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Effect of Methylphenidate and/or Levodopa Combined with Physiotherapy on Mood and Cognition after Stroke: A Randomized, Double-Blind, Placebo-Controlled Trial

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Key Words
Cognition · Mood · Rehabilitation pharmacology · Stroke

Abstract
Background/Aim: Stimulant medications can enhance mood and cognition in stroke rehabilitation, but human clinical trial results are inconclusive. We sought to prospectively study the effects of levodopa (LD) and/or methylphenidate (MPH) in combination with physiotherapy on mood and cognition following stroke in human subjects. ***Methods:*** Ischemic stroke patients were enrolled in our study 15 to 180 days after stroke onset. The patients were randomized into four medication groups (MPH, LD, MPH + LD, or placebo) and received a 15-day course of medication therapy (1 dose daily) and 45-min standard physiotherapy treatment daily. Mood and cognitive function were assessed at the study onset and 15, 90 and 180 days after study enrollment. ***Results:*** The strongest improvement of mood and cognition was found between baseline and the first follow-up immediately after the intervention. A significant improvement in mood was also found in the combined treatment group (MPH + LD) at 90 and 180 days, compared to the placebo group. ***Conclusions:*** A 15-day course of daily MPH + LD combined with physiotherapy over a 3-week period was safe and significantly improved mood status in ischemic stroke patients. Future studies are needed which determine the optimal therapeutic window for and dosage of psychostimulants as well as identify those stroke patients who might benefit the most from treatment.

Introduction

The physical and psychological sequelae caused by stroke can be devastating [1]. Post-stroke depression (PSD) is the most common neuropsychiatric consequence of stroke [2] and affects 6–79% of stroke survivors [3]. Early recognition and effective treatment of PSD leads to more favorable functional and psychosocial outcomes and reduces disease burden as well as morbidity and mortality [4]. In a recent systematic review, Hackett et al. [5] reported that antidepressants could reduce mood disorder symptoms among PSD patients but had no clear effect on prevention or remission of depressive illness after stroke. As deficits in central catecholamine levels are thought to play a major role in the etiology of PSD, en-

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hancement of central catecholaminergic levels via stimulant use has been proposed to be a therapeutic strategy for PSD [6]. Having catecholamine-stimulating properties, methylphenidate (MPH) and levodopa (LD) are both ideal pharmacologic agents to treat PSD due to cost considerations, favorable pharmacodynamics/pharmacokinetics, and side effect profiles relative to other stimulant medications [7–10]. Preliminary studies of stimulant medication use during stroke rehabilitation and PSD have been favorable [11], but randomized clinical trials in subacute and chronic phases are still needed to identify optimal pharmacotherapies. Accordingly, the aim of this study was to determine if LD and/or MPH in combination with physiotherapy could improve mood and cognition in stroke patients.

Methods

Patient Selection Criteria

Patients from 8 acute care hospitals located in Tehran and Qom, Iran, who presented and were diagnosed with ischemic chronic stroke and limb (arm or leg) paresis between March 2006 to September 2008, were enrolled. The enrollment window ranged from 15 to 180 days after stroke onset to permit acute management of stroke. Consenting patients were subsequently admitted for outpatient rehabilitation treatment at the Neurorehabilitation Clinic of Rofeydeh Hospital affiliated to the University of Social Welfare and Rehabilitation, Tehran, Iran. Demographic data collected from research participants included gender, age, established cerebrovascular risk factors, dominant paretic side, time of stroke onset, and history of previous stroke.

Patients were excluded if (a) they were unable to respond or directly consent; (b) they had comorbidities requiring strict blood pressure control and would be put at risk by the potential of hypertension from MPH therapy (history of hemorrhagic stroke, recent myocardial infarction within a 4-week period, decompensated cardiac insufficiency, tachycardia, uncontrolled hypertension, unstable metabolic disease, and glaucoma); (c) they may suffer adverse outcomes from the stimulant effects of MPH, including seizure and agitation; (d) they had major cognitive deficits that would prevent adequate study participation; (e) they are currently taking alpha-adrenergic agonists, antagonists, neuroleptics, benzodiazepines, MAO inhibitors, or anti-depressants, and (f) if they had a known hypersensitivity to MPH or LD.

The study was approved by the Ministry of Health in Iran and the Ethics Committee of University of Social Welfare and Rehabilitation. All patients provided written informed consent.

Randomization

Consenting patients were randomized into a double-blind, placebo-controlled trial with a 2 × 2 factorial design using a computerized randomization program. Initial randomization was performed by individuals unrelated to the study. Patients were divided into four groups, i.e. MPH, LD, MPH + LD, and placebo (P).

Physiotherapy

Patients received a daily 45-min session of standard physiotherapy treatment with a goal-oriented approach focusing on mobilization using selective movements (coordination exercises, strengthening exercises and active relaxation), lying, sitting and standing, balance using sensory and visual perceptual training and cognition, transfers, and ambulatory activities incorporating personal activities of daily living (ADL) and domestic ADL [12]. Movements were practiced with progressively more complex functional activities designed to promote the return of selective muscle control of the trunk and limbs [13]. All therapists provided the patients with a standardized rehabilitation program. The training content, but not duration, varied for each patient, depending on the severity of his or her paresis. Individuals also received additional rehabilitation such as speech therapy treatment, depending on their neurological impairments. The patients were monitored during all sessions to ensure that they received standard rehabilitation and that evaluations were performed adequately.

Pharmacotherapy

The drugs, i.e. MPH and/or LD and P, were randomly distributed in opaque boxes labeled 1–100. The drug protocol developed for this study was based on what was prescribed and suggested in previous studies [14] (MPH at a mean dose of 17 mg per day in PSD). In this four-group intervention model, drug treatment was given in the form of identical white tablets of 2 × 10 mg of either MPH or P and a tablet with either 125 mg LD or P. These tablets were administered at least 1 h before the training session to coincide with the timing of the peak pharmacological action of the drugs [15, 16]. Treatments were continued for 5 days per week for a total of 15 drug therapy sessions. Blood pressure and heart rate were monitored for 2 h before and after medication administration. In addition, patients were observed for known side effects of LD (cardiovascular symptoms, nausea, vomiting, and psychosis) and MPH (insomnia, nausea, or nervousness) during their rehabilitation.

Outcome Measures

Mood was assessed by the Geriatric Depression Scale (GDS) using the methods described by Johnson et al. [17] and Agrell and Dehlin [18]. The GDS measures changes in the affective rather than somatic components of depression and mood using a 15-item questionnaire. Depression was defined as a GDS of 7.8 or less, based upon previous ROC curve analysis (a sensitivity of 0.9 and a specificity of 0.84) [19]. Cognitive function was assessed by means of the Mini-Mental State Examination (MMSE) [20], an exam consisting of 19 questions scored 0 to 30 that addresses five areas of cognitive function: orientation to place and time, registration, attention and calculation, recall, and language. For the purposes of our study, we defined cognitive impairment as an MMSE score of 21 or lower. Previous efforts by Foroughan et al. [21] have shown this score to have an optimal balance with a sensitivity of 0.9 and a specificity of 0.84.

Statistical Analysis

Descriptive statistics calculated for continuous numeric data were means, standard deviations, frequencies, and percentages. Cognitive and depression scores were dichotomized to cognitive normality (MMSE >21) versus cognitive impairment (MMSE ≤ 21) and to non-depression (GDS <8) versus depression (GDS ≥ 8). The non-parametric one-sample Kolmogorov-Smirnov test

Table 1. Demographic characteristics for the four groups

	All	MPH	LD	MPH + LD	Placebo	p value
Mean age ± SD, years	64 ± 9.8	64.05 ± 10.8	66.3 ± 9.5	60.2 ± 9.1	65.3 ± 9.6	0.230
Gender, n						
Men	48	9	14	11	14	0.403
Women	30	10	6	8	6	
Mean time since stroke ± SD, days	65.6 ± 34.2	66.26 ± 40.7	67.8 ± 32.1	73.6 ± 41.5	54.9 ± 18.1	0.386
Prior stroke, n						
Yes	6 (7.7)	3 (15.8)	2 (10)	0	1 (5)	0.297
No	72 (92.3)	16 (84.2)	18 (90)	19 (100)	19 (95)	
Risk factors, n						
HTN	57 (73.1)	18 (31.6)	15 (26.3)	11 (19.3)	13 (22.8)	0.059
DM	44 (65.4)	9 (20.4)	14 (31.8)	6 (13.6)	15 (34.1)	0.021
HLP	39 (50.0)	12 (30.8)	8 (20.5)	10 (25.6)	9 (23.1)	0.500
HD	22 (28.2)	3 (13.6)	7 (31.8)	6 (27.3)	6 (27.3)	0.564
Smoking	18 (23.1)	5 (27.8)	5 (27.8)	4 (22.2)	4 (22.2)	0.959
Paretic side (right/left), n	45/33 (57.7/42.3)	10/9 (52.6/47.4)	13/7 (65/35)	11/8 (57.9/42.1)	11/9 (55/45)	0.874

Figures in parentheses indicate percentages. HTN = Hypertension; DM = diabetes mellitus; HLP = hyperlipidemia; HD = heart disease.

was used to identify the normality of variables, and logistic regression was used to calculate odds ratios relating age, gender, days since stroke onset, earlier history of stroke, paretic side, and risk factors. For each assessment time point (baseline, 15, 90 and 180 days), the MMSE and GDS scores were collected from each of the four treatment groups (MPH, LD, MPH + LD, and P) and were compared using ANOVA or Kruskal-Wallis test, based upon data normality. A repeated-measures ANOVA was used to identify improvements in MMSE and GDS scores with time among the four treatment groups and to identify differences in efficacy between the treatment groups at each time point.

Results

Among 1,043 stroke patients initially screened in Qom and Tehran, a total of 100 ischemic stroke patients met all inclusion criteria and consented for further study. 632 patients failed to meet the inclusion criteria due to excessive duration between stroke onset date and discharge from the acute care hospital. Of the 100 patients who participated in our study, 22 were lost to follow-up either due to death (n = 15; 4.2%) or participation failure (n = 7; 11.5%). The causes of death were related to the initial stroke and not found to be a result of the study intervention. The 22 patients lost to follow-up were not significantly different from the 78 individuals completing the study with respect to age, gender, or delay from stroke onset to treatment. Among the four randomized groups, no significant differences were observed concerning demographic (age and gender) or clinical characteristics (days since stroke onset, prior stroke, hyperlipidemia, heart disease, smoking, and paretic side of stroke; table 1). However, the incidence of diabetes mellitus was significantly different between the groups (p = 0.021). No negative side effects were observed in any group.

Outcome of Mood and Cognitive Function

Table 2 shows the scores and outcomes at baseline and at the three follow-up assessments of cognitive function. Baseline data of cognitive function (MMSE) and depression (GDS) were homogeneous and well balanced in all four groups.

No significant differences in the MMSE score were observed between the groups in general or with repeated measures. A post hoc t test revealed that the groups did not show any difference at any time of assessment concerning MMSE score ($p > 0.1$). Cognitive status, as measured by the MMSE, improved in all four treatment groups as time progressed ($F3, 74 = 156.914$, $p = 0.000$). Improvements were most substantial between baseline measures and the first follow-up at 15 days (table 2). When the patients were grouped based upon the presence of depression (GDS <8 and GDS ≥ 8, respectively), we found depressed patients to have significantly greater improvement in MMSE scores than patients who were not depressed.

Mood status, as measured by GDS, improved significantly and continuously in all four groups between baseline and the three follow-up assessments ($F3, 74 = 32.927$,

Table 2. MMSE scores at baseline and at the three follow-up assessments for the four groups

	Baseline	15 days	90 days	180 days
Cognitive impairment				
Mean of MMSE ± SD	17.9 ± 3.43	16.87 ± 3.7	17.31 ± 3.3	17.47 ± 3.5
n (%)	36 (46.1)	15 (19.2)	13 (16.7)	13 (16.6)
Cognitive normality				
Mean of MMSE ± SD	25.4 ± 2.36	25.7 ± 2.27	26.5 ± 2.33	26.7 ± 2.36
n (%)	42 (53.8)	63 (80.7)	65 (83.3)	65 (83.3)
MPH	21.1 ± 3	23.7 ± 2.9	24.7 ± 3.2	24.9 ± 3.3
LD	22 ± 5.2	24.4 ± 4.9	25.3 ± 4.8	25.3 ± 5
MPH + LD	23.5 ± 4	25.1 ± 3.7	26 ± 3.2	26.3 ± 3.4
Placebo	21.1 ± 6.1	22.8 ± 5.4	23.8 ± 5.3	24.2 ± 5.2
Group effect				
F	3.231	1.008	2.540	0.859
p	0.357[a]	0.394[b]	0.468[a]	0.466[b]
Time effect				
F			156.914	
p			0.000	
Group × time effect				
F			0.537	
p			0.659	
Post hoc comparison				
p	n.s.	n.s.	n.s.	n.s.
Post hoc comparison of time points, t value				
p	9.07[c]	0.000	6.668[f]	0.000
	11.609[d]	0.000	8.225[g]	0.000
	12.459[e]	0.000	2.377[h]	0.000

Figures are means ± SD, unless otherwise indicated. Higher scores of MMSE indicate better function. n.s. = Not significant.
[a] p value of χ^2 test. [b] p value of F test. [c] Baseline vs. 15-day follow-up. [d] Baseline vs. 90-day follow-up. [e] Baseline vs. 180-day follow-up. [f] 15-day vs. 90-day follow-up. [g] 15-day vs. 180-day follow-up. [h] 90-day vs. 180-day follow-up.

$p < 0.0001$; table 3). As in cognitive function, the most substantial improvements were observed between baseline and the first time point at 15 days (table 3). GDS scores improved significantly between baseline and 15-day assessments ($p < 0.05$), 15-day and 90-day assessments ($p < 0.05$), as well as between 90-day and 180-day assessments ($p < 0.05$; table 3). GDS scores differed significantly between the groups when performing two-way (group x time of assessment) ANOVA. A post hoc t test showed that the combined treatment (MPH + LD) differed significantly from the placebo treatment at 90 days ($p = 0.018$) and 180 days ($p = 0.006$; table 3).

Discussion

This study revealed that a 3-week regimen of physiotherapy and daily MPH and/or LD therapy significantly improved mood without eliciting major side effects or adversely affecting cognition in ischemic stroke patients. These findings suggest that dopaminergic neuromodulation combined with physical activity may enhance mood in ischemic stroke survivors.

The results of this study are consistent with those reported by Lazarus et al. [22] who demonstrated that over half of their study population (n = 53) experienced remission of depressive symptoms. In addition, they also demonstrated that response to MPH therapy was significantly faster than response to nortriptyline therapy (2.4 vs. 27 days). This is consistent with the clinical experience where traditional antidepressant therapy often fails due to intolerance in up to one third of patients [23] or delayed onset of action [24]. The prevalence of depression in our study population is in line with that reported in other studies where in females, depression ranged from 5.9 to 78.3% [25] and in males from 4.7% [26] to 65.2% [27]. We had a significantly higher prevalence of depression in females than in males at baseline,

Table 3. GDS scores at baseline and at the three follow-up assessments for the four groups

	Baseline	15 days	90 days	180 days
Depressed				
Mean of GDS ± SD	9.91 ± 1.46	8.62 ± 1.06	8.42 ± 0.79	8.57 ± 0.53
n (%)	33 (42.3)	8 (10.3)	7 (8.9)	7 (8.9)
Non-depressed				
Mean of GDS ± SD	4.4 ± 2	4.67 ± 1.4	4.34 ± 1.64	4.14 ± 1.77
n (%)	45 (57.7)	70 (89.7)	71 (91.1)	71 (91.1)
MPH	6.7 ± 3.5	5.1 ± 1.7	4.5 ± 1.9	4.3 ± 2
LD	7.2 ± 3.6	5.4 ± 1.9	4.8 ± 1.9	4.8 ± 2.4
MPH + LD	6.4 ± 2.6	4.1 ± 0.9	3.7 ± 1.3	3.4 ± 1.3
Placebo	6.5 ± 3.5	5.7 ± 2.1	5.7 ± 2.2	5.7 ± 2.1
Group effect				
F	0.199	11.944	3.683	4.694
p	0.896[a]	0.008[b]	0.016[a]	0.005[b]
Time effect				
F			32.927	
p			0.000	
Group × time effect				
F			1.564	
p			0.205	
Post hoc comparison (MPH + LD < placebo)				
p	n.s.	n.s.	0.018	0.006
Post hoc comparison of time points, t value				
p	5.447[c]	0.000	2.850[f]	0.006
	5.537[d]	0.000	3.414[g]	0.01
	5.714[e]	0.000	1.580[h]	0.118

Figures are means ± SD, unless otherwise indicated. Higher scores of GDS indicate worse function. n.s. = Not significant.
[a] p value of F test. [b] p value of χ^2 test. [c] Baseline vs. 15-day follow-up. [d] Baseline vs. 90-day follow-up. [e] Baseline vs. 180-day follow-up. [f] 15-day vs. 90-day follow-up. [g] 15-day vs. 180-day follow-up. [h] 90-day vs. 180-day follow-up.

but gender did not have a significant impact on outcome variables.

Rapid response time is a positive feature of MPH and LD when treating dysthymic stroke patients since they are often weakly motivated and poorly responsive to rehabilitation. Moreover, Grade et al. [11] found that stroke patients receiving 5–30 mg MPH daily for 3 weeks showed improvements in mood, although no differences between the MPH and placebo groups regarding cognitive function assessed by the MMSE could be observed. However, when we divided the patients into two groups based on whether or not they were depressed, we found that treated depressed patients showed a significantly greater improvement in MMSE scores than non-depressed patients. It seems that patients with stroke had partially reversible cognitive dysfunction when their depressive disorder was successfully treated [28].

Our finding that mood recovery is improved by a combined treatment (MPH + LD) accords with the result of a previous investigation in which there was a significant difference in the Barthel Index compared to placebo [29]. It seems that combination therapy may have a widespread effect on ADL and mood recovery by the presence of L-dopa, thereby causing increased dopamine levels. We found that patients with PSD had significantly less recovery in their ADL functions than the post-stroke non-depressed patients. The results of this study are consistent with those reported by Chemerinski et al. [30], who showed that in patients who recovered from PSD, a significantly greater improvement in ADL could be observed than in stroke patients whose depression did not remit. The mean or average daily dosage of MPH in other published trials varied between 8 and 30 mg [11, 31–33]. MPH and LD are mild psychostimulants structurally related to amphetamine and have similar qualities [34]. Effects peak 2 h after a single dose of MPH and LD and persist for 3–6 h [16, 35]. The ease of administration, the speed of response and the relatively few side effects could

make MPH an attractive alternative for the treatment of mood disorder in stroke patients [34]. The therapeutic effects of MPH in the treatment of depression has been attributed to its ability to improve mood, motivation and other cognitive functions including attention, working memory, and executive functions [36].

Cognitive impairment is frequently associated with mood disorder in stroke patients, and the nature of the relationship between cognitive impairment and PSD remains complex [37]. In our study, we found no group differences regarding cognition. However, the depressed patients showed significantly greater improvements in cognitive function than the non-depressed individuals, which is in line with earlier findings where stroke patients have partially reversible cognitive dysfunction when their depressive disorder is successfully treated [28].

We suggest that the lack of effect of MPH and/or LD on cognitive impairment might in part be related to the cognitive assessment scale, which is not sensitive enough to catch minor changes. The MMSE as a standardized scale for the assessment of cognitive function evaluates five areas of cognitive functions. Although it is sensitive to attention, recall, and language, it does not encompass all the cognitive deficits and is particularly weak in its ability to measure executive functions such as abstract thinking, judgment, problem solving, and perception [38].

Neuropsychiatric sequelae after stroke seem to have a natural recovery course [39]. The main theories recognized to date state that most spontaneous recovery tends to arise within the first 3 months after stroke onset, and that cognitive impairments are more likely than motor deficits to show spontaneous achievements beyond those months. In our study, the strongest improvement of time effect in mood and cognitive functions occurred during the first 15 days of treatment. However, it is difficult to differentiate spontaneous from therapy-induced recovery [40].

Some study limitations exist. The primary limitation was the small sample size. We experienced similar difficulties with patient recruitment as other studies due to a wide range of exclusion criteria. Although we chose wide inclusion criteria for stroke patients, more than 90% of the screened stroke patients did not meet the initial eligibility criteria and were therefore excluded. However, 78 patients of the 100 finally recruited patients completed the study. Although MPH and LD affected mood function significantly in our study, the effect size was not consistently large. Larger and perhaps more consistent effects may be achieved with a higher dose of active drugs, with a more frequent and longer duration of treatments, with recruitment of patients earlier after stroke onset, and by identifying patients prone to respond to treatment. Studies that showed a significant effect of MPH and LD on mood and cognition recruited patients early after stroke onset, i.e. 3–40 days after the stroke, while in our study patients entered the trial on average 65.6 days after stroke onset [11, 41, 42]. Nevertheless, the studies up to now are limited in a number of ways, and definitive conclusions cannot yet be drawn. The sample sizes were small, follow-up periods were either missing or relatively short, a wide range of drug doses was used, and the results were unconvincing or discrepant. Thus, further evaluation with large randomized, placebo-controlled, double-blind trials is needed to more clearly assess the role of MPH and LD in neuropsychiatric sequelae after stroke.

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