Medical Prophylaxis and Treatment of Cystoid Macular Edema after Cataract Surgery

The Results of a Meta-analysis

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Objective: The study aimed to determine the effectiveness of prophylactic medical intervention in reducing the incidence of cystoid macular edema (CME) and the effectiveness of medical treatment for chronic CME after cataract surgery.

Design: The study design was a systematic review and meta-analysis of published reports of randomized clinical trials (RCTs).

Participants: Sixteen RCTs involving 2898 eyes examining the effectiveness of medical prophylaxis of CME and 4 RCTs involving 187 eyes testing the effectiveness of medical treatment of chronic CME were used in the study.

Interventions: Medical prophylaxis of treatment (cyclo-oxygenase inhibitors or corticosteroids) versus control (placebo or active treatment) was performed.

Main Outcome Measures: Incidence of angiographically diagnosed CME, incidence of clinically significant CME, and vision were measured.

Results: Thirty-six articles reported testing a prophylactic medical intervention for CME after cataract surgery. The incidence of CME varied extensively across studies and was related to the study design used. Summary odds ratios (OR) indicated that prophylactic intervention was effective in reducing the incidence of both angiographic CME (OR = 0.36; 95% confidence interval [CI] = 0.28–0.45) and clinically relevant CME (OR = 0.49; 95% CI = 0.33–0.73). There also was a statistically significant positive effect on improving vision (OR = 1.97; 95% CI = 1.14–3.41). A combination of the results of the four RCTs testing medical therapy for chronic CME indicated a treatment benefit in terms of improving final visual acuity by two or more Snellen lines (OR = 2.67; 95% CI = 1.35–5.30). Assessment of the quality of the 20 RCTs included in the meta-analyses indicated problems in the design, execution, and reporting of a number of trials.

Conclusion: A combination of the results from RCTs indicates that medical prophylaxis for aphakic and pseudophakic CME and medical treatment for chronic CME are beneficial. Because most of the RCTs performed to date have problems related to quality, a well-designed RCT is needed to confirm this result, using clinical CME and vision as outcomes. *Ophthalmology 1998;105:397–405*

Cystoid macular edema (CME) remains a troublesome problem after cataract surgery[1–4] and other types of ocular surgical procedures,[5–8] and its etiology is not clear. Available therapeutic interventions, both for prophylaxis and for treatment of CME, are based on theories regarding the pathogenesis of the condition. Studies testing the efficacy of these interventions generally have not been well designed or conducted, and results have been inconsistent.

The majority of studies have not been randomized, many have had inadequate control groups, and most have had too few patients to detect small to moderate, but clinically important, differences between the treatments tested. In addition, relevant outcomes such as visual acuity have been used in only a few studies, and the outcomes that have been used more often are controversial. For example, many studies have used "angiographically determined CME" as an outcome and not the more rigorous (but also less consistently defined) "clinically significant CME." Angiographically determined CME inevitably will overestimate the incidence of clinical CME and will include many patients who have normal vision and experi-

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ence spontaneous resolution.[9-11] Patients with clinically significant CME, conversely, are more likely to have persistent visual impairment. Studies measuring only angiographically determined CME, therefore, do not provide information leading to reliable estimates of the efficacy of prophylactic intervention. They also often fail to provide information on patients' functional status (e.g., visual acuity, contrast sensitivity, color vision).

Our objectives were to review systematically and combine the results of similar published randomized clinical trials (RCTs) of CME after cataract surgery to (1) determine whether prophylactic medical intervention is effective in reducing the occurrence of CME and consequently in preventing visual loss in aphakic and pseudophakic patients and to (2) determine whether medical therapy appears to be an effective treatment in patients with chronic CME.

Methods

Literature Search

A search of the National Library of Medicine MEDLARS database MEDLINE was conducted to identify RCTs on prophylaxis of CME. The Medical Subject Headings (MeSH) MACULAR EDEMA, CYSTOID, and CATARACT/complications as well as the textword "macular edema" were used as search terms. Reports published from 1966 through 1996 in English, French, and German were retrieved and examined.

To identify studies evaluating a treatment effect in patients with chronic aphakic and pseudophakic CME, we searched MEDLINE (1966–1996) for RCTs on medical treatment of aphakic and pseudophakic CME. A MEDLINE search was done using the MeSH MACULAR EDEMA, CYSTOID; CYCLOOXYGENASE INHIBITORS; KETOROLAC; FENOPROFEN; INDOMETHACIN; and STEROIDAL AGENTS. We inspected the bibliographies of the collected articles to identify additional pertinent reports. The results of the two searches were screened, abstracts were reviewed by one of the authors (LR) to select potentially relevant articles, and copies were obtained.

Eligibility Criteria and Definitions

For the purpose of evaluating the effectiveness of medical prophylaxis, articles were eligible for review if they included at least ten patients reporting the incidence of aphakic or pseudophakic CME after cataract extraction. We excluded reports evaluating patients with other types of macular edema (unless data were presented separately for the different types of edema). Articles reporting on CME after surgery other than cataract extraction (e.g., perforating keratoplasty, yttrium–aluminum–garnet [YAG] capsulotomy, retinal surgery) also were excluded. For the purpose of assessing the effect of medical treatment, CME was defined as "chronic" if the report described it as lasting for at least 6 months. Only reports of RCTs were eligible for inclusion in our reviews.

A form was developed to document whether individual studies met eligibility criteria and to collect abstracted data regarding study design and methodologic quality,[12] the incidence of CME after cataract surgery, and final vision (available on request). Trials were deemed to be randomized if the text stated explicitly that the intervention was allocated randomly. All potentially relevant articles were reviewed and abstracted independently by two of the authors (LR, JC). The results of the review and abstraction were compared and disagreements resolved.

We defined clinical CME to include patients described in the reports as having clinical–ophthalmoscopic edema and those having angiographic edema classified as grade III according to the classification by Miyake et al.[13] Most articles did not present frequency distributions of final visual acuities. Rather, they tended to present simply the proportion of patients with a specified vision or better, or a specified number of lines improved. Thus, it was not possible to examine final vision as a continuous variable or use other categories of visual acuity or improvement or worsening. Final visual acuity was categorized as Snellen acuity 20/40 or better and worse than 20/40. In the meta-analysis of the effect of treatment on chronic CME, we defined vision to be "improved" if visual acuity increased by at least two Snellen lines. Although all studies used Snellen visual acuity, the methods of measuring vision no doubt varied across studies.

Estimation

Summary statistics relating to the incidence of angiographic and clinical CME were calculated using data from all eligible RCTs. Effects of the interventions are presented in terms of odds ratios (ORs). When the outcomes of interest are "negative" (e.g., clinical CME), a value less than 1.0 for the effect of an intervention would indicate that the odds of an adverse outcome are less in those given the test intervention than in those given the comparison intervention (e.g., placebo). Therefore, the test intervention is "protective." A value of more than 1.0 would indicate a "harmful" effect. Conversely, when the outcomes of interest are positive (e.g., in the case of vision, this would be an improvement in visual acuity or having "good" visual acuity), an OR of less than 1.0 indicates that the odds of vision improving are less in the treatment than the comparison group, and an OR greater than 1.0 indicates a beneficial effect. In either case, the 95% confidence intervals (CIs) for the ORs that do not include 1.0 correspond to ORs with an associated P value of less than 0.05, assuming a two-sided test of the null hypothesis that the OR equals 1.

Frequency analyses were performed using SAS (version 6.0 for personal computer, SAS Institute, Inc., Cary, NC). The Mantel–Haenszel–Peto method was used to obtain the summary OR, using specialized software by Joseph Lau, MD, Meta-Analyst, Version 0.998, New England Medical Center. When there were no CME events in either of the two study groups (e.g., incidence of CME was zero divided by number treated or studied for both treatment and control), 0.5 was added to the numerator and denominator of both study groups. This "correction" is adopted conventionally to obtain an estimate of the OR that otherwise would be unassessable. Results presented in Figures 1 and 2 are those with the 0.5 correction. For comparison with the results using the correction, we repeated the analyses, omitting those studies with zero events in both study groups. Heterogeneity among study ORs was tested with the chi-square statistic; in this case, a P value of 0.10 or less was considered to indicate heterogeneity.

Results

Efficacy of Prophylactic Medical Interventions for Surgically Induced Cystoid Macular Edema

Our literature search for reports of CME after cataract surgery identified 36 potentially relevant reports: 16 were RCTs, 13

Table 1. Weighted Average Incidence of Cystoid Macular Edema (CME) after Prophylaxis, by Study Design

Study Design	No. of Studies	Incidence of CME in Treated Group	Incidence of CME in Control	Rate Difference (%)
Studies assessing clinical CME				
Total studies	19	83/1708 (4.9%)	148/1465 (10.1%)	5.2
RCTs	12	52/1053 (5.0%)	61/748 (8.1%)	3.1
Non-RCT with control arm	7	30/655 (4.5%)	87/717 (12.1%)	7.6
Studies assessing angiographic CME				
Total studies	25	220/1977 (11.1%)	513/1606 (31.9%)	20.8
RCTs	15	137/1150 (11.9%)	215/842 (25.5%)	13.6
Non-RCTs with a control arm	10	83/827 (10.0%)	298/764 (39.0%)	29.0

RCTs = randomized clinical trials.

were nonrandomized controlled trials, and 7 were uncontrolled case series. Two of the 16 RCTs were identified from reference sections of published articles, and the other 14 were identified using electronic searching.

Data on the incidence of clinical CME (i.e., clinically diagnosed CME or grade III angiographic edemas) were available from 25 of 36 studies. The difference in incidence rates between the treatment and comparison groups varied by type of study design used: the nonrandomized studies tended to have a greater difference in incidence rates between groups than did the RCTs. A similar discrepancy in the rate difference was found between non-RCTs and RCTs for studies using angiographic CME as an outcome (Table 1). We decided on the basis of these findings to use only the results of RCTs to obtain a pooled estimate of treatment effect. Table 2 summarizes the main design and quality features for RCTs reporting on prophylactic treatment of CME. Almost all trials tested cyclo-oxygenase inhibitors (COIs) as the test prophylactic intervention. Nine of the 16 RCT reports did not state the method of randomization. Withdrawals appear to have been excluded from the analysis in 11 (69%) of 16 RCTs; overall, 29% of the randomized patients were lost to follow-up or were excluded.

In 15 of 16 RCTs evaluating a medical intervention for prophylaxis, the primary measure of outcome was the occurrence of angiographically diagnosed CME, defined as any amount of leakage in the macular region on the angiogram. The duration of follow-up was less than 3 months after surgery (i.e., less than 3 months after starting prophylactic intervention) in 9 of 15 of these trials, from 3 to 6 months in 5 trials, and 18 months in 1 trial. Statistical combination of the results from 15 RCTs measuring the effect of prophylactic intervention on angiographic CME showed a statistically significant positive effect, with a summary OR of 0.36 (95% CI = 0.28–0.45). The combined results from the 12 RCTs that presented data for prevention of clinical CME indicated that treatment is effective (summary OR = 0.49; 95% CI = 0.33–0.73) (Fig 1). Similar results were obtained, when the studies with zero events in both groups were omitted. Only 6 of 16 RCTs on prophylaxis presented data allowing the combination of results on visual acuity. The combined data show a statistically significant benefit of medical prophylaxis in terms of achieving a final visual acuity of 20/40 or better (summary OR = 1.97; 95% CI = 1.14–3.41) (Fig 2). When the study with no poor vision outcomes was omitted, similar results were obtained (summary OR = 1.97; 95% CI = 1.14–3.41). Results were in the same direction when the treatment effect was estimated in terms of a poor vision outcome: 4 (0.9%) of 439 patients receiving medical prophylaxis and 6 (1.8%) of 333 control subjects had a visual acuity of 20/200 or worse. Heterogeneity among studies was tested for all meta-analyses. In all cases, no statistically significant heterogeneity was found.

Efficacy of Medical Treatment for Chronic Cystoid Macular Edema

Twenty-four studies examining treatment of chronic CME and meeting our inclusion criteria were identified. The types of medical treatment included various COIs, steroidal agents (local and systemic), acetazolamide, cycloplegic agents, and hyperbaric oxygen. In the majority of studies (18 of 24), the treatment was tested without a concurrent comparison group.

Four of the six studies with a comparison group were RCTs and were included in our meta-analysis. All four were found using electronic searching. All four measured both visual acuity and improvement in fluorescein angiography as outcome variables. Table 3 lists some general features of the RCTs. The mean sample size of the trials was 47 (range, 14–120); none of the studies reported estimating the sample size before the study start. All four trials tested COIs versus placebo.

Figure 3 shows the combined results of the four trials. The summary OR using the Mantel–Haenszel–Peto method without a correction factor (OR = 2.67; 95% CI = 1.35–5.30) shows a positive effect favoring improved vision in patients receiving COIs. All four studies reported some patients excluded from the analysis, ranging from 13% to 27% of the total sample. Test results indicated no heterogeneity among study results.

Discussion

Several previous reviews have summarized the evidence from the published literature regarding medical interventions to prevent CME.[14–19] All agree that prophylactic medical intervention is effective in preventing angiographic edema but also that evidence is inconclusive regarding the efficacy of such interventions in preventing clinically diagnosed CME or loss of vision. The results from our quantitative synthesis indicate a benefit of prophylactic intervention for both angiographically diagnosed and clinically diagnosed CME. Moreover, medical prophylaxis appears to be protective against loss of vision in patients undergoing cataract surgery.

The incidence of CME varied considerably across studies that we examined. This observed variation may be explained by a number of factors, including different sur-

Table 2. Design and Quality Features of the Randomized Clinical Trials on Prophylactic* Treatment of Cystoid Macular Edema

	No.	(%)
Total RCTs	16	(100)
Design		
Patient inclusion criteria reported	16	(100)
Diagnostic criteria for CME		
Angiographic criteria only	4	(25.0)
Clinical/ophthalmoscopic criteria only	1	(6.2)
Angiographic and clinical criteria	11	(68.8)
Type of cataract extraction		
Intracapsular (ICCE)	9	(56.3)
Extracapsular (ECCE)	5	(31.3)
ICCE and ECCE	1	(6.2)
ECCE and phaco	1	(6.2)
IOL implantation		
Anterior chamber	3	(18.8)
Posterior chamber	5	(31.3)
Anterior and posterior chamber	1	(6.2)
No implantation	6	(37.5)
Not stated	1	(6.2)
Drugs for prophylaxis*		
Cyclo-oxygenase inhibitors		
Indomethacin	9	(56.3)
Suprofen	2	(12.5)
Ketorolac	1	(6.2)
Diclofenac	1	(6.2)
Piroxican	1	(6.2)
Hydroxyethyl-rutoside	1	(6.2)
Flurbiprofen	1	(6.2)
Corticosteroids	2	(12.5)
Type of comparison		
Placebo	15	(93.7)
Active treatment	1	(6.3)
Follow-up		
Mean duration of follow-up (mos)	4.6	(range 1–18)
>6 mos	3	(18.8)
Type of outcome assessed		
Incidence of CME	16	(100)
Visual acuity	12	(75)
Quality		
Sample size		
Total no. of eyes studied	2,898	
Mean	181	
Range	(20–695)	
A priori estimate of sample size		
Reported	0	—
Method of randomization		
Numbered vials	6	(37.5)
Table of random numbers	1	(6.2)
Not reported	9	(56.3)
Masking of patients and assessor		
Double masked	13	(81.3)
Not masked	2	(12.5)
No information	1	(6.2)
Handling of withdrawals		
Intention-to-treat analysis	0	—
Exclusion from analysis	11	(68.8)
No patients withdrawn	2	(12.5)
No information	3	(18.7)
Withdrawals		
≤10%	3	(18.7)
10–25%	4	(25)
>25%	6	(37.5)
Cannot tell	3	(18.7)
Median		30.5%
Range		0–41%

RCTs = randomized clinical trials; CME = cystoid macular edema; IOL = intraocular lens.

* All prophylactic schedules include the routine use of steroids, except for one RCT.[6]

Table 3. Design and Quality Characteristics of Randomized Clinical Trials Studying Efficacy of Medical Treatment for Chronic Cystoid Macular Edema

	No.	
Total RCTs	4	
Design		
Patient inclusion criteria		
Reported	4	
Definition of CME		
Reported	4	
Mean duration of CME at baseline		
>6 mos	3	
Not reported	1	
Treatment drugs		
Indomethacin	1	
Fenoprofen	1	
Ketorolac	2	
Type of comparison		
Placebo	4	
Duration of treatment (mos)		
1.5	1	
2	2	
3	1	
Mean duration of follow-up (mos)	3.5	
Type of outcome assessed		
Visual acuity	4	
Fluorescein angiography	4	
Quality		
Sample size		
Total no. of eyes studied	187	
Mean	47	
Range	(14–120)	
A priori estimate of sample size		
Reported	0	
Method of randomization		
Numbered vials	2	
Not reported	2	
Masking of patients and assessor		
Double-masked	4	
Handling of withdrawals		
No withdrawals	2	
Intention-to-treat analysis	0	
Exclusion from analysis	2	
Withdrawals		
Total	37	(20%)
Range	4–33	(13–27%)

RCTs = randomized clinical trials; CME = cystoid macular edema.

gical techniques and procedures used, rates of surgical complications, and methods used for diagnostic assessment. In addition, cataract surgery has changed significantly over the past 15 years. Outcomes and complication rates for intracapsular extraction are difficult to compare with modern extracapsular extraction and phacoemulsification.[20–22] Thus, variation among study results is no doubt influenced by variations in the procedure.[23]

Another possible source of the variation in incidence rates is bias. Nonrandomized trials had the highest incidence rates, and exaggerated treatment effects in nonrandomized studies usually are attributed to unintentional or intentional bias in reporting by the investigators; this interpretation also could be applied here. Although there were 36 published studies reported to have used medical prophylaxis for CME, fewer than half (44%) had used a proper design (e.g., RCT) to evaluate the effectiveness

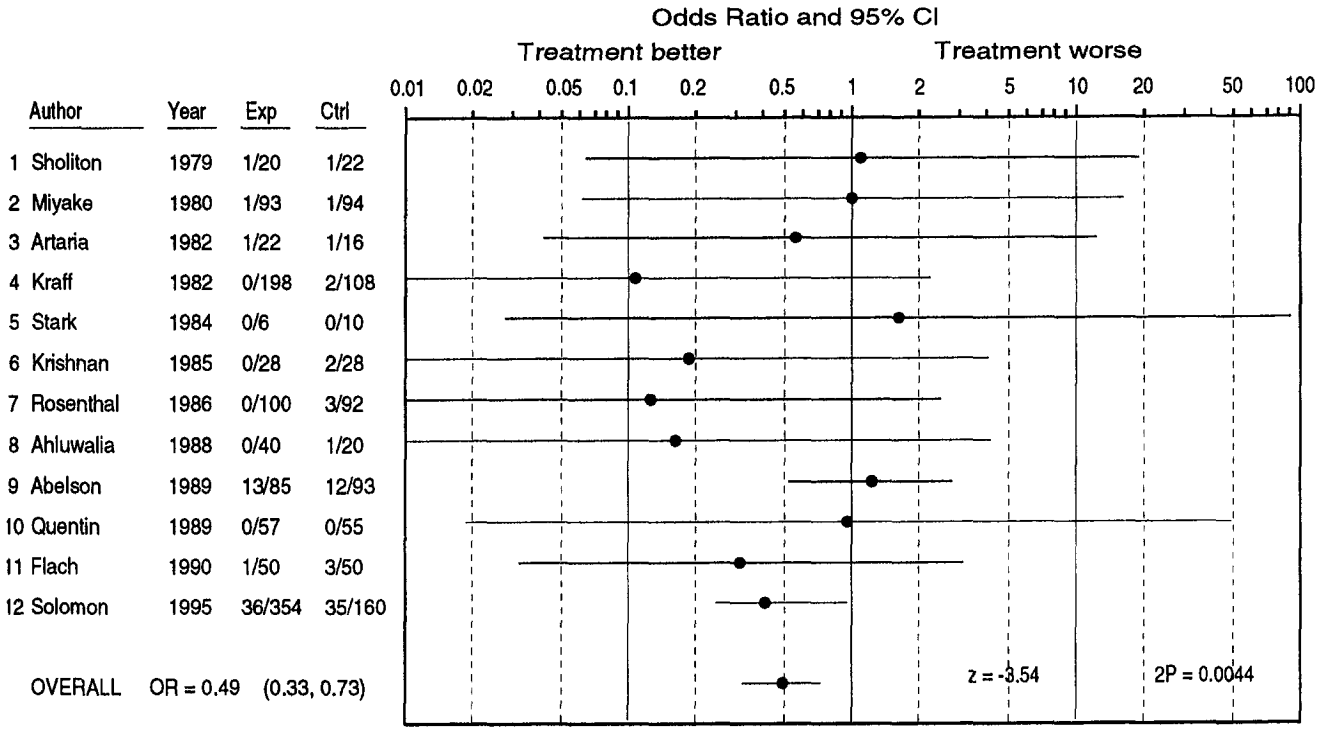

Figure 1. Individual and combined results from randomized clinical trials examining the association between prophylaxis and incidence of clinical cystoid macular edema. (Clinical cystoid macular edema includes the cases defined as "clinical–ophthalmoscopic edema" and all cases classified as grade III by Miyake classification (subjective symptoms, with a fluorescein retention of more than 2 mm in diameter on the angiogram, with definite changes in the macular area that may persist and lead to permanent disturbance.) Chi-square for hetereogeneity (11 degrees of freedom) = 15.94 (P = 0.15)

of the treatment tested. Despite considerable available literature urging the highest possible standards for design of studies assessing the effectiveness of treatment,[24] uncontrolled and nonrandomized clinical studies still are conducted often and their results published.

Even among the RCTs of medical prophylaxis for CME, there were important deficiencies related to study quality and opportunities for bias. Methods used to randomize, provide masked assessment of outcome, and handle withdrawals were our areas of major concern. The method of randomization was omitted from the Methods section in more than half (9/16) of the RCT reports in-

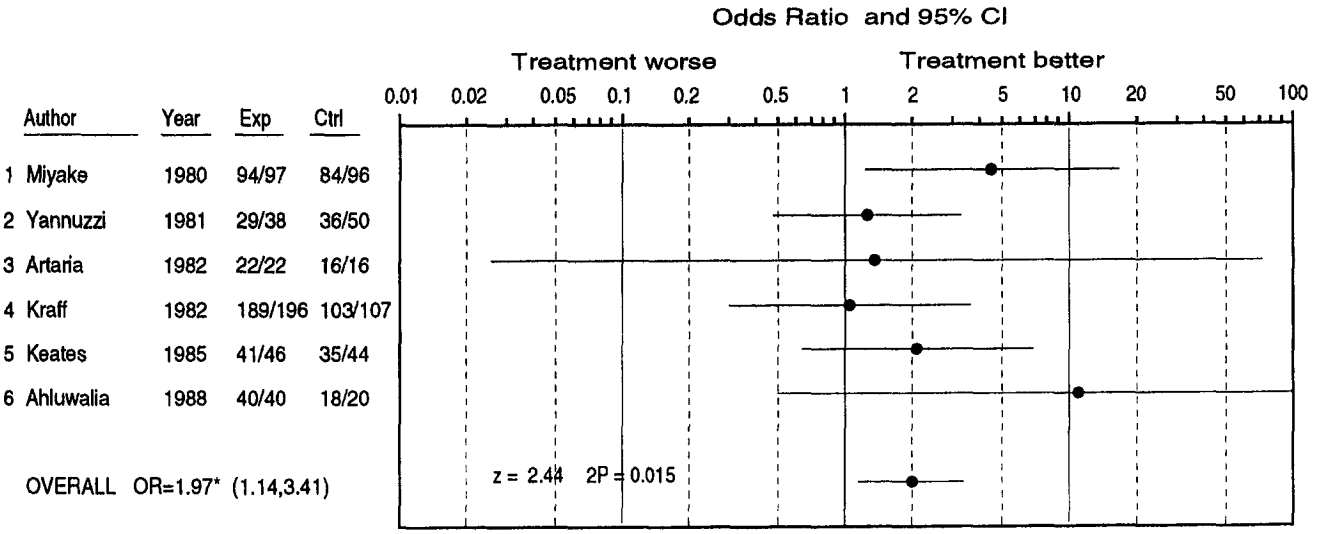

Figure 2. Individual and combined results from randomized clinical trials examining the association between prophylaxis and visual acuity of 20/40 or better. When a study with no outcomes of poor vision is removed from analysis, odds ratio = 1.83; 95% confidence interval = 1.01–3.29. Chi-square for hetereogeneity (5 degrees of freedom) = 8.52 (P = 0.145).

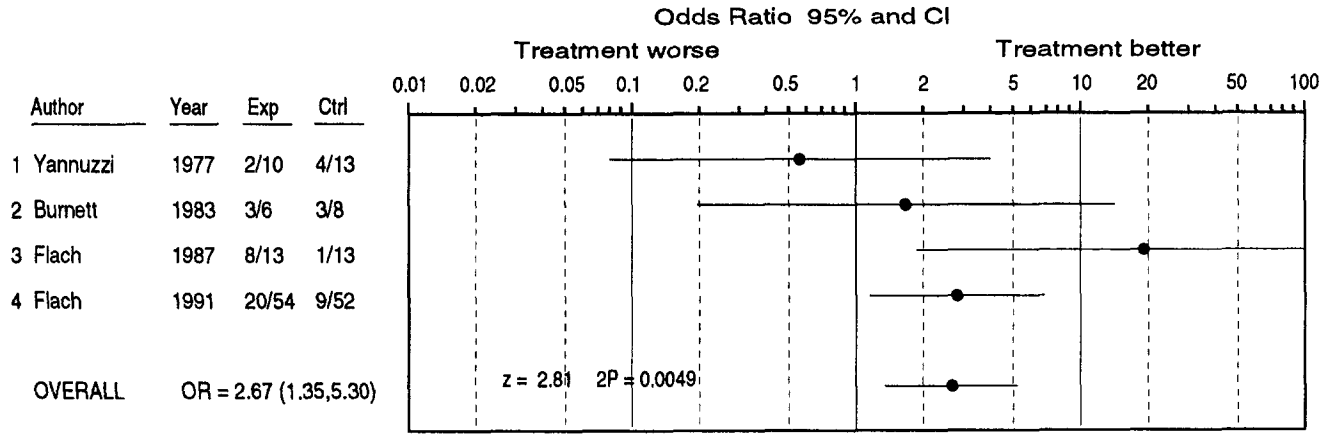

Figure 3. Individual and combined results from randomized clinical trials examining the association between treatment and improvement. Chi-square for hetereogeneity (3 degrees of freedom) = 3.58 (P = 0.25).

cluded, and 3 of 16 of the RCT reports described unmasked assessment of the outcome or did not report masking. A total of 715 (25%) of 2898 patients randomized were withdrawn and not included in the final analysis. Bias is introduced when the reason for "withdrawal" is related to the prognosis or outcome.

The outcome chosen for study in most of the RCTs covered by our meta-analysis, short-term angiographic changes, also is problematic. Most angiographically defined CME occurs in eyes with normal visual acuities, the condition often is self-limiting, and the angiographic leakage clears spontaneously with time. Recent studies have shown a significant decrease in contrast sensitivity in these patients however.[25,26] Visually threatening CME is much rarer.[9–11] We therefore consider our meta-analysis, which adopted angiographic CME as an outcome, to be limited in terms of providing information about the actual benefit of prophylactic treatment on CME. Almost all of the 15 angiographic RCTs individually showed a treatment effect of prophylaxis in reducing the incidence of angiographic changes within 6 months from cataract surgery; our meta-analysis of RCT results was necessary only to obtain a reliable estimate of the size of this effect. The summary OR indicates that treatment is protective against occurrence of CME. Long-term angiographic changes were reported in only one trial. In patients examined more than 6 months after surgery, there was a trend favoring treatment, but this was not statistically significant.[13]

Of the 12 RCTs that provided information on clinical CME as an outcome, only 1 showed a statistically significant effect of prophylaxis in reducing the incidence of CME. Combined data from the 12 RCTs indicated a statistically significant association between prophylactic intervention and reduced incidence of clinical CME (OR = 0.49; 95% CI = 0.33–0.73). This result is supported further by the combined results for visual outcome, which showed a statistically significant association between prophylaxis and measurement of "good" visual acuity. Thus, although the positive results for angiographic CME may not be reliable surrogates for a clinical effect, the treatment effects for the various outcomes are in concordance in terms of direction of the effect.

Almost all prophylactic RCTs tested COIs, and concurrent use of corticosteroids in the postoperative period was adopted in all but one trial.[27] Therefore, these studies actually report the efficacy of a combined corticosteroid and COI treatment. The possibility that there may be a synergistic effect[28,29] makes it difficult to draw strong conclusions about the efficacy of either of these drugs alone in preventing CME. The single trial that tested COI in the absence of concurrent corticosteroids showed a significant beneficial effect in preventing angiographic CME, as did the two studies in which topical corticosteroids alone were tested.[30,31]

The heterogeneity among some of the trials' findings calls into question whether the included studies can be safely summarized. From a statistical point of view, one approach is to test the heterogeneity among individual ORs. In all meta-analyses, heterogeneity was tested, and in no case was it found to be statistically significant. This implies that the combination of the studies' results is methodologically correct. This finding, however, should not prevent us from being cautious when interpreting the results of the meta-analysis.

Our pooled results indicate that treatment has a strongly positive effect on chronic CME. The four RCTs of chronic CME treatment used small sample sizes (total sample size < 100 in each group), probably explaining the broad range of individual estimates of treatment effect. This variability also might be because three different COIs were used and administered in different ways. Fenoprofen and ketorolac are water-soluble phenylalkanoic acids and were administered topically, whereas indomethacin is an indole derivative that is not soluble in water and was given by oral administration. When administered by topical application, the three drugs show comparable ocular penetration and a dose-dependent ability of inhibition of the blood–aqueous barrier breakdown.[32] It is well known that ocular penetration after systemic administration is much lower.[33] This could help to explain the ineffectiveness of indomethacin reported in the trial by Yan-

nuzzi et al.[34] It is worth mentioning the lack of RCTs testing the efficacy of corticosteroids in the treatment of chronic CME, despite their common use in the management of this condition. It is possible that additional trials on the topic have been conducted but that the results remain unpublished.[35] It also is possible that an important portion of the published literature was missed. This could be because the literature search was limited to English, French, and German trials and that search strategies used commonly do not generally provide comprehensive results.[36] If some relevant evidence was missed, this could have had a significant effect on a small meta-analysis such as ours.

In conclusion, meta-analysis of the results from the RCTs suggests that medical prophylaxis for aphakic and pseudophakic CME and medical treatment for chronic CME after cataract surgery is beneficial. However, the strength of our findings and the reliability of the estimate of the size of the effect are tempered by the need for additional data using clinical CME and vision as outcomes and the possibility that bias is present in the individual studies combined. A systematic review of this topic should be part of an ongoing system of reviews in ophthalmology that is kept up-to-date and can be used for setting treatment guidelines. Such a system has been proposed and is underway as part of the Cochrane collaboration.[37]

Appendix: Studies Included in Meta-analysis

Prophylactic Treatment for Cystoid Macular Edema

Randomized Clinical Trials

1. Sholiton DB, Reinhart WJ, Frank KE. Indomethacin as a means of preventing cystoid macular edema following intracapsular cataract extraction. Am Intraocul-Implant Soc J 1979;5:137–40.
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14. Quentin CD, Behrens–Baumann W, Gaus W. Prevention of cystoid macular edema with diclofenac eyedrops in intracapsular cataract extraction using the Choyce Mark IX anterior chamber lens. Fortschr Ophthalmol 1989;86:546–9.
15. Flach AJ, Stegman RC, Graham J, Kruger LP. Prophylaxis of aphakic cystoid macular edema without corticosteroids. A paired comparison, placebo-controlled, double masked study. Ophthalmology 1990;97:1253–8.
16. Solomon LD. Flurbiprofen—CME Study Group 1. Efficacy of topical flurbiprofen and indomethacin in preventing pseudophakic cystoid macular edema. J Cataract Refract Surg 1995;21:73–81.

Nonrandomized Clinical Trials

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