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A Comparison of the Effectiveness of Three Drug Regimens on Cognitive Performance of Patients with Parkinson's disease

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In the present study, the effectiveness of 3 drug regimen on cognitive performance of PD patients was compared. 12 patients who had been using pramipexole, levodopa and amantadine for at least 1 month entered the study and compared with those 12 who had been using trihexiphenidyle, levodopa and amantadine. There was also a control group including 11 patients who had been using only levodopa and amantadine. All 3 groups were asked to answer Montreal Cognitive Assessment in pretest phase. Then patients in experimental groups were asked not to use pramipexole or trihexiphenidyle for 72 hours and then all 3 groups were asked to answer the same questionnaire in post test phase. The results showed that patients who have used pramipexole had better performance in executive functions in post test. The findings suggest that pramipexole in combination with levodopa and amantadine may worsen the executive function in Parkinson's disease; however, there is almost neither adverse nor beneficial effect of trihexiphenidyl in such a combination on cognition in PD patients.

Parkinson's disease (PD) is categorized under the title of Movement Disorders (Sharma, 2008). But, although motor symptoms are the most common features of the disease, commorbid cognitive problems are also frequent (Bassett, 2005; Caviness, et al., 2007; Dcamp & Schneider, 2009; Jankovic, 2008; Koerts, et al., 2009; Lees, et al., 1983; Owen, 2004; Pagonabarraga, et al., 2008; Sollinger, et al., 2010; Starkstein & Merello, 2004; William-Gray, et al., 2007). William-Gray, et al., (2007) reported that about 62 percent of PD patients have at least mild cognitive problems at the onset of the disease, that may lead to dementia in about 10 percents of the

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cases after 4 years. Sollinger, et al., (2010) also reported a rate of 52.8 for mild cognitive impairment in PD.

The impaired abilities are those that based on frontal lobe functions'abilities such as executive functions, attention, visuo-spatial skills, and memory functions (Bassett, 2005; Cooper, et al., 1991; Pagonabarraga, et al., 2008; Rowe, et al., 2008). The impaired functions can interfere with occupational functioning and familial relationships, and may lead to loss of employment and family conflict (Bassett, 2005).

Depletion of dopamine supplies, in the lateral orbitofrontal and dorsolateral prefrontal circuits in PD is thought to be responsible for cognitive impairments in the disease (York & Alvarez, 2008).

It has been shown that cognitive functions can be influenced by various medications, either by worsening or improving those functions (Bassett, 2005). Two main classes of drugs, which are usually prescribed for PD are dopamine agonists and anticholinergic agents. Different studies have found different results on the effectiveness of these drugs on cognitive performance (e.g, Brusa, et al., 2003; Brusa, et al., 2005; Campbell, et al., 2010; Drag, et al., 2010; Ehrt, et al., 2010; Hamidovic, et. al, 2008; Konishi, et al., 2010; Levin, et al., 1995).

Levodopa and amantadine are two common drugs that are usually prescribed for PD patients. Different results are also found about their effectiveness on cognitive performance (De Letter, et al., 2012.; Graham, et al., 2009; Kobayashi, et al., 2004; Saletu, et al., 1992; Sánchez-Castañeda, et al., 2010).

Parkinson's disease patients usually don't treat with a single drug. Usually a drug regimen is prescribed for them. The combination of different drugs may lead to different results in cognitive performance of PD patients than a single drug. So it is essential to investigate the effectiveness of different drug regimen on cognitive functions.

In the present study it is intended to compare the effectiveness of one selected drug from each of the two classes on cognitive performance in PD patients in combination with levodopa and amantadine. For this purpose pramipexole, a D2/D3 agonist and trihexiphenidyle, an antimuscarinic agent were selected respectively.

METHOD

Participants. 35 Patients who entered the study were firstly diagnosed as having PD by a neurologist. They have been all administered a specific dose of medication for at least one month before the study. For one group (3 women, 9 men) pramipexole, levodopa and amantadine, and for another group (4 women, 8 men) trihexiphenidyle, levodopa and amantadine were prescribed respectively by the physician. Also there was a control group including 11 patients (3 women, 8 men) for them only levodopa and amantadine were prescribed. All 3 groups were matched for dosage of levodopa and amantadine. The exclusion criteria were M.R, severe psychiatric disorders, commorbid neurological illness, and using either psychoactive or benzodiazepine drugs. Tables 1 and 2 show a summary of the patient's demographic information.

Measurements

Montreal Cognitive Assessment (MoCA)

This test was developed by Nasreddin, et al., (2005) and assesses cognitive functions including executive functions (by an alternative trail making task, verbal fluency and abstraction), visuospatial function (by drawing a clock and copying a cube), short term memory (by learning 5 items and remember them after about 5 minutes), attention (by vigilance, subtracting serial 7s from 100, and backward and forward digit span), language (by naming 3 animals, sentence repetition and verbal fluency) and orientation (time and place). This scale use more and harder tasks for executive function, linguistic abilities, memory and visiospatial processing (Zadikoff, et al., 2008). Montreal Cognitive Assessment is more sensitive than MMSE in recognizing mild cognitive impairment and it takes only 10 to 15 minutes to administer (Gill, et al., 2008).

Its internal consistency, concurrent validity, specificity and sensitivity were reported to be acceptable in various research (Athilingam, 2007; Smith, et al., 2007; Wittich, et al., 2010; Wong, et al., 2009).

We have translated it to Farsi for the first time and we found a Cronbach alpha of 0.77 and a concurrent validity of 0.79 with MMSE for this test (Emsaki, et al., 2011).

Table 1. Summary of the patients' demographic information.

	groups	Mean (years)	Std deviation
Age	Pramipexole trihexiphenidyle control	62.08 58.16 57.36	5.90 8.67 6.80
Duration of the disease	Pramipexole trihexiphenidyle control	5 3.25 5.04	1.28 1.85 2.2
Years of education	Pramipexole trihexiphenidyle control	10.5 9.75 9.36	2.31 3.08 3.61

Table 2. Summary of patients' scores in BDI, BAI and UPDRS section III.

	groups	Mean	Std deviation
BDI	Pramipexole trihexiphenidyle control	9.25 8.75 7.54	2.41 5.72 3.58
BAI	Pramipexole trihexiphenidyle control	3.9 5.5 4.7	2.3 2.8 2.2
UPDRS	Pramipexole trihexiphenidyle control	8.41 7 8.82	2.68 2.7 2.96

Unified Parkinson's Disease Rating Scale (UPDRS)

This scale was developed in 1817 as a scale for incorporating elements of existing scales and providing a comprehensive scale for assessing PD related disabilities. UPDRS has four components: part I: mentation, behavior and mood; part II: activities of daily living; part III: motor; part IV: complications (Goetz, et al., 2003). Part III which was administered in this study assesses 14 motor abilities include: speech, facial expression, tremor at rest, action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternating movements of hands, leg agility,

arising from chair, posture, gait, postural stability, body bradykinesia and hypokinesia. Each ability is scored on a likert scale from 0 to 4. UPDRS internal and test retest reliability and facial and concurrent validity were reported to be acceptable in different studies (Goetz, et al., 2003; Siderowf, et al., 2002).

Beck Depression Scale (BDI)

This 21- item questionnaire was developed by Aeron T. Beck in 1967 for the assessment of depression (Shaver & Brennan, 1991). Its reliability and validity is reported agreeable in many researches (Marnat, 2009; Shaver & Brennan, 1991).

Beck Anxiety Inventory (BAI)

This self report 21- item questionnaire was also developed by Beck, et al., in 1988 to assess the severity of anxiety symptoms (Wilson, et al., 2004). Its internal consistency, test retest reliability, and concurrent validity were reported to be good in various studies (Beck, et al., 1988; Martin, et al., 2001).

Procedure

Patients were referred to the researchers by neurologist, according to inclusion and exclusion criteria. They were visited individually by one of the researchers. After the initial interview and explaining the aim and the qualification of the research, those patients who were volunteer to attend the study, were asked to answer Montreal Cognitive Assessment (MoCA) twice, once when they entered the study for the first time, and then 3 days later when they have stopped using pramipexole or trihexiphenidyle. Since depression, anxiety and motor disabilities can interfere with cognitive performance, BDI, BAI, and the motor part of the UPDRS were also administered to control their scores if there was a significant correlation with MoCA scores and cognitive functions.

RESULTS

It was necessary to test normality and homogeneity of variance, before applying the data to ANOVA. Shapiro-Wilk test of normality and Levene test of homogeneity of variance were not rejected and accordingly we were permitted to use this parametric test. To determine those variables that must be controlled, Pearson and Spearman correlation tests were

administered. The results showed that only the correlation between education (r=0.39, p<0.05) and MoCA pretest (r=0.91, p<0.05) and the total score of MoCA post test were significant. The results of ANCOVA showed that even after controlling the effect of pre test and education, there is a significant difference among 3 groups in total score of MoCA F(2,30)=7.817, p<0.05. The observed power of 0.93 showed that the sample size was enough for this conclusion. Table 3 shows ANCOVA results for investigating the difference in the total scores of MoCA among 3 groups.

Table 3. ANCOVA for investigating the difference in the total scores of MoCA among 3 groups (* p < 0.05).

Dependent variable	source	df	Mean square	F	Sig	Partial eta square	Observed power
MoCA post test	MoCA pre	1	88.96	132.198	0.001	0.815	1.00
	education	1	0.75	1.115	0.29	0.036	0.176
	group	2	5.26	7.817	0.002 *	0.34	0.93

ANCOVA was also administered to know in which subscales of MoCA this difference is significant. It showed that there is only a significant difference in executive function among 3 groups F(2,29)=1.902, p<0.05 and there was no significant difference in any other of the subscales. The power estimation of 0.98 showed that the sample size was enough for this conclusion.

The results of pairwise comparison of estimated marginal means in executive function showed that there is a significant difference between estimated marginal means of control and pramipexole groups (p= 0.001) and trihexiphenidyle and pramipexole groups (p= 0.004). But there is no difference between estimated marginal means of control and trihexiphenidyle groups (p=0.13). Table 4 and Figure 1 can better show these differences (table 4 shows pairwise comparison of estimated marginal means in executive function).

Table 4. Pairwise comparisons of estimated marginal means in executive function (*p < 0.05).

Dependent variable	Group	Estimated marginal means	Group	Estimated marginal means	sig
Executive function post test	control control pramipexole	72.1 72.1 63.2	trihexiphenidyle pramipexole trihexiphenidyle	006.2 63.2 006.2	0.13 0.001* 0.004*

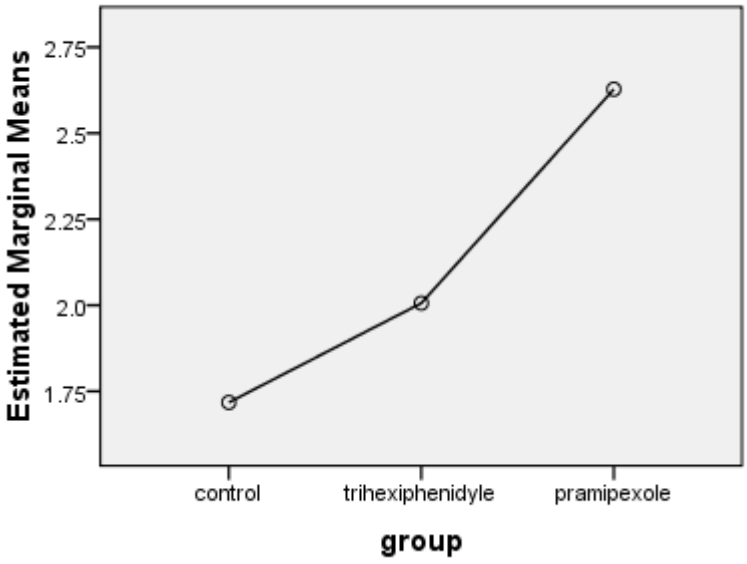

Figure 1. Difference among estimated marginal means of 3 groups.

DISCUSSION

The results showed that compared to control group and patients who were treated by trihexiphenidyle, those who used pramipexole had better performance in executive function in off treatment with this drug. This result is in agreement with those of Brusa, et al., (2003) who found that pramipexole leads to impairment in short term verbal memory, verbal

fluency and executive function and Hamidovic, et al., (2008), who investigated the effect of pramipexole on cognition of healthy volunteers and concluded that this drug leads to impairment in several subtests of the Automated Neuropsychological Assessment Metrics. But Levin, et al., (2009) in a 3 month study of influence of pramipexole in PD patients found that this drug leads to improvement in verbal fluency, but doesn't have any effect on other cognitive functions. Since the pathology of cognitive dysfunction in PD is related to dopamine depletion in nigrostriatal pathway and even the frontal cortex (Bosboom, et al., 2004; Leh, et al., 2010; Sawamoto, et al., 2008), a better performance in cognitive function was expected after using dopaminergic drugs. It is worth noting that none of these studies investigated the effect of pramipexole in combination with other drugs. But because of ethical issues we were not allowed to asked patients to quit all drugs, so patients in this experimental group used levodopa and amantadine in addition to pramipexole. According to Rowe, et al., (2008), "executive functions are mediated by distinct cortico- striato-thalamo- cortical circuits. In each circuit there is an optimal level of dopaminergic innervations, leading to a Yerkes-Dodson type U shape relationship between dopaminergic state and neural function". It can predict the impaired performance after dopaminergic treatment away from this optimum. Since levodopa, amantadine and pramipexole, all lead to dopamine enhancement, it may explain the worsened executive function after using these drugs.

The results also showed that there is no difference in cognitive functions of patients who had used trihexiphenidyle and control group. This result is in agreement with that of Drag and et al., (2010) who found that anticholinergic drugs was not associated with lower performance in cognitive functions. But most recent researches have shown that anticholinergic drugs lead to worsened cognitive performance including cognitive functions of PD patients (Campbell, et al., 2010; Ehrt, et al., 2010; Konishi, et al., 2010). Our results can be explained by pharmacokinetic and pharmacodynamic interaction with two other drugs. Considering that patients in this group of our research used levodopa and amantadine in addition to trihexiphenidyle, it could be said that concurrent using of these drugs that affect dopamine, reduce the undesirable effect of an anticholinergic agent on cognitive performance.

In conclusion, it is obvious that one of the drug regimens -pramipexole, levodopa and amantadine- can worsened the executive function of Parkinson's disease patients. But one of the limitations of our study was that we were not allowed to ask patients to cease all their drugs because of ethical issues and so we cannot conclude that worsening of

executive function is just due to pramipexole or trihexiphenidyle alone. This result can have some important implications. Informing patients and their families that the deficiency in some aspects of cognitive performance may occur due to the usage of these drugs, will help them not to panic when they finally encounter such disabilities. Another limitation of our study was that we couldn't have a follow up stage because patient's leakage. Comparing the results after one month could help us to understand whether this worsening will maintain after that period of using this regimen.

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