/kg/day plus high dose aspirin (80-100 mg/kg/day) or IVIG 400 mg/kg/day for four days plus high dose aspirin for the treatment of acute KD.[9]

Currently there are still variations among different centers in the use of IVIG, because i) the issue of the optimal dose of IVIG is not entirely resolved, ii) IVIG is not without risk and iii) IVIG is very expensive.

The aim of the following review is to evaluate evidence regarding:

i) the effectiveness of IVIG as compared to aspirin alone
ii) the optimal dose of IVIG
iii) the effectiveness of single versus multiple small infusions of IVIG
iv) the side effects of IVIG

The review is based on literature research on English journals from the MEDLINE and EMBASE databases from 1983 to 1999 and Cochrane Library databases. Only randomized control trials (RCT) with large number of patients were included in formulating recommendations. Reports in abstract form or in proceedings of meetings were excluded. Some important non-English articles particularly those in Japanese might be missed out but the meta-analysis by Terai[10] in this review had included non-English literatures.

I. Is IVIG Plus Aspirin More Effective Than Aspirin Alone?

Treatment at the acute phase of the KD is aimed at the suppression of inflammation. High dose (80-100 mg/kg/day) or lower dose (30-50 mg/kg/day) aspirin has become a standard treatment in the acute phase of KD, although its effectiveness has never been established by controlled trial. Studies that evaluate the effect of IVIG in KD always included aspirin in both the treatment and control arms.

We identified 3 RCTs in English in support of using IVIG in KD (Table1) .

It should be noted that the methods of the three trials were not uniform. Definitions of coronary artery abnormalities from each study were slightly different. The timing of starting therapy and the date of echocardiographic assessment were different. The doses of aspirin in combination with IVIG were not equal (ranging from 30-120 mg/kg/day). Newburger reported the prevalence[11] and the others reported the incidence of coronary artery lesions. In the Furusho study[8] the echocardiograms were not evaluated blindly. Despite the variations they all showed the efficacy of IVIG at high dose.

As the RCTs recruited patients who presented within 10 days of onset of illness it is questionable whether the efficacy of IVIG could be extrapolated to patients who presented beyond 10 days of onset. From the clinical point of view if signs of inflammation (e.g. fever) are still present, the disease is still at the acute stage and therefore IVIG should be useful.

Recommendation

There is sufficient evidence to recommend IVIG treatment in the acute phase of KD. IVIG plus aspirin is more effective than aspirin alone to prevent development of coronary artery abnormalities.

(Level I Evidence, Grade A Recommendation)

II. What is the Optimal Dose of IVIG?

The last section has shown that IVIG was effective in reducing the incidence of coronary artery lesions if given at

Table 1 Randomized control trials on IVIG treatment at the acute stage of Kawasaki disease

Trials	Treatment subgroup and number of patient		Timing of treatment	Percentage of CAL at subacute stage (≤30 days)			
				IVIG	Aspirin		
Furusho (1984)[8]	IVIG 400 mg x 5 days = 2 gm (total) + Aspirin 30-50 mg/kg/day (n=40)	Aspirin same dose (n=45)	≤7 days of onset	15%	42%	p<0.01	incidence of CAL within 29 days of onset of illness
Newburger (1986)[11]	IVIG 400 mg x 4 days = 1.6 gm (total) + Aspirin 80-120 mg/kg/day (n=74)	Aspirin same dose (n=75)	≤10 days of onset	6.8%	20%	p=0.02	prevalence of CAL at 14 days
Nagashima (1987)[12]	IVIG 400 mg x 3 days = 1.2 gm (total) + Aspirin 30 mg/kg/day (n=69)	Aspirin same dose (n=67)	≤10 days of onset	15.9%	37.3%	p<0.01	incidence of CAL up to 30 days after onset

Abbreviation: CAL=coronary artery lesion

a total dose of 1.2-2.0 gm/kg. To determine the optimal dose of IVIG many control trials had been organised.

Terai reported the results of a meta-analysis on this subject in 1997.[10] It was an analysis of 7 RCTs (including two studies in Japanese) comparing aspirin alone and different doses of IVIG plus aspirin. It revealed that the effectiveness of IVIG in reducing coronary artery lesions was dose-dependent (Table 2). An inverse relation between the dose of IVIG and the coronary artery lesion prevalence was demonstrated (adjusted $R^2 = 0.827$, $p = 0.021$ for subacute stage, adjusted $R^2 = 0.895$, $p = 0.01$ for convalescent stage) (Table 2).

Recommendation

Treatment with IVIG 2.0 gm/kg plus aspirin is more effective than lower IVIG dose plus aspirin in preventing development of coronary artery aneurysm.
(Level I Evidence, Grade A Recommendation)

III. Is It Possible to Select a Subgroup of High-Risk Patients with KD for IVIG?

The Harada scoring scheme was proposed in 1991 to select high-risk patients for IVIG treatment.[13] The children who within eight days of the onset of illness, satisfied at least four of the following criteria are regarded as high-risk:

1. White blood cell count more than 12,000/mm^3
2. Platelet counts less than 350,000/mm^3
3. C-reactive protein more than 3+
4. Haematocrit less than 35%
5. Serum albumin less than 3.5 gm/dL
6. Age under 12 months
7. Male sex

There have been very few prospective studies examining the specificity and sensitivity of the selection criteria. Sato's study in 1999 was the only RCT confirming the usefulness of the Harada score.[14] The study selected a subgroup of "low risk" KD patients for aspirin 30 mg/kg/day alone if the Harada score was ≤3. Fifty-eight patients were enrolled for treatment with aspirin only. Echocardiogram was obtained on admission, at four to five days after admission, then at approximately seven days after second check. None of the patients treated with aspirin alone developed coronary artery lesion in this 2-week period. The data from the report was quite reassuring. However the follow-up period was short. It is still possible that coronary artery aneurysm may develop beyond the 2-week period after onset of illness in the low risk group.

Therefore there is not enough evidence to exclude low risk patient from IVIG treatment.

IV. Is Single Infusion of IVIG More Effective than Multiple Small Infusions?

Two studies were conducted to investigate whether single infusion of IVIG has any advantage over the multiple small infusions.

In Newburger's 1991 study,[15] two regimens were compared: i) IVIG 2.0 gm/kg infused over eight to 12 hours + Aspirin 80-100 mg/kg/day and ii) IVIG 400 mg/kg/day infused over two hours for four days (1.6 gm total) + Aspirin same dose.

Although the single infusion group had a higher IVIG total dose (2.0 gm/kg) than the multiple infusions (1.6 gm/kg) it did not result in significantly lower prevalence of coronary artery lesion. The prevalence of coronary artery lesion among patients (excluding children with lesion at enrollment) treated with single infusion was 2.4% two weeks after enrollment as compared with 5.6% among patients treated with multiple infusions. At seven weeks the prevalence was 2.4% and 4.0% respectively. The differences

Table 2 Prevalence of CAL at subacute stage (30 days) and convalescent stage (60 days) in relation to IVIG dosage from Terai's meta-analysis

Regimens	No. of patients	Prevalence of CAL	
		30-day	60-day
Aspirin alone	195	23.5%	14.7%
total IVIG <1.0 gm/kg + Aspirin	275	12.2%	8.6%
total IVIG 1.0-1.2 gm/kg + Aspirin	400	13.7%	7.0%
total IVIG 1.6 gm/kg + Aspirin	365	5.7%	3.7%
total IVIG 2.0 gm/kg + Aspirin	573	3.6%	2.6%

Abbreviation: CAL=coronary artery lesion

of prevalence at two weeks and seven weeks were not significant (p=0.065 and p=0.313) between the two groups.

In Sato's 1999 study[14] 145 patients were selected for IVIG treatment. They were identified as having higher risk of developing coronary artery lesion according to the Harada score (see section III). Seventy-two patients received IVIG 2.0 gm/kg infused over 12 hours plus Aspirin 30 mg/kg/day and 73 received IVIG 400 mg/kg/day infused over two to three hours plus same dose of Aspirin for five days. The incidence of coronary artery aneursym and transient dilatation in the single infusion group was lower than the multiple small infusions group (4.17% vs 15.07%, p<0.026) within the two weeks period after onset of illness. However the follow up period in this study was limited to the first two weeks only. The incidence of coronary artery lesion at seven weeks was unknown.

These two studies demonstrated that the duration of fever after initiation of treatment was shorter in the single infusion group compared with the multiple infusion group. The difference in the mean duration of fever was 0.7 and 2.0 days in Newburger's and Sato's study respectively. Moreover in Sato's study the mean hospital stay was 2.8 days shorter in the single infusion group comparing with the multiple infusion group (13.1±6.0 days vs 15.9±7.2 days, P<0.05). Therefore IVIG given as a single infusion is more cost effective.

Recommendation

In children predicted to be at high risk of coronary artery disease the single infusion method is more effective than multiple small infusions to prevent coronary artery lesions at the acute stage (first two weeks). Also the single infusion method results in shorter duration of fever and has a potential to shorten hospital stay.

The evidence is in support of giving IVIG as a single bolus infusion.

(The IVIG infusion is normally given in 12 hours but the infusion rate may require adjustment in the presence of cardiac and renal insufficiency)

(Level I Evidence, Grade A Recommendation)

V. Is It Safe to Give IVIG Infusion to Children with Acute KD?

The incidence of side effects IVIG administration was about 3.8% from six studies (ranged from zero percent to 13%). All the adverse effects were transient and relatively minor.

Since IVIG is derived from donor plasma it has potential effect of anaphylaxis, haemolysis, disseminated intravascular coagulation and transmission of blood-borne pathogens. Parents should be well informed about the risk.

Table 3 Incidence of adverse effects of IVIG treatment

Trial	No. of patients enrolled	Adverse events			
		No. of patients	(%)	Major	Minor
Newburger 1991	549	15	(2.7)	9 mild heart failure 2 generalized oedema 1 extravasation	1 cough + nausea + nasal congestion 2 pruritus
Newburger 1986	84	7	(8.3)	3 mild heart failure 1 sepsis 1 neutropenia + splenomegaly	1 chills + pruritus 1 rash + fever + diffuse lymphadenopathy + splenomegaly
Sato 1999	145	0	(0)		
Nagashima 1986	69	9	(13)		8 fever + chills 1 rash
Furusho 1984	40	1	(2.5)		1 fever + chills
Morikawa 1994[16]	466	20	(4.3)	1 liver dysfunction (moderate) 1 agranulocytosis	2 liver dysfunction (mild) 1 hypertension (mild) 1 rash 8 shivering 5 fever 1 shivering + fever
Total	1353	52/1353	(3.8)	19	33

The infusion rate should also be adjusted in the presence of cardiac or renal insufficiency.

It can be concluded that IVIG is generally safe but not without risk.

Overall Recommendations

- IVIG should be given to all children with acute Kawasaki disease (Grade A)
- A single dose infusion of 2.0 gm/kg over 12 hours is preferred (Grade A)

VI. Issues not yet Resolved Regarding the Use of IVIG

The following issues are not addressed by the Guideline because there is not sufficient evidence to make recommendation.

1) Efficacy of different types of IVIG
2) Benefit of IVIG in patients with coronary artery lesions developed before treatment
3) Timing and dosage of IVIG retreatment in patients with persistent or recurrent fever
4) Alternative regimen of IVIG treatment
   While most centres in Hong Kong adopted the 2.0 gm/kg single dose regimen, a few centres used a more flexible approach in giving IVIG. An initial dose of 1.0 gm/kg IVIG was infused in five to six hours on the first day of treatment and followed by infusion of additional dose(s) of 1.0 gm/kg on subsequent day(s) if fever persisted or recurred. The treatment outcome as reported in two case series had been favourable[17-19] and only about 15% to 27% of patients treated with this regime required 2.0 gm/kg or more of IVIG. However, there is no randomised controlled trial on this flexible regime and hence not enough evidence to show whether it is superior or inferior to the 2.0 gm/kg single dose regime.

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