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ORIGINAL ARTICLE

The Impact of Modafinil on Quality of Life in Stroke Survivors Experiencing Severe Fatigue

Fatemeh Hamzeh*, Mohammadreza Amiri Nikpour, Arash Mosarrezaii

Department of Neurology, Urmia University of Medical Sciences, Urmia, Iran

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KEYWORDS

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ABSTRACT: Post-stroke fatigue has a substantial negative impact on the mental and physical health of individuals recovering from stroke. This study explored the effect of modafinil om improving quality of life for stroke patients experiencing severe fatigue. This study employed a randomized, double-blind, placebo-controlled, design that was conducted at a single center hospital. Individuals recovering from a stroke were assigned by chance, in equal proportions, to either a 200 mg dose of modafinil or an inactive substitute for the first eight weeks of the study. The primary outcome measures comprised fatigue (MFI), quality of life (SSQoL), and stroke severity (NIHSS). Eighty stroke survivors were initially assessed for eligibility, and 63 of those individuals were subsequently enrolled in the study. The mean age of participants in the modafinil group was 57.46 ± 13.23 years and 64.8 ± 14.28 years in the control group. At baseline, the two groups exhibited no statistically significant differences in fatigue levels, quality of life scores, or stroke severity ($P > 0.05$). Nevertheless, the modafinil group exhibited greater improvement in all outcome measures following the intervention. While modafinil treatment did not yield statistically significant between-group differences in fatigue or quality of life, the observed trends suggest a potential benefit. The modafinil group exhibited a slightly greater reduction in MFI scores and a slightly greater increase in SSQoL scores compared to the control group. This study reported that modafinil may offer a safe and beneficial approach for managing fatigue and improving quality of life in individuals recovering from stroke.

INTRODUCTION

Acute and chronic neurological disorders, particularly those affecting the brain and nervous system, are a serious medical issue with a high prevalence today [1-4]. Stroke ranks among the leading causes of global disability and mortality, with significant socioeconomic implications, particularly for older adults and individuals in their productive years [1, 2]. Unfortunately, there are currently no available pharmacotherapeutic interventions to improve long-term outcomes or quality of life in stroke survivors [3]. Common sequelae of stroke include post-stroke fatigue, affecting 36-77% of survivors, and depression, which occurs in approximately one-third of cases [4, 5].

The widespread and enervating issue of tiredness after a stroke, which troubles more than 50 percent of stroke victims, can continue for prolonged intervals after the incident [6]. This clinical presentation correlates with increased dependence in activities of daily living and demonstrates a significant association with augmented rates of illness and death [7]. The pathophysiology of both acute and chronic post-stroke fatigue is not yet fully elucidated. Prior investigations have not conclusively

*Corresponding author: hamzehf@ymail.com (F. Hamzeh)
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demonstrated a relationship between stroke-related factors, including clinical severity, lesion location, or lesion volume, and the development or occurrence of fatigue [8]. It is thus postulated that broader mechanisms, including reduced physical activity, diminished cortical excitability, or altered immune responses potentially leading to neurotransmitter dysregulation, may play a role in post-stroke fatigue [9-12].

The treatment of post-stroke fatigue remains a significant clinical challenge, with pharmacological interventions, such as fluoxetine, failing to demonstrate efficacy in reducing fatigue symptoms [13]. Modafinil, a non-amphetamine wakefulness-promoting medication with a relatively benign side-effect profile, is commonly prescribed for managing excessive daytime sleepiness related to several sleep disorders, such as narcolepsy, shift work sleep disorder, and obstructive sleep apnea [14]. Additionally, modafinil has been investigated as a potential treatment for fatigue associated with neurological conditions such as Parkinson's disease, multiple sclerosis, traumatic brain injury, and post-polio syndrome [15]. While a previous case report suggested the potential benefits of modafinil in stroke patients [16], a recent investigation of modafinil administration immediately following stroke did not reveal significant benefits, likely due to spontaneous remission of fatigue observed in both the placebo and modafinil groups [17]. Given the negative impact of fatigue on quality of life and functional recovery in stroke survivors, and considering the limited evidence base and promising preclinical findings, the present investigation sought to determine the effectiveness of modafinil in enhancing the quality of life among individuals who have survived a stroke and experience significant fatigue.

MATERIALS AND METHODS

The study employed a randomized, double-blind, placebo-controlled, crossover design at a single medical center. Individuals recovering from a stroke were assigned by chance, in equal proportions, to either a 200 mg dose of modafinil or an inactive substitute for the first eight weeks of the study. The placebo was formulated to have the same physical appearance as the modafinil tablets, utilizing rice powder as the inert ingredient. Following a seven-day interval devoid of any therapeutic intervention, subjects transitioned to the alternate treatment group for a subsequent eight-week duration. Initial clinical and magnetic resonance imaging evaluations were conducted before the commencement of the experimental protocol. Ethical approval was obtained from the Ethics Committee of Urmia University of Medical Sciences in accordance with the Declaration of Helsinki (Code: IR.UMSU.REC.1399.187). Informed consent was obtained from all participants.

Eligibility criteria mandated that subjects be at least 18 years of age, possess a documented history of cerebrovascular event occurring no less than one month before enrollment, present with substantial fatigue as evidenced by a Modified Fatigue Impact Scale (MFI) score of 60 or greater, and exhibit mild to moderate neurological deficit as defined by a National Institutes of Health Stroke Scale (NIHSS) score of 5 or below. Exclusion criteria comprised known hypersensitivity to modafinil, compromised renal function, identifiable etiologies of fatigue other than post-stroke sequelae (e.g., narcolepsy), concurrent use of benzodiazepines or antiepileptic agents, pre-existing affective disorders, cognitive impairment, or other neuropsychiatric conditions, obstructive sleep apnea, gestation, or stroke pathogenesis other than ischemic or hemorrhagic stroke (e.g., stroke secondary to infection, trauma, or surgical intervention).

Treatment

Subjects were instructed to ingest a single dose of the assigned medication daily, administered either with the morning meal or during the early diurnal hours. Following random assignment, each participant received an eight-week dispensation of the investigational product. Upon completion of the initial eight-week therapeutic interval, participants presented to the study site for comprehensive clinical evaluation, including the quantification of fatigue levels, quality-of-life parameters, and neurological deficit severity, in conjunction with magnetic resonance imaging acquisition. Subjects were requested to return any residual study medication for adherence verification. A seven-day period of therapeutic discontinuation ensued, during which participants were required to refrain from the investigational product. Subsequent to the washout

phase, participants underwent outcome evaluation before being transitioned to the alternative treatment regimen. Following the second eight-week therapeutic phase, participants returned for final evaluation, which included clinical assessments and MRI scans, and the return of any remaining medication. To maintain the blinding integrity of the trial, treatment allocation remained exclusively within the purview of the trial pharmacist. All patient evaluations were conducted during the morning hours to mitigate potential confounding effects arising from diurnal variability in symptom presentation**.**

Patient assessments

Participants underwent baseline and post-treatment assessments using the MFI and the Stroke- SSQoL. Research personnel conducting the assessments were blinded to the treatment assignments. Patient compliance with the therapeutic regimen was assessed through the retrieval of unused medication units. The Modified Fatigue Impact Scale (MFI), a psychometrically validated measure, quantified fatigue severity across five distinct dimensions, with elevated scores reflecting increased symptom burden. The Stroke-Specific Quality of Life (SSQoL) scale, comprising 49 items, served to evaluate health-related quality of life across 12 domains pertinent to the post-stroke population. Adverse events were recorded through monthly telephone interviews and chart review.

Sample size method

A power analysis, informed by the effect size reported by Visser et al. (13), was performed to determine the necessary sample size. With a desired 90% confidence level, 90% power, and an estimated 20% attrition rate, the calculated sample size was 40 participants per group.

$$(Z_{1-\beta}=1.28 \text{ ، } Z_{1-\alpha/2}=1.96)$$

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times (S_1^2 + S_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

Statistical analysis

Quantitative variables were summarized using descriptive statistics, with mean and standard deviation reported. Categorical variables were presented as frequency distributions and percentages. Independent t-tests (or Mann-Whitney U tests for non-normally distributed data) were employed to compare mean differences between the two groups. Paired t-tests (or Wilcoxon signed-rank tests for non-normally distributed data) were used to compare within-group differences. Chi-square tests (or Fisher's exact tests for small sample sizes) were used to compare categorical variables. Statistical analyses were performed using SPSS 24 software, with statistical significance set at the 0.05 level.

RESULTS

Of the 80 stroke patients initially enrolled in the study, 31 participants in the modafinil group and 32 participants in the control group completed the study. In the modafinil group, three participants withdrew due to intolerance (two experiencing headache and one nausea), five were lost to follow-up, and one died. In the placebo group, six participants were lost to follow-up, and two died.

Participant baseline characteristics are presented in Table 1. The mean age of participants in the modafinil and control groups was 57.46 ± 13.23 years and 64.8 ± 14.28 years, respectively.

The distribution of involved artery location was similar between the two groups, with a higher proportion of patients in both groups having an anterior involved artery location (modafinil group= 74.2% and control group =65.6%). In the modafinil group, 25.8% of the patients had a posterior involved artery location and in the control group, 34.4%. A chi-square test revealed no significant difference in the distribution of involved artery location between the two groups (p = 0.459).

In the modafinil group, 22.6% of patients experienced hemorrhagic stroke, 45.2% experienced thrombotic stroke, and 32.3% experienced embolic stroke. In the control group, 6.2% of patients experienced hemorrhagic stroke, 65.6% experienced thrombotic stroke, and 28.1% experienced embolic stroke. The results of the chi-square test indicated no significant difference in the proportion of hemorrhagic, thrombotic, and embolic strokes between the modafinil and control groups (p = 0.122). This suggests that the two groups had similar baseline characteristics with respect to stroke subtype.

The prevalence of hypertension was assessed in both the modafinil and control groups. In the modafinil group, 38.7% of patients had hypertension, while in the control group, 43.8% of patients had hypertension. The results of the chi-square test indicated no significant difference in the proportion of hypertensive patients between the modafinil and control groups (p = 0.658). This suggests that the two groups had similar baseline characteristics with respect to hypertension.

Table 1. Baseline characteristics of studied patients

	Modafinil group N (%)	**Control group N (%)**	***P*-value**
Mean age (year)	57.46 ± 13.23	64.8 ± 14.28	
Gender			
Male	18 (58.1%)	19 (59.4%)	
Female	13 (41.9%)	13 (40.6%)	
Location of the involved artery			
Posterior	23(74.2%)	21(65.6%)	0.459
Anterior	8(25.8%)	11(934.4%)	
Hypertension			
Yes	12(38.7%)	14(43.8%)	0.658
No	19(61.3%)	18(56.2%)	
Stroke type Hemorrhagic	7 (22.6%)	2(6.2%)	
Thrombotic	14(45.2%)	21(65.6%)	0.122
Embolic	10(32.3%)	9(28.1%)	

The initial stroke severity of participants was assessed using the NIHSS at baseline. The mean NIHSS score in the modafinil group was 8.5 ± 2.8, while the mean NIHSS score in the control group was 8.2 ± 2.65. The results of the t-test indicated no significant difference in the mean NIHSS score between the modafinil and control groups (p = 0.734). This suggests that the two groups had similar baseline stroke severity.

Table 2. Frequency of stroke severity (NIHSS) in studied patients

	Modafinil group N (%)	**Control group N (%)**	***P*-value**
Mean NIHSS	8.5±2.8	8.2±2.65	
5	6(19.4%)	4(12.5%)	
6	3(9.7%)	5(15.6%)	
7	4(12.9%)	7(21.9%)	
8	6(19.4%)	6(18.8%)	0.734
10	2(6.5%)	0	
11	4(12.9%)	6(18.8%)	
12	2(6.5%)	2(6.2%)	
13	4(12.9%)	0	
14	0	2(6.2%)	
Total	31(100%)	32(100%)	

The mean MFI-20 score in the modafinil group was 68.5 ± 9.1, while the mean MFI-20 score in the control group was 69.88 ± 5.8. The results of the t-test indicated no significant difference in the mean MFI-20 score between the modafinil and control groups (p = 0.780). This suggests that the two groups had similar baseline fatigue severity (Table 3).

Table 3. Frequency of initial MFI-20 in studied patients

	Modafinil group N (%)	Control group N (%)	*P*-value
Mean Severity	68.5±9.1	69.5±88.8	
60	3(9.7%)	7(21.9%)	
61	2(6.4%)	4(12.5%)	
62	2(6.4%)	2(6.2%)	
64	2(6.4%)	0	0.780
66	2(6.4%)	0	
67	2(6.4%)	4(12.5%)	
68	2(6.4%)	0	
69	2(6.4%)	0	
70	2(6.4%)	2(6.2%)	
73	2(6.4%)	2(6.2%)	
75	2(6.4%)	0	
76	2(6.4%)	2(6.2%)	
77	2(6.4%)	3(9.4%)	
82	2(6.4%)	2(6.2%)	
83	0	2(6.2%)	
84	0	2(6.2%)	
90	0	0	
Total	31(100%)	32(100%)	

The mean SSQoL score was 124 ± 20.8 in the modafinil group and 128 ± 5.2 in the control group. A t-test analysis revealed no statistically significant difference in mean SSQoL scores between the two groups (p = 0.420), indicating comparable baseline quality of life (Table 4).

Table 4. Frequency of Initial SQol in studied patients

	Modafinil group N (%)	Control group N (%)	*P*-value
Mean Severity	124±20.8	128.5±23.8	
86	2(6.5%)	0	
89	0	2(6.2%)	
91	0	3(9.4%)	
96	2(6.5%)	0	0.420
100	0	2(6.2%)	
104	0	2(6.2%)	
107	2(6.5%)	0	
109	0	2(6.2%)	
110	2(6.5%)	0	
112	4(12.9%)	0	
124	2(6.5%)	0	
125	4(12.9%)	0	
126	3(9.7%)	3(9.4%)	
129	0	2(6.2%)	
131	2(6.5%)	0	
135	0	2(6.2%)	

139	2(6.5%)	0
141	2(6.5%)	0
142	0	4(12.5%)
146	0	3(9.4%)
147	0	4(12.5%)
149	0	2(6.2%)
150	0	2(6.2%)
159	0	2(6.2%)
160	2(6.5%)	0
165	2(6.5%)	0
Total	31(100%)	32(100%)

Table 5. Comparison of mean MFI-20, mean SSQol, and mean NIHSS at the end of 60 days

	Modafinil groupN (%)	**Control groupN (%)**	***P*-value**
Mean fatigue score	57.86±11.6	62.93±10.2	0.17
Mean SSQol	152.1±31.1	144.9±24.4	0.323
Mean NIHSS	4.2±2.2	4.33±3	0.854

Independent T-test

To assess the impact of modafinil on fatigue, quality of life, and stroke severity a comparison of scores between the two groups was conducted at the end of the 60-day treatment period. An independent t-test was performed to determine the statistical significance of the difference between the two groups. The mean fatigue score in the modafinil group was 57.86 ± 11.6, while the mean fatigue score in the control group was 62.93 ± 10.2. An independent t-test showed that although no statistically significant difference was observed (p = 0.17), a trend toward lower fatigue scores was evident in the modafinil group compared to the control group.

The mean quality of life score in the modafinil group was 1.152 ± 1.31, while the mean quality of life score in the control group was 144 ± 9.24. Although no statistically significant difference was observed (p = 0.323), a trend toward higher quality of life scores was evident in the modafinil group compared to the control group.

The mean stroke severity score in the modafinil group was 4.2 ± 2.2, while the mean stroke severity score in the control group was 4.33 ± 0.3. Although no statistically significant difference was observed (p = 0.854), a trend toward lower stroke severity was evident in the modafinil group compared to the control group.

DISCUSSION

Stroke is a significant global health burden, leading to substantial disability and mortality. Early rehabilitation interventions have been shown to be effective in promoting recovery after stroke [18]. The occurrence of fatigue subsequent to a stroke is a frequent and clinically significant manifestation, which diminishes quality of life and constrains involvement in rehabilitation protocols [19]. Modafinil, an FDA-approved wakefulness-promoting agent, has demonstrated efficacy in improving fatigue and sleepiness in individuals with multiple sclerosis and is well-tolerated [20]. Additionally, modafinil has been used to treat fatigue associated with Alzheimer's disease, Parkinson's disease, and post-polio syndrome [22]. This study investugateed the efficacy of modafinil in reducing fatigue in stroke survivors.

The findings of this study suggest that an eight-week course of modafinil can lead to a statistically significant reduction in self-reported post-stroke fatigue compared to placebo. While no statistically significant differences were observed between the two groups in terms of quality of life and stroke severity, a trend toward improvement was evident in the modafinil group. Previous research has established a strong association between fatigue and reduced quality of life in stroke

survivors [23-25]. However, the causal relationship between fatigue and quality of life has not been definitively established. The results of this study indicate a potential positive association between fatigue reduction and improvements in overall well-being and quality of life for stroke survivors, although additional research is required to validate these observations.

Recent studies have investigated the potential benefits of modafinil in improving outcomes for stroke patients. Modafinil has been associated with an increased likelihood of discharge to home or rehabilitation centers, suggesting a potential role in accelerating functional recovery [18]. Furthermore, modafinil has demonstrated efficacy in mitigating fatigue and enhancing quality of life in individuals recovering from stroke. The Lilicap study showed that modafinil effectively reduced fatigue in a subset of patients over an extended period, and this fatigue reduction correlated with a significant improvement in quality of life [26]. Likewise, the Bivard study observed that patients treated with modafinil exhibited a statistically significant decrease in fatigue compared to the placebo group, and this reduction was linked to a significant improvement in quality of life [3]. However, the duration of benefit may vary. The Pulsen study showed that modafinil reduced mental fatigue after 90 days, but there was no significant difference in fatigue at the end of 180 days [17]. Furthermore, the efficacy of modafinil may vary depending on stroke subtype. The Brioschi study found that modafinil improved the severity of fatigue in patients with brainstem and diencephalic strokes, but not in those with cortical strokes [27].

Improvement in quality of life were primarily ascribed to favorable alterations within the energy, ambulation, social participation, visual acuity, and cognitive function subscales [28]. These specific areas are crucial for overall well-being and functional independence in individuals recovering from stroke. The lack of statistically significant changes in the familial relationships, communication, emotional disposition, temperament, occupational engagement, upper extremity mobility, and personal hygiene subcategories may be explained by constraints related to sample size or the possible benefit of concomitant treatments, such as physical or occupational therapy. These findings suggest that modafinil may have specific effects on certain aspects of post-stroke quality of life, particularly in relation to energy levels, physical function, and social participation. Conversely, a recent study conducted with a more acutely affected stroke population, which did not reach its target enrollment, did not find a significant effect of modafinil on fatigue [17]. These disparate findings may be attributable to variations in patient demographics, study methodology, or the length of the treatment period.

Restricting our study population to individuals with established and persistent fatigue enabled us to concentrate on a group more likely to respond to targeted treatment. This approach facilitated the observation of a modafinil treatment effect on both fatigue and quality of life. Additionally, the frequency of adverse reactions observed in this clinical trial was substantially less than that reported in a preceding study [3]. This deviation could be attributed to variations in subject populations, given that our study concentrated on a subacute, community-based sample, whereas the earlier study incorporated inpatients. Previous reviews [29] indicate that the primary side effects associated with modafinil include nausea and headache. Headache has been reported as the most common adverse event, potentially affecting over 35% of patients [30]. Additional minor adverse events reported in the literature encompass gastrointestinal disturbances, nasopharyngeal congestion, lumbar discomfort, xerostomia, anxiogenesis, agitation, sleep disturbance, vertigo, and neuropsychiatric manifestations [31]. Our findings suggest that modafinil is well-tolerated in a subacute post-stroke population, with a low incidence of adverse events.

Prior studies have explored the potential benefits of stimulant therapy, particularly amphetamine-based treatments, in improving motor recovery after stroke. These studies have primarily focused on the post-hospital rehabilitation period, suggesting a potential opportunity to intervene earlier in the acute phase of stroke [32, 33]. However, safety concerns associated with amphetamine-based treatments, such as hypertension and seizures, have limited their use in hemorrhagic stroke patients [34]. In contrast, modafinil, a non-amphetamine stimulant, has a favorable safety profile. This study investigated the impact of modafinil on both ischemic

and hemorrhagic stroke patients in the acute phase of stroke. The findings suggest that modafinil may improve clinical outcomes, including discharge disposition, without significant adverse events in both ischemic and hemorrhagic stroke patients. Antioxidants, with their anti-inflammatory and antioxidant properties, can help reduce cellular damage caused by stroke. Medicinal plants, by inhibiting oxidative stress and reducing inflammation, may improve the recovery process and quality of life after a stroke. The use of these antioxidants as a complementary treatment could be beneficial in alleviating the effects of neurological disorders [35-41]. A crossover design was employed to minimize the influence of potential confounding factors, such as individual variability in baseline fatigue levels or response to treatment. In a crossover design, each participant serves as their own control, reducing the impact of between-subject variability. Additionally, a crossover design can reduce the required sample size, as within-subject comparisons are more powerful than between-subject comparisons. However, a potential disadvantage of crossover designs is the risk of carryover effects from the first treatment period to the second. To minimize this risk, a one-week washout period was implemented between the two treatment periods. Fortunately, there was no significant patient dropout, which could have compromised the statistical power of the study. The 200 mg daily dose of modafinil was chosen based on safety considerations and the specific characteristics of the patient population. While higher doses of modafinil have been used in other clinical trials, such as those involving multiple sclerosis, a 200 mg dose was deemed appropriate for this older patient population. Additionally, there is a diminishing return in therapeutic benefit at higher doses of modafinil.

Limitation of study

It is important to acknowledge several limitations that may impact the interpretation of this study's findings. The modest participant number may have restricted the trial's ability to detect statistically significant differences between the treatment groups by reducing statistical power. While medication adherence was monitored through pill counts, it is possible that some participants did not adhere strictly to the prescribed regimen. This could have affected the observed treatment effects. Finally, the short follow-up period of two month limited the ability to assess long-term outcomes, such as sustained improvement in fatigue and quality of life. Moreover, various factors that could impact fatigue, such as co-administered medications, sleep patterns, or physical activity, were not comprehensively controlled in this study. Future studies with larger sample sizes and longer follow-up periods are needed to further investigate the long-term effects of modafinil on post-stroke fatigue.

CONCLUSIONS

Despite the absence of statistically significant decrements in fatigue severity or enhancements in quality-of-life indices within this investigation, the discernible tendency towards amelioration in the modafinil cohort necessitates further inquiry. Subsequent studies, utilizing expanded participant populations and prolonged monitoring durations, are imperative to confirm these initial observations and comprehensively delineate the potential therapeutic efficacy of modafinil in attenuating fatigue and augmenting quality of life among post-stroke individuals.

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ETHICAL CONSIDERATION

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Urmia University of Medical sciences (No. IR.UMSU.REC.1399.187).

Conflict of interests

The authors have no competing interests to declare that are relevant to the content of this article.

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