COMPARISON BETWEEN BROMOCRIPTINE AND SELEGILINE IN TREATMENT OF PARKINSON

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ABSTRACT

Parkinson's disease is a common degenerative disease that causes rigidity, bradykinesia and rest tremor in patients. Available treatments include levodopa (the major drug) and other supplementary drugs (bromocriptine or selegiline) which can reduce such disabilities, but because of the necessity of their uses for a long term treatment, many side effects are being expected. Thus, due to lack of sufficient reports about efficacy and side effects of such supplementary drugs, this experimental study was carried out. Seventy seven patients (50 men and 27 women) with the average age of 68±8.42 years were divided into three groups. In group A, levodopa and trihexyphenidyl (Artan®) were administered to 18 patients. In group B, selegiline (Deprenyl®) was used as a supplementary and was administered with levodopa and trihexyphenidyl for 25 patients. In group C, bromocriptine was used in place of selegiline, for 34 patients. In a three year period, the patients were followed up, in conformity with UPDRS (Unified Parkinson's Disease Rate Scale). In this experimental study, group C showed better physical activities in comparison with group A and group B, in spite of having better conditions at the first year showed totally little differences in comparison with group A. With a view to side effect particularly dyskinesia; there was little side effect in group C. On the basis of results of this investigation it appears that bromocriptine as a supplementary drug in comarison to selegiline has fewer side effects.

Keywords: Parkinson's disease, Dyskinesia, Levodopa, Selegiline, Bromocriptine.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that affects an estimated 1 million people in the US and tens of millions worldwide (1). The main symptoms of Parkinson's disease are slow movements, resting tremor and early fatigueness due to muscle stiffness (2). From the physiopathological point of view, Parkinson's disease is caused by degeneration of nigrostriatal dopaminergic pathways which leads to reduction of dopamine synthesis in mesencephalon (substantial nigra), and affect putamen (Basal Ganglions) (3,4). Medication therapy has made significant advances and improvements especially over the last 10 years. A number of new treatments and new strategies have emerged and the quality of life for the average patients has improved (1). The basis of treatment has been decrease in dopamine deficiency at the striatum (2,5,6). Taking into consideration that dopamine can't penetrate through blood brain barrier, levodopa, its metabolic precursor is being used. Long-term use of levodopa, however, is associated with development of motor fluctuations including dyskinesia (1) Further-more, a dopa decarboxylase inhibitor has been used to prevent the dopa decarboxylase transformation of levodopa to dopamine in peripheral circulation, which has resulted in a 75% decrease in levodopa dosage. The effect of levodopa, that is the principal treatment in Parkinson's disease is on the bradykinesis and following disabilities. The major side effects of this drug are gastrointestinal and cardiovascular such as orthostatic hypotension. Other dyskinesia complications such as chorea, athetosis and other abnormal movements are revealed after a long term of the levodopa treatment. ON-OFF phenomenon, which is sever fluctuation of symptoms such as sever rigidity and tardiness motion or intensive increase in movement and decrease in muscle tones (choreathetosis) may be observed between two consecutive dosages of the drug (7) In order to reduce these side effects, the dosage of the drug should be decreased which has its own complications. Some drugs such as bromocriptine and selegiline have been used, for this purpose, to reduce the dosage of levodopa. Bromocriptine is a dopamine agonist and acts directly on dopaminergic receptors; therefore when it is used in combination with levodopa, its dosage can be reduced (8). Selegiline is a specific monoamine-oxidase (B) inhibitor, may have a dual effect: reducing the catabolism of dopamine and limiting

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the formation of the free radicals which are neurotoxin (9). The pharmacokinetics of selegiline is highly variable; it has low bioavailability and large volume of distribution (9). Since it selectively decrease metabolism of levodopa (10), it doesn't have any complication on the blood pressure (11). There are some reports which indicate that the use of selegiline may prevent Parkinson's disease progression by reducing morphological changes in sabstantianigra (7,12), but other studies haven't confirmed these findings. (13,14). Anti-cholinergic drugs have also been used in treatment of symptoms, and in this study trihexyphenidyl (Artan) which has been used for treatment of rest tremors was used for all of our patients. The purpose of this study was to compare the efficacy and side effects of bromcriptine and selegiline in these groups of patients.

MATHERIALS AND METHODS

This prospective randomized clinical trial carried out on 105 patients (M=69, F=36) with the average age of 68+8.42, who referred to Neurologist offices in 1377. The inclusion criterion was Parkinson's disease diagnosis. The exclusion criteria were: death, taking other drugs especially cardiac drugs (because of the drug interaction), and cases who did not follow the treatment. After diagnosis and taking the written consent, the patients were divided into three Groups. Group A: treated by levodopa & artan; Group B: treated by levodopa &artan & selegiline and Group C: treated by levodopa, trihexy-phenidyl and bromocriptine.

Initially, low doses of drugs were prescribed and the amount of the doses were slowly increased up to sufficient therapeutic dosage. Levodopa was prescribed as 125 mg three times a day; trihexyphenidyl 2 mg three times a day; selegiline 5 mg two times a day and bromocriptine 2.5 mg two times a day (4).

The study took 36 months and evaluation of treatment included relief of symptoms, motor activity remission and doing daily activities that were in conformity with UPDRS tables (15, 16), which has three parts.: the first part is mental, behavioral and psychological disorders, the second part was related to daily routine activity and the last part was examination of motor activities of patients. In each part degree of disability rate scored from 0-4.

The higher score demonstrate severity of disease and the maximum score was 199, which indicated total disability of patient, versus zero, that indicated complete ability of patient. In this study variables of the second and third parts were considered more, and among the side effects of drugs, the neurological complications such as dyskinesia were investigated specifically. Due to interaction of amino acids and levodopa in small intestine absorption, a low protein diet was advised to patients. The samples were simple randomize selected from 1999 to 2001. On the basis of the uniform use of trihexy-phenidyl in three groups, the main purpose of the study was comparison of the efficacy of bromo-criptine and selegiline which were administered with levodopa to patients. Patients were inspected and examined quarterly at first year and twice a year during the second and third years. Considering difficulties in obtaining drugs by patients, the numbers of samples in three groups are not equal. Finally, 10 male and 7 female patients from group A, 8 male and 2 female patients from the group B and one male from group C were excluded from the study and study was completed with total of 77 patients. Comparison of variables in three groups was achieved by the use of χ^2 and nonparametric t-test and a $p<0.05$ was considered statistically significant For comparison of drug side effects ratio at first, real difference between ratios were measured with confidence interval of 95% and compared with each other with Z one sided test (α= 5%).

RESULTS

Of all patients, 77 participants with the average age of 68±8.42 completed the study (Table 1). As shown in figures 1 and 2 there was a significant relief in all groups but the patients in Group A had higher degree of functional disabilities than other groups .Although the side effect in group B were less than those of group A in the first year, but they increased and reached to the levels in group A during the second year and even more than group A during the third year .After the first year, rate of changes and fluctuation and frequency of UPDRS scores alteration were the high mostly in group B, and was low in group C and the patients of this group had more relief (Table 2). One of the most important Side effects in this investigation was dyskinesia

DISCUSSION

Although the main mechanism of selegiline is MAO inhibition, but it has some other effects such as decrease in the oxidative radicals' production and cellular apoptosis (which may protects the neurons from some toxins) (17,18). other effects of the drug is amphetamine like effect, increase in the release, and inhibition of dopamine reuptake by having these properties it has been claimed that this drug prevents the progression of Parkinson's disease (19-21).

Table 1. Age distribution of the patients with Parkinson's disease treated with three different drugs (levodop and selegiline and brompcriptine)

Groups	Frequency		Mean age ± SD	
	Male	Female	Male	Female
A*	12	6	62±6.84	66.67±6.47
B**	15	10	68.33±8.27	65.50±8.44
C***	23	11	67.61±5.2	68.64±7.62
Total	50	27	66.48±6.92	67.4±7.55

*Group A (levodopa and artan); **Group B (levodopa, artan and selegiline); ***Group C (levodopa, artan and bromocriptine)

Table 2. degree of changes in UPDRS (Unified Parkinson's Disease Rate Scale) scores in three groups of Parkinson's disease patients during three years.

Month	Scale of disease			Degree of changes		
	Group A*	Group B**	Group C***	Group A	Group B	Group C
3	2.1	1.9	2.2	2.1	1.9	2.2
6	2.8	3.3	3.1	0.7	1.4	0.9
9	3	3.8	3.5	0.2	0.5	0.4
12	2.7	2.9	3.3	-0.3	-0.9	-0.2
18	2.4	3.3	3	-0.3	0.4	-0.3
24	2.1	2.8	2.8	-0.3	-0.5	-0.2
30	1.5	2.3	2.2	-0.6	-0.7	-0.6
36	1.3	1.5	1.9	-0.2	-0.8	-0.3

*Group A (levodopa and artan); **Group B (levodopa, artan and selegiline); ***Group C (levodopa , artan and bromocriptine)

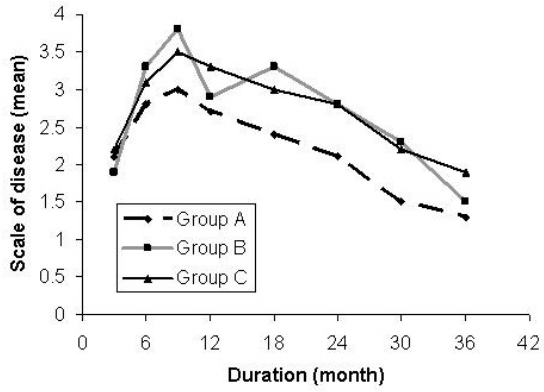

Figure 1. Comparison of scale of disease between Parkinson's disease patients groups according to UPDRS (Unified Parkinson's Disease Rate Scale).
Group A (levodopa and artan); Group B (levodopa, artan and selegiline); Group C (levodopa, artan and bromocriptine)

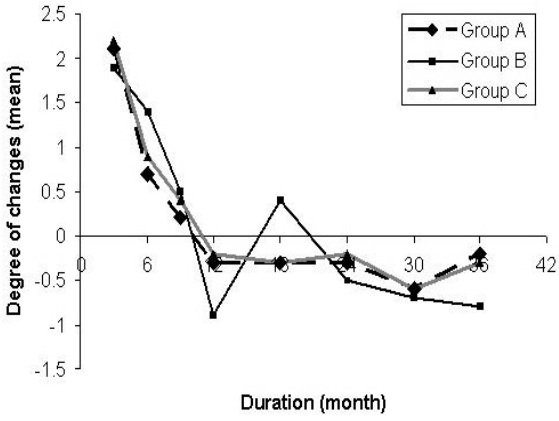

Figure 2. Comparison of the score alteration of the disease between Parkinson's disease patients groups according to UPDRS (Unified Parkinson's Disease Rate Scale) .
Group A (levodopa and artan); Group B (levodopa, artan and selegiline); Group C (levodopa, artan and bromocriptine)

Bromocriptine is a synthetic derivative of ergotamine and acts directly on dopamine receptors and increases the dopaminergic system activities in basal ganglia. Orthostatic hypotension is one of the side effects of bromocriptine but in long term use this side effects does not have any importance. Retroperitoneal fibrosis resulting from the use of this drug is uncommon. In this study, beneficial effects of selegiline, which were observed in the first year, gradually disappeared and as a result, levodopa dosage in group B patients had to be increased to levels higher than Group A (levodopa without any adjunct). Besides, the patients in Group B had the most fluctuations in clinical situations and more side effects in comparison to other groups.

Insufficient efficacy of selegiline (22,23) and its inability in prevention of the progress of the disease has been reported in other studies (11). However, the patients in group C (bromocriptine) had less complications and side effects in comparison with other groups. The required dose of levodopa for acquisition of best movement position was least in this group compared with other groups which, is in agreement with results of other studies (24,25).

On the basis of the reduction in levodopa dosage when it is used in combination with bromocriptine, as well as lower side effects and fluctuation of symptoms in this regimen, use of this drug during all stages of disease is recommended. When levodopa is used in combination with selegiline, in a short period of time (under one year), patients need lower amounts of levodopa in order to gain the balance point of motion, however beneficial effects of selegiline are for short term and due to the consequent side effects, its uses for a long time is not recommended.

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