PREDICTORS OF INTRAVENOUS IMMUNOGLOBULIN RESISTANCE IN KAWASAKI DISEASE IN A TERTIARY CHILDREN'S HOSPITAL

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ABSTRACT

BACKGROUND AND OBJECTIVE: Kawasaki Disease (KD) is the leading cause of acquired heart disease in children in developed countries. We aimed to determine the predictors of intravenous immunoglobulin (IVIG) resistance based on clinical manifestations and laboratory parameters.

METHODOLOGY: This was a retrospective cohort study of classic KD patients.

RESULTS: Two hundred and ten patients were included in the study. The mean age was 2.0 $\pm$ 1.8 years old with slight female predominance at 51.4%. Seven (3.3%) cases were found to be IVIG resistant. There was no significant difference in age, clinical manifestations or fever duration. Univariate analysis revealed that IVIG resistant group had a heavier weight with mean of 16.4 kg $\pm$ 12.2 compared to the IVIG responder group 12.2kg $\pm$ 4.8. The IVIG resistant group had a higher white blood cell count of 23.9 $\pm$ 7.8 compared to the responder group of 17.9 $\pm$ 6.5.

CONCLUSION ANDRECOMMENDATIONS: There is an IVIG resistance rate of 3.3% among classic KD patients. A high white blood cell count and weight are probable predictors for IVIG resistant KD. We recommend a larger sample size of resistant cases and a case-control multicenter study.

KEYWORDS: Kawasaki Disease, Intravenous Immunoglobulin, IVIG resistant Kawasaki

INTRODUCTION

Kawasaki Disease (KD), also known as mucocutaneous lymph node syndrome, is the leading cause of acquired heart disease in children in developed countries.[1]It is a febrile illness and a probable infectious cause was postulated, but its etiologic cause has not yet been elucidated. It generates vasculitis, with predilection to the coronary arteries, inducing ectasia and aneurysms. A genetic role has been implicated, and there is a higher propensity for the Asian population.The disease is self-limiting, however the long-term complications of KD involve the coronary arteries, making this illness a source of further research for its prevention and treatment.

Standard treatment for KD is intravenous immunoglobulin (IVIG) and aspirin, ideally started within 10 days from disease onset. Although the exact action of IVIG in KD is still poorly understood, it has been used as the first line treatment regimen. This approach is effective in symptom resolution in up to 90% of cases, bringing down the risk for coronary artery abnormalities to 2-4% compared to 20-25% with aspirin alone.[1] However, according to studies, there is a 10-20% chance that a patient may not respond to IVIG, and may need additional IVIG or some other form of treatment such as methyprednisolone and infliximab.[2,3,5]This subset of individuals is at a greater risk of acquiring coronary artery abnormalities. Therefore, delays in recognition and treatment may be detrimental.

Increased detection of KD has revealed increasing incidence of IVIG resistant cases.[2]A number of recent studies from Asia tried to elicit possible predictors of IVIG resistance by comparing responders to nonresponders.[2,4,5,7,9] They have identified demographic and laboratory parameters, including age, day of

illness, hemoglobin, platelet count, neutrophil count, serum total bilirubin level, serum albumin level, alanine aminotransferase, lactate dehydrogenase, C-reactive protein and erythrocyte sedimentation rate as predictors of IVIG resistance.[3,4]However these studies have conflicting results, hence this local study has been proposed.

We aimed to determine the variables which predict IVIG resistance in patients with Kawasaki disease.Identifying probable IVIG resistant cases will help physicians give a more accurate prognosis and modify treatment plan. Timely and adequate treatment will decrease the risk of coronary artery abnormalities, which may cause significant morbidity and mortality. A number of laboratory tests are initially requested to support the diagnosis; hence this study may help point to the most cost-effective tests. Local policy makers will be guided in allocating and prioritizing funds to the most crucial tests needed to predict IVIG resistant KD.

The incidence of Kawasaki disease in South Korea is 86.4/100,000 population, compared to that of Japan which is 134.2/100,100.[5]Tremoulet, A et al reported increasing IVIG resistant KD in their center since 2006.[3]This is a vast number of children at risk for developing coronary artery problems. Such coronary artery abnormalities may become stenotic, develop thrombi, ischemia and cause sudden death.Kawasaki disease without IVIG treatment results in about 20-25% occurrence of coronary artery aneurysm. Although this is significantly decreased to about less than 5% with treatment, there is significant percentage, 10-20%, who will not respond to initial IVIG. These non responders are at increased risk of coronary artery complications, and thus need additional treatment either with another cycle of IVIG infusion or alternative medications (e.g. methylprednisolone).[6]Fever in Kawasaki disease is correlated to the development of complications. It is postulated to be the effect of ongoing vascular inflammation due to continued release of inflammatory cytokines. Hence, IVIG resistance is based on this clinical finding. Failure to respond is defined as persistent or recrudescent fever equal to or more than 36 hours after the initial IVIG infusion. However, many practitioners re-treat based on fever alone, which may be caused by other factors such as a recent infection.[7] Hence, there is a need for more objective parameters to determine the indication for IVIG re-treatment.

Recent studies have focused on parameters thatpredict IVIG resistance. This would allow proper prognostication, adept anticipation, and may help develop new hypotheses as to pathogenesis and treatment. Higher bilirubin, AST, percent segmenters (PMN) and decreased platelets are independent predictors of persistent or recrudescent fever in KD in Korea.[5] In a retrospective study by Lee, et al among 91 Korean children with KD, it was pointed out that fractional change CRP might be an important value for predicting IVIG resistance.[8] This was supported with a study by Hyun Cho, et al, when they reviewed 234 complete and 77 incomplete Kawasaki cases. Moreover, they added that elevated percent of segmenters as well as NT-proBNP predicted early IVIG resistance.[9]These validated a prospective study done on 129 KD patients in the same population by Kwon KH, et al, which demonstrated that CRP, NT-proBNP, and percent neutrophils were independent parameters of retreatment. There were no differences between the groups in age, gender distribution, and duration of fever prior to IVIG in this study population. Furthermore, this study proposed the following treatment recommendations: 1) Retreat patients who remain febrile despite IVIG therapy and have high values of CRP, NT-proBNP and/or percent neutrophils; 2) When patients become febrile but with normal laboratories, observe for 1-2 days for defervescence; 3) When patient is afebrile and has abnormal laboratories, do not re-treat. However, conducting larger scale prospective studies on these guidelinesare recommended.[7]Meanwhile, Young, JHM et al concluded that a low serum albumin level and a high neutrophil percentage are independent predictors of IVIG resistance in Chinese children.[4]

A scoring system for predicting IVIG resistant KD was previously formulated by

Egami, et alobtained from Japanese children and was applied by TremouletA, et alin a retrospective study conducted in San Diego County from October 1998 to September 2006, to determine its predictive value in an ethnically diverse population. However, the system missed over 60% IVIG resistant cases. The same scoring system was also applied to the Asian population and yielded specificity of 89.3% and sensitivity of 33.3%.[3]Sleeper, et al utilized the risk scoring systems for IVIG resistance developed in Japan (Egami, Kobayashi and Sano) and revealed<45% sensitivity and87% specificity when applied North American children.[10] Genetic variations as to race play a major role in KD that may be affecting disease severity and outcome.[3]

We aimed to determine the predictors of IVIG resistance in Kawasaki Disease in a tertiary children's hospital. Specifically, we wished to determine the predictors of resistance to IVIG of patients diagnosed with KawasakiDisease as to initial clinical manifestations and laboratory parameters

METHODOLOGY

This is a retrospective cohort study of Kawasaki Disease patients admitted at a tertiary children's hospital from 2004-2014.All patients admitted from January 2004 to December 2014 who fulfilled the American Heart Association Diagnostic Guidelines for complete or classic Kawasaki Disease were included in the study. Classic KD patients who were not given IVIG and incomplete or atypical Kawasaki Disease patients were excluded.

Responders were defined as patients with defervescence 48 hours after completion of IVIG infusion. Non responders were those with persistent or recrudescent fever 48 hours after completion of IVIG infusion. Using Epi Info version 7, the minimum sample size requirement was estimated to be at 156 based on the 20% incidence of IVIG resistance as reported by Cha, Yoon et al with 95% confidence level and 5% margin of error.[5]

All medical records of patients with classic KD from 2004 to 2014 were retrieved. A data collection form was used to record all pertinent data. The form included the demographic data, initial clinical manifestations and initial laboratory results of every patient with KD. Demographic data included age, sex and weight. Clinical manifestations such as day of fever, changes in extremities and oral cavity, rash, conjunctivitis, and cervical lymphadenopathy were noted. The initial laboratory results of complete blood count (white blood cell count, neutrophils and platelet count), liver function tests (alanine aminotransferase, aspartate aminotransferase, total bilirubin and albumin), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and presence or absence of 2-dimensional echocardiogram (2D echo) findings were recorded.Data analysis was done using Stata SE version 13. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated as frequency and percentage. Comparison of characteristics between responders and resistant were done using independent t-test for quantitative variables, and Fisher's exact test for qualitative variables. The study was reviewed and approved by the Ethics committee prior to commencement.

RESULTS

Two hundred and ten patients with classic KD admitted and treated with IVIG from January 2004 to December 2014 were included. Baseline clinical characteristics are shown in Table 1, and lab parameters in Table 2.

Table 1. Baseline Demographic and Clinical Characteristics of Classic Kawasaki Disease Patients Admitted from January 2004 to December 2014

Characteristics (N = 210)	$\overline{x} \pm SD$ or n(%)
Age (years)	2.0 $\pm$ 1.8
Sex: Male Female	 102 (48.6%) 108 (51.4%)
Weight (Kg)	12.3 $\pm$ 5.2
Rash	197 (93.8%)
Cervical lymphadenopathy	179 (85.2%)
Hand manifestations	168 (80%)
Oral manifestations	196 (93.3%)
Conjunctivitis	186 (88.6%)
Fever duration before treatment (days)	8.9 $\pm$ 3.3

Table 2. Baseline Laboratory Parameters of Classic Kawasaki Disease Patients admitted from January 2004 to December 2014

Laboratory Parameters (N = 210)	$\overline{x} \pm SD$ or n(%)
WBC	18.2 $\pm$ 6.6
Neutrophils	0.63 $\pm$ 0.16
Platelet count	504.6 $\pm$ 191.4
Bilirubin	33.8 $\pm$ 46.6
Albumin	32.2 $\pm$ 6.1
ALT	119.2 $\pm$ 79.9
AST	80.8 $\pm$ 46.5
CRP	93.4 $\pm$ 97.8
ESR	91.4 $\pm$ 30.3
2D echo findings: Positive Negative	 90 (55.9%) 71 (44.1%)

The study included 7 (3.3%) IVIG resistant cases.The demographic, clinical and laboratory parameters of IVIG responder and resistant Kawasaki patients were compared (Table 3). There were no significant differences noted in age, clinical manifestations, fever duration and in mostinitial laboratory parameters.There were significant differences identified in terms of weight and initial WBC count. Univariate analysis using two-sample t test revealed that IVIG resistant group had a heavier weight with mean of 16.4 kg $\pm$ 12.2 compared to the IVIG responder group 12.2kg $\pm$ 4.8. Also, the IVIG resistant group revealed to have a higher WBC count of 23.9 $\pm$ 7.8 compared to the responder group of 17.9 $\pm$ 6.5.

Table 3. Comparison of Characteristics between IVIG Responders and Resistant KD

Variables	IVIG Responders (n = 203)	IVIG Resistant (n = 7)	P value
Age (years)	2.0 ± 1.8	2.7 ± 2.8	0.36
Sex: Male Female	 96 (47.3) 107 (52.7)	 6 (85.7) 1 (14.3)	0.059
Weight (Kg)	12.2 ± 4.8	16.4 ± 12.2	0.035
Rash	190 (93.6)	7 (100.0)	1.00
Cervical lymphadenopathy	174 (85.7)	5 (71.4)	0.28
Hand manifestations	163 (80.3)	5 (71.4)	0.63
Oral manifestations	189 (93.1)	7 (100.0)	1.00
Conjunctivitis	180 (88.7)	6 (85.7)	0.58
Fever duration before treatment	8.9 ± 3.1	10.4 ± 6.4	0.24
WBC	17.9 ± 6.5	23.9 ± 7.8	0.02
Neutrophils	0.63 ± 0.15	0.65 ± 0.24	0.82
Platelet count	503.3 ± 185.6	541.6 ± 334.5	0.60
Bilirubin	-	-	-
Albumin	32.4 ± 6.3	31.6 ± 6.5	0.86
ALT	118.4 ± 84.4	125.5 ± 38.9	0.91
AST	-	-	-
CRP	94.7 ± 99.5	62.4 ± 32.2	0.47
ESR	92.2 ± 29.8	70.5 ± 39.6	0.09
2D echo	85 (55.2)	5 (71.4)	0.47

DISCUSSION

In this retrospective cohort study, there was only 3.3% IVIG resistance rate observed within the 10-year period. This figure was low compared to the reports from other countries, which ranged from 7.5% to 38%.[4]We aimed to determine clinical and biochemical predictors to IVIG resistance that may help to prevent fatal complications and to pave way for additional or innovative anti-inflammatory therapies. Several studies have reported distinct predictors of IVIG resistance and many have developed a scoring system. Egami et al analyzed 320 Japanese children and derived a bedside score that designated one point for each of the following: (1) infants less than 6 months old; (2) diagnosed before four days of illness;(3) platelet count ≤300 x 109/L; and (4) CRP ≥80 mg/L, Lastly, the score also designated two points for ALT ≥80 IU/L. Using a cut-off point of three, the prediction score was shown to single out IVIG resistance with 78% sensitivity in this study group.[4]However, in our study, the resistant cases were not comparable based on age (2.7 years ± 2.8), duration of fever (10.4 days ± 6.4), platelet count (541.6 ± 334.5), CRP (62.4 ± 32.2) and ALT (125.5 ± 38.9) levels.

A study of Young et al proposed a high neutrophil percentage as an independent predictor of IVIG resistance. Aninhibited neutrophil apoptosis in the acute phase of Kawasaki results in an increase in number of circulating neutrophils.Consequently, the prolonged neutrophil life span may contribute to the pathogenesis of vasculitis with autotoxic mediators released by neutrophil into thecirculation, thus worsening the inflammation.[4] However, this was not observed in our study with only 0.65 ± 0.24 neutrophil count and is not significant compared to IVIG responders instead our study revealed significant difference between responders (17.9 ± 6.5) and resistant cases (23.9 ± 7.8) with the WBC while Young reported it was not significant.

No study has proposed sex and weight as independent predictors, however our study showed significance between the weight of IVIG responders (12.2 kg ± 4.8) and IVIG non responders (16.4 kg ± 12.2). There was a

predominance of male gender in the IVIG resistant group 85.7% (6 out of the 7 cases); however, it showed no significant difference compared to the responder group.

CONCLUSION

In conclusion, our study reported an IVIG resistance rate of 3.3% among admitted classic KD patients for a period of 10 years. They all fulfilled the diagnosis of classic Kawasaki Disease and received IVIG. Our study showed that high WBC and weightas probable predictors for IVIG resistant Kawasaki disease.

The limitation of this study is the small sample size of IVIG resistant cases. Further analysis to determine other probable predictors was impossible with the 7 resistant cases. A case-control study design could had been done to compare IVIG responders and resistant cases using multivariate analysis; and possibly strengthen high white cell count and weight as probable predictors for IVIG resistance. A territory-wide and multi-centered collaboration is essential to further investigate for possible predictors and help develop a locally applicable scoring system with more significant clinical or biochemical predictors.

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