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Multicenter Clinical Trial for Evaluating Methylprednisolone Pulse Treatment of Idiopathic Optic Neuritis in Japan

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Background: A randomized, controlled clinical trial was conducted in 1991 to compare an intravenous megadose of methylprednisolone with a control drug (mecobalamin) for treating acute idiopathic optic neuritis.

Cases: Sixty-six cases from 22 clinical centers throughout Japan were examined to evaluate the treatment on visual function parameters, such as visual acuity, visual field, color vision, contrast sensitivity, and critical flicker frequency.

Observations: The methylprednisolone pulse treatment group showed faster recovery of visual function, particularly the visual acuity at 1 week ($P < .05$), Humphrey field analyzer mean deviation at 3 weeks ($P < .05$), and color vision at 1 week ($P < .05$). Recovery of contrast sensitivity at several different spatial frequencies was significant in the pulse treatment group at 1 ($P < .01$), 2 ($P < .05$), and 4 weeks ($P < .05$) after the start of treatment. Visual function test results at 12 weeks and 1 year were essentially the same in the two treatment groups. Side effects appeared more frequently in the pulse treatment group than in the control ($P < .05$).

Conclusions: Pulse treatment does not appear effective for idiopathic optic neuritis even though visual function in the pulse treatment group of this trial recovered more quickly during the initial phase compared to the controls. More effective and specific treatment should be established for optic neuritis. **Jpn J Ophthalmol 1999;43:133–138**

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Introduction

Idiopathic optic neuritis (optic neuritis) is characterized by an acute onset with a higher incidence in young people, and is a common optic nerve disease. Visual loss attending the disease is usually treated with systemic corticosteroids in Japan,[1,2] probably for the anti-inflammatory and immunosuppressive effects. Perkin and Rose[3] reported 87% of patients with optic neuritis recovered their vision to better than 0.5 after a minimum follow-up period of 6 months. Numerous other authors have indicated high values for recovery of visual acuity following resolution of optic neuritis. However, no prospective, controlled clinical study has been conducted to fully clarify the effects of corticosteroids in the treatment of optic neuritis. A study group in the USA has reported the results of a clinical trial using corticosteroids for optic neuritis.[4] Demographic differences in the occurrence and treatment of the disease in Japan and the US have been demonstrated.[5]

To evaluate the efficacy of a pulse treatment by corticosteroid for the disease, a multicenter cooperative research group with participants from 30 universities throughout Japan undertook a clinical treatment trial study on idiopathic optic neuritis in 1991.[6] The results of visual function tests subsequent to methylprednisolone pulse treatment are compared with those for the control treatment group.

Methods

The criteria for eligibility were the same as specified previously.[5] Participating patients provided signed informed consent and the treatment was randomly assigned by the envelope method. The two treatments used in this trial consisted of intravenous methylprednisolone (1 g/day) for 3 days, followed by oral corticosteroid for 7–10 days (pulse treatment group) or intravenous mecobalamin (500 μg/day) for 3 days, followed by oral mecobalamin for at least 7 days (control treatment group). Intravenous administration was carried out over 45–60 minutes once a day, usually in the morning.

In this study, it was the policy to inform neither the patient nor examiner which treatment was being used, although it was known by the attending physician.

Visual function tests were conducted to determine parameters such as visual acuity, visual field, color vision, contrast sensitivity, and central critical flicker fusion frequency (CFF) before and at 1, 3, 4, 12 weeks, and 1 year after the initiation of treatment. Testing procedures were the same as in the previous study.[5] Visual acuity was measured, subsequent to full refractive correction, using Landolt rings as the target at a viewing distance of 5 m and the results were expressed as decimal acuity.

For perimetry during the follow-up, program 30-2 with the Humphrey field analyzer (HFA) was used. For statistical analysis, mean deviation less than −3.00 dB was regarded as abnormal. The 38 Ishihara Pseudoisochromatic International Color Plates (Kanehara, Tokyo) were used for color vision assessment of the affected eyes. Scores (0–32)[5] were used to evaluate color vision and a correct score of 32 was considered normal. The Vision Contrast Test System (VCTS, Vistek Consultants, Dayton, OH, USA) was used to measure contrast sensitivity at a testing distance of 1 m.[7] Contrast sensitivity within the range stipulated by the VCTS recording chart at any of six frequencies was considered normal. The instrument developed at Osaka University[8] (CFF Test Apparatus II, Matsumoto Medical Instruments, Osaka) or that at Kitasato University[9] (Handy Flicker HF, Neitz Instruments, Tokyo) was used to measure CFF. Any value exceeding 35 Hz was considered as normal, based on the normal value stipulated by the authors.

The patients were always encouraged to report side effects. Blood tests to determine glucose, cholesterol, and triglyceride were conducted once a week throughout the course of treatment. During treatment, patients were questioned each day by an ophthalmologist about possible side effects specified on a checklist.

Optic neuritis was indicated when a patient reported new visual loss confirmable by visual acuity data and at least one other visual function test. Statistical analysis was made using chi-square or Student's *t*-test.

Results

Data for 70 patients were analyzed in the baseline study.[5] Four patients were subsequently eliminated just before the start of treatment ($n = 2$) or during treatment ($n = 2$), because they had decided not to give their consent. A final evaluation of the clinical data for the remaining 66 patients (14–58 years, male:female ratio, 1:2) was made during follow-up period; 33 patients were in the pulse treatment group and 33 were in the control treatment group. Before treatment, the visual function test results for the two groups were essentially the same.

Corrected visual acuity was measured for all 66 patients. Although a nonstatistical difference ($P = .08$) was noted at 1 week after the start of treatment, the average visual acuity for the two groups was basically the same throughout the follow-up. The ratio of visual acuity before and after treatment, however, showed that in the pulse treatment group, visual acuity was significantly high in the week 1 of treatment ($P = .03$). Visual acuity better than 1.0 was much more frequent at 1 week in the pulse treatment group, as compared with controls ($P = .04$), as shown in Figure 1. The incidence of poor visual acuity (<0.2) in the two groups was essentially the same throughout the follow-up period. Visual acuity better than 1.0 after 1 year was noted in 76% of the pulse treatment group and 70% of the controls. Eight patients (24%) in the pulse treatment group and 6 control patients (18%) showed poor visual acuity of 0.1 or less after 1 week of treatment ($P > .1$), while poor visual acuity was 2–6% after 4 weeks and 1 year in both groups.

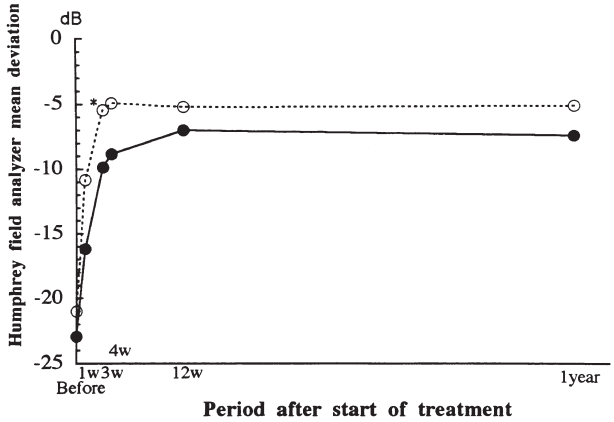

Figure 2. Average mean deviation of Humphrey field analyzer (program 30-2) in the two treatment groups at each examination. −○−: pulse ($n = 21$), −●−: mecobalamin ($n = 25$), $^*P < .05$.

HFA mean deviation could be determined for only 46 cases. The average mean deviation data are shown in Figure 2. This parameter for the pulse treatment group was not significantly higher than for the controls at 1 week ($P = .07$) and only marginally higher at 3 weeks of treatment ($P = 0.49$). The incidence of eyes with normal mean deviation in the pulse treatment group was significantly higher at 4 weeks than in the control group ($P = .01$), but at no other times.

Color vision could be examined in 52 eyes in the first 12 weeks of the study, and the average score in the pulse treatment groups was significantly higher than in controls at 1 week ($P = .01$), but at no other times, as evident in Figure 3. The incidence of eyes

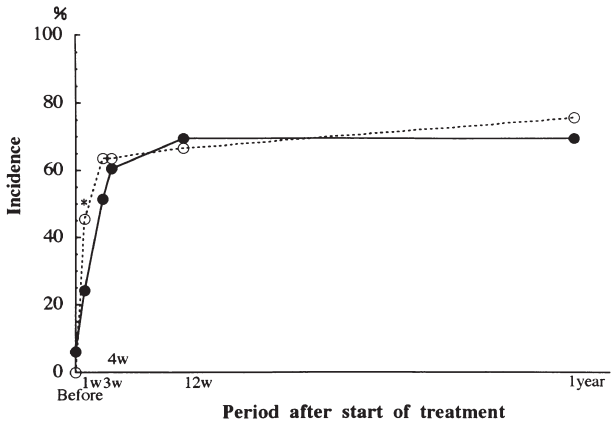

Figure 1. Incidence of affected eyes with normal visual acuity (>1.0) in the two treatment groups at each examination. −○−: pulse ($n = 33$), −●−: mecobalamin ($n = 33$), $^*P < .05$.

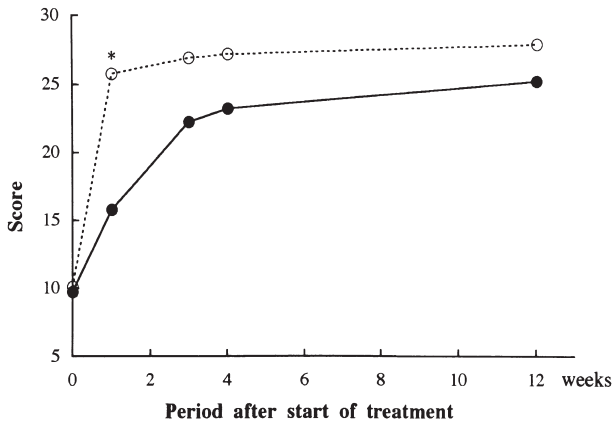

Figure 3. Average correct score obtained using Ishihara pseudisochromatic plates in the two treatment groups at each examination. −○−: pulse ($n = 25$), −●−: mecobalamin ($n = 27$), $^*P < .05$.

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with correct scores (n = 32) in the pulse treatment group was not significantly higher than in the controls at 1 week (P = .098).

Contrast sensitivity data were obtained for 37 eyes. The incidence of eyes with normal sensitivity at all spatial frequencies was essentially the same in the two groups throughout the follow-up (Figure 4). At 1 week, the incidence of eyes with normal contrast sensitivity in the two study groups differed significantly at 1.5, 3, and 12 cycles per degree (CPD); at 3 weeks, they differed at 3 and 12 CPD; and at 4 weeks, at only 1.5 CPD (Table 1).

CFF was measured for 51 eyes. Average CFF in the pulse treatment group was not significantly higher than in controls at any time during the follow-up. The incidence of eyes with normal CFF in the pulse treatment group was slightly high at 4 weeks (P = .073), but at no other times (Figure 5).

The incidence of eyes with normal visual function at 1 year was: 72.7% of all affected eyes in visual acuity (>1.0), 41.3% in HFA mean deviation (>−3.00 dB), 64.2% in correct score of color vision (n = 32), 83.8% in contrast sensitivity and 74.5% in CFF.

Side effects were detected in 9 patients (28.1%) in the pulse treatment group and 2 patients (6.0%) in the controls. This difference is statistically significant (P < .05). Hyperglycemia was seen in 4 pulse treatment patients; constipation, diarrhea, acneiform eruption, and hyperlipidemia in 2; and headache and increasing fever in 1. Two patients with hyperglycemia had to be referred to a specialist for treatment and management. Two control patients developed transient diarrhea. No patient was required to drop out of the study.

Four pulse treatment patients (6%) and 2 controls (3%) had at least one new episode of optic neuritis in either eye during the 12-month follow-up.

Table 1. Incidence of Eyes With Normal Contrast Sensitivity at Each Spatial Frequency (%).

Spatial Frequency (CPD)	Before	1 W	3 W	4 W	12 W	1 Y
1.5						
P	13.3	71.4**	85.7	92.9*	100	100
C	7.7	21.7	52.2	65.2	78.3	90.9
3						
P	6.7	85.7**	100*	100	100	100
C	7.7	34.8	69.6	78.3	87	100
6						
P	6.7	50	71.4	71.4	78.6	100
C	0	21.7	47.8	56.5	73.9	81.8
12						
P	13.3	85.7**	92.9*	100	100	100
C	11.5	39.1	65.2	78.3	82.6	100
18						
P	13.3	85.7	100	100	100	100
C	23.1	52.2	78.3	82.6	91.3	100

C: Control group, CPD: cycles per degree, P: pulse treatment group, W: week, Y: year.

Discussion

In the US optic neuritis treatment trial, the pulse treatment group had slightly better visual fields, contrast sensitivity, and color vision but not visual acuity at 6 months.[4] A German study to determine the effects of oral prednisolone indicated that the visual

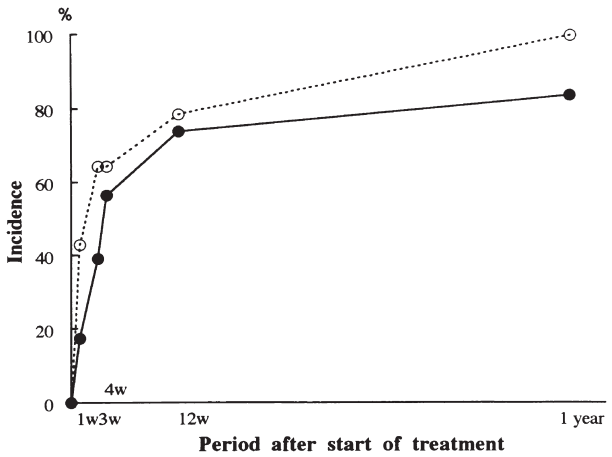

Figure 4. Incidence of affected eyes with normal contrast sensitivity at all five spatial frequencies in the two treatment groups at each examination. −○−: pulse (n = 14), −●−: mecobalamin (n = 23).

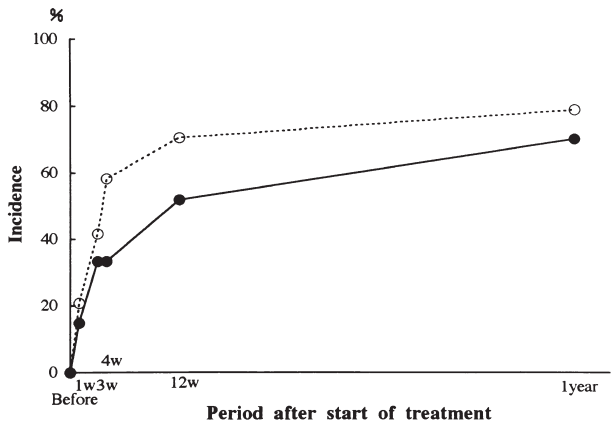

Figure 5. Incidence of affected eyes with normal CFF (>35 Hz) in the two treatment groups at each examination. −○−: pulse (n = 24), −●−: mecobalamin (n = 27).

function of patients with optic neuritis improved rapidly during the initial phase of treatment.[10] Oral prednisolone was found ineffective and, in fact, resulted in greater recurrent risk of optic neuritis in the US study.[4,11]

In Japan, pulse treatment with methylprednisolone for optic neuritis has become widespread and is the treatment of choice at 30% of medical institutions.[2] A retrospective pilot study using a small number of patients has failed to indicate any beneficial effects of pulse treatment.[1]

Methylprednisolone pulse treatment followed by a short oral tapering period was conducted in the present study and was found to render maximal corticosteroid effects in minimal side effects. Our study group considered it unethical in Japan to use a placebo for this disease, and mecobalamin was thus used as the control drug because it can be administered either orally or intravenously and promotes recovery of experimentally induced neuronal degeneration.[12,13]

Differences in visual function test results for the two treatment groups became evident as early as 1–4 weeks and then less apparent with time. Recovery of visual acuity, HFA mean deviation, correct scores on the Ishihara pseudochromatic plates, and contrast sensitivity all showed essentially the same rate of recovery with statistically significant differences at 1, 3, or 4 weeks. Visual acuity, central visual field, and color vision may possibly bear a close relationship to the parvocellular system,[14] and pulse treatment should thus contribute to recovery of this system in the initial phase of treatment. Significantly higher contrast sensitivity in the pulse treatment group was apparent at low spatial frequencies, such as 1.5 and 3 during 1–4 weeks. There also appeared to be a recovery of the low–spatial-frequency pathway, which is related to the magnocellular system,[14] in the pulse treatment group during the initial phase. Therefore, the initial effect of pulse treatment on retinal ganglion cells appears nonselective and diffuse.

The two treatment groups showed no differences in visual function at 12 weeks, while the pulse treatment group in the US had significantly better visual function, but not visual acuity, at 6 months as compared with the placebo group.[4] There is a difference in the time course of recovery but faster recovery of visual function by the pulse treatment group than by the controls was noted in the US study.[4]

CFF, as another visual function test, was conducted in the Japan study but not in the US study. CFF is used fairly often as a visual test in Japan, particularly for optic neuritis, owing to its high sensitivity for detecting visual dysfunction of the optic nerve. Recovery of CFF is generally delayed in patients with optic neuritis.[7] No significant differences could be found in the present CFF results throughout follow-up. A conspicuous, though not significant, difference was noted at 4 weeks ($P = .073$), suggesting slower CFF recovery in the controls as compared with the pulse treatment group. This is in contrast to the results of the other tests, thus showing that CFF possibly reflects a specific visual function of the optic nerve.

The results for the pulse treatment group at 12 weeks and 1 year of follow-up were basically the same as those for the controls. Pulse treatment for patients with optic neuritis is thus shown to expedite recovery of visual function, although not necessarily with better final outcome. As shown by the incidence of eyes with normal HFA mean deviation at 1 year (41.3%), HFA was the most sensitive of all five tests for assessing visual function; in the US study it had an even higher value of 55.9%.[15] Therefore, full recovery did not occur in more than half the Japanese optic neuritis patients by either mode of treatment even at 1 year after the start of treatment.

Trobe[16] stated that pulse treatment, which may not be helpful for vision, is advised when MRI scans show two or more 3-mm–diameter signal abnormalities. This is because the treatment was noted to retard the development of multiple sclerosis in the US study.[17] This was after 2 years of follow-up, but the 5-year cumulative probability of clinically definite multiple sclerosis did not differ by treatment group.[18] We cannot judge whether this guideline would also be acceptable for Japanese patients because they develop multiple sclerosis infrequently.

The incidence of side effects in pulse treatment was much higher than expected. Although side effects were neither fatal nor severe, the high incidence is noteworthy because in the present study only patients without risk of side effects were treated with corticosteroid and only for a short period.

Pulse treatment was not shown to be very effective for treating idiopathic optic neuritis. More effective treatment should be established. However, until such time, pulse treatment may be permitted only in cases where quick recovery is strongly desired by the patient.

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