Relative Efficacy of Intravenous Methylprednisolone and Oral Prednisolone in the Treatment of Acute Relapse in Multiple Sclerosis

MULTİPL SKLEROZDA AKUT ATAĞIN TEDAVİSİNDE İNTRAVENÖZ METİLPREDNİZOLON VE ORAL PREDNİZOLONUN ETKİNLİĞİ

Hatice TANKİŞİ*, Neşe ÖZTEKİN*, Bülent GÜVEN*,
Fevzi ÖZTEKİN*, Şenay ÖZBAKIR**, Hayat GÜVEN*

* Dept. of Neurology SSK Ankara Hospital,
** Dept. of Neurology Ankara Numune Hospital, Ankara, TURKEY

Summary

61 patients with multiple sclerosis in the acute phase enrolled this study. 31 of them were treated with Ig intravenous methylprednisolone (IVMP) daily for 5 days followed by prednisolone in gradually decreasing doses (MP+P Group); 18 of them were treated only with tapering doses of prednisolone (P Group) and 12 patients were treated with a Jive day course of IVMP without a subsequent course of prednisolone (MP Group). Clinical assessments were repealed at 1, 2, 4 and 8 weeks after starting treatment. In patients with relapse, there was a significant difference in the rate of recover)', but there was no difference in the final outcome between MP+P and P groups. In MP treated group the rate of recovery was same as MP+P group but the final outcome was significantly worse than the other two groups.

Key **Words:** Multiple sclerosis, Metyhlprednisolone, Prednisolone

T Klin J Med Res 1998, 16:54-57

Özet

Bu çalışmaya akut atakta 61 mıltipl sklerozla hasta alındı. Hastaların 31 'i 5 gün boyunca I gr günlük intravenöz metilprednizolonu (İVMP) takiben dereceli olarak azaltılan dozlarda prednizolon ile tedavi edildi (MP+P Grubu), hastaların 18'ine sadece azaltılan dozlarda prednizolon (P Grubu) ve 12'sine prednizolon verilmeksizin 5 günlük IVMP (MP Grubu) tedavisi verildi. Klinik değerlendirmeler tedaviye başlandıktan sonra I, 2, 4 ve 8'inci haftalarda tekrarlandı. Atağı olan hastalarda MP+P ve P grupları arasında iyileşme hızında anlamlı fark var, fakat sonuçta fark yoktu ve MP'la tedavi edilen grupta iyileşme hızı MP+P grubu ile aynı, fakat sonuç diğer iki gruptan anlamlı derecede daha kötü idi.

Anahtar Kelimeler: Mıltipl skleroz, Metilprednizolon, Prednizolon

T Klin Araştırma 1998, 16:54-57

Multiple sclerosis is a disease ot'multifactorial pathogenesis in which immunologic alterations are important, including abnormal CNS synthesis of IgG (1-3).Because of this observation, the design of new treatments for the disease has been focused on immunomodulatory agents such as IFN-P (4), high-dose immunoglobulins (5), Copolymer 1 (Copaxone) (6), linomide (7) and oral tolerization techniques (8). Although several new treatment regimens have

been developed, the importance of steroids could not be denied (9). There has been much speculations as. to how steroids exert their effect in acute relapse. Possible mechanisms include the resolution of edema, a direct neurophysiologic effect, or an immunologically mediated mechanism. It is likely that the main mechanism is the resolution of edema (1,10). Prednisolone has been extensively used to treat severe MS relapses and many reports have suggested that pulsed thcraphy with large doses of methylprednisolone may also be effective in relapsing multiple sclerosis (11-13,9,10). We have investigated whether combined treatment with IVMP followed by oral prednisolone in gradually decreasing doses was superior to oral prednisolone and MP alone.

Methods

Sixty-one patients with definite MS, according to the Poser criteria (14) were prospectively investigated in this study. 49 had relapsing-remitting disease, and in 12 patients the acute relapses were superimposed on a chronic progressive course. All patients were in an exacerbation for less than 8 weeks and more than 10 days without evidence of spontaneous improvement. Patients with any other neurologic disorder, pregnancy, immunosupressive theraphy, severe disability and any contraindication to steroid theraphy arc excluded. The disease course, sex, age at entry, disease duration and clinical rating according to Kurtzke's Expanded Disability Status Scale (EDSS) (15), arc summarized in Table 1. The patients were chosen randomly. In the 1st group, 31 patients were treated with mcthylprcdnisolone administered intravenously for 2 hours in a dose of lg daily for 5 consecutive days followed by oral prednisolone starting with 1 mg/kg daily, in gradually decreasing doses. In the 2nd group 18 patients were treated only with oral prednisolone in the same doses. In the 3rd group patients were treated with a 5 day course of 1 gr IVMP without a subsequent course of prednisolone. Routine laboratory tests were performed before the treatment, weekly for the first two weeks and then every month during treatment. Clinical assessment was repeated in 1st, 2nd, 4th and 8th weeks.

Results

61 patients entered this study. 31 of them received IVMP and prednisolone, 18 of them were treated with prednisolone and 12 of them with MP alone. There was no significant difference between the three groups in sex distrubition, age of onset and severity of disease, but the mean age and the duration of disease were different at each group (Tabic 1). Student's t test was used for comparing mean scores and mean change in scores for each functional system and for overall disability at each assessment for the three modes of treatment. Minor side effects were noted during parenteral MP administration such as slight weight gain and minimal edema in 10 and slight flushing in 5 patients. More important adverse effects were associated with chronic oral prednisolone, weight gain and edema

Table 1. Prctrcatment comparison of the study groups

	MP+P		MP
Male/Female	13/18	7/11 .	7/5
Age at entry*	3t.9±8.8	35.2±9.3	27.5±7.3
Age at First symptom[2]	25.2±6.6	26.9±9.4	23.3J 8.5 I
Duration of disease (years)*	7.l±7.4	9.5+±6.0	5.2+±7,l
Disability (Kurtzke)*	4.9±1.2	45=l=l.1	4.3Ü.4
Disease course	RR:25	RR: 16	RR:8
	RR+CP:6	RR+CP:2	RR+CP:4

Mean ± *staiulart deviation*
MP.Methylprednisolone P:Prednisolone
RR : relapsing-remitting
RR+CP:relapse superimposed on choronic progressive course

were reported in 12, mild hyperglycemia in 3 and hypertension in 2 patients.

In IVMP+oral prednisolone (MP+P) group, most of the patients reported subjective improvement 1 to 3 days after starting treatment and 20 of 31 patients improved significantly on the 1st week of the treatment (4.9±1.2 versus 4.1±1.0). This initial rapid response was followed by further clinical improvement. In prednisolone treated group, patients improved slower than the MP+P group over the 1st week and that this difference was maintained at week two (p<0.05). However, at 8 weeks there was no longer significant difference between the two groups (p>0.05). In the 3rd group most of the patients improved significantly in the 1st week (4.3+1.4 versus 3.7+1.2) like the patients in the MP+P group, but at 8 weeks the final outcome was significantly worse than the other two groups (p<0.05). None of the patients in the 1st and 2nd groups had any other bout during the 8 weeks period but two of the 12 patients in group 3 suffered from a second bout after the end of steroid treatment. The most significant improvement was seen in pyramidal and cerebellar functional systems on each group. The comparison of mean EDSS in patients on each group over the 8 week course of the study is shown in Figure 1.

Discussion

This study confirms previous reports that pulse therapy with high dose intravenous methylpred-
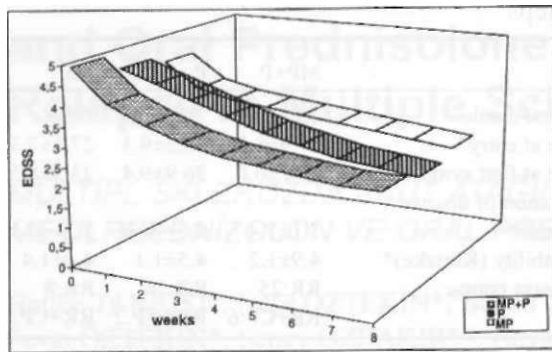
Figure 1. The comparison of mean Kurtzke disability status scales in patients on MP i-P, P and MP groups over the 8-wceks course of the study.

nisolone is an effective treatment for patients with multiple sclerosis in relapse (11,12,16,17). In this study clinical improvement was rapid in onset during relapse and the main decrease in disability scores occured within one week after starting IVMP treatment although most patients were aware of subjective improvement after the third dose. There was no significant difference in the final outcome between those on a 5-day course of high-dose IVMP followed by oral prednisolone in gradually decreasing doses and those on a 3-4 week course of tapering doses of prednisolone alone.

Prednisolone has been extensively used to treat severe MS relapses (exclusive of optic neuritis) although its efficacy has never been tested in a randomised, blinded, placebo-controlled clinical trial (9). And, recently some authors have been inclined to treat severe MS attacks (predominantly motor and cerebellar involvement) with a 3-to 5-day course of IVMP generally without a subsequent course of prednisolone and they have accepted this mode of treatment as safe and well tolerated but there is no data to support that this approach is superior to prednisolone or ACTH (9). We treated 12 patients with MP without a subsequent course of prednisolone and we observed that the final outcome was worse in this group than the other two groups. This might be because of our limited number of patients in group 3 and the two patients who suffered from a second bout. As there is some evidence that disease activity is continuous throughout the entire course of multiple sclerosis, even in re-

lapsing cases, it seems logical to suggest that combined treatment with IVMP followed by a long term maintenance therapy might be more effective than either agent alone (17). The rapid onset of recovery obtained with IVMP is particularly desirable for patients in acute relapse and achieves useful clinical improvement in the shortest possible time without the adverse effects encountered with prolonged administrations by other routes (11,12). In addition, this treatment shortens the duration of hospital admission for patients in relapse (12,16,18). Although the effect of MP is rapid in onset, it docs not prevent further relapse or progression of the disease (17-19). This study has confirmed the more rapid clinical response that occurs with methylprednisolone but fails to show any significant longer term benefit when compared to the conventional oral prednisolone regimen.

Methylprednisolone was easily administered, well tolerated and surprisingly free from serious adverse effects. Slight flushing, transient ankle swelling and a metallic taste in the mouth during infusion were the most frequently reported side effects but these were mild and never as severe as prolonged courses of oral corticosteroids (11,12, 17,19). In this study only minor side effects were noted during MP treatment and more serious side effects were associated with oral prednisolone regimen. But no patient dropped out of the study because of side effects.

This study presents the short term preliminary resuts; the results of the follow up period will be published at the end of the 2nd year.

In conclusion, our study shows that high dose MP seems to be safe, efficient, and acceptable mode of steroid administration and IVMP with a subsequent course of prednisolone might be more effective than either agent alone.

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