Arq Neuropsiquiatr 2008;66(2-B):350-353

BENEFIT WITH METHYLPREDNISOLONE IN CONTINUOUS PULSETHERAPY IN PROGRESSIVE PRIMARY FORM OF MULTIPLE SCLEROSIS

Study of 11 cases in 11 years

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Abstract – Primary progressive multiple sclerosis (PPMS) is defined clinically with a progressive course from onset. There is no approved treatment for the PPMS. Methylprednisolone IV (MP) hastens the recovery from MS relapses. We studied 11 patients that met the MacDonald's diagnostic criteria for PPMS. The dose of MP was 30 mg/kg in 250 mL of glucose solution in three consecutive days during the first week, two doses during the second and one dose in the third week. One weekly session for eight consecutive weeks was given. After, a once-a week/ eight-week interval was maintained. The medium EDSS before treatment was 6.2, and after 11.2 years of treatment, the EDSS was 4.9. Although we studied a small sample of PPMS we may conclude that therapy with IVMP prevents clinical worsening of MS in the majority of patients with improvement in EDSS scores.

KEY WORDS: progressive primary form, multiple sclerosis, methylprednisolone.

Benefício do uso de pulsoterapia contínua com metilprednisolona na forma primária progressiva da esclerose múltipla: estudo de 11 casos em 11 anos

Resumo – A forma progressiva da esclerose múltipla (FPEM) é definida como progressiva desde o início. Não há tratamento eficaz para esta forma. A metilprednisolona por via endovenosa (MPEV) é usada para os surtos de exacerbação da EM. Estudamos 11 pacientes que preenchiam os critérios de MacDonald para FPMS. A dose inicial de MPEV foi de 30 mg/kg em 250 mL de soro glicosado por três dias consecutivos na primeira semana, duas doses na segunda e uma dose na terceira semana. Seguiu-se uma sessão semanal por oito semanas. Após manteve-se uma dose semanal a cada oito semanas. A média do EDDS foi 9,6 antes e 4,9 após 11,2 anos de tratamento. Embora tenhamos estudado número reduzido de casos, podemos dizer que o uso de MPEV impede a progressão da FPEM na maioria dos pacientes estudados com melhora do EDDS.

PALAVRAS-CHAVE: forma primária progressiva, esclerose múltipla, metilprednisolona.

Multiple sclerosis (MS) might be considered a disease with different clinical phenotypes rather than an entity encompassing several distinct diseases[1] and the primary progressive multiple sclerosis (PPMS) is defined clinically with a progressive course from onset with no distinct relapses[2].

A study with 1844 patients with MS, 58% had relapsing-remitting (RRMS), 27% had secondary progressive (SPMS), 6% progressive relapsing (PRMS) and 9% PPMS forms. Median age at onset of progressive phase was similar in SPMS and in PPMS cases from onset[1,2]. In another study the mean age at onset was 40.1 years in the PPMS type and 29.2 years in the RRMS. The initial symptoms were motor in 57%, cerebellar or brainstem in 24%; sensory in 15%; and optic neuropathy in 5% of the PPMS form[3,4]. The disability was similar in PPMS, PRMS and SPMS cases and probably the mechanisms of demyelinating was common in all forms of MS[4]. There is a consensus that intravenous methylprednisolone (IVMP) hastens the recovery from MS relapses[1-3]. Nowadays it is considered the standard treatment for relapses of MS[1-3].

There is some suggestion that IVMP treatment may change the natural history of RRMS. The Optic Neuritis Treatment Trial (ONTT)[5,6] suggested that IVMP delays the

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Received 16 January 2008, received in final form 24 March 2008. Accepted 16 April 2008.

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Table 1. Identification, sex, years of beginning treatment, number and main syndromes and years before starting IVMP.

N	Sex	Y/beginning	Age	Syndromes	Main syndromes	Other syndromes	Years B IVMP
1	F	1975	32	4	SC,C	ON	17
2	F	1979	23	2	SC,C	ON	10
3	M	1979	25	4	SC,C	ON, IO	14
4	F	1979	25	3	SC,C	ON	13
5	F	1980	27	4	SC	IO	10
6	F	1982	31	4	SC,C	IO	12
7	M	1984	32	3	SC	SD, ON	17
8	M	1987	43	4	SC,C	COG	5
9	F	1991	51	3	SC	–	2
10	M	1993	36	3	SC,C	ON	3
11	F	1993	36	4	SC,C	SD, ON	3

F, female; M, male; Y, years; SC, spinal cord; C, cerebellar; ON, optic neuritis; IO, Internuclear oftalmoplegia; SD, sphincter disturbance; COG, cognitive; B, before; IVMP, intravenous methylprednisolone.

development of clinically definite MS following optic neuritis. There is some doubts if the ONTT results could be generalized to clinically isolated syndromes other than optic neuritis or to RRMS[5-7]. In patients with RRMS, treatment with pulses of IVMP prevents or delays disability progression and in the magnetic resonance image (MRI) make slowly the development of T1 black roles, prevents or delays whole-brain atrophy[8], and reduces the gadolinium enhancement in T1[9]. Sloka and Stefanelli[10] conclude that IVMP acts in different ways decreasing the inflammatory cycle: dampening the inflammatory cytokine cascade, inhibiting the activation of T cells, decreasing the extravasations of immune cells into the central nervous system, facilitating the apoptosis of activated immune cells, and indirectly decreasing the cytotoxic effects of nitric oxide and tumor necrosis factor alpha[10].

We usually use IVMP in isolated optic neuritis, cerebellitis and mielitis as in RRMS. As many patients referred improvement of chronic symptoms and signs, we decided to use IVMP in the PPMS form. In the present study we evaluate the use of IVMP in 11 patients with PPMS.

METHOD

We studied 11 patients with PPMS. All patients met the clinical and laboratorial adapted for MacDonald's diagnostic criteria for MS. All of them were submitted to MRI and analysis of CSF obtained by lumbar puncture. In all of them there was a raised IgG index. Other diagnoses were excluded: vitamin B_{12} deficiency, syphilis, schistosomiasis, HIV, HTLV 1,2, degenerative, hereditary disease, adrenomyeloleucodystrophies, CADASIL, dural arteriovenous malformation, cervical spondylosis, intrinsic or extrinsic tumors, neurosarcoidosis, paraneoplastic syndromes and granulomatous diseases, as well as vasculitides. For the case studies, we used the patient's medical register: name, sex, age of onset, year of onset, clinical syndromes, number of syndromes and topography. The comparison between pre-and-post-treatment EDSS scores was our reference points. Duration of illness between the beginning/start of treatment up until the latest follow-up consultation was also considered. The patients didn't use other immunosupressor or immunomodulating drugs. The patients were advised and warned as possible side effects regarding corticoids use. Arterial blood pressure was verified at the beginning and at the end of each session. Before IVMP patients were evaluated and considered normal for cardiologic, di-

Table 2. Age of beginning.

Age of begining- years		
51 (maximum)	23 (minimum)	33 (average)

Table 3. Main syndromes.

Number patients	Syndromes
4	Spinal
7	Spinal / cerebellar

Table 4. Periodicity of IVMP.

Number of patients	Days
2	10
4	15
1	20
4	30

Table 5. EDDS before and after IVMP, years of treatment and IVMP intervals.

N	Before IVMP	After IVMP	Years of treatment	IVMP intervals (days)
1	7	6.5	14	10
2	6.5	6.5	10	15
3	7.5	5.5	13	20
4	6.0	3.0	14	30
5	6.5	6.5	12	30
6	5.0	4.0	12	15
7	6.5	5.5	5	10
8	6	3	14	30
9	5.5	4.5	13	30
10	6	4.5	8	15
11	6	4	9	15

IVMP, intravenous methylprednisolone.

gestive and respiratory functions. Patients were also submitted to routine laboratory tests (parasitological, urinary and blood chemistry as well as chest X-ray).

Table 1 shows the 11 patients. Seven patients were female and 4 were male. The patients are listed in decreasing order of year duration of MS. Patient one has the largest of duration time (31 years) while patient 11 has the lowest disease time (13 years). Six patients had four syndromes; four patients had three syndromes and one patient with two syndromes. In Table 2, we see that the maximum age of onset was 51 years and the youngest age of onset was 23 years, with an average age of 33 years old. Table 3 shows that four patients had the spinal form of MS, while 7 patients had both spinal and cerebellar forms. The spinal form predominated in 11 patients.

RESULTS

Treatment was consistently applied on an out-patient basis and by skilled nursing teams. The initial dose of MP was 30 mg/kg or 1.5 grams per treatment session, diluted in 250 mL of 5% glucose (dextrose) solution in three consecutive days during the first week (one daily dose), and two doses during second week in two consecutive days, and one dose during the third and final week. If the initial therapy proved beneficial, we recommend one weekly session for eight consecutive weeks. As long as treatment proved satisfactory, with additional positive results, the once-a week/ eight-week would be maintained. With the stabilization of clinical symptoms, the treatment regimen would then be modified, every three months, to intervals of 10, 15, 20 and 30 days (Table 4). If there were worsening of symptoms, we return to the original eight-week regimen.

Table 5 shows migrations of EDSS before treatment for EDSS in course of treatment as well as the periodicity in days of IVMP in last evaluation. Then in two patients the IVMP was given every 10 days, in four from 15/15 days, in one every 20 days and in 4 every 30 days. The duration of treatment varied from five years (patient 5) to 14 years (patients 3 and 7).

There were no side effects inherent to treatment with corticosteroids, but almost them present unwanted effects such as insomnia and metallic taste during the infusion and in the days following the IVMP

DISCUSSION

In 1992 we made a protocol for continuous treatment of MS with IVMP pulses. We were encouraged by the following evidences: a) diseases mediated immunologically are treated by similar way with benefits[11], with the doses of IVMP (30 mg/kg)[12]; b) there are few undesirable or collateral effects concerning to the chronic use of oral corticoids; c) the periodicity between the applications is initially indicated on periods of each seven days. The change in the periodicity depends on clinical and MRI improvement; d) the results were available by the EDSS[13-15]; e) the patients have active participation in the treatment.

In British Columbia, Tremlett et al.[3] reports that 352 patients with MS took an average of 13.3 years to reach a sustained EDSS score of 6 (requires care), which was somewhat longer than reported in other studies, notably by Confavreux and Vukusic[1] : 7.1 years (n=282).

Treatment brought measurable benefits in EDSS scores to 9 patients. Two patients (cases 2 and 5) (Table 5) remain clinically stable, and were found to be more competent motor wise in skills not measured by the EDSS scale, since EDSS is not sufficiently sensitive in evaluating certain motor functions and skills. Continuation of IVMP therapy was always an option for maintaining previously acquired clinical benefits.

The patients with the predominantly spinal form of PPMS (cases 2, 5, 7 and 9) had least benefit with IVMP, according to EDSS scale scores. Patients with the predominantly cerebellar form had better outcome (cases 3,4,6,8 and 11). Patient 4 presented most benefit regarding EDSS score variation. In 13 years of disease evolution, his EDSS score was 6, and after 14 years of treatment changed to 3. Improvement in this patient as well as in all patients proved to be uniformly gradual and slow. Patients 2, 3, 7 and 8 had their treatment discontinued for up to 1 year. All patients had worsening of symptoms and signs, and after reassuming treatment had new improvement. No relapse was observed in any of our patients.

There is no approved treatment for the PPMS. Nevertheless, some important clinical benefits have been observed after treatment of PPMS with high-dose methylprednisolone alone or in association with mitoxantrone or cyclophosphamide[16-18]. There is a need for further studies establishing optimal treatment standards in PPMS with IVMP. Unsolved questions relate to the optimal dose whether tapering is beneficial, as well as possible differences between biological responses to gluco-corticoides. Higher doses of IVMP are associated with more pronounced clinical improvement when compared to the more commonly used doses of 500 to 1000 mg/day, but it is still not clear if these differences translate into meaningful differences in clinical efficacy[19-25].

As for periodicity of IVMP applications, patients 2, 6, 10 and 11 currently receive MP every 15 days between applications, of their own desire, since widening of treatment-free intervals cause clinical worsening of their symptoms. The remainders are in the process of possibly widening their treatment free intervals, depending upon their future clinical stability. Patient 4 currently receives treatment every 30 days, and with possible widening, due to excellent clinical stability presented, as well as regarding RMI results.

Although we studied a small sample of PPMS, we think that we may conclude that: 1) the continued therapy with IVMP prevents clinical worsening of PPMS in the majority of patients with improvement in EDSS scores; 2) the intervals of treatment will depend upon the individual need of each patient, varying in accordance with his/her evolution; 3) the improvement is slow and gradual; 4) the patients worsen when the treatment was discontinued and improved when IVMP was resumed; 4) the patients with the cerebellar form of PPMS improve better than those with the spinal form; 5) there were no side effects with IVMP ; 6) a treatment protocol using IVMP for PPMS should be established; 7) as the PPMS is a rare form of MS, a multicentric study with continuous IVMP is needed to determine the efficacy of this treatment.

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