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The Effect of Levodopa on Motor Function Outcome in Patients with Ischemic Stroke: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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ABSTRACT

Levodopa enhances neuronal plasticity and functional recovery and modulates anatomical and functional variations in central nervous system. The present study was aimed to evaluate the effect of levodopa-C on motor function recovery of patients experienced a stroke. This was a randomized, placebo-controlled, double-blind clinical trial conducted on 114 patients with ischemic middle cerebral artery stroke. The patients after the first day of stroke were randomly divided into two groups: the levodopa-C group and placebo group. In addition to the intervention, the patients received the stroke routine medications during the study. The patients received 100 mg daily medication for 3 weeks. A significant improvement was observed in motor function criteria of Rivermead mobility index (RMI) ($p = 0.006$) and Barthel index (BI) ($p = 0.009$) after 21 days in the levodopa-C group (79.1 %), compared to the placebo group (49 %). A review was carried in the subgroups, which indicate that patients with cortical stroke in the levodopa group had a significant improvement, compared with the placebo group ($p = 0.005$). The basic motor functions of about 79 % of the levodopa-C patients ($n = 35$), compared with the 44% in the placebo group, were enhanced by 25% according to the BI and RMI criteria ($p = 0.008$). Most of these patients had cortical stroke. Our findings showed significant therapeutic effect of levodopa-C in the patients with cortical stroke. Larger clinical trials containing larger sample size with cortical ischemic stroke are needed to better assess the impact.

Keywords: Ischemic stroke, levodopa–C, Motor Function Improvement, Middle Cerebral Artery, Rivermead Mobility Index, Barthel Index Clinical Trials, Placebo..

INTRODUCTION

Stroke is the third most common cause of death after cardiovascular and cancer diseases and is one of the most common causes of disability in adults. The overall mortality of stroke in the most advanced medical centers is about 12%. Those who survive often lose their performance and economy and would impose a psychological burden to family and society[1]. During the recent years many studies have been conducted to develop effective drugs that meet the desired safety and convenient availability. Therefore, some drugs such as simvastatin[2], and methylphenidate[3] (Ritalin) have been studied, but the results of clinical trials were controversial and have not verified the efficacy of these drugs in terms of performance of motion recovery[4,5]. However a survey on patients with ischemic stroke who were treated with methylphenidate in combination with levodopa, the

drug-treated groups significantly improved motor function was seen with placebo[6].

Currently, the only option available for the recovery of motor function in patients who are developing disability caused by stroke, is practical techniques of physiotherapy and occupational therapy, but even in the centers equipped with beds for stroke and numerous sessions and suitable for physiotherapy, 36% of patients at the time of discharge, will have moderate to severe decline[7]. Therefore, drugs that can affect the central nervous system, can improve the rehabilitation and completion of new neural circuits. Several studies during the past few years have developed drugs affecting noradrenergic transmission system, including levodopa which has shown neuroprotective and neurotrophic effects in animal and human samples[8]. Appropriate pharmacokinetics, high safety, and little side effects make this drug a good candidate for modulating the dopaminergic system in Parkinson's disease[9-16]. It is also able to reduce the effects of toxic factors and stimulates the secretion of Brain Derived Neurotrophic Factor (BDNF) and Vascular Endothelial Growth Factor (VEGF)[17]. In addition to the main features of neuroprotective, these factors increase neurogenesis and modulation of neuronal plasticity, nerve growth, inflammation, and elimination. Levodopa possesses these properties[17]. Neuronal plasticity is one of the protective processes of brain tissue after a stroke[7-10]. These factors also contribute to the regulation of cell survival and differentiation of neurons. Fibroblast growth factor: FGF-2 is useful for the repair of nervous tissue function in pathophysiological conditions such as chemical neurotoxicity, mechanical trauma and cerebral ischemia and protects cortical synaptic terminals, against amyloid and oxidative stresses dependent on the transport of glucose, glutamate and mitochondrial function[17]. The mechanisms of action of levodopa includes modulating neuronal plasticity which is facilitated through influencing the activity of dopamine receptors in the primary motor cortex[15].

In the brain levodopa is metabolized to dopamine (95%) and norepinephrine (5%). According to studies, increased motor function recovery occurs by increasing concentrations of norepinephrine in synapses[11]. Levodopa is rapidly decarboxylated so that a small part of it is available to cross the blood-brain barrier (BBB) and enter the central nervous system which is then converted into dopamine. Therefore, to increase the effectiveness of Levodopa in the brain, usually levodopa with a peripheral inhibitor of dopadecarboxylase such as carbidopa is given that decreases the dose required for this medication and its side effects (e.g., vomiting, arrhythmia, etc). Drug availability, reasonable price, and fewer complications are the main interesting factors of levodopa. In addition, previous studies have shown its beneficial effects on rehabilitation of disabled stroke patients. Therefore, this drug can significantly reduce the treatment costs, reduce the complications associated with morbidity, quality of life and ultimately can prolong the useful life of patients. Further studies on levodopa, especially evaluating the conditions and limitations of treatments and medical facilities like -tPA are of prime importance to establish it as a standard treatment option for stroke patients. The aim of this study was to investigate the usefulness of levodopa in improving motor function in patients with ischemic stroke.

MATERIALS AND METHODS

At first, those patients diagnosed with depression according to diagnostic criteria of DSM-4 and cardiovascular disease (based on examination of the heart, electrocardiography and echocardiography underwent treatment with selective serotonin reuptake inhibitors: SSRIs and tricyclic antidepressants were excluded from the study. Then, patients with ischemic stroke in the middle cerebral artery (MCA) with a 1:1 ratio were randomly included in the study. They were assigned in two groups of levodopa or placebo with the knowledge of a member of the research team who was not involved in the survey questionnaire to determine the clinical outcome.

A total of 114 patients were studied in two equal groups. In the placebo group one patient died due to aspiration pneumonia on the sixth day of the treatment and was excluded. In both groups patients were treated with the standard regimen of stroke (including aspirin 80 mg per day, atorvastatin 100

mg per day, and folic acid 10 mg per day), along with *physiotherapy* sessions per month. In the levodopa group, in addition to the above regimen, immediately after the occurrence of stroke, Patients with treated with levodopa-C tablets (containing 100 mg levodopa and 25 mg carbidopa) for a period of 21 days. In the placebo group, patients, in addition to a standard diet, received a placebo in a shape similar with the drug levodopa - C, but no clinical effect or interaction. Placebo was prepared from talc material by the School of Pharmacy.

After the 21-day treatment period, the motor function performance of the patients of two groups were assessed and compared using Rivermead mobility index (RMI) and Barthel index (BI) for life quality. The relatives of the patients were instructed to cut medication consumption for the patient if patient had any clinical complaints such as nausea, vomiting, anorexia, lethargy, psychosis, depression, weakness, palpitations, restlessness, and hallucinations and the host supervisor should be notified quickly through a special telephone line for the patient's family.

In this study none of the patients were excluded because of the adverse effects, and only in the placebo group on the sixth day of treatment, one patient died due to aspiration pneumonia and was excluded.

Data Collection

The RMI and BI were used to assess the motor function performance of the patients. RMI is a standard questionnaire designed to assess disability from stroke. This questionnaire measures the mobility potency of the patient from slight movements in the bed to running potency so that the normal condition is expressed with score 15 and more motor impairment is associated with lower scores where for perfect disability it is zero.

BI is a questionnaire for accurate assessment of quality of life of patients with stroke that assesses their ability to perform simple daily activities such as eating, personal hygiene, urination, and defecation. The scoring criterion is 0-10 and the higher the score the higher the patient's motor. In this study, the scores of both groups were compared with each other based on both criteria. Due to the descriptive nature of both criteria and non-compliance with the normal distribution, a *non-parametric test* (*Mann-Whitney U test*) was used for data analysis. C*hi-square* test was used to compare qualitative variables and *Kolmogorov–Smirnov* test (K–S test) to determine whether the sample data is normally distributed. In all tests the statistical significance level of 0.05 was set.

RESULTS

During the study, 709 patients with stroke in the middle cerebral artery (MCA) were evaluated in terms of the inclusion of screening and 114 patients were identified as eligible for inclusion and assigned to the levodopa-C or placebo groups (n = 57 in each group). Of these people 113 (57 in the levodopa group; 56 in the placebo group) have completed the study. Generally, after 21 days of treatment, a significant difference in motor function improvement was observed in the levodopa-C (79%) group, compared with the placebo group (49%) (p=0.030). For further analysis, the groups were subdivided based on the cerebral stroke type (cortical stroke versus non-cortical). Forty three patients with stroke had a cortical involvement in MCA that 35 patients in the levodopa group and eight patients in the placebo group were treated. The results obtained after 21 days of treatment with levodopa-C showed that patients with the cerebral cortical stroke in terms of improvement in motor

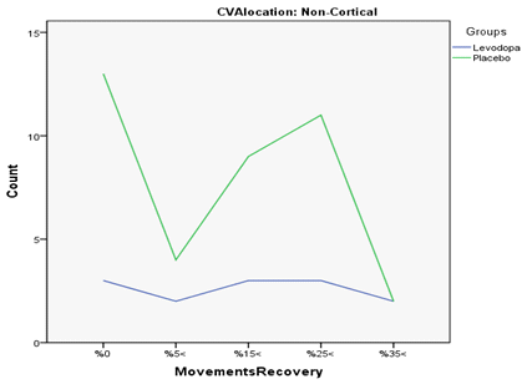

Fig. 1: Comparison of motor function performance between the levodopa-C and placebo groups for non-cortical stroke patients.

function in both RMI and BI measures, had a significant difference compared to their baseline values, the patients with non-cortical stroke did not show any significant difference (Fig. 1). Re-analysis of the data cortical versus non-cortical cerebral stroke showed that the difference is attributed to the patients with cortical stroke in the levodopa-C group (Fig. 2).

Fig. 2: Comparison of motor function performance between the levodopa-C and placebo groups for cortical stroke patients.

DISCUSSION

Results showed that early treatment with low doses of levodopa-C (ration 4:1) to 100 mg levodopa and 25 mg *carbidopa* improved the motor function performance of patients with ischemic stroke and this improvement significantly depends on the lesion site (cortical or non-cortical stroke). Improvement in the scores of RMI and BI of patients with cortical ischemic stroke in the levodopa-C group compared to the placebo group was significant, while no significant improvement was observed in both groups of patients with non-cortical ischemic stroke. Therefore, the next question is whether the dependence of improvement on the location of stroke has a scientific justification? Previous studies have indicated that functional outcome improvement in cortical ischemic strokes is better than non-cortical ischemic strokes[18].

However, fewer responses of patients with non-cortical ischemic stroke to levodopa-C (8.23%) and the differences observed in the amount of motor function improvements in patients with cortical ischemic stroke in the levodopa-c group than patients with the same stroke in the placebo group is explainable. Therefore, an overview of the Neuroprotective and neurotrophic mechanisms of levodopa and its neuronal plasticity process (by acting on receptors of dopamine[17]) may help to clarify this issue. Besides these effects, some studies have found that increasing concentrations of norepinephrine in synapses that in turn stimulate norepinephrine receptors can reduce the effects of acquired brain injury[19, 20].

Levodopa can reduce the effects of toxic factors and stimulates the secretion of brain-derived neural growth factor (BDNF) and cell growth regulator factor)VEGF (that an activated toxicity process has an essential role in the damage of neurons and the pathogenesis of ischemia[21, 22]. It should be noted that this phenomenon occurs in the early hours of the occurrence of ischemia (approximately six hours after the occurrence of ischemia)[23]. Administration of levodopa in the first day patients and because the plasma concentration of the drug 1-2 hrs after oral consumption, reach a maximum, if patients refer in a timely manner in the early hours of the occurrence of the cerebral stroke, some patients may use neuroprotective effects of levodopa that is containing effects of anti-active toxic inclusion. On the other hand, levodopa has neurotrophic effects mainly through the inhibition of GSK-2B and activating *cAMP-response element-binding protein* (*known as CREB*), which leads to an increased incidence of neuronal secretion of *BDNF*. BDNF is normally secreted by neurons in the gray matter and glial cells after ischemic injury[24, 25]. The findings of animal studies support that BDNF plays a role in improving motor function and response to rehabilitation[26] and also stimulate and strengthen neuroplasticity and reorganize cortex that is necessary to restore and improve function after stroke[27, 28].

Given the above and taking into account the experimental results that levodopa can significantly increase the BDNF levels secreted from the cortical cells within three days of exposure, it can be concluded that the mechanism of action of levodopa is likely its neurotrophic actions of.

Furthermore, our findings showed that the site of ischemic injury in all patients with cortical cerebral stroke was frontal and prefrontal motor lobe nearby it that could help explain why a significant motor improvement in the subgroup of patients with cortical stroke after three weeks was more.

CONCLUSION

Our findings in line with previous in vitro and in vivo studies on cell cultures, laboratory animals, and human subjects with stroke demonstrated that levodopa exerts neuroprotective, neurotrophic, and *neuroplasticity mediating effects which in turn can improve the* motor function outcome in the stroke patients, at least in a subgroup of patients with cortical stroke. Furthermore, the results of this study confirmed that the use of low-dose levodopa-c is a safe treatment for use as an adjunctive therapy with the standard regimen for treatment of ischemic stroke.

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