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Pediatrics 2005;116:989-995

DOI: 10.1542/peds.2005-0504

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/116/4/989>

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American Academy of Pediatrics

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Effect of Initial Corticosteroid Therapy on Coronary Artery Aneurysm Formation in Kawasaki Disease: A Meta-analysis of 862 Children

Angela C. Wooditch, MD, and Stephen C. Aronoff, MD

ABSTRACT. *Objective.* Kawasaki disease is an acute vasculitis of infancy and childhood. When untreated, 15% to 25% of patients develop coronary artery aneurysms. Although the use of aspirin and intravenous immune globulin (IVIG) as initial therapy is well established, the role of corticosteroids is uncertain. The objective of this study was to identify clinical trials that compared the rate of coronary aneurysm formation after initial therapy with corticosteroids or an appropriate control and to determine the overall efficacy of corticosteroid therapy for the initial treatment of Kawasaki disease.

Methods. Published studies were identified by searches of the Medline and the Cochrane Central Register of Controlled Trials databases as well as hand searches of selected references. Studies were included when (1) all subjects had a stated diagnosis of Kawasaki disease; (2) a corticosteroid preparation was included as part of the initial management of the disease process; (3) a therapeutically matched control group was included for the entire study, or subsets of patients that received a therapeutic intervention identical to the experimental group except for the inclusion of a corticosteroid compound could be identified; and (4) 2-dimensional echocardiography or coronary artery catheterization was performed at least 2 weeks after therapy to detect the presence of coronary aneurysms. Included studies were evaluated for quality and heterogeneity. Meta-analysis was performed using a fixed-effects model.

Results. Eight studies fulfilled criteria for inclusion. Because 2 of these studies provided adequate detail to permit evaluation of 2 subgroups each, a total of 10 groups were available for evaluation. The significant heterogeneity that existed among the 10 studies ($Q = 21.9$, $I^2 = 59.0$) was eliminated when 2 studies with markedly different study designs were removed ($Q = 5.59$, $I^2 = 0.00$). Meta-analysis of the remaining 8 studies revealed a significant reduction in the incidence of coronary artery aneurysms among patients who received corticosteroid therapy plus aspirin \pm IVIG compared with aspirin \pm IVIG alone (odds ratio [OR] 0.546; 95% confidence interval [CI]: 0.371–0.803); the benefit of corticosteroid therapy was maintained when study subsets of aspirin alone (OR: 0.601; 95% CI: 0.392–0.921) or aspirin + IVIG (OR: 0.352; 95% CI: 0.136–0.909) were compared with matched regimens that contained corticosteroids.

Conclusion. The inclusion of corticosteroids in aspirin-containing regimens for the initial treatment of Kawasaki disease reduces the incidence of coronary aneurysms. *Pediatrics* 2005;116:989–995; *Kawasaki disease, corticosteroids, coronary aneurysms, complications, therapy.*

ABBREVIATIONS. IVIG, intravenous immunoglobulin; OR, odds ratios; SE, standard error; CI, confidence interval.

First described in English in 1974, Kawasaki disease is an acute vasculitis of infancy and early childhood characterized by fever of >5 days' duration, nonpurulent conjunctivitis, rash, unilateral cervical lymphadenopathy, oropharyngeal mucositis, and edema or erythema of the hands and feet.^{1–3} Development of coronary artery aneurysms is the major cardiac morbidity from this disease.⁴

Aspirin and intravenous immunoglobulin (IVIG) reduce the incidence of coronary artery aneurysms in Kawasaki disease.^{3,5} The utility of corticosteroids in Kawasaki disease is less clear. Shulman⁶ noted that some reports address "rescue" therapy (corticosteroid administration in children who fail IVIG therapy), whereas others address "primary" therapy (corticosteroid administration as a component of first-line therapy). The most recent guidelines for the management of Kawasaki disease do not endorse the use of corticosteroids as primary therapy³; the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association withheld its recommendation on the basis of the low level of supporting evidence. Because no systematic review addressed the use of corticosteroids as primary therapy for Kawasaki disease, the present study was undertaken to identify clinical trials that compared the rate of coronary aneurysm formation after initial therapy with corticosteroids or an appropriate control and to determine the overall efficacy of corticosteroid therapy for the initial treatment of Kawasaki disease.

METHODS

Study Identification

The Medline and the Cochrane Central Register of Controlled Trials databases were searched using both the Ovid and PubMed search engines, covering the period from 1966 to February 2005. Search terms included "Kawasaki," "steroid," "corticosteroid," "treatment," and "controlled trials." The reports were screened for relevance using the title and abstract. The bibliographies of selected articles and editorials were also reviewed.

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Accepted for publication May 5, 2005.

doi:10.1542/peds.2005-0504

No conflict of interest declared.

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Study Selection and Data Analysis

Studies were included when they met the following criteria: (1) all subjects had a stated diagnosis of Kawasaki disease; (2) a corticosteroid preparation was included as part of the initial management of the disease process; (3) a therapeutically matched control group was included for the entire study, or subsets of patients that received a therapeutic intervention identical to the experimental group except for the inclusion of a corticosteroid compound could be identified; and (4) 2-dimensional echocardiography or coronary artery catheterization was performed at least 2 weeks after therapy to detect the presence of coronary aneurysms. The methods sections from candidate articles were separated from the text, all references to the authors or the location of the study were hidden, and the methods were reviewed by one of the authors (S.C.A.) for compliance with inclusion criteria. The other author reviewed the methods section unblinded. Conflicts were resolved by discussion until consensus was reached.

The quality of each article was rated using the following schema:

1. Were the criteria for the diagnosis of Kawasaki disease stated explicitly (defined as (a) a statement that all patients met the diagnostic criteria of the American Heart Association; (b) a statement that all patients met the criteria of the Japanese Ministry of Health, or (c) fever for 5 days plus any 4 of the following: conjunctivitis, mucositis of the oral pharynx, peripheral edema, unilateral lymphadenopathy, and rash) (yes = 1; 0 = no)?
2. Was an experimental study design used (randomized, controlled, prospective, study with defined protocol = 2; controlled, defined protocol only = 1; none = 0)?
3. Was follow-up coronary imaging performed after enrollment (≥ 4 weeks = 2; 2–4 weeks = 1; not stated = 0)?
4. Was coronary imaging interpreted in a blinded manner (yes = 1; no or not stated = 0)?

Each article was scored by the authors. Conflicts in scoring were resolved by consensus.

Data Abstraction

Information from each article was abstracted using a standardized tool. For each study, data for a group that was treated with corticosteroids and data for a comparable control group were identified. Reports that evaluated multiple therapeutic protocols were treated as separate studies when appropriate control groups could be identified. Details of the patient population were recorded. For each study, the dosage and the duration of aspirin therapy and the dosage and the duration of IVIG therapy for the control group were recorded. For the corresponding experimental group, the compound, dosage, and duration of corticosteroid therapy were recorded. Only studies or study subsets in which aspirin and IVIG therapy were identical between the control and experimental groups were included. Additional therapies were permitted when administered to both groups of patients. Outcome data were expressed as the proportion of patients per group with aneurysms (maximum number of patients with coronary aneurysms detected during follow-up/total number of patients in the group).

Statistical Analysis

The proportion of patients who developed coronary aneurysms in each study was converted to odds ratio (OR), and the variance was calculated; in cases in which no events occurred in a cell, a value of 0.5 was used.⁷ The protocol for dealing with heterogeneity, publication bias, and method for statistical analysis was determined before the capture of any data.

The inclusion of a subset of studies that differ from the majority of studies in method, population, or therapeutic specifics affects not only the model used for meta-analysis but also its outcome.^{7,8} Heterogeneity among the studies and study subgroups was assessed by calculating Cochran's Q statistic, applying it to a χ^2 distribution and calculating the associated *P* value⁹; *P* < .05 suggested significant heterogeneity. For determining the percentage of heterogeneity across studies, *I*² was calculated.¹⁰ Outlying studies were identified from plots of the *z* statistic versus the reciprocal of standard error (SE; Galbraith plots) and by linear regression.^{8,11} Suspected sources of heterogeneity were confirmed by subset

analysis.¹² If the heterogeneous studies contained significant variations in protocol or method from the remaining studies, then the offending studies could be excluded from the database. In the absence of such explanations, an attempt to combine the studies would be of questionable validity.⁸

Assessment of publication bias (the tendency to find published articles with positive findings more often than those with negative findings) was determined graphically from a plot of SE versus OR (funnel plot).¹³ The number of studies that were needed to increase the *P* value above .05 (fail-safe *N*) was also calculated.¹⁴

In the absence of significant study-to-study heterogeneity, the model of Mantel and Haenszel is the method of choice for combining studies.¹⁵ This method assumes a fixed treatment effect from study to study; variations in outcomes among studies are assumed to be the result of randomness within each study. The model of DerSimonian and Laird¹⁶ assumes a random distribution of treatment effects around an unidentified mean. This method yields larger SDs than fixed effects methods and ignores the issue of heterogeneity.

Calculations, forest plots, and funnel plots were performed with meta-analysis software (Comprehensive Meta-Analysis, Version 2 [β]; Biostat, Inc, Englewood, NJ, www.meta-analysis.com). Linear regression and Galbraith plots were performed with standard spreadsheet software (Excel Office 2000; Microsoft Corp, Redmond, WA).

RESULTS

Study Inclusion and Selection

Online searches of public databases and hand searching of selected bibliographies yielded 168 citations. Initial screening of titles and abstracts identified 26 relevant articles. Twelve of these articles did not contain original data and represented topical reviews. The methods sections of the remaining 14 articles were analyzed for compliance with the meta-analysis protocol. Six studies were excluded:

1. Three studies examined the use of corticosteroid therapy in children who failed initial treatment with standard therapy.^{17–19}
2. One study failed to include a control group that received comparable therapy to the corticosteroid recipient group.²⁰
3. One study evaluated the role of corticosteroid therapy in treating existing coronary aneurysms secondary to Kawasaki disease.²¹
4. One study represented a preliminary report of a later study that was included in the analysis.²²

Eight reports fulfilled criteria for inclusion^{23–30}; 2 were written in Japanese, and 1 was written in German. Two of the studies were separated into 2 subgroups each. Kato et al²⁴ enrolled 92 patients into 1 of 5 treatment regimens during the first 4 weeks of illness. One subgroup consisted of 25 patients who received cephalexin alone (control) and 17 patients who received cephalexin and prednisolone (experimental). The second subgroup consisted of 36 children who received aspirin alone (control) and 7 children who received aspirin and prednisolone (experimental). Shinohara et al²⁸ reviewed the records of 299 patients with Kawasaki disease and divided them into 4 groups. One subgroup consisted of 42 children who received aspirin, dipyridamole, and propranolol (control) and 170 children who received aspirin, dipyridamole, propranolol, and prednisolone (experimental group). The second subgroup consisted of 25 children who received aspirin, dipyridamole, propranolol, and IVIG (control) and 62

children who received aspirin, dipyridamole, propranolol, IVIG, and prednisolone. Table 1 summarizes the 10 groupings included in the analysis.

Quality of Studies

The quality of the 8 studies included in the database is shown in Table 2. The study by Kusakawa et al²⁵ failed to meet any of the quality criteria. This was a retrospective report, and none of the patients followed a uniform treatment or follow-up protocol. Only 2 of the studies stated that patients were randomly assigned to treatment arms^{27,30}; no statement as to how patients were assigned treatment was noted in the remaining studies.

Analysis of Heterogeneity

When all 10 of the groups were combined using the fixed-effects model, significant heterogeneity as a result of differences across studies was identified ($Q = 21.9, P = .0009, I^2 = 59.0$). Figure 1 is a plot of the z statistic ($\log OR/SE$) against a surrogate measure of sample size ($1/SE$). Two points appeared as outliers from the line defined by the majority of the studies. Kusakawa et al²⁵ described an aggregate of cases that were identified retrospectively and reported to the Japanese Welfare Ministry by 13 hospitals spread throughout the country. Although an aspirin and an aspirin plus corticosteroid group were reported, the duration and the dosage of medications were not recorded. There is no description of a uniform protocol applied to these patients. A prospective study that was contained in the same report compared 3 treatment protocols: (1) aspirin alone, (2) flurbiprofen alone, and (3) prednisolone plus dipyridamole. Because a matched control for the prednisolone-treated group was not identified, these data were unacceptable for inclusion in the database. Subgroup 1 in the study by Kato et al²⁴ was the only study not to include aspirin in both arms of the study. Linear regression of the Galbraith plot of the remaining 8 studies was significant (slope = $-0.56, b = 0, r = -0.95$). The removal of these 2 studies eliminated all of the across-study heterogeneity ($Q = 5.59, P = .588, I^2 = 0.00$).

Publication Bias

Figure 2 is a funnel plot of the remaining 8 groupings identified for this study. The increased spread in outcome with increasing SE is consistent with the absence of publication bias. Calculation of the fail-safe N found that 9 studies with no effect would be needed to raise the P value beyond .05.

Meta-analysis

When the outcomes of the 8 groups were combined using the model of Mantel and Haenszel, significantly fewer patients who received corticosteroid therapy in addition to standard therapy (aspirin with or without IVIG or other therapies) experienced coronary artery aneurysms than those who received matched standard therapy alone (OR: 0.546; 95% confidence interval [CI]: 0.371–0.803; $P = .002$; Fig 3). To control for IVIG as a confounding variable, we also performed subset analyses. Five groups com-

pared aspirin plus prednisolone with aspirin alone. In this subset, significantly fewer prednisolone and aspirin recipients experienced coronary artery aneurysms than those who received aspirin alone (OR: 0.601; 95% CI: 0.392–0.921; $P = .019$). In the remaining 3 groups, patients received aspirin plus IVIG, or aspirin, IVIG, and corticosteroid therapy. In this subset, fewer patients who received corticosteroid therapy experienced coronary artery aneurysms than matched control subjects (OR: 0.352; 95% CI: 0.136–0.909; $P = .031$).

DISCUSSION

The role of corticosteroids in the initial management of Kawasaki disease has not been established. From the data presented in this meta-analysis, corticosteroids combined with aspirin seem to reduce significantly the incidence of coronary artery aneurysms when used as initial therapy for Kawasaki disease. This effect is maintained when IVIG is added to the initial therapy. Individual clinical trials that evaluated the clinical efficacy of corticosteroid therapy in Kawasaki disease were not of sufficient size to draw valid conclusions. The process of meta-analysis permits the combination of individual trials into an overall study with markedly increased power. As such, statistical significance may be demonstrated through meta-analysis when single small trials were unable to produce results.

The ability of meta-analyses of small trials to predict the results of large, randomized, clinical trials is controversial. LeLorier et al³¹ compared the predictions of 19 meta-analyses of small clinical trials with the results of 12 definitive, large, randomized, controlled studies. When 40 pairs of outcomes between meta-analyses and large clinical trials were compared, meta-analyses were found to have positive and negative predictive values of 68% and 67%, respectively. Statistically significant differences in point estimates of effects among pairs of meta-analyses and clinical trials occurred in only 12% of cases, whereas differences in direction of effect occurred in 20% of the comparisons. Cappelleri et al³² identified 101 meta-analyses that contained at least 1 large, randomized, clinical trial as defined by patient size (>1000) or power (>0.80). The relative risks of the meta-analysis:large trial pairs correlated closely ($r = 0.75$). Fifteen disagreements in outcome between meta-analysis:clinical trial pairs were observed: 5 resulted from differences in control group event rates, 1 resulted from suspected publication bias, 4 resulted from significant differences in study protocol such as comparability of study populations and blinding, and 5 had no identifiable cause. Finally, Sterne et al¹³ noted that meta-analyses may be subject to "small study effects." Because studies with statistically significant differences are more likely to be published than those with "insignificant differences," greater effect sizes are needed in small studies to achieve statistical significance. Although none of the small studies described in the present report achieved statistical significance on their own, the magnitude of the clinical effect expected with corticosteroids in a

TABLE 1. Summary of Studies

Study	Patient Characteristics				Standard Therapy			Corticosteroid Therapy				
	Total Patients, <i>n</i>	Male, <i>n</i>	Mean Age, yr	Age Range, y	Maximum Days of Symptoms Before Enrollment	Aspirin (mg/kg per day)	IVIG mg/kg per dose	No. of Doses	Additional Therapy	Drug Preparation	Dosage (mg/kg per day)	Duration
Kan, 1990 ²³	315	201	2.08	NS	9	50	0	0	Dipyridamole 5 mg/kg × 1 mo	Prednisolone	2	Variable
Kato et al., 1979 ²⁴												
Subgroup 1	42	NS	NS	NS	7	0	0	0	None	Prednisolone	2-3	28-48 days
Subgroup 2	42	NS	NS	NS	7	30	0	0	None	Prednisolone	2-3	28-48 days
Kusakawa, 1983 ²⁵	294	NS	NS	NS	NS	Variable	0	0	None	Variable	Variable	Variable
Neudorf, 1993 ²⁶	35	28	1.5	NS	NS	80-100	0	0	None	Prednisolone	NS	NS
Okada et al., 2003 ²⁷	32	18	2.75	NS	9	30	1000	2	None	Prednisolone	6	Defervescence
Shinohara et al., 1999 ²⁸												
Subgroup 1	212	NS	NS	NS	9	30	0	0	Propranolol 1 mg/kg	Prednisolone	6	Defervescence
Subgroup 2	87	NS	NS	NS	9	30	200 or 400	5	Propranolol 1 mg/kg	Prednisolone	6	Defervescence
Sone, 1987 ²⁹	110	64	2.08	0.8-9	NS	30	0	0	Dipyridamole 2 mg/kg Propranolol 1 mg/kg	Prednisolone	2	1-3 wk
Sundel et al., 2003 ³⁰	38	27	4.4	0.4-13.5	10	20-25	2000	1	None	Methylprednisolone	30	1 dose

TABLE 1. Continued

Study	Coronary Imaging		Outcomes	
	Type of Imaging	Follow-up Period	Total Control Patients, <i>n</i>	Total Steroid Patients, <i>n</i>
Kan, 1990 ²³	2D	3 mo	60	255
Kato et al., 1979 ²⁴			17	45
Subgroup 1	Cath	4-8 wk	5	11
Subgroup 2	Cath	4-8 wk	4	0
Kusakawa, 1983 ²⁵	Cath	Variable	43	20
Neudorf, 1003 ²⁶	2D	NS	3	0
Okada et al., 2003 ²⁷	2D	3 wk	0	0
Shinohara et al., 1999 ²⁸				
Subgroup 1	2D	NS	8	21
Subgroup 2	2D	NS	6	1
Sone, 19087 ²⁹	Cath	2 mo	20	24
Sundel R, et al., 2003 ³⁰	2D	6 wk	9	6

NS indicates not stated; 2D, 2D echocardiography; Cath, cardiac catheterization.

TABLE 2. Quality Assessment of 8 Studies Selected for the Meta-analysis

Study	Diagnostic Criteria	Study Design	Imaging Follow-up	Blinded Outcome	Total
Kan, 1990 ²³	1	1	2	0	4
Kato et al., 1979 ²⁴	1	1	2	0	4
Kusakawa, 1983 ²⁵	0	0	0	0	0
Neudorf, 1993 ²⁶	0	1	2	0	3
Okada et al., 2003 ²⁷	1	2	2	0	5
Shinohara et al., 1999 ²⁸	1	1	2	0	4
Sone, 1987 ²⁹	0	1	2	0	3
Sundel et al., 2003 ³⁰	1	2	2	1	6

See text for scoring.

Fig 1. Galbraith plot of 10 studies identified for meta-analysis.

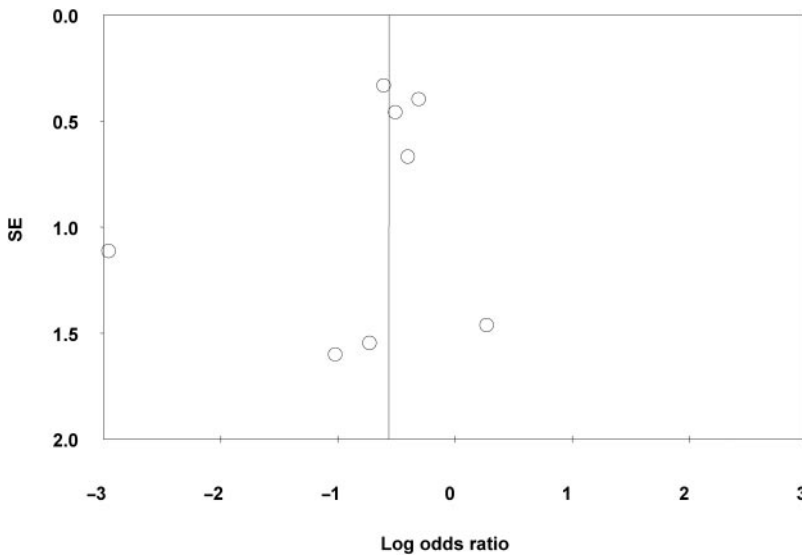
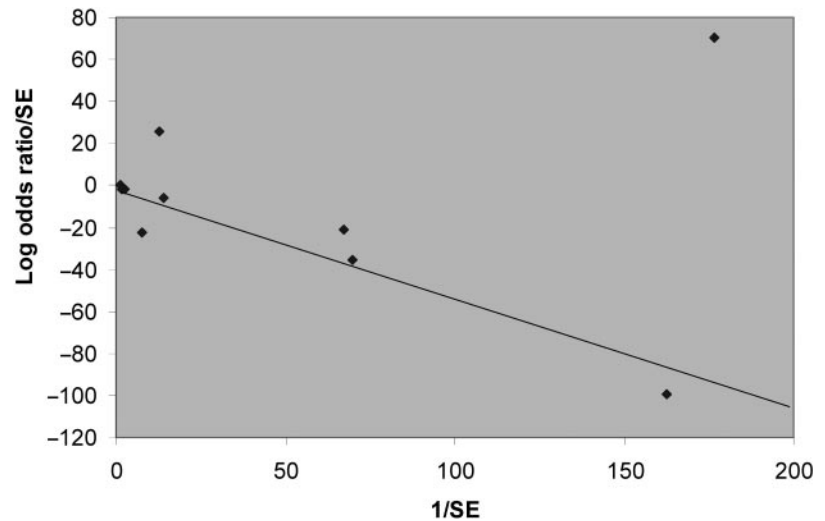


Fig 2. Funnel plot of 8 studies identified for meta-analysis.

large clinical trial may be overestimated by this meta-analysis.

Disparate study design and lack of randomization and blinding are other potential sources of bias in the present study. Commentaries by Shulman and Newburger^{6,33} have noted the variability in outcomes and the limitations of the method used in most of the existing studies that examined the use of corticosteroids in the initial management of this disease. The present review, which includes the studies addressed by both Shulman and Newburger, also

found significant flaws in the study design of most of the studies included. Only 2 studies used a prospective, randomized, appropriately controlled design.^{27,30}

Finally, only 1 of the studies included in the present report used currently recommended dosages of IVIG³⁰; 2 studies used lower dosages of IVIG, and the remaining 5 used aspirin alone. Moreover, the dosage, duration, and form of corticosteroid therapy varied greatly among the studies included in the meta-analysis. As such, this analysis does not pro-

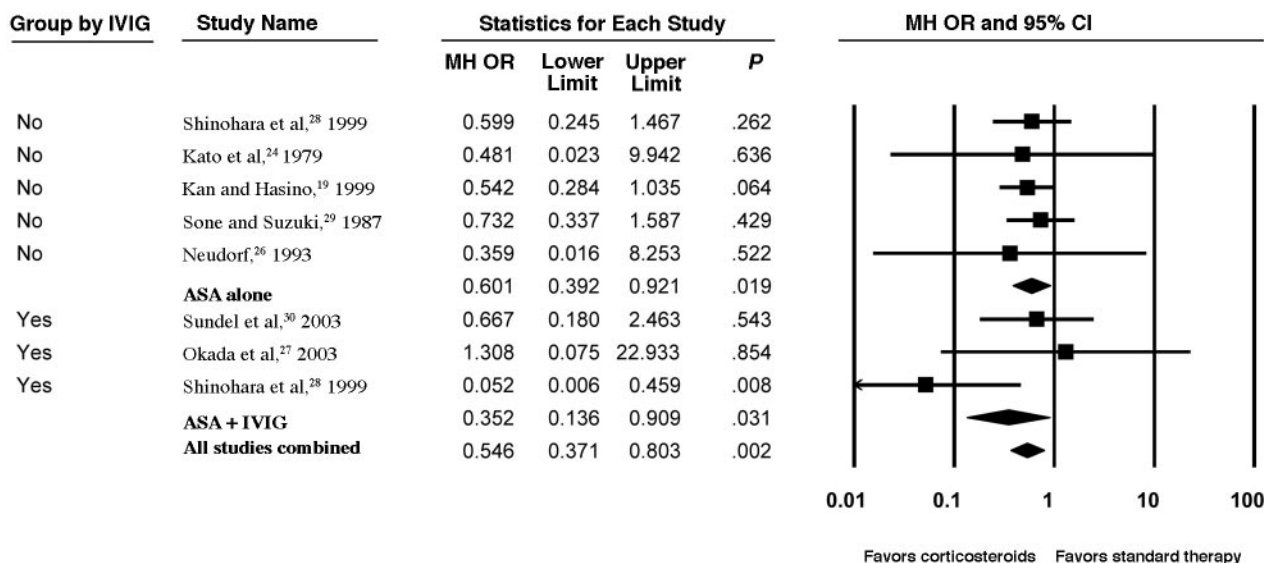


Fig 3. Overall meta-analysis ($n = 8$) and meta-analyses of aspirin (ASA; $n = 5$) and ASA combined with IVIG ($n = 3$) subgroups.

vide a basis for a specific drug form, dosage, or duration.

In summary, IVIG and aspirin remain the standard of therapy for the treatment of Kawasaki disease. The present study demonstrates that when combined with aspirin-containing regimens as initial therapy, corticosteroids significantly reduce the incidence of coronary artery aneurysms. An ongoing multicenter study should provide additional evidence to address the use of corticosteroids in combination with contemporary dosages of IVIG and aspirin as initial therapy for Kawasaki disease.³

ACKNOWLEDGMENTS

We thank Drs Satoru Eguchi and Alexander Davidson for translating several of the studies.

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AWASH IN INFORMATION, PATIENTS FACE A LONELY, UNCERTAIN ROAD

“A generation ago, patients argued for more information, more choice and more say about treatment. To a great extent, that is exactly what they have received: a superabundance of information, often several treatment options and the right to choose among them. As this new responsibility dawns on patients, some embrace it with a sense of pride and furious determination. But many find the job of being a modern patient, with its slog through medical uncertainty, to be lonely, frightening and overwhelming. . . . The job of being a modern patient includes not only decision making, of course, but, often, coordinating doctors, medical records and procedures, as well as negotiating with insurance companies, who are often the ultimate arbiters over which treatment options will be covered. . . . Increasingly, that soul-healing doctor-patient relationship has become harder to sustain. Whipsawed by insurance plans, patients frequently switch physicians. Pressed by diminishing reimbursements, those doctors are building ever larger, more unwieldy practices, with less time for each patient. The strain has left doctors themselves feeling exhausted, angry and heartbroken. . . . Until the late 1960’s, patients perceived doctors, then almost exclusively white men, as unassailable figures of authority. They knew best. But during the social and cultural upheaval that ushered in the women’s rights, civil rights and consumers’ rights movements, the paternalistic authority of the physician became deeply suspect.”

Hoffman J. *New York Times*. August 14, 2005

Submitted by Roger Soll, MD

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Pediatrics 2005;116:989-995

DOI: 10.1542/peds.2005-0504

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