Comparative effectiveness of intravenous immunoglobulin from different manufacturing processes on Kawasaki disease

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Review article

Background: **The comparative effectiveness of intravenous immunoglobulin (IVIG) for Kawasaki disease was regarded as inconclusive in the international guidelines. However, several new evidences have been published in recent years.**

Data sources: **A literature search of PubMed was conducted using key words of "Kawasaki disease or mucocutaneous lymph node syndrome" and "immunoglobulin" in combination. Only original articles published after 2004 were selected. A total of 813 papers were found in PubMed. These papers were screened manually by their titles and abstracts.**

Results: **Patients treated with IVIG prepared by beta-propiolactonation might have worse outcome (a higher non-responsive rate in one report and a higher rate of coronary aneurysm in two reports). Storage of IVIG in acidic solution might be correlated with a higher rate of coronary aneurysm (two reports).**

Conclusions: **Different processes of preparation and conditions of preservation of IVIG may have profound effects on its clinical effectiveness. Randomized controlled studies are needed to further elucidate this issue.**

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Key words: **coronary aneurysm; immunoglobulin; Kawasaki disease; treatment outcome**

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Introduction

Kawasaki disease was first described by Dr. Tomisaku Kawasaki in Japan in 1967.[1-4] Now, the disease is widely reported in young children of different ethnic populations.[3] It is also the most common cause of acquired heart disease among children in most industrialized countries.[5-13] It is capable of inducing carditis and vasculitis, which result in long-term sequelae involving the coronary arteries. Thus, it is currently the subject attracting the attention of researchers.

For the management of Kawasaki disease, most physicians follow the guidelines of the American Academy of Pediatrics (AAP) and American Heart Association (AHA) published in 2004, which include the rapid infusion of high-dose intravenous immunoglobulin (IVIG) (2 gm/kg) in 12 hours, together with oral aspirin.[3] As such, IVIG is regarded as the most important medication for the treatment of Kawasaki disease in the acute stage.[14] Although the influence of different manufacturing processes on differences in IVIG effectiveness was briefly described in the AAP and AHA guidelines, the guidelines concluded that "potentially important product-manufacturing differences exist. But the results of clinical studies....conflicted".

Almost 10 years have passed since the publication of these guidelines and several interesting studies have been published since then. This article aimed to review new evidences regarding this issue. PubMed was searched for articles by using the key words "Kawasaki disease or mucocutaneous lymph node syndrome" and "immunoglobulin" in combination. Only original articles published after the year 2004 were selected. A total of 813 articles were found in PubMed. These articles were screened manually by their titles and abstracts.

The mechanisms of immunoglobulin therapy in Kawasaki disease

Because Kawasaki disease is recognized as vasculitis

of the coronary artery, it is almost impossible to obtain a human sample except for a few autopsy cases. Related literature on the pathology of Kawasaki disease is also quite limited[15-20] and most of the reports focus on vasculitis of the coronary artery. Such inflammatory process can trigger further remodeling of blood vessels, which can last for years.[15,19,20] This may somehow explain why Kawasaki disease induces long-term sequelae on the coronary artery. Meanwhile, some studies found that vasculitis not only occurs in the coronary artery but also in all medium-sized arteries.[16-19]

The mechanism of IVIG in the treatment of Kawasaki disease is still obscure. Researchers found that part of the effectiveness comes from an immuno-modulatory effect on the host immune system by binding the constant region (Fc portion) of host immunoglobulins.[3] IVIG can significantly inhibit the release of interleikin-1 by monocytes in peripheral blood but does not decrease cytotoxic anti-endothelial antibodies.[21] It may also reduce the release of interleukin-1 of macrophages via interaction with their Fc receptors.[22]

In short, IVIG may decrease the interleukin release of host immune cells via interaction with the Fc portion of host immunoglobulins. Thus, the inflammatory storm of Kawasaki disease is subsequently suppressed.

Differences in the effectiveness among immunoglobulins

Although IVIG is undoubtedly the major medication for acute-stage Kawasaki disease.[14] It is extracted from blood of many donors. The World Health Organization have established standards for the manufacture of immunoglobulins (at least 1000 donors, 90% of IgG preserved, the sub-categories consistent with normal population, and screening for hepatitis viruses B, hepatitis viruses C, and human immunodeficiency virus).[23] However, among different manufacturers of IVIG, there are still differences in the manufacturing processes, purification, IgA concentration, and conditions of preservation (Table 1).[23-29] Minor differences may cause side effects and complications, for instance, slightly higher concentrations of IgA or IgM induce severe anaphylactic reactions.[27,30] Moreover, hepatitis transmission results in defects in the manufacturing process.[31,32]

With regard to efficacy, a retrospective case control study (n=45) conducted in the United States of America comparing the efficacy of two brands, Venoglobulin I and Iveegam, has been published in 1995. This study found that Iveegam shortened febrile days and had less side effects,[33] but did not infer the practical reasons for the results. Unfortunately, the retrospective design and limited case numbers limited the value of this study. But the study was cited by the AHA and AAP guidelines in 2004.

After the publication of the guidelines, Tsai et al[26] compared the effectiveness of four brands of IVIG, including Venoglobulin S, Gamimune, Intraglobin F, and SNBTSPF Center CBSF in 2006. They found that Intraglobin F had a higher non-responsive rate and

Table 1. Brands, manufacturing processes, and characteristics of immunoglobulins*[26,28,29]

Brand name	Gamimune N	Intraglobin F	Venoglobulin-S	Flebogamma	"TBSF" human immunoglobulin for intravenous use	Iveegam	Gamimune
Manufacturer	Talecris Biotherapeutics, INC.	Biotest Pharma GMBH	Alpha Therapeutic Corp.	Instituto Crifols S.A.	CSL Limited	Baxter Corporation Bio Science Division	Bayer Health Care Biologic Products Division
Country	NC, USA	Germany	LA, USA	Spain	Australia	IL, USA	NC, USA
Preparation	Cold etheanol-PEG precipitation, diafiltration/ acidification	Cold etheanol-PEG precipitation, β-propiolactonation	Cold etheanol-PEG precipitation, DEAE-Sephadex fractionation	Cold etheanol-PEG precipitation, nanofiltration down to 20 nm	Cold etheanol-PEG precipitation, chromatographic fractionation	Cold ethanol fraction phosphoethylene glycol trypsin treatment	Cold ethanol fraction phosphoethylene glycol diafiltration/ acidification
IgA conc. (μg/mL)	270	≤2500	15.1	<50	<25	10	270
IgM conc. (μg/mL)	76±15	≤600	<11.1	Trace	Trace	N/A	N/A
Osmolality (mOsmol/kg)	274	N/A	N/A	N/A	Isotonic	240 mOsm/L	274 mOsm/L
pH	4.0-4.5	6.6	Non acidic	5.0-6.0	4.25	6.4-7.2	4.0-4.5
Sugar content	None	Glucose	Sorbital	Sorbital	Maltose	5 g/mL glucose	None
IgG MWD	Mono 99%, dimer <1%	Mono+dimer >90%	Mono+dimer >95%	Mono >99.8%	Mono+dimer >90%	N/A	N/A

MWD: molecular weight distribution; conc.: concentration; N/A: not available; PEG: phosphoethylene glycol; DEAE: diethylaminoethyl. *: no data available for brand E-com.

more coronary aneurysms in the convalescent phase, which was attributed to beta-propiolactonation during IVIG purification. Beta-propiolactonation might change the Fc portion of IVIG, thereby interfering with its binding with the host macrophages. This subsequently decreased the ability of IVIG to inhibit interleukin-1 release. At last, the immuno-modulatory effect of high-dose IVIG was weakened.[26] This study collected certain case numbers, but the patients came from only one institution and the four groups of patients were not collected in the same period. Moreover, the significantly different numbers in each groups and the lack of long-term follow-up became the weak points of the study.

In 2007, Kuo et al[34,35] found no differences in brands of IVIG, using data from a single hospital. However, they used a surrogate endpoint, eosinophil counts, instead of real clinical outcomes. The statistical power was also not enough because of limited case numbers, which make the results less persuasive.

In 2010, Manlhiot et al[28] compared two brands of IVIG, Iveegam (non-acidified) and Gamimune (acidified) and found that Gamimune was associated with a lower non-responsive rate and a shorter hospital stay, but a higher incidence of coronary artery aneurysms. They inferred that this phenomenon of Gamimune, which was preserved in acidic solution, could damage the elastin protein, especially when coronary arteries were involved in an inflammatory process, subsequently causing more coronary aneurysms. On the other hand, the lower non-responsive rate was attributed to differences of concentration. Gamimune was prepared in a higher concentration (10%) compared to Iveegam (5%). This would allow physicians to have an easier delivery of high-dose IVIG in 12 hours. Although the cases came from several hospitals, the case distributions were significantly unequal. Care quality and outcome definition may vary from hospital to hospital. Moreover, the results only reached borderline statistical significance even after propensity score adjusting. Long-term follow-up data were also lacking.[36-38]

Our research team published a nationwide cohort study in 2013.[29] We found that beta-propiolactonation increased the IVIG non-responsive rate during the acute phase. Acidified IVIG might increase the rate of coronary aneurysm but it decreased the IVIG non-responsive rate. The long-term results (need for medication after 6 months) were correlated with IVIG non-responsiveness in the acute stage. The observed higher non-responsive rate of beta-propiolactonation IVIG was consistent with the results of Tsai et al.[26] Although the increased rate of acute aneurysm and decreased refractory rate of acidified IVIG were similar to the observations by Manlhiot et al,[28] the concentration differences in Canada were not noted in Taiwan. The authors also did not explain why acidified IVIG was more effective. With regard to the effectiveness of IVIG, this study had the largest case numbers to date. It was also the first study to provide long-term follow-up data. However, the study had certain weak points stemming from the fact that the data were for insurance claims data. No validation could be provided in consideration of patient privacy. Moreover, the claims data of the Taiwan National Health Insurance lacked laboratory results and imaging reports.[39,40]

Some patients with Kawasaki disease developed hyponatremia during the acute phase. The pathogenesis was considered to be correlated with syndrome of

Table 2. Summary of studies comparing the efficacy of different brands of immunoglobulins

Authors	Brands	Study design	Periods	Sample size	Endpoints	Results	Comments
Tsai et al.[26]	Venoglobulin S, Gamimune N, Intraglobin F, CBSF Human immunoglobulin	Case series	1998-2003	437 (91, 182, 93, 71)	Prolonged fever (non-responsive), CAA incidence	IVIG, prepared with beta-propiolactonation (Intraglobin F) having higher CAA rate	Different periods in single center no longitudinal data
Kuo et al.[35]	Gamimune N, Intraglobin F, E-com	Case series	1999-2005	45 (19, 20, 6)	Eosinophil counts	No difference among brands	Limited statistical power
Manlhiot et al.[28]	Iveegam, Gamimune	Case series	1990-2007	954 (862, 92)	Prolonged fever (non-responsive), CAA incidence	Lower IgA content and non-acidic storage IVIG (Iveegam) having lower CAA rate; acidified IVIG having shorter hospital stay	Different periods in single center, no longitudinal data, unbalanced case numbers between groups
Lin et al.[29]	Gamimune N, Intraglobin F, Venoglobulin-S, Flebogamma	Cohort study	1997-2008	3830 (1894, 617, 1081, 238)	Non-responsive, CAA incidence, needing choric medication	Beta-propiolactonation having higher treatment failure and needing chronic medication rate; acidification increasing CAA rate	The only study providing long-term follow up data; lacking of data validation and laboratory results

CAA: coronary artery aneurysm; IVIG: intravenous immunoglobulin.

inappropriate antidiuretic hormone secretion and cytokine release.[41,42] Hyponatremia was also recognized as an index of disease severity and a predictor of coronary complications.[41,43] Immunoglobulin therapy was found to effectively reverse hyponatremia in Kawasaki disease.[42] Although immunoglobulins without sodium were reported to have an adverse effect on hyponatremia in patients with Kawasaki disease, their clinical efficacy was equivalent to that of those with a high sodium concentration.[44]

The four studies are summarized in Table 2. It might be better to perform a meta-analysis to confirm the different effectiveness by different manufacturing processes. However, it is not possible at present because of few papers published and lack of randomized controlled trials.

Conclusions

The immuno-modulatory effect of IVIG plays an important role in suppressing the inflammatory storm of Kawasaki disease. Different preparation processes (beta-propiolactonation or cold-ethanol-PEG precipitation) and conditions of preservation (acidified or not) of IVIG may exert profound effects on its clinical effectiveness. Randomized controlled studies are needed to elucidate this issue.

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Contributors: Lin MC proposed the study and wrote the draft.

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