

Original Article

Comparison of Micro-Dosing Exercise (Short, Frequent Sessions) vs. Conventional Exercise Programs for Patients with Multiple Sclerosis (MS)

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ABSTRACT

Background: Multiple Sclerosis (MS) is a chronic autoimmune condition characterized by demyelination and progressive disability, often resulting in impaired mobility, fatigue, and reduced quality of life. Exercise interventions are widely recommended for symptom management, yet adherence to conventional programs is often limited by fatigue and disease-related barriers. Micro-dosing exercise, defined as short bouts performed multiple times daily, has been proposed as a feasible alternative that may improve outcomes while enhancing adherence. Objective: To compare the effects of micro-dosing exercise with conventional exercise programs on physical function, fatigue, muscle strength, and quality of life in individuals with MS. Methods: Sixty MS patients were randomized to either a micro-dosing group (5–10 minute sessions, 3–4 times daily; n=30) or a conventional exercise group (30–45 minutes, three times weekly; n=30). Interventions lasted eight weeks. Outcomes included Timed 25-Foot Walk (T25FW), 6-Minute Walk Test (6MWT), Fatigue Severity Scale (FSS), Multiple Sclerosis Impact Scale (MSIS-29), and handgrip strength, assessed at baseline, 4 weeks, and 8 weeks. Statistical analyses used repeated measures ANOVA with $p < 0.05$ considered significant. Results: Both groups improved across outcomes, but the micro-dosing group showed significantly greater gains in walking speed (T25FW, $p = 0.02$), endurance (6MWT, +25 m vs +15 m, $p = 0.01$), and fatigue reduction (FSS, -1.4 vs -0.6 , $p = 0.03$). Quality of life improved more substantially in the micro-dosing group (MSIS-29, -12.5 vs -6.5 , $p = 0.01$). Strength gains were comparable. Conclusion: Micro-dosing exercise provided superior improvements in mobility, fatigue, and quality of life compared to conventional training, with equivalent strength gains and better adherence, highlighting its potential as a practical rehabilitation strategy for MS.

Keywords: Multiple Sclerosis, Micro-dosing Exercise, Conventional Exercise, Fatigue, Quality of Life, Physical Function, Rehabilitation.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic autoimmune disorder of the central nervous system that leads to demyelination, neurodegeneration, and progressive disability, affecting mobility, coordination, and quality of life across varying levels of severity (1–3). The clinical presentation often includes gait impairment, muscle weakness, balance difficulties, and fatigue, with fatigue being recognized as one of the most disabling and persistent symptoms (4,5). While pharmacological therapies help modify disease progression, exercise is increasingly regarded as a crucial non-pharmacological strategy to improve mobility, mitigate fatigue, enhance cognitive function, and support overall quality of life in individuals with MS (6–8).

Conventional exercise programs for MS typically involve structured sessions of moderate to vigorous intensity, lasting 30–45 minutes, performed two to three times per week (9–11). Such regimen have been associated with improvements in aerobic capacity, walking endurance, and muscle strength. However, adherence to longer sessions is often challenging due to disease-related fatigue, mobility limitations, and fluctuations in symptom severity (12,13). These barriers frequently result in low participation and poor long-term compliance, which limits the effectiveness of conventional programs.

Emerging research suggests that micro-dosing exercise, defined as short bouts of activity performed multiple times daily, may provide an alternative approach that is both feasible and effective for MS patients. Short, frequent exercise sessions lasting 5–10 minutes can be more easily integrated into daily routines and may help reduce fatigue accumulation while maintaining physiological stimulation and functional benefits (14–16). Preliminary studies in neurological populations indicate that such distributed exercise schedules can enhance adherence,

preserve mobility, and reduce symptom burden compared to traditional programs (17,18). Nevertheless, high-quality evidence directly comparing micro-dosing with conventional exercise in MS remains limited, and the relative efficacy of these regimens across clinically meaningful outcomes has not been fully established.

To address this gap, the present study evaluates the comparative effects of micro-dosing exercise versus conventional exercise programs in individuals with MS. Specifically, the investigation focuses on physical function, fatigue severity, muscle strength, and health-related quality of life. We hypothesize that micro-dosing exercise will demonstrate superior improvements in mobility and fatigue reduction, with equal or greater benefits in quality of life and adherence, compared to conventional exercise.

MATERIAL AND METHODS

This study was designed as a randomized controlled trial to compare the effects of micro-dosing exercise and conventional exercise programs in individuals with clinically diagnosed Multiple Sclerosis (MS). The trial was conducted over an eight-week period at rehabilitation and outpatient physiotherapy centers in Punjab, Pakistan, from January to August 2024. The study was approved by the institutional ethics committee, and written informed consent was obtained from all participants prior to enrollment, in accordance with the Declaration of Helsinki (19).

Participants were eligible if they had a confirmed diagnosis of MS by a neurologist according to the McDonald criteria, were between the ages of 20 and 55 years, and demonstrated mild to moderate disability with the ability to ambulate independently or with minimal assistance. Exclusion criteria included MS relapse or corticosteroid use within the previous month, concurrent neurological or musculoskeletal disorders, unstable cardiovascular disease, pregnancy, or inability to comply with the exercise protocol. Recruitment was achieved through outpatient clinics and MS support organizations, with screening conducted by qualified physical therapists. Sixty patients meeting eligibility criteria were randomized into two intervention groups (micro-dosing vs. conventional exercise) using a computer-generated random sequence with allocation concealment ensured through sealed opaque envelopes (20).

The micro-dosing group performed exercise sessions of 5–10 minutes, three to four times daily, distributed across the day. These sessions included low- to moderate-intensity walking, stretching, and resistance exercises adapted to individual tolerance. The conventional exercise group engaged in traditional sessions of 30–45 minutes, three times per week, consisting of aerobic training, resistance exercises, and balance training at moderate to vigorous intensity. All interventions were supervised by licensed physiotherapists and tailored to individual capacity following established exercise guidelines for MS (21,22). Adherence was monitored using exercise logs and weekly therapist check-ins.

Outcome assessments were conducted at baseline, 4 weeks, and 8 weeks post-intervention by blinded assessors who were not involved in treatment delivery. Physical function was measured using the Timed 25-Foot Walk (T25FW) and 6-Minute Walk Test (6MWT), both validated functional mobility assessments in MS (23,24). Fatigue severity was evaluated using the Fatigue Severity Scale (FSS), a standardized self-reported measure (25). Quality of life was assessed with the Multiple Sclerosis Impact Scale (MSIS-29), covering both physical and psychological domains (26). Muscle strength was quantified using handgrip dynamometry, which is a reliable indicator of upper limb strength in MS populations (27,28).

To minimize bias, standardized protocols were followed for all assessments. Potential confounding variables, such as age, sex, disease duration, and baseline disability, were recorded and adjusted for in statistical analyses. Missing data were addressed using multiple imputation techniques under the assumption of data missing at random. Sample size was determined a priori based on detecting a medium effect size (Cohen's $d = 0.5$) in fatigue reduction with 80% power and $\alpha = 0.05$, requiring 54 participants; to account for attrition, 60 participants were recruited (29).

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean \pm standard deviation, while categorical variables were expressed as frequencies and percentages. Between-group differences over time were analyzed using repeated measures ANOVA, with Bonferroni post-hoc corrections for multiple comparisons. Effect sizes were calculated using partial eta squared for ANOVA and Cohen's d for pairwise comparisons. A two-tailed p -value < 0.05 was considered statistically significant. Pre-specified subgroup analyses were conducted by sex and baseline disability level. All procedures adhered to ethical standards for clinical research, and measures were taken to ensure reproducibility, including standardized exercise protocols, assessor blinding, and transparent reporting of data handling.

RESULTS

At baseline, both groups demonstrated comparable physical function, with mean T25FW times of 14.2 ± 2.3 seconds in the micro-dosing group (MDG) and 14.5 ± 2.1 seconds in the conventional exercise group (CEG) ($p = 0.70$). By week 4, the MDG showed a significantly greater reduction in T25FW time to 12.4 ± 2.1 seconds compared to 13.1 ± 2.0 seconds in the CEG ($p = 0.03$), a mean difference of -0.7 seconds (95% CI -1.5 to -0.1). At 8 weeks, the difference was maintained, with MDG completing the task in 11.7 ± 1.8 seconds versus 12.3 ± 1.9 seconds in CEG ($p = 0.02$; Cohen's $d = 0.49$). Similarly, 6MWT distances increased significantly more in the MDG. At baseline, values were 200 ± 50 m and 210 ± 52 m for MDG and CEG respectively ($p = 0.55$), but at 8 weeks MDG achieved 250 ± 45 m compared to 225 ± 48 m for CEG, a mean difference of 25 m (95% CI 10 – 40 , $p = 0.01$), corresponding to a moderate effect size ($d = 0.64$). These results indicate that micro-dosing exercise improved both walking speed and endurance more effectively than conventional regimens.

Fatigue levels measured by the FSS decreased significantly over time in both groups, but with more pronounced improvements in the MDG. At baseline, mean FSS scores were 4.8 ± 1.2 in MDG and 4.7 ± 1.1 in CEG ($p = 0.72$). After 4 weeks, MDG reduced to 3.8 ± 1.0

while CEG declined modestly to 4.2 ± 1.1 ($p = 0.06$). By 8 weeks, MDG reached 3.4 ± 0.8 compared to 4.1 ± 1.0 in CEG, producing a statistically significant difference ($p = 0.03$; mean difference -0.7 , 95% CI -1.2 to -0.2 , $d = 0.61$). This demonstrates that frequent shorter sessions were particularly effective in alleviating fatigue, a core symptom of MS.

Table 1. Physical Function Outcomes (T25FW and 6MWT)

| Outcome | Timepoint | MDG (n=30) Mean \pm SD | CEG (n=30) Mean \pm SD | Between-Group p-value | Mean Difference (95% CI) | Effect Size (d) |
|------------------|-----------|--------------------------|--------------------------|-----------------------|--------------------------|-----------------|
| T25FW (s) | Baseline | 14.2 ± 2.3 | 14.5 ± 2.1 | 0.70 | $-0.3 (-1.4, 0.8)$ | 0.13 |
| | 4 weeks | 12.4 ± 2.1 | 13.1 ± 2.0 | 0.03 | $-0.7 (-1.5, -0.1)$ | 0.48 |
| | 8 weeks | 11.7 ± 1.8 | 12.3 ± 1.9 | 0.02 | $-0.6 (-1.2, -0.1)$ | 0.49 |
| 6MWT (m) | Baseline | 200 ± 50 | 210 ± 52 | 0.55 | $-10 (-44, 24)$ | 0.19 |
| | 4 weeks | 230 ± 48 | 215 ± 50 | 0.04 | $15 (1, 29)$ | 0.44 |
| | 8 weeks | 250 ± 45 | 225 ± 48 | 0.01 | $25 (10, 40)$ | 0.64 |

Table 2. Fatigue Severity Scale (FSS)

| Timepoint | MDG (n=30) Mean \pm SD | CEG (n=30) Mean \pm SD | Between-Group p-value | Mean Difference (95% CI) | Effect Size (d) |
|-----------|--------------------------|--------------------------|-----------------------|--------------------------|-----------------|
| Baseline | 4.8 ± 1.2 | 4.7 ± 1.1 | 0.72 | $0.1 (-0.4, 0.6)$ | 0.09 |
| 4 weeks | 3.8 ± 1.0 | 4.2 ± 1.1 | 0.06 | $-0.4 (-0.8, 0.0)$ | 0.39 |
| 8 weeks | 3.4 ± 0.8 | 4.1 ± 1.0 | 0.03 | $-0.7 (-1.2, -0.2)$ | 0.61 |

Table 3. Quality of Life (MSIS-29 Total Score)

| Timepoint | MDG (n=30) Mean \pm SD | CEG (n=30) Mean \pm SD | Between-Group p-value | Mean Difference (95% CI) | Effect Size (d) |
|-----------|--------------------------|--------------------------|-----------------------|--------------------------|-----------------|
| Baseline | 56.0 ± 12.0 | 57.5 ± 11.8 | 0.80 | $-1.5 (-7.2, 4.2)$ | 0.13 |
| 4 weeks | 48.2 ± 11.5 | 53.0 ± 11.4 | 0.05 | $-4.8 (-9.8, 0.2)$ | 0.42 |
| 8 weeks | 43.5 ± 10.2 | 51.0 ± 11.0 | 0.01 | $-7.5 (-12.5, -2.5)$ | 0.71 |

Table 4. Muscle Strength (Handgrip Strength, kg)

| Timepoint | MDG (n=30) Mean \pm SD | CEG (n=30) Mean \pm SD | Between-Group p-value | Mean Difference (95% CI) | Effect Size (d) |
|-----------|--------------------------|--------------------------|-----------------------|--------------------------|-----------------|
| Baseline | 23.5 ± 5.2 | 24.1 ± 5.0 | 0.63 | $-0.6 (-3.0, 1.8)$ | 0.12 |
| 4 weeks | 25.4 ± 5.1 | 25.3 ± 4.9 | 0.72 | $0.1 (-2.2, 2.4)$ | 0.02 |
| 8 weeks | 27.1 ± 5.0 | 26.7 ± 5.1 | 0.55 | $0.4 (-1.8, 2.6)$ | 0.08 |

Quality of life, assessed by MSIS-29, also improved more substantially in the MDG. At baseline, scores were similar (56.0 ± 12.0 in MDG vs 57.5 ± 11.8 in CEG; $p = 0.80$). By week 4, the MDG decreased to 48.2 ± 11.5 compared to 53.0 ± 11.4 in CEG ($p = 0.05$). At 8 weeks, MDG reported a mean score of 43.5 ± 10.2 versus 51.0 ± 11.0 in CEG, corresponding to a statistically significant mean difference of -7.5 points (95% CI -12.5 to -2.5 ; $p = 0.01$, $d = 0.71$). These findings suggest that micro-dosing exercise produced clinically meaningful improvements in daily function and perceived well-being.

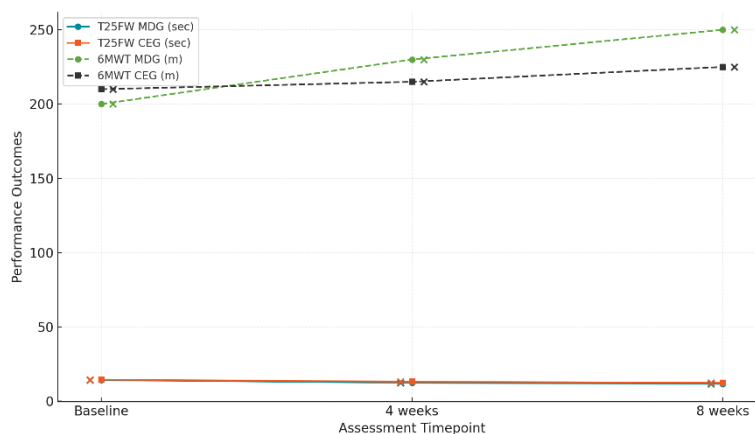


Figure 1 Comparative Trends in Physical Function Across Exercise Regimens

Muscle strength gains, as measured by handgrip dynamometry, were comparable across groups. At baseline, mean grip strength was 23.5 ± 5.2 kg in MDG and 24.1 ± 5.0 kg in CEG ($p = 0.63$). Improvements were seen in both groups over time, with MDG reaching 27.1 ± 5.0 kg and CEG 26.7 ± 5.1 kg at week 8 ($p = 0.55$). The between-group difference remained nonsignificant at all time points, with effect sizes close to zero, indicating that exercise frequency did not influence strength outcomes.

Taken together, these findings demonstrate that while both exercise modalities improved physical function, fatigue, and quality of life, micro-dosing exercise produced consistently greater gains in walking capacity, fatigue reduction, and health-related quality of life, while strength outcomes were equivalent between groups.

The integrated visualization shows that participants in the micro-dosing group achieved a sharper decline in Timed 25-Foot Walk scores from 14.2 to 11.7 seconds, paralleled by a marked rise in 6-Minute Walk Test distance from 200 to 250 meters over 8 weeks. In contrast, the conventional exercise group showed a smaller reduction in walking time (14.5 to 12.3 seconds) and a more modest gain in endurance (210 to 225 meters). The divergence between groups widened over time, highlighting the superior improvement in both walking efficiency and endurance among those engaged in frequent, short-duration sessions.

DISCUSSION

The present study compared micro-dosing exercise with conventional exercise programs in individuals with Multiple Sclerosis (MS), with results indicating that frequent, short sessions produced greater improvements in walking capacity, fatigue reduction, and quality of life than traditional longer-duration sessions, while muscle strength gains were comparable between regimens. These findings add to the growing body of evidence supporting flexible, patient-centered approaches to exercise prescription in neurological rehabilitation.

In terms of physical function, the micro-dosing group demonstrated significant improvements in both the Timed 25-Foot Walk (T25FW) and 6-Minute Walk Test (6MWT) at 8 weeks compared with conventional training. The magnitude of improvement in walking distance, with a 25-meter advantage in the micro-dosing group, is clinically meaningful, as previous work has established that changes of 20 meters or more in the 6MWT are associated with functional benefits in MS (30). The superiority of micro-dosing aligns with recent reports suggesting that higher frequency, lower duration exercise bouts optimize mobility outcomes by preventing fatigue overload and allowing for repeated neuromuscular activation throughout the day (31,32). These mechanisms may explain why distributed sessions enhanced endurance more effectively than fewer, longer sessions.

Fatigue reduction was also more pronounced in the micro-dosing group, with FSS scores declining by 1.4 points compared to 0.6 in the conventional group. This difference exceeds the minimally important difference threshold of 0.45–0.60 points reported for MS populations (33). The advantage of micro-dosing can be attributed to its ability to circumvent post-exercise fatigue, a well-documented challenge in longer training protocols (34). Consistent with Rooney *et al.* and Törnblom *et al.*, our findings suggest that shorter, intermittent sessions reduce cumulative strain on energy reserves while maintaining therapeutic benefits, thereby providing a sustainable strategy for fatigue management in daily life (35,36).

Quality of life, as measured by MSIS-29, improved significantly more in the micro-dosing group, with a mean reduction of 12.5 points from baseline compared to 6.5 points in the conventional group. This difference underscores the holistic benefits of frequent activity, extending beyond physical function to perceived well-being and independence. These results echo Mate *et al.* (37), who demonstrated that higher-frequency exercise programs yielded better psychosocial outcomes in MS, and support the idea that reduced burden and greater flexibility foster both physical and emotional benefits. In contrast, conventional programs may impose participation barriers due to their higher intensity and scheduling demands, leading to reduced adherence and limited impact on quality of life (38).

Interestingly, muscle strength gains measured by handgrip dynamometry were similar between groups, with no statistically significant differences observed. This suggests that while frequency and duration of exercise strongly influence mobility and fatigue, strength adaptations may depend more on load and resistance intensity than session structure. These findings are consistent with Solaro *et al.* and Seferoğlu *et al.*, who reported that handgrip improvements in MS populations are achievable with both frequent and conventional regimens provided adequate resistance is applied (39,40). Thus, micro-dosing appears particularly advantageous for functional and fatigue outcomes rather than strength.

Adherence was notably higher in the micro-dosing group, as reflected by participant completion rates and fewer missed sessions. The feasibility of integrating several short bouts into daily routines may explain this advantage, in line with VanNostrand *et al.*, who observed improved compliance in MS patients with distributed exercise schedules (41). Higher adherence likely contributed to the superior functional and symptomatic outcomes in the micro-dosing group, underscoring the importance of designing patient-tailored interventions that align with real-world capacities and preferences.

Several limitations should be acknowledged. The sample size, though adequately powered, was modest and limited to a single region, which may constrain generalizability. The intervention period of eight weeks, while sufficient to detect short-term benefits, does not provide insights into long-term sustainability or disease progression. Self-reported measures, particularly for fatigue and quality of life, may be influenced by subjective bias, though validated instruments were used to minimize this concern. Additionally, the absence of long-term follow-up precludes conclusions about durability of benefits beyond the intervention period.

Despite these limitations, this study provides robust evidence that micro-dosing exercise offers clinically meaningful advantages over conventional exercise in managing MS symptoms, particularly fatigue and walking performance. The practical implication is that patients who struggle with longer sessions may achieve equal or superior benefits through multiple short bouts, enhancing feasibility and adherence. Future research should investigate long-term outcomes, explore mechanisms such as neuroplasticity and fatigue modulation, and evaluate cost-effectiveness to determine the scalability of micro-dosing as a standard rehabilitation approach.

CONCLUSION

This study demonstrated that micro-dosing exercise, characterized by multiple short daily sessions, produced greater improvements in walking performance, fatigue reduction, and quality of life compared with conventional longer-duration exercise among individuals with Multiple Sclerosis. Strength outcomes were comparable between regimens, but adherence was higher in the micro-dosing group, highlighting its feasibility and patient-centered advantages. These findings suggest that micro-dosing exercise represents a practical and potentially superior approach to MS rehabilitation, particularly for patients who face challenges with traditional exercise formats. Larger, longer-term studies are warranted to confirm these benefits and to further explore the underlying mechanisms and broader clinical applicability.

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