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A RANDOMIZED, CONTROLLED TRIAL OF CORTICOSTEROIDS IN THE TREATMENT OF ACUTE OPTIC NEURITIS

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Abstract *Background and Methods.* The use of corticosteroids to treat optic neuritis is controversial. At 15 clinical centers, we randomly assigned 457 patients with acute optic neuritis to receive oral prednisone (1 mg per kilogram of body weight per day) for 14 days; intravenous methylprednisolone (1 g per day) for 3 days, followed by oral prednisone (1 mg per kilogram per day) for 11 days; or oral placebo for 14 days. Visual function was assessed over a six-month follow-up period.

Results. Visual function recovered faster in the group receiving intravenous methylprednisolone than in the placebo group; this was particularly true for the reversal of visual-field defects (P = 0.0001). Although the differences between the groups decreased with time, at six months the group that received intravenous methylprednisolone still had slightly better visual fields (P = 0.054), contrast sensitivity (P = 0.026), and color vision (P = 0.033) but not better visual acuity (P = 0.66).

The outcome in the oral-prednisone group did not differ from that in the placebo group. In addition, the rate of new episodes of optic neuritis in either eye was higher in the group receiving oral prednisone, but not the group receiving intravenous methylprednisolone, than in the placebo group (relative risk for oral prednisone vs. placebo, 1.79; 95 percent confidence interval, 1.08 to 2.95).

Conclusions. Intravenous methylprednisolone followed by oral prednisone speeds the recovery of visual loss due to optic neuritis and results in slightly better vision at six months. Oral prednisone alone, as prescribed in this study, is an ineffective treatment and increases the risk of new episodes of optic neuritis. (N Engl J Med 1992; 326:581-8.)

OPTIC NEURITIS is an acute demyelinating disease of the optic nerve. It may occur in a patient with confirmed multiple sclerosis or as an isolated neurologic finding, in which case it may represent a forme fruste of multiple sclerosis.[1] The typical clinical profile consists of sudden loss of vision, which can vary in severity from a slight deficit in the field of vision to complete loss of light perception, followed by spontaneous improvement over several months. Most patients have lasting symptoms of visual impairment, and even when visual acuity returns to normal, abnormalities are common in other aspects of visual function, such as the visual field, color vision, and contrast sensitivity.[2,3]

The efficacy of corticosteroids and corticotropin as treatments for optic neuritis has been debated since these drugs were introduced into clinical practice in the 1950s. Numerous anecdotal reports have suggested that they are effective, but randomized trials have not demonstrated a benefit. Three randomized trials of corticotropin[4-7] and one of retrobulbar triamcinolone[8] have been inconclusive primarily because of their small samples of patients. Neither oral nor intravenous corticosteroids have been evaluated in randomized trials. In the past decade, case reports have suggested that intravenous corticosteroids hasten recovery from optic neuritis.[9]

Despite the paucity of evidence about the efficacy of corticosteroids and their potential for causing adverse reactions, many ophthalmologists and neurologists prescribe them as treatment for optic neuritis. In 1986 a mail survey of ophthalmologists and neurologists in Michigan and Florida indicated that 65 percent of the ophthalmologists and 90 percent of the neurologists prescribed corticosteroids (almost always in oral form) for optic neuritis (unpublished data).

To evaluate corticosteroids as treatment for optic neuritis, we designed a multicenter, randomized clini-

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*The major participants in the Optic Neuritis Study Group are listed in the Appendix.

cal trial to answer the following questions: Does treatment with either oral prednisone or intravenous methylprednisolone improve visual outcome in acute optic neuritis? Does either treatment speed the recovery of vision? What are the complications of treatment in relation to its efficacy?

Methods

The design of the study (the Optic Neuritis Treatment Trial) has been described in part previously,[10] and details of the criteria for eligibility, treatment protocols, testing procedures, and quality-control measures are given in the trial manual.[11]

Patient Recruitment and Eligibility Criteria

Physicians in the vicinity of each clinical center were asked to refer patients to the study investigators. Patients were evaluated with ocular and neurologic examinations, visual-function testing, magnetic resonance imaging of the brain, antinuclear-antibody and fluorescent treponemal-antigen determinations, and chest radiography. To be eligible for the study a patient had to be between the ages of 18 and 46 years, have a history consistent with acute unilateral optic neuritis with visual symptoms lasting eight days or less, and have evidence of a relative afferent pupillary defect and a visual-field defect in the affected eye on examination. Patients were excluded if they had previously had optic neuritis in the same eye or had clinical evidence of a systemic disease, other than multiple sclerosis, that might cause optic neuritis. Eligible patients signed a form giving informed consent that had been approved by the investigational review board of each institution.

Treatment Assignment

A permuted-blocks design with a separate sequence for each clinical center was used to assign patients randomly in equal numbers to three treatment groups. The first group received intravenous methylprednisolone (Solu-Medrol, 250 mg every 6 hours for 3 days) followed by oral prednisone (Deltasone, 1 mg per kilogram of body weight per day [rounded to the nearest 10 mg] for 11 days) and is referred to as the intravenous-methylprednisolone group; the second group received oral prednisone (1 mg per kilogram per day for 14 days) and is referred to as the oral-prednisone group; the third group received oral placebo on the same schedule as the oral-prednisone group. Each treatment period was followed by a short period during which the oral dose was tapered, to 20 mg on day 15 and to 10 mg on days 16 and 18. Patients in the intravenous-methylprednisolone group were hospitalized for the three days of treatment. Oral treatment was given in a single morning dose. Patients in the oral-prednisone and placebo groups were blinded to their treatment assignment, whereas those in the intravenous-methylprednisolone group were not.

Compliance in taking oral medication was assessed by counting the number of pills remaining in each bottle when it was returned.

Determination of Outcome

Visual field and contrast sensitivity were the primary measures of outcome; visual acuity and color vision were secondary measures. Unlike visual acuity, which measures the eye's ability to resolve small targets (high spatial frequency), contrast sensitivity as tested in this study assesses the eye's ability to recognize large targets (peak spatial frequency).

Follow-up visits were scheduled on or about days 4, 15, and 30, weeks 7, 13, and 19, months 6 and 12, and then yearly. The data collected at the six-month visit were the major measurements of visual outcome. At each visit, we took an interval history, performed a refraction, and measured visual acuity (with a retroilluminated Snellen ETDRS letter chart), contrast sensitivity (with the Pelli–Robson chart), and visual field (with the Humphrey Field Analyzer). At the six-month visit and all subsequent visits, we also performed the Farnsworth–Munsell 100-hue color-vision test and a neurologic examination.

The personnel assessing visual function were always unaware of whether the patient was assigned to the placebo or prednisone group, and as often as possible they were unaware of whether the patient was receiving methylprednisolone.

Adverse Effects and Intercurrent Events

At each visit the patients were weighed, and on days 4 and 15 they were asked about potential side effects of their medication. A new attack of optic neuritis was diagnosed if a patient reported new visual loss in either eye that was documented on visual-function testing and verified by the study chairman's review of records. Treatment for new attacks was given at the physician's discretion. Multiple sclerosis was diagnosed on the basis of the clinical criteria of Poser et al.[12] for definite multiple sclerosis.

Statistical Analysis

The necessary sample size was projected to be 145 patients per group, on the basis of the following assumptions: the proportion of patients in the placebo group with abnormal contrast sensitivity at six months would be 75 percent, the expected reduction in this percentage by treatment would be 30 percent, the alpha error would be 0.02, and the power of the study would be 90 percent. The calculated sample size was increased by 20 percent to allow for withdrawal and noncompliance.

In all analyses, each steroid group was compared with the placebo group. All reported P values are two-tailed. Because of differences between the groups in the degree of visual loss at base line (a strong predictor of visual outcome), all comparisons of visual func-

Table 1. Randomization, Compliance with Medication, and Follow-up of the Treatment Groups.

	All Groups	Placebo	Intravenous Methylprednisolone	Oral Prednisone
		no. of patients		
Randomization	457	150	151	156
Patients ineligible but randomized*	9	5	1	3
Compliance with medication				
Study medication withdrawn because of toxicity or medical contraindication	3	0	3†	0
Patient discontinued medication before end of course, without medical justification	5	1	3‡	1
Treatment completed but >5 pills not taken§	11	4	3	4
Treatment assignment unmasked	3	2	—	1
Follow-up				
Patient dropped out				
Before end of treatment	6	1	2	3
Between end of treatment and 6 mo	2	2	0	0
After 6 mo	26¶	9	9	8
		percent		
Missed-visit rate‖	3.4	3.9	3.3	3.0
		no. of patients		
Patients completing 6-mo visit	438	143	144	151
Patients completing 1-yr visit	354	112	121	121
Patients completing 2-yr visit	205	65	66	74

*All patients continued to be followed, except two patients withdrawn because of misdiagnosis.

†Prednisone was discontinued during the oral phase in two of the three patients.

‡Prednisone was discontinued during the oral phase in one of the three patients.

§According to counts of returned pills.

¶Includes eight patients in whom follow-up was discontinued when the San Diego clinic was moved to San Francisco.

‖For the seven visits in the first six months.

tion were stratified according to base-line visual acuity. All results reported here are adjusted values; the results shown in the tables and figures are both adjusted and unadjusted values. The distributions of the data on visual function in each group at six months were compared by a univariate Wilcoxon rank-sum test,[13] and all four measures were combined for the Wei–Lachin test of stochastic ordering.[14] The relative risk that each measure would demonstrate recovery of function to normal was calculated from the cumulative incidence of return to normal within the six-month follow-up period with the Mantel–Haenszel method.[15] The rate of recovery was analyzed for the entire six months by life-table analysis with the Kruskal–Wallis test for censored data.[16]

The treatment groups were compared in terms of the side effects of medication by the chi-square test of association in contingency tables, and in terms of weight gain by analysis of variance with two contrasts (each steroid group vs. the placebo group).

Using all our follow-up data (follow-up, 6 to 24 months for each patient), we assessed the differences between the groups in the rate of new episodes of optic neuritis and the rate of development of multiple sclerosis by the Kaplan–Meier product-limit method[17] with a Mantel log-rank test,[18] and we calculated relative risks by proportional-hazards analysis.

Results

Four hundred fifty-seven patients were enrolled between July 1, 1988, and June 30, 1991. The number enrolled at individual clinical centers ranged from 15 to 46. The status of all patients and their base-line characteristics are summarized in Table 1 and Table 2, respectively. After randomization, two patients were found to have a compressive optic neuropathy rather than optic neuritis; two other patients who did have optic neuritis were found to have connective-tissue diseases. During the 6 to 24 months of follow-up, no other patients had signs of a systemic disease, other than multiple sclerosis, that could be considered a cause of the optic neuritis (e.g., sarcoidosis, systemic lupus erythematosus, or syphilis).

Compliance with Medication and Side Effects

The full course of treatment was completed by all but 3 percent of the patients. An additional 2.4 percent of the patients took at least five pills fewer than prescribed during the entire treatment period (Table 1).

In general, the side effects of the treatments were mild. Two patients in the intravenous-methylprednisolone group had serious adverse side effects: one patient had an acute transient depression that required psychotropic drugs, and the other had acute pancreatitis. In both patients the adverse effect resolved without sequelae. Minor side effects were more common in both steroid groups than in the placebo group. The patients in the steroid groups more often reported sleep disturbance, mild mood change, stomach upset, and facial flushing and had a greater mean percentage of weight gain than did the patients in the placebo group ($P<0.001$ for each comparison).

Follow-up Visits and Masking

The overall rate of visits missed among the seven scheduled follow-up visits in the first six months was 3.4 percent. When examining visual function in the patients in the intravenous-methylprednisolone group, technicians were unaware of the patients' treatment assignment during 86 percent of all follow-up visits overall and 94 percent of the six-month visits. When examining the oral-prednisone and placebo groups, the technicians were unaware of whether the patients were in the intravenous-methylprednisolone group or one of the other two groups during 85 percent of all visits and 86 percent of the six-month visits.

Visual Outcome

Intravenous Methylprednisolone versus Placebo

Analysis of life-table curves indicated that the rate of return of vision to normal was higher in the intravenous-methylprednisolone group than in the placebo group ($P = 0.0001$ for visual field, $P = 0.02$ for contrast sensitivity, and $P = 0.09$ for visual acuity) (Fig. 1 and Table 3). The differences between these two groups in the distributions of measures of visual function were greatest on day 4 and day 15 (data not

Table 2. Demographic and Clinical Characteristics of the Patients at Study Entry.*

Characteristic	All Patients (N = 457)	Placebo (N = 150)	Intravenous Methylprednisolone (N = 151)	Oral Prednisone (N = 156)
Sex — % female	77	75	77	79
Race — % white	85	84	81	90
Age —yr	32.0±6.7	31.3±6.4	32.4±7.1	32.2±6.6
Median weight — kg (range)	70 (42–182)	70 (44–151)	68 (42–148)	72 (44–182)
Duration of visual symptoms before entry — days	5.0±1.6	5.0±1.7	5.0±1.6	5.0±1.6
Ocular pain present — %	92	89	95	92
Optic disk swollen — %	35	34	35	37
Multiple sclerosis diagnosed — (%)	6	7	3	7
Visual acuity — no. of patients				
20/40 or better	162	59	50	53
20/50 to 20/190	129	40	43	46
20/200 or worse	166	51	58	57
Visual function — median (quartiles)				
Contrast sensitivity — line number	9 (3.5, 12)	10 (4, 12)	9 (3, 12)	9 (3, 12)
Mean visual-field deviation — dB	−23.02 (−31.90, −12.25)	−20.68 (−31.01, −10.79)	−24.73 (−31.89, −12.90)	−25.67 (−32.28, −13.15)
Visual acuity — Snellen equivalents	20/80 (20/640, 20/25)	20/63 (20/640, 20/25)	20/80 (20/800, 20/32)	20/80 (20/640, 20/32)
Color vision — error score	667 (1338, 266)	538 (1338, 244)	757 (1338, 302)	648 (1338, 266)

*Plus–minus values are means ±SD. There were no significant differences ($P<0.01$) between either steroid group and the placebo group in any characteristic, according to chi-square tests, t-tests, and Wilcoxon rank-sum tests, as appropriate.

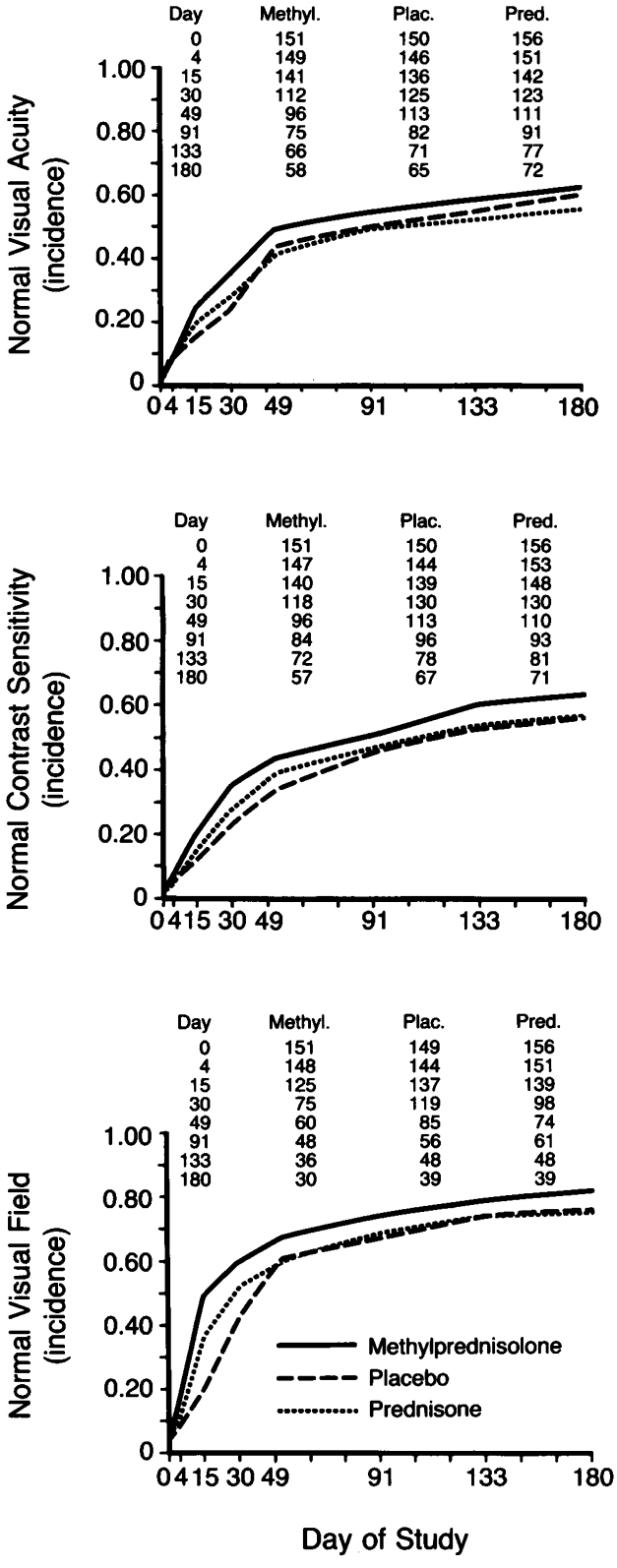


Figure 1. Life-Table Analysis Showing Cumulative Rates of Recovery of Normal Visual Function over the Six-Month Follow-up Period, According to Treatment Group.

The number of patients in each treatment group without recovery to normal before each visit is shown in each panel; Methyl. denotes methylprednisolone, Plac. placebo, and Pred. prednisone. The curve for each steroid group was compared with that for the placebo group by the Kruskal–Wallis test for censored data; the results are shown in Table 3.

shown). Although thereafter the differences between the groups decreased, as Table 4 demonstrates, at six months the distributions for contrast sensitivity (P = 0.026), visual field (P = 0.054), and color vision (P = 0.033) were still significantly different, although those for visual acuity were not (P = 0.66). The P value for the stochastic-ordering summary statistic for all four measures was 0.029.

Although the 95 percent confidence intervals for the relative risk of recovery of normal function included 1.0 for three of the four measures, the cumulative incidence of recovery was greater in the intravenous-methylprednisolone group than in the placebo group for all four measures (the relative risk was 1.17 for contrast sensitivity, 1.09 for visual field, 1.07 for visual acuity, and 1.21 for color vision). For each of the four measures, the relative risk of recovery was lowest among patients whose vision was 20/40 or better at base line, higher among those whose vision ranged from 20/50 to 20/190, and highest among those whose vision was 20/200 or worse (Table 5).

Oral Prednisone versus Placebo

When the oral-prednisone group was compared with the placebo group, there were no significant differences in the rate of recovery (P>0.05 for each measure) or the distribution of any of the outcome measures at six months (P = 0.54 for contrast sensitivity, P = 0.83 for visual field, P = 0.35 for visual acuity, and P = 0.58 for color vision; P = 0.87 for the stochastic-ordering statistic) (Table 4). The relative risk of recovery (oral prednisone vs. placebo) was slightly above or below 1.0 for each of the four measures (Table 5).

Poor Visual Acuity at Six Months

The number of patients in each group who had a poor visual outcome was similar. At six months only 9 patients (6.0 percent) in the intravenous-methylprednisolone group, 11 (7.1 percent) in the oral-prednisone group, and 8 (5.3 percent) in the placebo group had visual acuity of 20/50 or worse.

New Attacks of Optic Neuritis

Twenty patients (13 percent) in the intravenous-methylprednisolone group, 42 (27 percent) in the oral-prednisone group, and 24 (15 percent) in the placebo group had at least one new episode of optic neuritis in either eye during the 6 to 24 months of follow-up. At least one new episode occurred in affected eyes (i.e., those affected at entry) in 14 patients (9 percent) in the intravenous-methylprednisolone group, 23 (15 percent) in the oral-prednisone group, and 16 (10 percent) in the placebo group, and at least one occurred in contralateral eyes in 8 (5 percent), 25 (16 percent),

Table 3. Results of Kruskal–Wallis Test Comparing Recovery Rates in the Steroid Groups with Rates in the Placebo Group.

Treatment Group	Visual Acuity	Contrast Sensitivity	Visual Field
		chi-square	
Methylprednisolone			
Unadjusted	1.45 (P = 0.23)	3.27 (P = 0.07)	12.68 (P = 0.0004)
Adjusted	2.93 (P = 0.09)	5.91 (P = 0.02)	16.27 (P = 0.0001)
Prednisone			
Unadjusted	0.03 (P = 0.61)	0.27 (P = 0.61)	2.34 (P = 0.13)
Adjusted	0.06 (P = 0.39)	0.75 (P = 0.39)	3.16 (P = 0.08)

and 11 (7 percent) patients, respectively. Analysis of the length of time to the first new episode of optic neuritis in either eye demonstrated that the rate of new episodes was significantly higher in the oral-prednisone group (P = 0.02), but not the intravenous-methylprednisolone group, than in the placebo group (Fig. 2). When compared with the placebo group, the oral prednisone group had a relative risk of a new episode that was 1.79 (95 percent confidence interval, 1.08 to 2.95) for either eye, 1.40 (95 percent confidence interval, 0.74 to 2.65) for the affected eye, and 2.50 (95 percent confidence interval, 1.15 to 5.46) for the contralateral eye. In the intravenous-methylprednisolone group, the relative risk of a new episode was 0.81 (95 percent confidence interval, 0.45 to 1.47) for either eye, 0.86 (95 percent confidence interval, 0.42 to 1.76) for the affected eye, and 0.65 (95 percent confidence interval, 0.23 to 1.81) for the contralateral eye.

Development of Multiple Sclerosis

Multiple sclerosis was newly diagnosed during follow-up (6 to 24 months) in 20 patients (14 percent) in the intravenous-methylprednisolone group, 35 (24 percent) in the oral-prednisone group, and 28 (20 percent) in the placebo group. The relative risk of multiple sclerosis was 0.65 (95 percent confidence interval, 0.37 to 1.16) in the intravenous-methylprednisolone group and 1.17 (95 percent confidence interval, 0.71 to 1.93) in the oral-prednisone group, when each group was compared with the placebo group.

Discussion

In our randomized, placebo-controlled trial, patients who received intravenous methylprednisolone followed by oral prednisone recovered vision faster than patients given placebo, but their visual outcome at the end of the six-month follow-up period was only slightly better than that in the placebo group. Oral prednisone alone provided no benefit in terms of either the rate of recovery or the outcome at six months. Unexpectedly, patients in the oral-prednisone group had a higher rate of new attacks of optic neuritis than did patients in the other two groups.

Table 4. Distributions of Measures of Visual Outcome at Six Months.*

Outcome Measure and Base-Line Visual Acuity	Placebo	Intravenous Methylprednisolone			Oral Prednisone		
	median (25th, 75th quartiles)	median (25th, 75th quartiles)	P value†		median (25th, 75th quartiles)	P value†	
			unadjusted	adjusted		unadjusted	adjusted
Contrast sensitivity — line number							
20/40 or better	14.5 (14, 15)	15 (14, 15)			15 (14, 15)		
20/50 to 20/190	14 (14, 15)	15 (14, 16)			15 (14, 16)		
20/200 or worse	14 (13, 14)	14 (12, 15)			14 (12, 14)		
Total	14 (14, 15)	15 (14, 15)	0.049	0.026	14 (13, 15)	0.620	0.538
Visual field mean deviation — dB							
20/40 or better	−1.50 (−2.48, −0.24)	−1.83 (−2.62, −0.30)			−1.72 (−3.56, −0.78)		
20/50 to 20/190	−2.20 (−4.75, −0.55)	−1.00 (−2.24, 0.16)			−1.15 (−2.22, −0.35)		
20/200 or worse	−3.03 (−5.64, −1.81)	−2.07 (−4.95, −1.01)			−3.50 (−11.03, −1.59)		
Total	−2.18 (−4.48, −0.62)	−1.81 (−2.91, −0.46)	0.071	0.054	−1.91 (−4.32, −0.81)	0.823	0.825
Visual acuity — Snellen equivalents							
20/40 or better	20/16 (20/16, 20/13)	20/16 (20/20, 20/13)			20/16 (20/16, 20/13)		
20/50 to 20/190	20/16 (20/20, 20/13)	20/16 (20/20, 20/13)			20/16 (20/20, 20/13)		
20/200 or worse	20/20 (20/20, 20/16)	20/16 (20/25, 20/16)			20/20 (20/32, 20/16)		
Total	20/16 (20/20, 20/13)	20/16 (20/20, 20/13)	0.764	0.664	20/16 (20/20, 20/13)	0.395	0.350
Color vision — error score							
20/40 or better	71 (144, 40)	72 (94, 37)			84 (164, 34)		
20/50 to 20/190	90 (158, 44)	69 (143, 36)			91 (141, 38)		
20/200 or worse	129 (373, 78)	89 (318, 52)			151 (532, 47)		
Total	94 (182, 50)	82 (119, 44)	0.055	0.033	100 (220, 37)	0.648	0.576

*The number of patients in each stratum is shown in Table 2.

†P values are for Wilcoxon rank-sum tests comparing each steroid group with the placebo group.

Table 5. Relative Risk of Recovery of Normal Visual Function within Six Months.*

Outcome Measure and Base-Line Visual Acuity	Placebo	Intravenous Methylprednisolone				Oral Prednisone			
	% Normal within 6 mo	% Normal within 6 mo	Relative Risk†			% Normal within 6 mo	Relative Risk†		
			unadjusted	adjusted	95% CI		unadjusted	adjusted	95% CI
Contrast sensitivity									
20/40 or better	69.5	78.0	1.12		0.89–1.41	75.5	1.09		0.86–1.37
20/50 to 20/190	60.0	69.8	1.16		0.85–1.60	63.0	1.05		0.75–1.47
20/200 or worse	33.3	43.1	1.29		0.80–2.10	31.6	0.95		0.55–1.64
Total	54.7	62.3	1.14	1.17	0.98–1.41	55.8	1.02	1.05	0.86–1.26
Visual field									
20/40 or better	88.1	88.0	1.00		0.87–1.15	83.0	0.94		0.81–1.10
20/50 to 20/190	75.0	83.7	1.11		0.90–1.39	87.0	1.16		0.94–1.42
20/200 or worse	58.8	70.7	1.20		0.91–1.59	56.1	0.95		0.69–1.32
Total	74.7	80.1	1.07	1.09	0.97–1.23	74.4	0.97	1.01	0.89–1.14
Visual acuity									
20/40 or better	81.4	72.0	0.89		0.72–1.09	73.6	0.90		0.74–1.11
20/50 to 20/190	57.5	62.8	1.09		0.77–1.55	63.0	1.10		0.78–1.55
20/200 or worse	33.3	50.0	1.50		0.95–2.36	29.8	0.90		0.51–1.56
Total	58.7	60.9	1.04	1.07	0.90–1.28	54.5	0.93	0.96	0.80–1.15
Color vision									
20/40 or better	72.9	82.0	1.13		0.92–1.38	66.0	0.91		0.71–1.16
20/50 to 20/190	52.5	62.8	1.20		0.82–1.74	63.0	1.20		0.82–1.74
20/200 or worse	41.2	56.9	1.38		0.94–2.04	42.1	1.02		0.65–1.60
Total	56.7	66.9	1.18	1.21	1.02–1.44	56.4	1.00	1.01	0.84–1.23

*The normal ranges for the measures of visual function were based on 95 percent confidence intervals, as follows: visual acuity, >20/20; contrast sensitivity, ≥line 15; visual-field mean deviation, ≥−3.00 dB; and color vision, ≤110 error score.

†The relative risk of recovery of normal function on the outcome measure at any visit within six months in each steroid group as compared with the placebo group. Totals have been adjusted for base-line visual acuity. A relative risk greater than 1.0 indicates that a higher percentage of patients in the steroid group recovered normal function than in the placebo group. A relative risk of less than 1.0 indicates that a lower percentage of patients in the steroid group recovered normal function than in the placebo group. CI denotes confidence interval.

The regimen of intravenous methylprednisolone was generally well tolerated; only two patients had serious side effects, both of which resolved without sequelae. As compared with placebo, methylprednisolone was most beneficial during the first 15 days of follow-up and less so subsequently, so that by the end of 7 weeks the differences between the two groups in visual function were small. At six months, when all improvement due to treatment should have been evident, the intravenous-methylprednisolone group was still slightly better, as compared with the placebo group, in contrast sensitivity, visual field, and color vision but not in visual acuity. This differential effect of treatment on the measures of visual outcome was not unexpected, since contrast sensitivity, visual field, and color vision are more sensitive indicators of optic-nerve function than is visual acuity.[2,3]

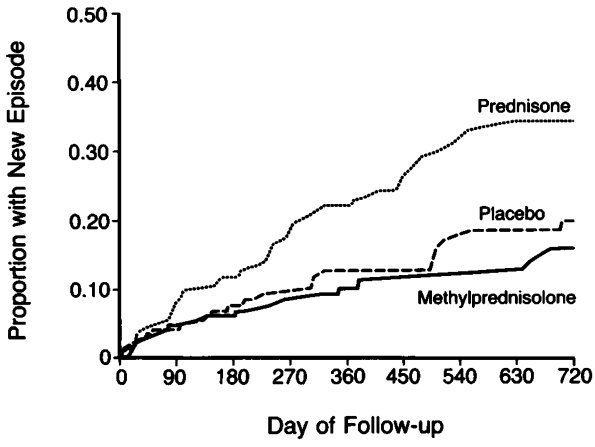
When the oral-prednisone group was compared with the placebo group, there were no differences in either the rate of recovery or the visual outcome at six months as assessed by any of the measures of visual function. In view of our sample size of 156 patients in the oral-prednisone group and 150 in the placebo group, frequent follow-up visits, and excellent rate of completion of blinded follow-up visits, we have a high degree of confidence that the use of oral prednisone alone as prescribed in this study has no benefit.

The patients in the oral-prednisone group faced a risk, not previously reported, that we consider serious. New attacks of optic neuritis occurred during the 6 to 24 months of follow-up in 42 patients (27 percent) in this group, as compared with 24 patients (15 percent) in the placebo group and 20 patients (13 percent) in the intravenous-methylprednisolone group. Although we do not have a biologic explanation for the higher rate of new episodes in the oral-prednisone group, the likelihood that this finding was a chance occurrence is small.

There were no significant differences between the placebo group and the steroid groups in the rate of development of definite multiple sclerosis. Our data provided no support for the contention of a previous study that multiple sclerosis may develop at an increased rate among patients with optic neuritis who receive intravenous methylprednisolone.[19]

For this study, we selected oral prednisone because it is widely prescribed for optic neuritis, and intravenous methylprednisolone because our clinical experience and that of others had suggested that it might be more effective than oral corticosteroids. The total dose of methylprednisolone in relation to body weight was several times greater than that of prednisone; we selected the dose of each to approximate the usual quantities prescribed in clinical practice.

The patients in the intravenous-methylprednisolone group were not masked as to their treatment assignment, because ethical and economic considerations prevented the inclusion in the trial of a treatment group that received intravenous placebo. We consider it unlikely that our finding of differences between the intravenous-methylprednisolone group and the placebo group resulted from the lack of masking of



Methylpred.	151	140	126	112	91	60	60	60	37
Prednisone	156	141	122	102	86	60	54	52	40
Placebo	150	140	120	105	86	62	58	57	44

Figure 2. Kaplan–Meier Curves Showing Cumulative Incidence of New Episodes of Optic Neuritis in Either Eye, According to Treatment Group.

The number of patients in each treatment group who were still at risk for a first new episode of optic neuritis in either eye at the beginning of each three-month period is shown at the bottom of the figure. The curves for the oral-prednisone and placebo groups differed significantly according to the Mantel log-rank test (chi-square = 5.20, P = 0.02), but the curves for the intravenous-methylprednisolone and placebo groups did not (chi-square = 0.44, P = 0.51).

the patients, since the personnel examining visual function were usually unaware of the patients' treatment assignments and the differences between groups were evident in several measures of outcome and over the range of follow-up visits.

Although a more rapid rate of recovery was detected in the intravenous-methylprednisolone group on day 4 — i.e., on completion of the course of methylprednisolone (and in most cases before the initiation of the course of prednisone), we cannot determine whether a group of patients who received methylprednisolone alone would have had the same visual outcome as our group that received both methylprednisolone and prednisone. We also cannot determine whether administering a higher dose of methylprednisolone, such as the dose of 30 mg per kilogram suggested for treatment of acute spinal-cord injuries,[20] or initiating treatment sooner after the onset of symptoms might have produced even greater benefit than we found with the dose used in this trial.

The results of our study may have a bearing on the treatment of multiple sclerosis with corticosteroids. There is ample evidence that optic neuritis is a manifestation of multiple sclerosis.[1] Measures of visual function, as assessed in this study, are more easily quantified than most other measures of neurologic function used in previous trials of treatment for multiple sclerosis. Previous studies of corticosteroid treatment for this disorder have been inconclusive.[21] The results of our study indicate the need for a placebo-controlled trial to assess the efficacy of such treatment.

The demographic characteristics of our cohort are similar to those of previously described groups of patients with optic neuritis[22,23]; most patients with a first episode of acute optic neuritis would meet the criteria for eligibility used in our trial. Therefore, we believe that our results are applicable to the care of most patients with a first episode of optic neuritis who are examined within eight days of the onset of visual symptoms.

Although our study was not designed to evaluate the effects of treatment in subgroups, we believe that treating optic neuritis does not benefit vision if visual acuity is 20/40 or better, assuming that visual-field loss is slight. If vision during the first eight days after the onset of visual symptoms is worse than 20/40, treatment with intravenous methylprednisolone followed by oral prednisone must receive consideration. In deciding whether to prescribe this treatment, physicians should weigh the potential for more rapid recovery of vision and slightly better visual outcome at six months against the small risk of serious adverse effects, as well as the inconvenience to the patient and the cost of treatment, particularly if hospitalization is necessary. Since adverse effects of treatment were uncommon, intravenous therapy on an outpatient basis may be feasible. Future studies should assess the efficacy of intravenous doses given once or twice daily, since such a schedule would enhance the feasibility of outpatient treatment.

Oral prednisone, as tested in this trial, not only is ineffective against optic neuritis but also increases the risk of new episodes. On the basis of our results, we believe that there is no role for oral prednisone alone in the treatment of patients with initial episodes of optic neuritis of presumed demyelinative origin.

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Appendix

A complete listing of the members of the Optic Neuritis Treatment Trial Study Group has been published previously.[10] The following are the major participants in the study group.

Central Units. Study Chairman's Office, University of South Florida, Tampa: R. Beck and B.J. Sellers; Data-Coordinating Center, George Washington University, Biostatistics Center, Rockville, Md.: P. Cleary, J.C. Backlund, D. Kenny, N. Loring, S. Campbell, P. Gilbert, W. Watson, and J. Zablotny; Visual-Field Reading Center, University of California, Davis: J. Keltner, C. Johnson, J. Spurr, and L. Shapiro; Magnetic Resonance Image Reading Center, University Diagnostic Institute, Tampa, Fla.: R. Murtagh and J. Arrington; National Eye Institute, Bethesda, Md.: C. Atwell.

Clinical Centers. University of Arkansas, Little Rock: M. Brodsky, B. Lyon, S. Nazarian, W. Jay, A. Luther, and R. Ford; Cullen Eye Institute, Baylor College of Medicine, Houston: J. McCrary, B. Slight, R. Gross, L. Rolak, and P. Frady; Pacific California Medical Center, Smith–Kettlewell Eye Research Institute, San Francisco: B. Katz, N. Hawker, O. Paul, M. Swenson, N. Loey, and N. Kelly; Duke University, Durham, N.C.: E. Buckley, M. Anderson, Jr., G. Valentine, S. Pollock, W. Massey, L. Duncan, K. Kossover, and L. Griffin; University of North Carolina, Chapel Hill:

B. Grimson, N. Tripoli, J. Messenheimer, and D. Fletcher; University of Florida, Gainesville: J. Guy, D. Shamis, S. Zam, L. Hamed, J. Malone, and M. Willingham; Center for Sight, Georgetown University, Washington, D.C.: G. Chrousos, S. Lauber, J. Kattah, and E. Coyle; University of Illinois, Chicago: J. Goodwin, E. Sullivan, C. Winterbotham, J. Nichols, L. Skorin, Jr., P. Bobak, and J. Putz; University of Iowa, Iowa City: J. Corbett, S. Thompson, C. Musser, R. Kardon, P. Johnston, G. Mitchell, J. Delsing, and C. Fountain; Wills Eye Hospital, Thomas Jefferson University, Philadelphia: P. Savino, M. Devlin, R. Sergott, T. Bosley, C. Cantor, K. Santa-Maria, and S. Ward; Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore: N. Miller, C. Krich Putzulo, M. Repka, D. Buchholz, S. Reich, and L. West; Kellogg Eye Center, University of Michigan, Ann Arbor: J. Trobe, C. Caudill, W. Cornblath, L. Kruscke, and B. Michael; Michigan State University, East Lansing: D. Kaufman, J. Froehlich, T. Moore, G. Ristow, B. Zendler, J. Kokinakis, E. Rosick, and M. Barris; New York University, New York: M. Kupersmith, A. Addessi, F. Warren, and S. Wahba; Devers Eye Institute, Good Samaritan Hospital, Portland, Ore.: W. Shults, L. Diehl, R. Dreyer, J. Zilis, R. Wilson, R. Herndon, D. Gibbs, H. Leonard, C. Beardsley, J. Arends, K. Steffen, B. Royce, and D. McKenna; University of Washington, Seattle: C. Smith, P. Ernst, J. Orcutt, R. Mills, W. Longstreth, S. Smith, B. Lawrence, D. Bjorn, and Y. Cady.

Data and Safety Monitoring Committee: M. Fisher (chair), P. Alguire, J. Carl, G. Rubin, J. Weinstein, V. Smith, and J. Dunbar-Jacob.

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