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# Physical rehabilitation has a positive effect on disability in multiple sclerosis patients

[Articles]

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## Outline



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# Article abstract^

Background: Although physical rehabilitation is commonly administered to MS patients, its efficacy has not been established.

Objective: We assessed the efficacy of an inpatient physical rehabilitation program on impairment, disability, and quality of life of MS patients with a randomized, single-blind, controlled trial.

Methods: Fifty ambulatory MS patients were assigned to 3 weeks of inpatient physical rehabilitation (study treatment) or exercises performed at home (control treatment). Patients were evaluated at baseline and at 3, 9, and 15 weeks by a blinded examining physician.

Results: No changes in impairment occurred in either group, as measured by the Expanded Disability Status Scale. At the end of the intervention the study group improved significantly in disability, as assessed by the Functional Independence Measure (FIM) motor domain, compared with controls ($p = 0.004$), and the improvement persisted at 9 weeks ($p = 0.001$). The effect size statistic was usually large or moderate in all scale scores of the FIM motor domain at 3 weeks and moderate to fair thereafter. The study group also improved in overall health-related quality of life profile compared with controls; however, the difference was significant only for the mental composite score at 3 ($p = 0.008$) and 9 weeks ($p = 0.001$).

Conclusions: Despite unchanging impairment, physical rehabilitation resulted in an improvement in disability and had a positive impact on mental components of health-related quality of life perception at 3 and 9 weeks.

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The leading nontraumatic cause of neurologic disability in young adults is MS, with various combinations of impairments affecting different MS patients or the same patient over time. Physical rehabilitation is generally accepted as useful for such MS patients. A wide range of physiotherapeutic approaches is employed, ranging from more traditional strategies to newer techniques emphasizing the learning and practice of functional motor skills within a "task-specific" context.[1,2] However, there is no compelling evidence that physical rehabilitation is effective in MS. It is also important to identify the optimal approach for a given patient, determine how long the effects last, and estimate the cost-effectiveness. Studies verifying the efficacy of physical rehabilitation require reliable, valid, and practical outcome measures.[3] Furthermore, because physical rehabilitation is concerned with overall physical disability and handicap and not simply with impairment in individual functions, comprehensive measures of overall disability and handicap are at least as important as impairment measures.

To our knowledge, only two studies have been published on the efficacy of physiotherapy in MS. The study by Freeman et al.[4] examined the efficacy of an inpatient physical rehabilitation program but did

not have a control intervention. The study of Petajan et al.[5] was a randomized clinical trial assessing the impact of aerobic training on fitness and quality of life.

The current study, which is ongoing, reports the interim results of a randomized, single-blind, controlled study to determine the efficacy of an inpatient physical rehabilitation program in clinically definite, out-of-exacerbation MS patients.

**Methods.** *Patients*. All consecutive hospitalized patients and outpatients seen at the Istituto Nazionale Neurologico C. Besta, Milan, Italy, between January 1995 and April 1997 were considered for inclusion in the study. Selection criteria were clinically definite or laboratory-supported MS, Expanded Disability Status Scale (EDSS) score at inclusion between 3.0 and 6.5, and age between 18 and 65 years.[6,7] Exclusion criteria were as follows: one or more exacerbations in the preceding 3 months; cognitive impairment likely to interfere with adherence to the study, as determined by a Mini-Mental State Examination score of <= 23.8, after adjustment for age and education; history of cardiovascular, respiratory, orthopedic, psychiatric, or other medical conditions precluding participation; pregnancy; treatment with immunosuppressants, interferons, copolymers, 4-aminopyridine, or experimental drugs in the 6 months before enrollment; and rehabilitation therapy in the 3 months before admission (one or more rehabilitation sessions a week for at least 4 consecutive weeks).[8,9]

Patients were required to abstain from interferons, copolymer, cyclophosphamide, 4-aminopyridine, and IV steroid pulse therapy during the trial. Psychotropic drugs and symptomatic medications for spasticity, tremor, and bladder disturbances could not be initiated, but if they were already being prescribed, doses and schedules had to be held constant during the 15-week study period. Any other prescribed medication had to be reported by the referring physician (see following) along with dosage, administration dates, and reason for use.

All eligible patients agreed to randomization to physical rehabilitation or control treatment and signed informed consent forms. Patients were first stratified by EDSS score (3.0 to 4.5 or 5.0 to 6.5) and then assigned by telephone call to the randomization unit, to rehabilitation or control treatment.

Randomization employed a computer-based pseudorandom number generator. Patients assigned to the control treatment were offered the inpatient rehabilitation program at the end of the study.

*Neurologic examinations*. Examinations took place at baseline and weeks 3, 9, and 15. Three physicians were responsible for the patients during the study. The referring physician recorded patients' general information, clinical data, and follow-up history. The treating physician was responsible for the rehabilitation program. The evaluating physician, who was blinded to treatment assignment, administered the evaluation scales, which consisted of Kurtzke's EDSS, Hauser's Ambulation Index, the Functional Independence Measure (FIM), and the Hamilton Rating Scale for Depression.[7,10-13] Health-related quality of life was assessed by the self-administered 36-item Short Form Health Survey Questionnaire (SF-36).[14-17] The SF-36 contains 36 items divided into 8 multi-

item scales: physical functioning (PF), role limitation-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitation-emotional (RE), and mental health (MH). An additional one-item measure of self-evaluated change in health status is also available. SF-36 also assesses two major health concepts, physical and mental, with two composite scores, the physical composite score (PCS) and the mental composite score (MCS). The physical scales (PF, RP, BP, and GH) make up the PCS, and the remaining four scales (MH, RE, VT, and SF) make up the MCS.[15]

Scores for all scales were assembled using the Likert method for summated ratings, and the raw scores were then linearly transformed to 0 to 100 scales.[17] Higher transformed scores indicate better health. A large-print version of the form was used, and patients were assisted if they were unable to complete it alone.

To reduce interobserver variability, all but two patients were assessed by one neurologist (A.S.); the two remaining patients were assessed by another neurologist (G.F.).

*Rehabilitation program*. The inpatient rehabilitation program lasted for 3 consecutive weeks and consisted of twice-daily exercise periods, each 45 minutes long. At the end of the period, the patients were instructed in a self-executed exercise program to perform at home. The control treatment consisted of the home exercise program only.

The physical rehabilitation program, which has been described in detail elsewhere,[18] was devised and coordinated by the treating physician (P.G.) and administered by qualified physiotherapists at the Rehabilitation Department of the Ospedale S. Spirito. Briefly, the therapeutic approach differed according to the patient's level of impairment and disability, and included passive (stretching, mobilization) and active interventions. For patients with an EDSS score <= 4.5, the main goals were normalization of postural control, facilitation of a normal gait pattern, increasing the range of movement, and maximizing muscle power and endurance. For patients with an EDSS score > 4.5, instruction on appropriate use of mobility aids and orthoses as well as refinement of compensatory strategies were also part of the program.

Control patients received a 1-day session of individual instruction from a physiotherapist concerning their home exercises as well as written instructions devised by the treating physician. Patients with an EDSS score > 4.5 were also trained in the use of mobility aids and orthoses. The control treatment was adapted from a self-performed program devised by the Swiss Multiple Sclerosis Society.[19,20]

*Statistical analysis*. There were two primary outcome measures. The first was the effect of the rehabilitation program on disability as measured by the motor domain of the FIM. This comprises self-care, transfers, and locomotion scales. A change of two or more levels was considered clinically significant. The second main outcome measure was change in neurologic impairment as assessed by the EDSS. Change in the SF-36 score was a secondary efficacy end point.

The required population size was calculated for the EDSS primary end point. Forty-five patients per

group were required to detect, with a power of 80%, a difference of 20% in the proportion of patients changing by at least one EDSS step after 3 weeks. An interim analysis after recruitment of the first 50 patients was planned, and the results of this analysis are the subject of this paper. Data were analyzed according to the randomization assignment (intention-to-treat).

Proportions were compared by the $[chi]^2$ or Fisher's exact test. Continuous data were compared using Wilcoxon rank sum test. The clinical impact of the intervention was assessed by the effect size statistic, calculated as mean change in study group minus mean change in controls, divided by the pooled standard deviation of the baseline mean.[21] A value of 0.2 for the effect size statistic is considered a small effect, 0.5 is moderate, and 0.8 is large.[22] All statistical tests were two-tailed; *p* values <= 0.05 were considered significant. Statistical analyses were carried out using Stata Statistical Software, release 5.0.

**Results.** Between January 1995 and April 1997, 304 patients were screened and 50 were enrolled in the study, with 27 patients assigned to study treatment and 23 to control treatment. A total of 254 patients did not meet the inclusion criteria: 110 (43%) had an EDSS score out of range; 44 (17%) were already receiving physical rehabilitation; 26 (10%) were receiving immunosuppressants and 6 (2%) were receiving interferons; 33 (13%) were in exacerbation; 12 (5%) resided in central/southern Italy; 14 (6%) had overt copathology; and 9 (3%) patients refused to participate.

Patient characteristics at baseline are summarized in table 1. The physiotherapy and control groups were well matched for all variables. Five patients withdrew from the study before the end of the 15-week study period, three from the rehabilitation program and two from the control treatment. One control patient failed to present for the last examination, one study-group patient had an exacerbation 2 weeks after entry, and three others (one control, two intervention) deteriorated clinically and were given steroids between the 9th and 15th week. All these patients were included in the analysis (figure 1).

Table 1 Baseline characteristics of 50 MS patients randomly assigned to receive inpatient rehabilitation or self-performed exercises

Figure 1. Profile of the randomized controlled trial.

At 3 and 15 weeks the evaluating physician was asked to guess what type of treatment patients were receiving. She correctly guessed that two control patients (9%) were receiving control treatment and two intervention patients (7%) were receiving rehabilitation, whereas three rehabilitation patients (11%) were incorrectly thought to be receiving the control treatment. No opinion was expressed for the remaining 43 patients.

In this interim study the results presented do not include changes in individual functional systems or nonmotor domains of the FIM.

*Impairment.* The changes in EDSS scores clustered closely around 0 in both groups at the end of the rehabilitation period and at 9 and 15 weeks. An improvement by one EDSS step, considered clinically significant, occurred in only one patient assigned to the study treatment 9 weeks after enrollment. Three weeks from enrollment, seven intervention patients (26%) and two control patients (9%) improved by one-half step; 9 weeks from enrollment, two intervention patients (7%) and one control patient (4%) improved by one-half step; at 15 weeks, two control patients (9%) improved by one-half step and no intervention patient improved.

*Disability.* The other main outcome measure was the FIM motor domain, for which an improvement of two or more steps was considered clinically significant. Thirteen intervention patients (48%) improved by two or more steps at 3 weeks compared with two (9%) in the controls (Fisher's exact test, $p = 0.004$). Twelve intervention patients (44%) and one control were still improved at 9 weeks (Fisher's exact test, $p = 0.001$). One intervention patient (4%) and 2 of 22 control patients (9%, one patient did not present for the last examination) were still improved at 15 weeks (Fisher's exact test, $p = 0.6$).

All scale scores of the FIM motor domain differed significantly in the two groups at 3 and 9 weeks, and differed significantly in two scales, self-care and locomotion, at 15 weeks (table 2). The effect size statistic was usually large or moderate at 3 weeks-0.9 for mobility and self-care, and 0.5 for locomotion. At 9 weeks the values were 0.9 for self-care and 0.3 for mobility and locomotion; at 15 weeks the values were 0.6 for self-care, 0.7 for locomotion, and 0.5 for mobility.

Table 2 Change in Functional Independence Measure motor domain

*Quality of life.* The baseline SF-36 results are shown in figure 2 in comparison with Italian normative data from 1,636 individuals aged 23 to 68 years. There were no differences between the two patient groups in any health scale at baseline. Figure 3 shows score changes at 3 weeks relative to baseline. Overall, the SF-36 profile improved for patients who underwent the study treatment in all but the BP scale. The difference between study-group patients and controls was statistically significant for GH and MH (at 3, 9, and 15 weeks), VT (at 3 and 15 weeks), and RE and SF (at 9 weeks). As shown in table 3, the PCS changes at 3, 9, and 15 weeks were consistently higher in the study group than they were in controls; however, these differences were not statistically significant. The rehabilitation group achieved significant improvements in the MCS at 3 and 9 weeks, with mean (±SD) changes of 5.2 ± 7.0 at 3 weeks and 4.8 ± 9.9 at 9 weeks compared with corresponding changes in the controls of -0.8 ± 7.3 at 3 weeks (Wilcoxon rank sum test, $p = 0.008$) and -5.3 ± 14.8 at 9 weeks (Wilcoxon rank sum

test, $p = 0.001$). At 15 weeks, the groups no longer differed significantly in the MCS, when mean (±SD) changes were 2.1 ± 9.7 in the rehabilitation group and -1.8 ± 7.7 in the controls.

Figure 2. Mean 36-item Short Form Health Survey Questionnaire scores at baseline in comparison with Italian normative data on 1,636 subjects aged 23 to 68 years. Values on the y axis are scores. PF = physical functioning; RP = role limitation-physical; RE = role limitation-emotional; VT = vitality; MH = mental health; SF = social functioning; BP = bodily pain; GH = general health.

Figure 3. Mean changes in 36-item Short Form Health Survey Questionnaire scores at 3 weeks. Values on the y axis are score changes. PF = physical functioning; RP = role limitation-physical; RE = role limitation-emotional; VT = vitality; MH = mental health; SF = social functioning; BP = bodily pain; GH = general health. *Wilcoxon rank-sum test.

Table 3 Change in SF-36 composite scores

**Discussion.** We found that impairment, as assessed by the EDSS, was not affected by the rehabilitation program. However, 48% of physiotherapy patients improved by two or more steps on the FIM motor domain at 3 weeks, and 44% were still improved at 9 weeks. The corresponding figures were significantly lower in controls (9% at 3 weeks, 4% at 9 weeks). Furthermore, the degree of improvement in disability brought about by physiotherapy was clinically useful, as indicated by increased scores in all FIM motor domain scales, with large or moderate effect sizes in most scales; the improvement persisted at 9 and 15 weeks.

Overall, the SF-36 profile improved for patients who underwent the study treatment; however, the difference was statistically significant only for the MCS at 3 and 9 weeks. This finding should be interpreted in light of the limited power of the study (power calculations were not based on the SF-36, which was a secondary outcome) and a probable floor effect with regard to the PCS and its determinants, as indicated by the low baseline scores (see figure 2).[23] Thus an improvement in health perception was not detected in the PF and RP scales in physically compromised patients, probably because of the unipolar limitation of these scales.[24]

When the study was designed, only the SF-36, a general quality of life questionnaire, was available; it is not disease-specific and not sufficiently sensitive to physical changes in disabled patients. Since June 1996 we have been using the Multiple Sclerosis Quality of Life-54 survey that includes the SF-36 and a disease-specific module for MS patients. It has been recently translated and adapted for Italian patients.[25,26]

Our data are consistent with the recently published waiting-list randomized study of Freeman et al.[4] on progressive MS patients. This study differs from ours in that it admitted nonambulatory patients, and a control intervention was lacking. Furthermore, the rehabilitation program included occupational, cognitive, and speech therapies. Despite these differences, both studies showed a positive effect on disability (as assessed by the FIM) and negligible effect on impairment.

The randomized, single-blind study by Petajan et al.[5] found that ambulatory MS patients benefited from aerobic training in terms of fitness, reduced fatigability, improved quality of life perception (Sickness Impact Profile), and bowel and bladder function on the EDSS. In contrast to the study of Petajan et al., our investigation did not demonstrate a significant effect of rehabilitation on the physical dimension scales of the SF-36. This may be because the patients of Petajan et al. had a low level of disability (they could perform regular aerobic training), thus a floor effect was less likely to affect their results.

We believe our interim findings are encouraging and indicate that physical rehabilitation has a positive effect on disability, which persisted after 9 weeks. An effect on the overall quality of life profile and the MCS (at 3 and 9 weeks) was also detected.

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