Multi-center clinical study of Parkon® efficiency

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Abstract

The double-blind placebo-controlled trial was performed in four scientific and clinical centers in Moscow: Russian Medical Academy of Postgraduate Education; Russian State Medical University Center of Neuro-Muscular Pathology; Neurosurgery Research Center named after N. Burdenko and Department of Human and Animal Physiology, Biological Faculty, Lomonosov Moscow State University, Moscow,

The purpose of the study was to investigate the efficacy of Parkon as the compound for the effect on motor disturbances in treatment of both Parkinson's disease (PD) and neuroleptic-induced parkinsonism. The main active ingredient of Parkon® is low concentrated hydrogen peroxide [1-3,7].

It has been shown that intranasal use of highly diluted solutions of hydrogen peroxide suppresses the activity of endogenous MAO-A and MAO-B and reduces oxidative stress both in the hypothalamus and in the basal ganglia of healthy and damaged MPTP animals (in press, p. Also [8, 9]. These experimental data, together with data on the influence of micromolar concentrations of H2O2 on the regulation of BBB permeability in animals [5, 6] served as the basis for the development of drugs for the treatment of the Parkinson's disease and neuroleptic parkinsonism.

In this article, we present the results of a multicentre, double-blind, placebo-controlled study of the therapeutic efficacy of the new patented Parkon® antiparkinsonian drug, which contained micromolar concentrations of hydrogen peroxide H_2O_2.

Endonasal use of Parkon® in patients with neuroleptically induced Parkinsonism and Parkinson's disease in levels from 1.0 to 2.5 on the Hoehn and Yahr [4] scale has been found to have moderate to good therapeutic effects.

There have been demonstrated positive effects in patients with predominantly trembling and predominantly rigid forms of the disease. Most of the improvements noted were also seen in the improvement of autonomic symptoms.

Key words: Parkinson's disease, treatment, active oxygen forms, neuroprotection

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The study was performed on 120 patients who met all inclusion and exclusion criteria.

Criteria for inclusion into the study

- PD, stages 1.0-2.5 (Hoehn & Yahr)
- Disease duration of not more than 8 years
- Drug induced parkinsonism, stages 1.0 - 3.0 (Hoehn & Yahr)
- Both genders, ages 40-75 years
- No medical treatment of PD or use of L-dopa containing medications for less than 3 years or/and use of anticholinergic drugs for less than 5 years
- Doses of antiparkinsonian drugs were stable during the month before the study
- No disappearance or partial disappearance of PD symptoms after taking L-dopa or anticholinergic drugs
- Women were post-menopausal or women of childbearing age were using at least one non-hormonal method of contraception during at least one month before the study. Confirmed abstinence was considered a method of contraception
- Women of childbearing age who had normal menstrual cycle during a period of 3 months preceding the

inclusion in the study and who had negative pregnancy test at the time of randomization (first visit) before first application of Parkon

- Written consent

Criteria for exclusion from the study

- Use of L-dopa containing medications or dopamine agonists for more than 3 years or/and use of anticholinergics for more than 5 years
- Use of amantadine, antidepressants, sedative, antihistamine and soporophic drugs; drugs with hypnotic effect, P-blockers used to treat tremor, methyldopa or reserpine at any time during 6 weeks prior to the study
- History of epilepsy
- Use of MAO-B inhibitors (jumex, deprenyl, selegiline) at any time during 4 weeks prior to the study
- PD stages of 3.0 - 5.0 (Hoehn & Yahr) or drug induced parkinsonism stages 4.0-5.0 (Hoehn & Yahr)
- Parkinsonism caused by poisoning by CO gas or manganese, encephalitis, or other neurodegenerative disorders
- Presence of surgical stereotaxic operation in anamnesis
- Pregnancy or breastfeeding
- Any clinically important disorders of cardiovascular and respiratory systems, liver, kidney, gastrointestinal, progressive neurological (except for PD) disorders, that were in decompensating stage and that required variable therapy other than Parkon or other interferences that could influence the results of the study
- Clinically significant pathological changes in EKG (during the past 2 months)
- Any tumor during a period of 5 years prior to the study
- Presence of narcotic dependence (including alcohol) in anamnesis or positive test results for the presence of narcotic drugs in the blood
- Participation in the other clinical studies during a period of 2 months prior to the study
- Any information that lead to believe that patient was not conscientious (that he/she might not follow the therapy accordingly)
- Inability to administer the drug independently or impossibility to administer the drug with assistance
- Intolerance to Parkon's ingredients

The subjects received Parkon or placebo in the form of intranasal spray according to a schedule for 4 weeks. The schedule was as follows:

- Gradual dosage escalation in 3 days
- Use of stable (fixed) dose for 30 calendar days
- Stop the drug administration without a period of dosage de-escalation

Clinical evaluation of the patients included:

- Detailed anamnesis
- Investigation of neurological and somatic status using UPDRS scale [4],
- Investigation of mental status using Mini Mental State Examination (MMSE)

Clinical evaluation was performed 4 times during the study: before the treatment (1st visit), 2 weeks after the start

of the treatment (2nd visit), 4 weeks after the start of the treatment (3rd visit) and 2 weeks after the end of the treatment (4th visit and end of study). Patients receiving Parkon were referred to as ***Parkon Group*** and patients receiving placebo as ***Placebo Group*** or ***Control Group.*** The study included a total of 120 patients (60 in Parkon Group and 60 in Placebo Group). Overall, there was a good tolerance to the treatment by Parkon in both groups. 56 people in Parkon Group and 58 people in Placebo Group participated in the study till the end. The frequency of side effects (headaches and/or allergic reactions) was 12 (20%) in Parkon Group and 5 (8.3%) in Placebo Group ($p>0.05$). 6 people had to stop the treatment due to side effects: 4 (6.6%) from Parkon Group and 2 (3.3%) from Placebo Group ($p>0.05$).

In Parkon Group, 2 people developed allergic rhinitis with a discharge from the eyes, stuffy nose, itchy throat, cough, which caused not only to suspend the treatment but also to prescribe antihistamine medications; 2 patients developed intense headaches and itchy throat.

In Placebo Group, the subjects had to discontinue the treatment due to conjunctivitis (1 case) and severe headache (1 case).

In addition to the side effects that caused a discontinuance of the treatment,

- 8 (13.3%) patients in Parkon Group developed light to moderate headache in the morning that disappeared several hours later without any medication
- In Control Group, among 3 people who developed side effects that did not cause the discontinuation of treatment, 1 person developed an allergic reaction and 2 people developed a headache.

No other side effects, including abnormal changes in EKG or orthostatic hypotension, were observed. Table 1 summarizes the results of 114 patients who participated in the study till the end.

Table 1. General characteristic of patients. Comparison on a stage of the illness (Hoehn and Yahr, 1967)

Groups, n		Stages of PD (Hoehn & Yahr)			
		1.0-1.5	**2.0**	**2.5**	**Total**
Parkon Group	Before treatment	12	25	23	60
	End of study	11	24	21	56
Control Group	Before treatment	10	26	24	60
	End of study	10	25	23	58

The subjects in the study had the following major symptoms:

- Akinesia (bradykinesia, oligokinesia),
- Muscle rigidity of torso and extremities (one- or two-sided according to the Hoehn & Yahr scale),
- Resting tremor (patients with predominately tremor form or, to the less extent, patients with rigid form of PD), also one or two-sided according the stage on Hoehn & Yahr.

Depending on prevalence of certain symptoms, patients were divided into several subgroups:

- With predominately shaking form

- With predominately rigid form
- With akinetic-rigid (hypokinetic) form

In addition, some patients had the following:

- bradyphrenia combined with light symptoms of depression and moderate emotional-volitional disturbances;
- vegetative disturbances, such as hypersalivation, seborrheia and constipation;
- stiffened face and monotonous speech;
- changes in handwriting such as micrography and slowness of writing.

Among concomitant somatic disorders the most common were hypertension, angina pectoris (functional class II-III), chronic diseases of gastrointestinal tract (colitis, cholecystopancreatitis, and diabetes type II, compensated).

The patients were distributed according to their disease stages as follows: 21 people had stages 1-1,5 on Hoehn & Yahr, 49 people had stage 2.0, and 44 people had stage 2.5.

Table 2. General characteristic of the patients in Parkon and Control Groups according to stages of PD (Hoehn & Yahr) and clinical forms

Group	Stage Hoehn & Yahr Scale	Clinical Form		
		Predominantly Tremor Form	Predominantly Rigid Form	Akinetic-Rigid Form
Parkon	1.0-1.5	10	0	1
	2.0	11	10	3
	2.5	11	8	2
	Total	32	18	6
Control	1.0-1.5	9	0	1
	2.0	11	9	5
	2.5	13	10	0
	Total	33	19	6

Parkon Group consisted of 56 people (mean age 62.6±10.6 years) who were diagnosed with Parkinson's disease or drug-induced parkinsonism; 32 patients had tremor form, 18 patients had rigid form, and 6 patients had akinetic-rigid form; in terms of stages of PD evaluated on Hoehn & Yahr scale, 11 patients had stages 1.0-1.5, 24 patients had stage 2.0, and 21 patients had stage 2.5. 24 people from Parkon Group never used L-dopa containing medications, 16 used L-dopa containing medications for a period of not more than 2 years, and 16 used it for more than 2 years (Table 3.)

Control Group was similar to Parkon Group in terms of age (mean age was 62.9±8.5 years), conditions, level of movement disturbances, forms and stages of PD and consisted of 58 people receiving placebo; 33 of them had predominately tremor form, 19 - predominately rigid form and 6 of them akinetic-rigid form. In terms of stages of PD evaluated on Hoehn and Yahr scale, 10 patients had stages 1.0-1.5, 25 patients had stage 2.0, and 23 patients had stage 2.5. 22 patients in control group never used L-dopa containing medications, 19 patients used it for a period of not more than 2 years, and 17 patients used it longer than 2 years.

Table 3. Distribution of patients in Parkon and Control Groups based on use of L-dopa containing medication

Group, n	Distribution based on use of L-dopa		
	Never used	Used not more than 2 years	Used more than 2 years
Parkon	24	16	16
Control	22	19	17
Total	46	35	33

There was a positive clinical effect as a result of the treatment with Parkon in terms of a decrease in major neurological symptoms of PD (resting tremor, rigidity, akinesia), which led to the overall improvement in movement ability (improvement in movement initiation and walking), decrease in postural instability, increase in daily activities and level of self-support. In addition, there were certain improvements in emotional-volitional sphere: increase in overall activity and initiative in day-to-day activities and decrease in depressive symptoms.

Control Group also exhibited certain improvements, such as decrease in rigidity, akinesia and tremor, facilitation of movement initiation and walking, but the improvement was less noticeable compared to Parkon group.

Before the start of the treatment, the average UPDRS score was 53.4±15.4 in Parkon Group and 52.8±14.7 in Control Group. At the end of the study patients in Parkon Group showed a statistically significant ($p<0.001$) reduction in the UPDRS score to 37.6±12.1. Control Group also showed significant improvement ($p<0.01$), but it was less apparent: mean UPDRS score at the end of the treatment was 45.2±15.2 (Table 4).

Table 4. Dynamics of clinical manifestation in patients in Parkon and Control Groups (Mean value on UPDRS scale)

Groups	Mean UPDRS value in the Dynamics (M±SD)				p values		
	1st visit Before treatment	2nd visit 2 weeks after start of treatment	3rd visit 4 weeks after start of treatment	4th visit 6 weeks end of study	1 vs. 2 2 vs. 3	1 vs. 3 2 vs. 4	1 vs. 4 3 vs. 4
Parkon Group (n = 56)	53.4L15.4	45.3±12.0	38.0L13.0	37.6±12.1	<0.005 <0.005	<0.001 <0.005	<0.001
Control Group (n = 58)	52.8±14.7	49.8±12.1	45.3±14.0	45.2±15.2		<0.001	<0.001

It's important to note that statistically significant ($p<0.005$) improvement in Parkon Group was assessed just after 2 weeks of taking Parkon, compared to the Control Group where significant ($p<0.01$) improvement was observed only after 4 weeks. Therefore, 2 weeks after the beginning of the treatment there was a significant difference ($p<0.005$) between Parkon and Control Group, and that difference remained statistically significant ($p<0.005$) at the end of the study (6 weeks). There was no withdrawal syndrome observed in Parkon and Placebo Groups.

Statistically significant improvement, demonstrated as a decrease in UPDRS score, was observed in patients with predominantly tremor and rigid forms of PD. Patients with tremor form demonstrated the greatest improvement.

In Parkon group patients with mainly tremor form of PD, and stages 1.0-1.5 (Hoehn & Yahr), statistically significant ($p<0.05$) improvement of symptoms was observed, mean values on UPDRS scale were 29.96±11.58

before the treatment and 20.0±9.16 at the end of the study (Table 5). In Control group patients with mainly tremor form of PD, and stages 1.0-1.5 (Hoehn & Yahr), no statistically significant improvement was observed and mean values on UPDRS scale were 30.2±14.48 before the treatment and 29.02±14.08 at the end of the study. (Table 5.).

Table 5. Dynamics of clinical manifestation in Parkon and Control Group patients with a predominantly tremor form of PD and stages 1.0-1.5 on Hoehn & Yahr

	UPDRS values (M ± SD)				
Group	**Before treatment**	**End of treatment (4 weeks)**	**End of study (6 weeks)**	**P 1 vs. 2**	**P 1 vs. 3**
Parkon (n=10)	29.96±11.58	20.15±9.1	20.0±9.16	<0.05	<0.05
Control (n=9)	30.2±14.48	29.2±14.1	29.02±14.08	-	

In Parkon Group patients with primarily tremor form of PD and stage 2.0 on Hoehn & Yahr, statistically significant ($p<0.05$) improvement of the symptoms was observed, the values on UPDRS scale were 39.78±11.49 before the treatment and 27.44±10.24 at the end of the study. In Control Group patients with primarily tremor form of PD and stage 2.0, no statistically significant improvement ($p< 0.3$) was noted and the UPDRS score was 38.36±13.58 before the treatment and 32.5±11.74 at the end of the study (Table 6).

Table 6. Dynamics of clinical manifestation (mean value on UPDRS scale) in Parkon and Control group patients with stage 2.0 on Hoehn & Yahr scale

Subgroup A. Patients with a predominantly tremor form

	UPDRS values (M ± SD)				
Group	**Before treatment**	**End of treatment (4 weeks)**	**End of study (6 weeks)**	**P 1 vs. 2**	**P 1 vs. 3**
Parkon (n=ll)	39.78±l.47	28.11±0.52	27.44±0.24	<0.05	<0.05
Control (n=ll)	38.36±3.58	33.1±2.65	32.5±l.74	-	-

Subgroup B. Patients with a predominantly rigid form

	UPDRS values (M ± SD)				
Group	**Before treatment**	**End of treatment (4 weeks)**	**End of study (6 weeks)**	**P 1 vs. 2**	**P 1 vs. 3**

Parkon (n=10)	48.6±11.8	36.48±13.82	36.17±14.31	<0.05	<0.05
Control (n=9)	49.33±15.54	43.03±16.24	42.73±16.24	·	·

Parkon group patients with a predominantly rigid form and stage 2.0 demonstrated statistically significant (p<0.05) improvements, which were slightly less apparent than improvements in patients with predominantly tremor form, and their UPDRS scores were 48.6±11.8 before the treatment and 36.17±14.31 at the end of the study. The Control Group (the same subgroup) did not demonstrate a statistically significant improvement (the UPDRS scores were 49.33±15.54 before the treatment and 42.73±16.24 at the end of the study) (Table 6).

Patients with a predominantly tremor or predominantly rigid forms of PD and Hoehn & Yahr stage 2,5 also demonstrated a statistically significant (p<0.05) dynamic of the mean score on UPDRS scale. The changes of the UPDRS values in Control Group were not statistically significant. In Parkon Group patients with stage 2.5 on Hoehn & Yahr, mean value on the UPDRS scale was 64.4±20.62 before the treatment and 47.0±18.2 at the end of the study in patients with a predominantly tremor form (p<0.05) and 63.28±13.75 before and 48.8±13.1 at the end of the study in patients with a predominantly rigid form of PD (Table 7). No statistically significant changes were observed in Control group patients with stage 2.5 on Hoehn & Yahr. (Table 7).

Table 7. Dynamics of clinical manifestation (mean value on UPDRS scale) in Parkon and Control groups patients with stage 2.5 on Hoehn & Yahr scale

Subgroup A. Patients with a predominantly tremor form

	UPDRS values (M ± SD)				
Group	**Before treatment**	**End of treatment (4 weeks)**	**End of study (6 weeks)**	**P 1 vs. 2**	**P 1 vs. 3**
Parkon (n=ll)	64.4±20.6	47.34±7.5	47.0±18.2	<0.05	<0.05
Control (n=13)	62.38±18.9	55.0±18.1	54.73±17.9	·	·

Subgroup B. Patients with a predominantly rigid form

	UPDRS values (M ± SD)				
Group	**Before treatment**	**End of treatment (4 weeks)**	**End of study (6 weeks)**	**P 1 vs. 2**	**P 1 vs. 3**
Parkon (n=8)	63.28±13.75	49.0±12.75	48.8±13.1	<0.05	<0.05
Control (n=10)	61.44±13.45	57.2±14.4	56.0±14.89	·	·

Thus, as a result of a comparative analysis of the dynamics of mean values on UPDRS scale, in Parkon group, statistically significant improvement (p<0.05) noted, while in Control group, no statistically

significant improvement was noted in any subgroup of Control group patients.

Patients with akinetic-rigid form (stages 1.5-2.5 on Hoehn & Yahr scale) demonstrated positive dynamics as a result of treatment with Parkon, but no statistically significant results were observed in either Parkon group or Control group; mean UPDRS score was 41,5±9.71 before the treatment and 34.0±12.6 at the end of the study for Parkon group, and 42.17±13.20 before the treatment and 36.5L7.6 at the end of the study for Control group (Table 8).

Table 8. Dynamics of clinical manifestation (mean value on UPDRS scale) in Parkon and Control group patients with akinetic-rigid form of PD and stage 1.5-2.5 on Hoehn & Yahr

	Mean UPDRS values (M ± SD)				
Group	**Before treatment**	**End of treatment (4 weeks)**	**End of study (6 weeks)**	**P 1 vs. 2**	**P 1 vs. 3**
Parkon (n=6)	41.5±9.71	35.0±11.8	34.0±12.6	<0.4	<0.3
Control (n=6)	42.17±13.2	37.66±8.51	36.5±7.6	<0.5	<0.4

Conclusion

Thus, as a result of the double-blind placebo-controlled trial, it was determined that treatment with Parkon leads to a decrease in clinical manifestation of on motor disturbances in treatment of both Parkinson's disease (PD) and neuroleptic-induced parkinsonism.

In particular, in patients with Parkinson's disease there was a statistically significant decrease in the average UPDRS ($p < 0.05$) in patients with a stage of 1.5-2.5 on the Hoehn & Yahr scale of predominantly tremor and predominantly severe forms. Patients with stages 1.5-2.0 had a more pronounced dynamics than patients with stage 2.5. No withdrawal syndrome was noted. Similarly, patients with less severe symptoms of antipsychotic parkinsonism were more sensitive to Parkon's treatment.

Side effects in the form of allergy or headaches were more frequent in patients who were treated with Parkon than in patients who took placebo, but the difference was not statistically significant.

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