Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 1, pp. 15-26 January-June 2022
Cano CU, Ley-Chua T, Garcia RD. A Systematic Review and Meta-Analysis on the Safety and Efficacy of Second Dose Immunoglobulin Versus High Dose Pulse Methylprednisolone in Refractory Kawasaki Disease
https://doi.org/10.56964/pidspj20222301005

ORIGINAL ARTICLE

A SYSTEMATIC REVIEW AND META-ANALYSIS ON THE SAFETY AND EFFICACY OF SECOND DOSE IMMUNOGLOBULIN VERSUS HIGH DOSE PULSE METHYLPREDNISOLONE IN REFRACTORY KAWASAKI DISEASE

Catherine Uy Cano, MD,[1] Teldy Ley-Chua, MD, FPPS[1] and Robert Dennis Garcia, MD, MHSA[1,2]
[1]Department of Pediatrics, Cardinal Santos Medical Center, [2]Department of Pediatrics, Makati Medical Center
1st PLACE 2022 PIDSP RESEARCH CONTEST

ABSTRACT

Background: There is limited information available regarding the management of IVIG-refractory Kawasaki Disease (KD).

Objectives: This study aimed to evaluate the safety and efficacy of a second intravenous immunoglobulin (IVIG) infusion versus intravenous methylprednisolone (IVMP) in patients with IVIG-refractory KD.

Methodology: Cochrane Library, PubMed, Medline, Elsevier (Science Direct), Springer Link and BMJ databases were searched from May 1, 2020 to December 31, 2020. We included randomized controlled trials (RCTs) and high-quality prospective and retrospective studies, with population restricted to children 0 months to 18 years, with KD refractory to initial IVIG at 2g/kg, who remained febrile for 24-48 hours after completion of initial IVIG, and who received second-line monotherapy with either a second dose IVIG or IVMP. We conducted a meta-analysis using Review Manager [RevMan] 5.4.1 software.

Results: A total of six studies (n=188 patients) were analyzed. The incidence of coronary artery lesions was comparable between a second dose of IVIG and IVMP (RR 0.82, 0.34-1.96, P=0.66) in patients with IVIG-refractory KD. The rate of fever resolution to a second IVIG, compared to IVMP, was not significantly different between groups (RR 0.97, 0.84-1.13, P=0.72). There was a significantly higher incidence of adverse events in the IVMP group (RR 0.42, 0.26-0.57, P=0.0002), but these were all transient and resolved without further treatment.

Conclusions: There is no significant difference in the incidence of coronary artery lesions and rate of fever resolution post-retreatment with a second dose of IVIG versus IVMP in IVIG-refractory KD. More adverse events were reported in the IVMP group.

KEYWORDS: *Mucocutaneous Lymph Node Syndrome, Kawasaki Disease, Refractory Kawasaki Disease, Immunosuppressant, Intravenous Immunoglobulin, Methylprednisolone, Second IVIG Infusion*

Correspondence:
Dr. Catherine U. Cano
Email: caihong14pchs@gmail.com

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 1, pp. 15-26 January-June 2022
Cano CU, Ley-Chua T, Garcia RD. A Systematic Review and Meta-Analysis on the Safety and Efficacy of Second Dose Immunoglobulin Versus High Dose Pulse Methylprednisolone in Refractory Kawasaki Disease
https://doi.org/10.56964/pidspj20222301005

INTRODUCTION

Kawasaki disease (KD) is an acute, self-limited, medium-vessel vasculitis which most commonly affects infants and young children less than 5 years of age.[1,2] The current standard therapy for KD is a combination of intravenous immunoglobulin (IVIG) and acetylsalicylic acid.[3] However, approximately 10-20% of patients fail to respond to IVIG and remain febrile ≥ 36 hours following completion of IVIG infusion.[4] These patients are considered to have IVIG-refractory KD and have a nine-fold higher risk of coronary lesions compared to those who respond to initial treatment.[5]

Corticosteroid is the treatment of choice for most vasculitides but its use in KD remains controversial.[6] Furukawa, et al. reported that among 65 patients with IVIG-refractory KD, 68% of patients treated with intravenous methylprednisolone (IVMP) became afebrile within one day of therapy compared to 63% of patients treated with a second dose of IVIG.[7] The difference in the incidence of coronary abnormalities was insignificant between the two groups, suggesting that IVMP is a viable treatment option for IVIG-refractory KD.[7] In another retrospective study by Kim, et al. on 38 patients with IVIG-refractory KD, all three who were given corticosteroid monotherapy, without a second IVIG treatment, developed coronary artery lesions, although the difference between the two groups was not statistically significant.[8] The inconsistencies and absence of significant differences between treatment arms in these studies may be due to inadequate sample size and the low frequency of IVIG-refractory KD.

The treatment goal for patients with KD is to suppress systemic inflammation as early as possible because prolonged elevation of serum inflammatory cytokines is associated with the development of coronary artery lesions (CALs).[8,9]

Miura, et al. found that IVMP use was associated with significantly lower plasma levels of tumor necrosis factor-alpha and monocyte chemoattractant protein-1, compared to levels in children who were given a second dose IVIG.[9] The American Heart Association recommends a second dose IVIG as reasonable therapy in IVIG-refractory KD patients and IVMP as an alternative, or as a third-line treatment, when there is resistance to a second dose of IVIG.[10] The role of IVMP in IVIG-refractory KD has not been firmly established due to inadequate clinical trials on its efficacy compared to a second dose of IVIG.[11] This study aimed to evaluate the safety and efficacy of a second IVIG infusion versus IVMP in children with IVIG-refractory KD using a meta-analysis approach. It is hypothesized that IVMP will be as effective, or more effective, than retreatment with a second dose of IVIG in patients who fail to respond to the initial IVIG dose. Incidence of CALs, post-retreatment fever resolution, and occurrence of adverse events were the specific parameters compared.

METHODOLOGY

Database Search Strategy

We searched the following databases from May 1, 2020 until December 31, 2020: Cochrane Library, PubMed, Medline, Elsevier (Science Direct), Springer Link and BMJ Journals. The search strategy used a combination of the following keywords - "Kawasaki disease / mucocutaneous lymph node syndrome AND intravenous immunoglobulin/intravenous gamma-globulin / immunoglobulin AND resistant / unresponsive / refractory / intractable / failure AND intravenous methylprednisolone / high pulse methylprednisolone OR steroid AND treatment / retreatment / therapy / management."

Filters were applied to retrieve only the studies available in English with full texts and published from the year 2000 to 2020. Manual review of references from published articles was also done to identify additional relevant studies.

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 1, pp. 15-26 January-June 2022
Cano CU, Ley-Chua T, Garcia RD. A Systematic Review and Meta-Analysis on the Safety and Efficacy of Second Dose Immunoglobulin Versus High Dose Pulse Methylprednisolone in Refractory Kawasaki Disease
https://doi.org/10.56964/pidspj20222301005

Selection Criteria and Process

We included RCTs, high-quality prospective and retrospective studies, with population restricted to children 0 months to 18 years, with KD refractory to initial IVIG at 2g/kg, who remained febrile ≥ 36 hours after completion of initial IVIG, and who received second-line monotherapy with either a second dose IVIG (1-2g/kg) or IVMP (30mg/kg/dose x 3 days). We included only original peer-reviewed, full-text publications with at least five patients. We excluded studies that were published prior to 2005, written in a language other than English, duplicate data, abstract proceedings and reviews, basic science studies, combination therapy, alternate dosing of initial IVIG or second-line therapy, and case reports or case series with < 5 patients. Screening and selection of articles was performed by the primary investigator.

Data Collection and Outcome Measures

Data extraction was performed by 1 primary and 2 co-investigators. Information collected included year of publication, country of origin, study characteristics, number of subjects, and the outcomes of interest - incidence of CALs (including coronary artery dilatation and coronary artery aneurysm), fever resolution and adverse events. Coronary artery dilatation is identified if the coronary artery diameter is ≥ 3mm in a child < 5 years old, or ≥ 4mm in a child ≥ 5 years old. Small coronary aneurysm is present when the coronary artery diameter is ≥ 4mmin a child < 5 years old, or an internal diameter of a segment measuring 1.5 to 4 times that of an adjacent segment if the child is ≥ 5 years old.

Giant aneurysm is present when the coronary artery diameter is ≥ 8mm or if the child is > 5 years old, an internal diameter of a segment measuring > 4 times that of an adjacent segment.[8,10,13]

Transient coronary artery dilation refers to lesions that disappear within 28 days of illness.[10] Since only three out of six articles gave definitions for coronary artery lesions, the Japanese classification scheme on coronary artery abnormalities was adopted in this meta-analysis.[7,8,14] The assumption is that the AHA classification scheme on coronary artery abnormalities is based on Z-scores, while the Japanese classification is based on absolute or relative internal lumen diameter. Fever resolution is defined as temperature < 37.8°C, or a significant decrease in temperature in a patient with persistent fever, within 3 days of completing the drug infusion, and for which there is no other explanation for fever resolution. Adverse events included death or near-death, or any serious or non-serious medical event that may or may not warrant additional medical treatment to prevent another serious event. Data were retrieved as reported from the studies. In one study where the outcome of interest was indirectly reported, analysis of reported numbers was done to extract the desired information.[8]

Assessment of the Risk of Bias in Included Studies

The methodological quality of included RCTs and prospective studies were assessed using the Cochrane collaboration tool for the risk of bias. The Methodological Index for Non-Randomized Studies (MINORS) guidelines was used to assess methodological quality of all non-RCTs. The overall quality of evidence and strength of recommendations were evaluated using the GRADE system. Three investigators independently assessed the risk of bias per study and a consensus was generated among the reviewers.

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 1, pp. 15-26 January-June 2022
Cano CU, Ley-Chua T, Garcia RD. A Systematic Review and Meta-Analysis on the Safety and Efficacy of Second Dose Immunoglobulin Versus High Dose Pulse Methylprednisolone in Refractory Kawasaki Disease
https://doi.org/10.56964/pidspj20222301005

Statistical Analysis

A traditional pair-wise, meta-analysis was conducted. All statistical analyses and risk of bias assessment were performed using the Review Manager [RevMan] 5.4.1 software. The risk of bias assessment was performed in accordance with the guidelines outlined in the Cochrane Handbook (version 6.1). Risk ratios (RR) and 95% confidence interval (CI) for dichotomous outcomes were estimated and a random-effects model was used. Sensitivity analyses were performed to evaluate the effect of each study on the pooled RR. Between-study heterogeneity was tested using Chi-square and was considered significant at $I^2 > 50\%$ or $P < 0.1$. Funnel plot was not utilized to examine publication bias as it was deemed unnecessary.[15] Forest plot was employed to represent estimated results from studies. The desired sample size was calculated at 300 as derived from a priori estimated treatment effects.

RESULTS

Study Selection and Description

We retrieved 824 potentially eligible studies (Figure 1), six of which were published between 2005 and 2016 and were included in the meta-analysis following the inclusion and exclusion criteria (Table 1). Two studies were RCTs, two prospective and two retrospective studies. Neither the blinding nor the allocation concealment method was mentioned in any of the reports (Table 3). Recurrent or persistent fever in IVIG-refractory KD was defined in three studies as a body temperature of more than or equal to 37.5°C within 48 hours of receipt of IVIG, while two studies defined it as a body temperature of more than 38.0°C within 24 to 36 hours of initial IVIG treatment (Table 2). One study did not specify the body temperature used as the basis for fever, but defined treatment resistance as fever persistence or relapse within 36 hours of initial IVIG treatment. The six selected studies included 188 patients.

The control and treatment groups had similar baseline characteristics, including sex, ethnicity, age at fever onset, time from fever onset to diagnosis, and time from first treatment to retreatment. All studies reported a higher proportion of males than females, with an average age at diagnosis between two to three years old. The average day of illness upon initial treatment was between 4 - 5 days. The average day of retreatment was during the seventh to ninth day of illness. From the included studies, the rate of resistance to initial IVIG treatment was reported between 13-17%.

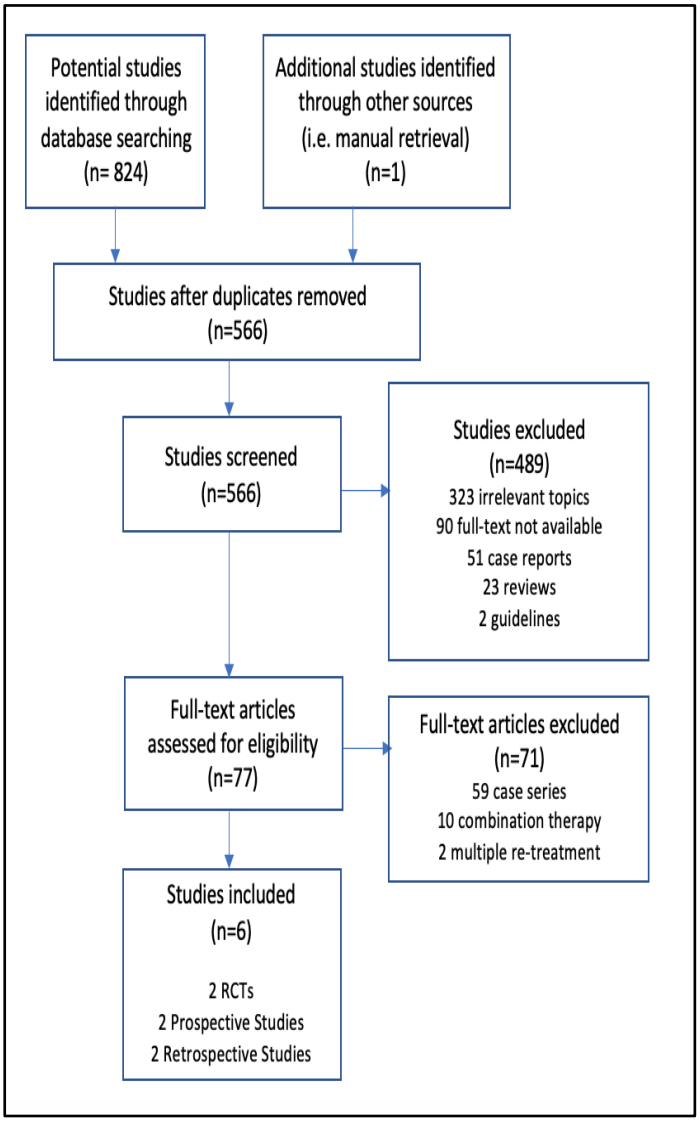

Figure 1. PRISMA Study flow diagram

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 1, pp. 15-26 January-June 2022
Cano CU, Ley-Chua T, Garcia RD. A Systematic Review and Meta-Analysis on the Safety and Efficacy of Second Dose Immunoglobulin Versus High Dose Pulse Methylprednisolone in Refractory Kawasaki Disease
https://doi.org/10.56964/pidspj20222301005

Table 1. Characteristics of included studies

AUTHOR, YEAR	COUNTRY	DESIGN OF STUDY	TOTAL PATIENTS	SEX (MALE %)	AGE (YEAR)	INITIAL TREATMENT		RATE OF RESISTANCE TO INITIAL IVIG	RE-TREATMENT		FF UP PERIOD POST RE-TREATMENT
						DAYS OF ILLNESS UPON TREATMENT			DAYS OF ILLNESS UPON TREATMENT		
						GROUP A (2ND IVIG)	GROUP B (IVMP)		GROUP A (2ND IVIG)	GROUP B (IVMP)	
MIURA 2005	JAPAN	RCT	22	NR	NR	NR	NR	NR	NR	NR	1 WEEK
FURUKAWA 2007	JAPAN	RETROSPECTIVE*	63	54%	2.4	5 (2-9)	4 (3-5)	13%	7 (6-8)	8 (5-11)	4 WEEKS
MIURA 2008	JAPAN	RCT	15	67%	2.6	4 (4-4)	5 (4-7)	NR	8 (6-9)	9 (8-10)	1 WEEK
OGATA 2009	JAPAN	PROSPECTIVE#	27	64%	2.5	4 ± 1.3	5 ± 0.3	16%	8 ± 2.4	7 ± 1.3	PRIOR DISCHARGE
TERAGUCHI 2013	JAPAN	PROSPECTIVE*	41	59%	2.3	NR	NR	17%	7 (6-10)	8 (5-14)	4 WEEKS
KIM 2016	KOREA	RETROSPECTIVE#	20	76%	2.7	NR	NR	NR	NR	NR	8 WEEKS

*Subjects who refused steroids were assigned to the IVIG group.
#Subjects were assigned to 2nd IVIG vs. IVMP based on location of care.
NR= not reported

Table 2. Characteristics of included studies

AUTHOR, YEAR	INITIAL IVIG TREATMENT				RE-TREATMENT					
	IVIG (G/KG/DOSE) [HRS] *	ASA (MKDAY)*	INITIAL IVIG RESISTANCE DEFINITION	RATE OF RESISTANCE TO INITIAL IVIG*	GROUP A			GROUP B		
					2ND IVIG		ASA*	IVMP		ADDITIONAL TX*
					(G/KG/DOSE)	# OF	(MKDAY)	(MKDAY)	# OF DAYS	
MIURA 2005	2 [NR]	NR	T≥37.5C W/IN 48HRS	NR	2	1	NR	30	3	HEPARIN 15-20U/KG/HR
FURUKAWA 2007	2 [12-24]	30	RELAPSE W/IN 36HRS	13%	1 TO 2	1	30	30	3	PRED (1) X 7D
MIURA 2008	2 [24]	NR	T ≥ 37.5C W/IN 48HRS	NR	2	1	NR	30	3	NR
OGATA 2009	2 [24]	30	T ≥ 37.5C OR DECREASE IN CRP <50% W/IN 48HRS	16%	2	1	30	30	3	NR
TERAGUCHI 2013	2 [24]	30	T≥38C W/IN 36HRS OR DECREASE IN CRP <50% IF T 37.5-38C	17%	2	1	NR	30	3	HEPARIN 10U/KG + PRED (1) X 7D
KIM 2016	2 [10-12]	50	T>38C W/IN 24-36HRS	NR	1 TO 2	1	50	30	3	TAPERING ORAL PRED

NR= not reported

Table 3. Quality assessment of included studies

AUTHOR, YEAR	RANDOMIZATION	BLINDING	ALLOCATION CONCEALMENT	LOST TO FF UP/ WITHDRAWAL	GRADE	MINORS
MIURA 2005	YES	NR	NR	NO	B	N/A
FURUKAWA 2007	NO	NR	NR	NO	C	19
MIURA 2008	YES	NR	NR	NO	B	N/A
OGATA 2009	NO	NR	NR	NO	C	20
TERAGUCHI 2013	NO	NR	NR	NO	C	20
KIM 2016	NO	NR	NR	NO	C	19

Risk of Bias of Included Studies

The four non-RCTs had scores ranging from 19 to 20 points according to the MINORS guidelines (Table 3), hence, all of these were marked as high quality studies. Additionally, the risk of bias assessed by the Cochrane collaboration tool (Figure 2) suggested possible sources of selection, performance and detection bias. In the two RCTs included, the papers discussed randomization, without providing information on allocation concealment or blinded measurements.

The published methodology, including outcome measures reported by the included studies, was consistent with that reported in the respective results section. The risk of selective reporting bias for these studies has been coded as low.

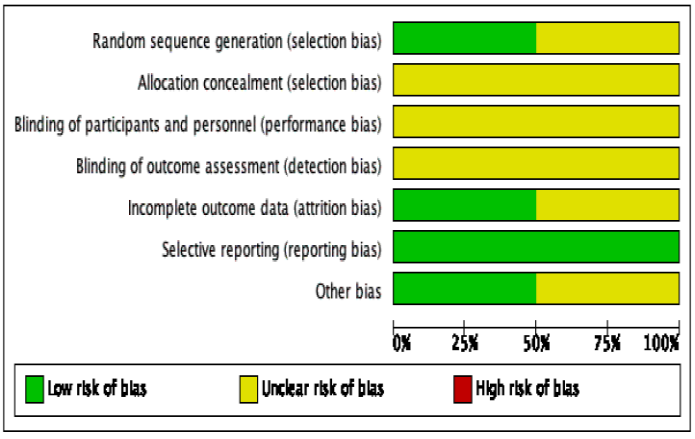

Figure 2. Assessment of the risk of bias

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 1, pp. 15-26 January-June 2022
Cano CU, Ley-Chua T, Garcia RD. A Systematic Review and Meta-Analysis on the Safety and Efficacy of Second Dose Immunoglobulin Versus High Dose Pulse Methylprednisolone in Refractory Kawasaki Disease
https://doi.org/10.56964/pidspj20222301005

Evaluation of Outcomes

CALs

Incidence of coronary artery lesions was not significantly different between a second IVIG infusion versus IVMP treatment in patients with refractory KD (RR 0.82, 0.34-1.96, P=0.66).

No significant heterogeneity was observed among the studies (I^2=38%, P=0.16) (Figure 3). The follow-up time point at which echocardiography was performed ranged from study entry to eight weeks post-treatment.

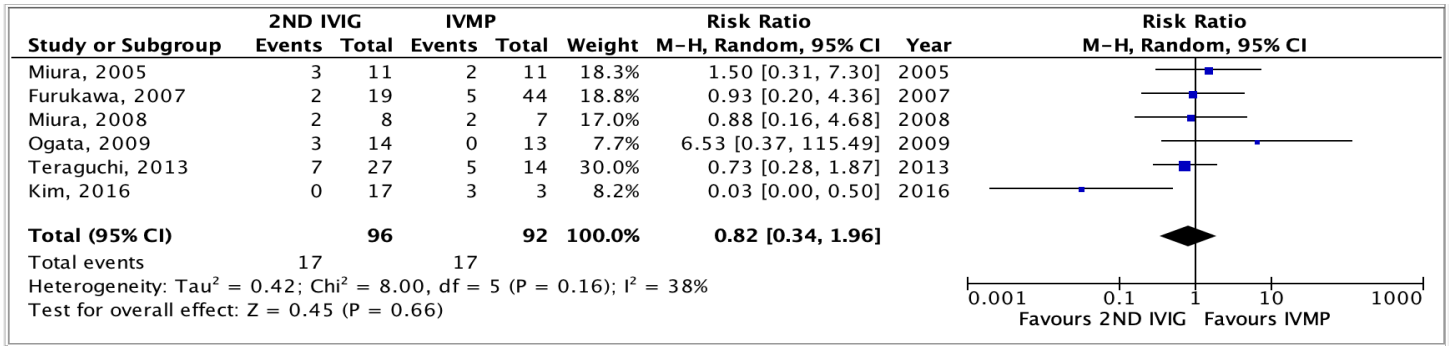

Figure 3. Forest plots of a traditional pair-wise meta-analysis of CALs post-retreatment in patients with refractory KD

Fever resolution

The rate of fever resolution was not significantly different after a second IVIG versus IVMP treatment in patients with refractory KD (RR 0.97, 0.84-1.13, P=0.72).

No significant heterogeneity was observed among the studies (I^2=12%, P=0.34) (Figure 4).

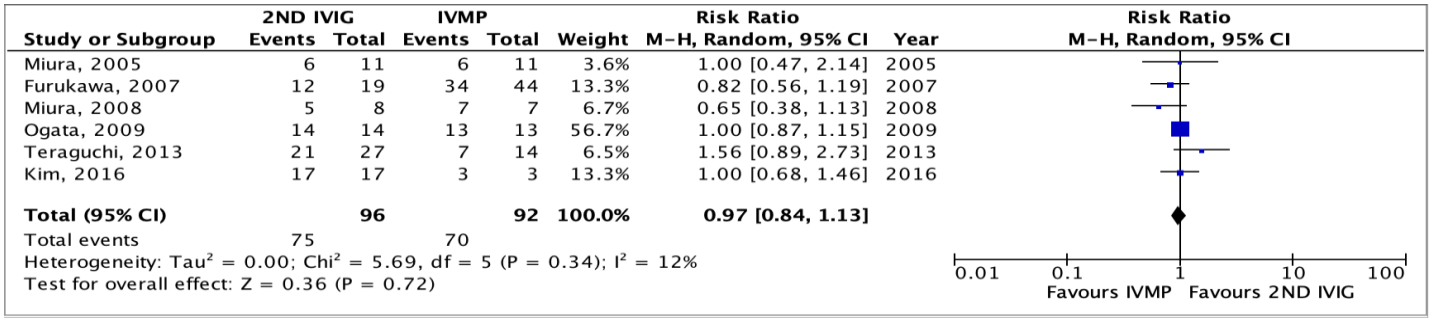

Figure 4. Forest plots of a traditional pair-wise meta-analysis of fever resolution post-retreatment in patients with refractory KD

Adverse events

Four studies reported adverse events during treatment. Miura, et al. and Furukawa, et al. reported more adverse effects in the IVMP group, particularly bradycardia (RR 0.26, 0.11-0.61, P=0.002), hypertension (RR 0.64, 0.42-0.97, P=0.04), and hypothermia (RR 0.32, 0.06-1.81, P=0.20).[7,9,16] The incidence of hyperglycemia (RR 0.07, 0.01-0.46, P=0.006) was also significantly higher in the IVMP group.

Gastrointestinal bleeding and nerve palsy were also reported in the IVMP group.[7,14] No significant heterogeneity was observed within each subgroup of adverse events (All I^2=0%, P>0.10). Overall effect revealed a significantly higher incidence of adverse events in the IVMP group (RR 0.42, 0.26-0.57, P=0.0002) (Figure 5).

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 1, pp. 15-26 January-June 2022
Cano CU, Ley-Chua T, Garcia RD. A Systematic Review and Meta-Analysis on the Safety and Efficacy of Second Dose Immunoglobulin Versus High Dose Pulse Methylprednisolone in Refractory Kawasaki Disease
https://doi.org/10.56964/pidspj20222301005

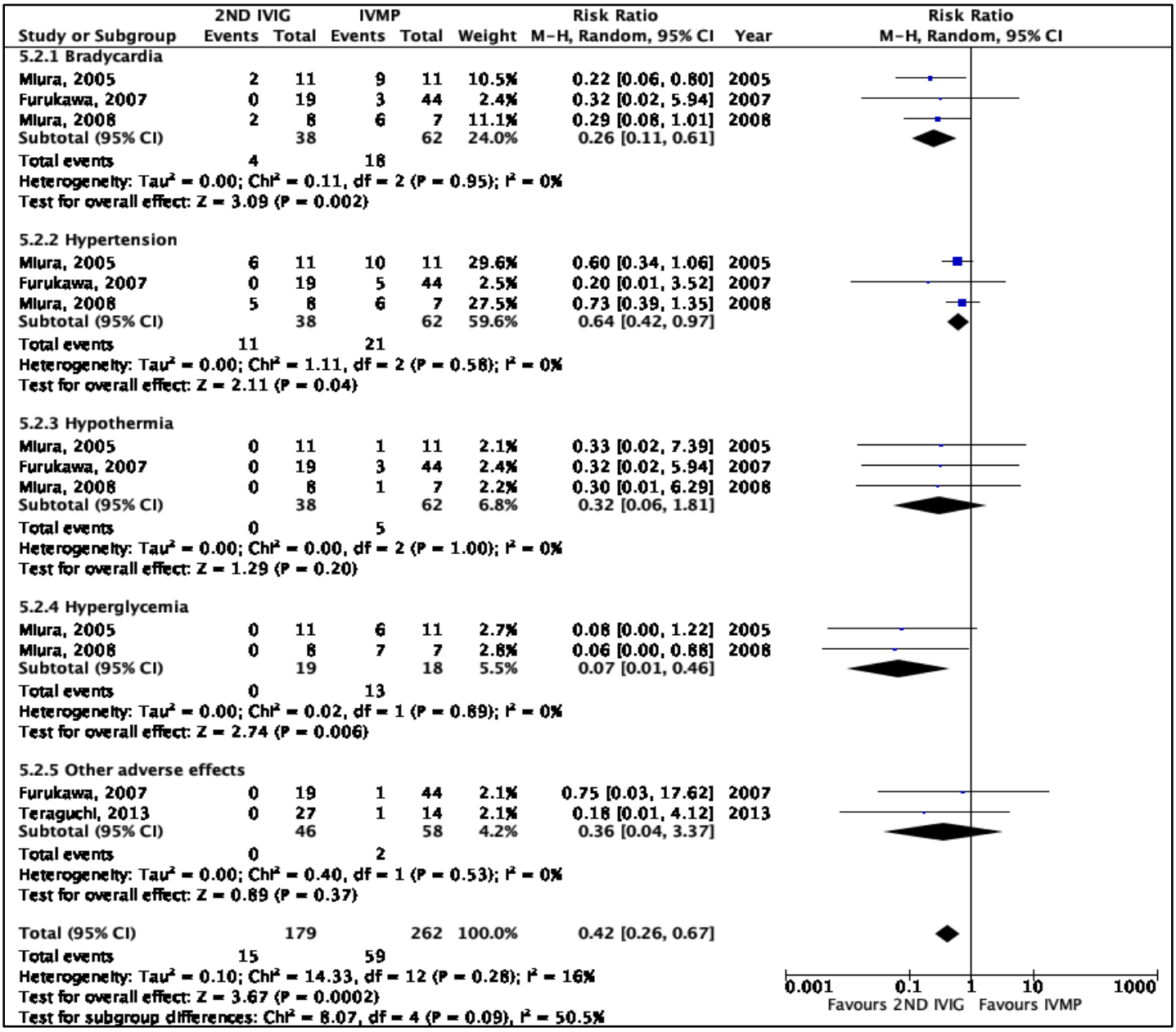

Figure 5. Forest plots of a traditional pair-wise meta-analysis of variable AEs during retreatment

Sensitivity Analysis and GRADE Evidence Profile

There is no significant heterogeneity observed among the included studies in terms of incidence of CALs, fever resolution, or adverse effects. Data reported by the studies of Ogata, et al. and Kim, et al. for CALs, and by Teraguchi, et al. for fever resolution, were outside of the range reported in the rest of the studies.[8,14,17] Sensitivity analysis showed no significant impact of individual outcomes on the overall results (Figure 6 and 7).

Heterogeneity was noted to have totally vanished (I^2=0% from 34%) in the analysis of CAL incidence when the study of Kim, et al. was excluded (Figure 6).

According to the GRADE system, the working group grades of evidence were moderate (Grade B) for incidence of CALs and rate of fever resolution, and low (Grade C) for the total rate of adverse events measured.[12]

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 1, pp. 15-26 January-June 2022
Cano CU, Ley-Chua T, Garcia RD. A Systematic Review and Meta-Analysis on the Safety and Efficacy of Second Dose Immunoglobulin Versus High Dose Pulse Methylprednisolone in Refractory Kawasaki Disease
https://doi.org/10.56964/pidspj20222301005

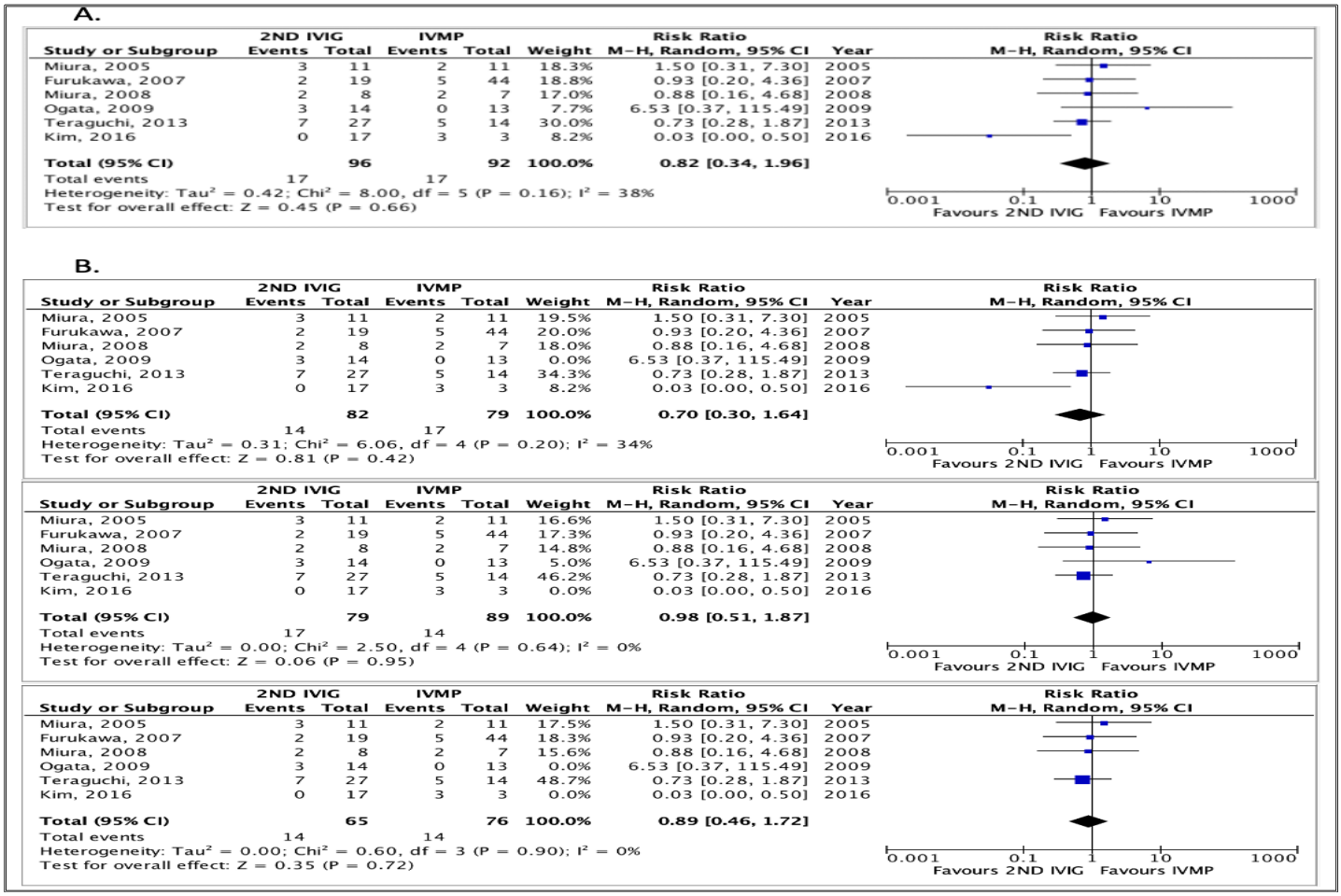

Figure 6. Forest plots of a traditional pair-wise meta-analysis on incidence of CALs post-retreatment of refractory KD patients: (A) before and (B) after sensitivity analysis

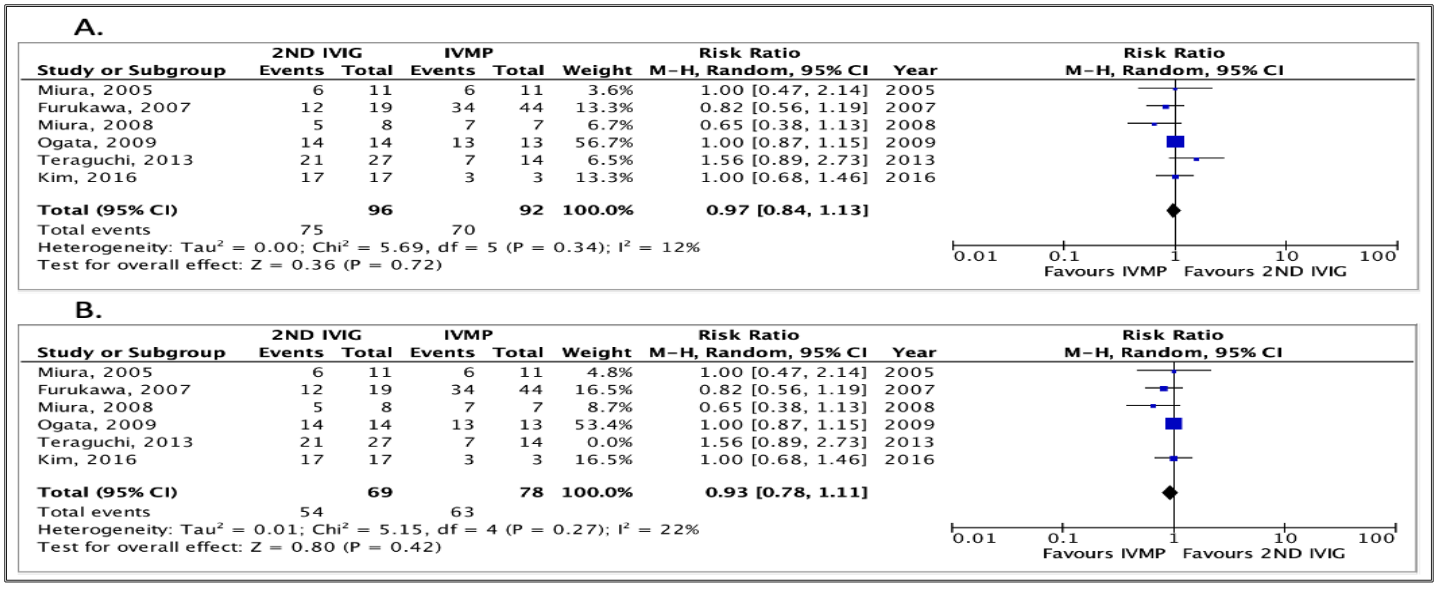

Figure 7. Forest plots of a traditional pair-wise meta-analysis on fever resolution post-retreatment of refractory KD patients: (A) before and (B) after sensitivity analysis

Publication Bias

There were only six studies included in this meta-analysis and screening of publication and reporting bias through funnel plot asymmetry or meta-regression analyses was unnecessary.[15]

DISCUSSION

This meta-analysis compared the outcomes of second-line IVIG versus IVMP in the treatment of children with IVIG-refractory KD. No significant differences between the two groups were seen in terms of incidence of CAL and rate of fever resolution. More adverse events were reported in those who received IVMP than those who were given a second dose of IVIG.

The incidence of CAL was similar in those who received a second IVIG infusion versus those given high-dose IVMP for IVIG-refractory KD. The longest follow-up period for repeat 2D echocardiography was eight weeks after re-treatment. The incidence of CAL for the different studies averaged around 20%-25% for both re-treatment groups, excluding the findings of one study which was out of the range of the other five. A sensitivity analysis showed a disappearance of heterogeneity, with the overall outcome being unaffected when the study of Kim, et al. was excluded. A Cochrane review based on seven randomized controlled trials evaluated the impact of corticosteroid use on the incidence of CALs in KD, as either first-line or second-line treatment, and found that the addition of corticosteroids significantly reduced the subsequent occurrence of CALs without serious adverse effects.[18] However, the review included some RCTs with participants predetermined to be high-risk for IVIG-refractory KD, which may be a possible source of bias in favor of steroid treatment. Zhu, et al., in their meta-analysis on the effect of corticosteroid therapy in Kawasaki disease, found no difference in the incidence of coronary artery aneurysms, with and without steroid therapy, irrespective of whether it was used as a primary or as an additional treatment for IVIG-refractory KD.[3]

Kobayashi, et al. reported that patients who were stratified as low-risk for IVIG-refractory KD, using the Kobayashi risk scoring system, had similar clinical and coronary outcomes despite the addition of corticosteroids to standard treatment, while significantly lowering the incidence of treatment failure and coronary artery abnormalities among high-risk patients, with corticosteroid use.[19] More recent meta-analyses also reported inconsistent findings.[4,11,20] Crayne, et al. analyzed 388 patients with IVIG-refractory KD from 8 papers, including comparative studies on second IVIG versus IVMP, or second IVIG versus infliximab, and noncomparative studies involving only second IVIG or infliximab. The study reported no significant differences in the incidence of persistent non-giant aneurysms at 4-8 weeks after re-treatment across the three treatment groups, but found second IVIG to have significantly reduced the presence of giant aneurysms by 90% versus IVMP (RR=0.1; [95% CI, 0.01-0.9], p=0.01).[4] Chan, et al. had the same objective as Crayne, et al. and analyzed 12 studies with 372 IVIG-refractory KD patients. They found that neither infliximab nor IVMP was significantly more effective than second IVIG infusion in lowering CALs (infliximab, 0.85, 0.43-1.69; IVMP, 0.99, 0.52-1.88).[11] Yang, et al. focused on comparison between second IVIG with IVMP in IVIG-refractory KD patients, and analyzed 4 studies with 127 patients. The study found no significant difference in the incidence of CALs between second IVIG and IVMP (odds ratio=1.55, 95% CI: 0.57-4.20, p=0.39).[20] This study reports similar findings as Yang, et al. and Chan, et al. Both studies reported no significant difference in terms of incidence of CALs between second IVIG and IVMP in IVIG-refractory KD.

The fever resolution rate was similar, post-re-treatment, with either IVMP or second dose IVIG. The antipyretic effect of IVMP has been shown to be superior than a second IVIG infusion in refractory KD in several studies.[3,7,9,11,16,17,20]

Fever resolution is defined as a significant decrease in temperature in a patient with persistent fever, within three days of completing the drug infusion, without another explanation for the fever other than Kawasaki disease. Although fever resolved faster in the IVMP treated group, recurrence of fever was identified in some studies, so the proportion of responsive patients was similar between the two groups.[7,9,14,16] Our study considered fever recurrence as an indication of non-response to treatment. Re-treatment resistance is therefore the reciprocal of fever resolution rate. Analysis of the final fraction of febrile patients revealed no significant difference in incidence of fever resolution and therefore treatment resistance between IVMP and second dose IVIG (Figure 4). The discrepancy of findings in this paper with previous studies is likely secondary to dissimilar fever resolution rates which were taken for comparison.[3,7,9,16,17,20] A recent meta-analysis compared the initial fever resolution rates between the two re-treatment groups despite fever recurrence in the IVMP group.[20] Other than fever, other objective quantifiable parameters, including 2-D echocardiogram findings, were also considered as possible proxies for outcomes when comparing the two treatment groups. In the assessment of included articles however, the 2-D echocardiography data provided were very disparate and incomplete to allow comparison of findings between the two treatment groups.

One of the articles in this meta-analysis, by Miura, et al., found that children who received IVMP had cytokine levels that decreased faster than those seen in children who received a second IVIG initially, but with similar levels subsequently.[9] Monocyte chemo-attractant protein 1 (MCP-1), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) were significantly lower in IVMP-treated patients, compared with the IVIG-treated group, on day 4 but not on day 7. Rebounds in cytokine levels may possibly explain the fever recurrence after treatment for KD.

This is the reason why a tapering course of oral prednisone is suggested for continuation therapy, after systemic corticosteroid has been given, to prevent rebound inflammation.[9,10] Past reports have shown that MCP-1 is expressed at the sites of coronary arteritis of fatal KD patients and that the expression of MCP-1 genes persisted or was increased into the convalescent phase in KD patients with coronary artery lesions.[21,22] Serum level of TNF-α has also been reported to be higher in KD patients with coronary artery lesions than in those without coronary artery lesions.[23] Oral steroids, after the systemic doses, is therefore suggested to continuously suppress cytokine levels to reduce the chance of fever recurrence and the incidence of coronary artery lesions in children who receive IVMP.[9, 24]

The IVMP group reported more adverse events during treatment, including bradycardia, hypertension and hyperglycemia. These are common side effects of high dose IVMP therapy and these were all transient and non-serious.[7,9,16,25] Chan, et al. pointed out a possible reporting bias as methylprednisolone has been extensively reported in several studies as an anti-inflammatory drug administered to IVIG-refractory KD patients.[20] Other adverse events reported in the IVMP group included a case of gastrointestinal bleeding and a case of nerve palsy.[7,14]

Relevance and Implications

The Philippine Health System is dominated by the private health sector and patients are often burdened by out-of-pocket payments for health services. IVIG is an expensive treatment. For patients with IVIG-refractory KD, the current recommendation of giving a second dose of IVIG imposes a significant financial burden. The efficacy of methylprednisolone, as non-inferior to a second dose of IVIG, can have significant utility as an acceptable, relatively inexpensive, and reliable choice, as a second-line treatment for IVIG-refractory KD.

Although this study did not address cost-effectiveness of the two treatment options, it is well known that IVIG is very expensive, while corticosteroids are relatively inexpensive medications.

Limitations of the Study

IVIG-refractory KD is rare, making an adequately powered prospective randomized controlled trial difficult to conduct.[4] Only two of the included studies in this report were randomized controlled studies. The dosage and administration of corticosteroids, immunoglobulins, acetylsalicylic acid and other additional drugs in all included studies, as presented in Table 2, demonstrated minimal variation which can also affect the outcomes for accurate comparison. Furthermore, the studies included small samples and could contribute to bias. The follow-up periods of each study were relatively short, which may not truly reflect the coronary artery outcomes post-retreatment. In a meta-analysis, it can be difficult to avoid publication bias. Nevertheless, short of adequately powered studies among published data, this type of evidence review is the best effort to improve the test power by combining several small clinical trials into a seemingly large clinical trial. The risk of selective reporting bias is deemed low as the published methodology, including outcome measures reported by the included studies, was consistent with that reported in the respective results section. The desired sample size of a meta-analysis is at least that of a large well-designed clinical trial.[26] The target sample size for this study was calculated at 300. Due to limited available evidence, the identified eligible studies accrued only to a total of 188 patients. The review process of the articles was done by three investigators independently, but the screening and retrieval of the included articles was solely done by the primary investigator which could have contributed to selection bias. More than one independent investigator involved in the retrieval of articles is ideal to limit the chance of missing out on relevant articles.

CONCLUSION

This study found no significant difference in the incidence of coronary artery lesions and the rate of fever resolution post-retreatment with IVMP versus a second dose of IVIG in IVIG-refractory KD patients. More adverse events were reported in the IVMP group, although all were noted to be transient and to have resolved without additional management.

ACKNOWLEDGEMENTS

We thank Ms. Kristine Calvario, Mr. Roy Alvin Malenab and Dr. Ivy Cloma for their invaluable contributions in the conduct of this study.

REFERENCES

1. Burns JC, Glode MP. Kawasaki syndrome. *Lancet* [Internet]. 2004 Aug 7 [cited 2021 Jan 4];364(9433):533-44. Available from: https://pubmed.ncbi.nlm.nih.gov/15302199/ DOI: 10.1016/S0140-6736(04)16814-1
2. Marrani E, Burns JC, Cimaz R. How should we classify Kawasaki disease? *Frontliers in Immunology* [Internet]. 2018 Dec 14 [cited 2021 Jan 5];9:2974. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2018.02974/full
3. Zhu B, Lv H, Sun L, Zhang J, Cao L, Jia H, et al. A meta-analysis on the effect of corticosteroid therapy in Kawasaki disease. *Eur J Pediatr.* 2012171(3):571-578.
4. Crayne C, Mitchell C, Beukelman T. Comparison of second-line therapy in IVIG refractory Kawasaki disease: a systematic review. *Pediatr Rheumatol* [Internet]. 2019 Nov 27 [cited 2021 Jan 4];17:77 . Available from: https://ped-rheum.biomedcentral.com/articles/10.1186/s12969-019-0380-z DOI: 10.1186/s12969-019-0380-z
5. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/ Canadian Kawasaki syndrome study group. *Pediatr Infect Dis J*. 1998 Dec;17(12):1144–1148.
6. Saneeymehri S, Baker K, So T. Overview of pharmacological treatment options for pediatric patients with refractory Kawasaki disease*. J Pediatr Pharmacol Ther.* 2015;20(3):163–177.
7. Furukawa T, Kishiro M, Akimoto K, Nagata S, Shimizu T, Yamashiro Y. Effects of steroid pulse therapy on immunoglobulin resistant Kawasaki disease. *ArchDis Child.* 2008 Feb;93(2):142–146.
8. Kim HJ, Lee HE, Yu JW, Kil HR. Clinical outcome of patients with refractory Kawasaki disease based on treatment modalities. *Korean J Pediatr.* 2016 Aug 24;59(8):328-334.

9. Miura M, Kohno K, Ohki H, Yoshiba S, Sugaya A, Satoh M. Effects of methylprednisolone pulse on cytokine levels in Kawasaki disease patients unresponsive to intravenous immunoglobulin. *Eur J Pediatr*. 2008 Jan 4;167(10):1119-1123.
10. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term Management of Kawasaki Disease: a scientific statement for health professionals from the American Heart Association. *Circ* [Internet]. 2017 [cited 2021 Jan 3];135(17): e927–e999. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000484 DOI: 10.1161/CIR.0000000000000484
11. Chan H, Chi H, You H, Wang M, Zhang G, Yang H, Li Q. Indirect-comparison meta-analysis of treatment options for patients with refractory Kawasaki disease. *BMC Pediatr* [Internet]. 2019 May 17 [cited 2021 Jan 6];19(158):1-15. Available from: https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-019-1504-9
12. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations [Internet]. [No publication place]: The GRADE Working Group; 2013 [cited 2021 Jan 6]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html
13. JCS Joint Working Group. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2008)--digest version. *Circ* [Internet]. 2010 [cited 2021 Jan 3];74(9):1-10. Available from: https://www.jstage.jst.go.jp/article/circj/74/9/74_CJ-10-74-0903/_article DOI: 10.1253/circj.cj-10-74-0903
14. Teraguchi M, Ogino H, Yoshimura K, Taniuchi S, Kino M, Okazaki H, et al. Steroid pulse therapy for children with intravenous immunoglobulin therapy-resistant Kawasaki Disease: A prospective study. *Pediatr Cardiol.* 2013 April;34:959-963.
15. Higgins JPT, Green S. Cochrane Handbook for systematic reviews of interventions, Version 6.1.0. [Internet]. London: The Cochrane collaboration; 2020 [cited 2021 Jan 7]. Available from: https://training.cochrane.org/handbook
16. Miura M, Ohki H, Yoshiba S, Ueda H, Sugaya A, Satoh M, et al. Adverse effects of methylprednisolone pulse therapy in refractory Kawasaki disease. *Arch Dis Child.* 2005 Oct;90(10):1096–1097.
17. Ogata S, Bando Y, Kimura S, Ando H, Nakahata Y, Ogihara Y, et al. The strategy of immune globulin resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. *J Cardiol.* 2009 Feb;53(1):15–19.
18. Wardle AJ, Connolly GM, Seager MJ, Tulloh RM. Corticosteroids for the treatment of Kawasaki disease in children Cochrane Database Syst Rev[Internet] 2017 Jan 27 [cited 2021 Jan 2];1(1):CD011188. Available from: https://pubmed.ncbi.nlm.nih.gov/28129459/ DOI: 10.1002/14651858.CD011188.pub2
19. Kobayashi T, Inoue Y, Otani T, Morikawa A, Kobayashi T, Takeuchi K, et al. Risk stratification in the decision to include prednisolone with intravenous immunoglobulin in primary therapy of Kawasaki disease. *J Pediatr Infect Dis*. 2019 Jun;28(6):498-502.
20. Yang X, Liu G, Huang Y, Chen S, Du J, Jin H. A meta-analysis of re-treatment for intravenous immunoglobulin-resistant Kawasaki disease. *Cardiol Young*. 2015 Aug;25(6):1182-1190.
21. Teari M, Jibiki T, Harada A, Terashima Y, Yasukawa K, Tateno S, et al. Dramatic decrease of circulating levels of monocyte chemoattractant protein-1 in Kawasaki disease after gamma globulin treatment. *J Leukoc Biol.* 1999 May;65(5):566–572.
22. Wong M, Silverman ED, Fish EN. Evidence for RANTES, monocyte chemotactic protein-1, and macrophage inflammatory protein-1 beta expression in Kawasaki disease. *J Rheumatol.* 1997 Jun;24(6):1179–1185.
23. Lin CY, Lin CC, Hwang B, Chiang BN. Cytokines predict coronary aneurysm formation in Kawasaki disease patients. *Eur J Pediatr.* 1993 Apr;152(4):309–312.
24. Gong GWK, McCrindle BW, Ching JC, Yeung RSM. Arthritis presenting during the acute phase of Kawasaki disease. *J Pediatr.* 2006 Jun;148(6):800–805.
25. Darling HS, Marwah V, Rajput AK, Varma PP, Singh KK. Low Dose Methylprednisolone Induced Bradycardia. *J Assoc Physicians India* [Internet]. 2013 Dec [cited 2021 Jun 21];61. Available from: https://www.japi.org/q27484/low-dose-methylprednisolone-induced-bradycardia
26. Thorlund K, Mills EJ. Sample size and power considerations in network meta-analysis. *Syst Rev* [Internet]. 2012 Sept 19 [cited 2021 Jun 21];1(4):1-2. Available from: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-1-41 DOI:10.1186/2046-4053-1-41