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Research Article

# Effects of Neural Progenitor Cells on the Clinical Course of Parkinson's Disease in Patients with Motor Fluctuations

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## ABSTRACT

**Objective:** Assessment of dynamic pattern of Motor Fluctuations (MFs) in the patients with Parkinson's Disease (PD) after complex therapy using intrathecal (endolumbar) route of injecting of cryopreserved stem cells of fetal brain with inclusion of classical treatment and adherence to all therapy prescriptions.

**Materials and methods:** Comparative study for 68 patients who had primarily diagnosed PD underwent treatment and had been under observation at the Cell Therapy Center EmCell, Kyiv for at least 5 years. All of them had characteristic MFs and manifestation of dyskinesia. A range of disease specific phenomena with motion activity and motor fluctuations during a day were studied. During investigation, the patients had been receiving basic treatment with levodopa. The Main Group (MG) constituted 38 patients who along with standard therapy received intrathecal injection containing fetal stem cells harvested from 7-11 weeks gestation human fetuses. The Control Group (CG) included 30 patients. Both groups had been compared according to sex and the age of patients, features of MFs and the stage of disease.

**Results and discussion:** Authors proved positive effects of intrathecal injections in preparation containing cryopreserved fetal stem cells on the grade of motor fluctuation, life quality and daily activity of PD patients with developed MFs, if included into standard treatment. Over 3 and 6 months after treatment, a significant decrease of dyskinesia and the other specific phenomena were reported by the MG patients, whereas their life quality significantly increased. Thus, over 6 months the treatment results were significantly better in the patients of the MG, if compared to the same in the CG.

**Conclusion:** Intrathecal administration of neural progenitor cells is safe and effective method of treatment which can be used in complex therapy together with antiparkinsonian medicines in patients having MFs.

**Keywords:** Parkinson's disease; Fetal stem cells; Intrathecal route of administration; Dyskinesia; Motor fluctuation; Wearing off; On-off phenomena; Freezing phenomena

## INTRODUCTION

Parkinson's Disease (PD) is one of the most frequently occurring neurology diseases in the elderly. Though an ongoing search for medicines in therapy of PD lasting more than two centuries, until present day there are no efficient drugs or therapy methods to slow down PD progression or somewhat influence the neuronal death as the pathology base of the disease.

Thus, at the beginning of 60s (the XX century) Oleg Gornikevich, Austrian and Ukrainian-born doctor, who worked together with neurologist Walther Birkmayer, after determining a sharp decrease in dopamine levels produced by the brain among the patients with Parkinsonism, established that levodopa drugs significantly reduce PD signs [1,2]. Further studies concerning levodopa treatment were carried out by George Kotsias, who also proved that specifically high doses of this medicine had been effective in PD. A broad application of levodopa in clinical practice started at the end of 60s, immediately after the scientific results of such a research had been

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published [3]. Until presently, Levodopa (l-DOPA) preparations had been the most effective treatment method for PD patients.

Medicines of l-DOPA demonstrate effectiveness during the whole clinical course of disease; nevertheless, if the drug has been continuously used, its therapeutic potential is decreased. This happens because as far as PD progresses, different neurology symptoms are developing and increasing in the patients; however, at the beginning such individuals only partially respond to treatment with levodopa. Besides, following several years of levodopa therapy prescribing, vast majority of PD patients reported changes in their reaction to the drugs and they complained of Motor Fluctuations (MFs). The episodes of dyskinesia, as well as specific phenomena characterized by fluctuation in motor activity during the day, belong to the principal signs of MFs [3]. The phenomenon of "wearing off", "on-off", and "freezing" can be referred to the specific phenomena in the PD cases. Different types of dyskinesia include: "on-off" dystonia, peak-dose dyskinesia, biphasic dyskinesia, paroxysmal unpredictable dyskinesia and the others. The above symptoms occur as early as after 5-6 years of treatment with l-DOPA in 50-80% of the PD patients and the peak-dose dyskinesia develops most frequently. Such dyskinesia episodes increase each year by 10% on the background of therapy by use of l-DOPA [4,5]. Furthermore, the episodes with peak-dose dyskinesia make impossible additional increase of the doses of l-DOPA causing unfavorable effects on life quality in the treated patient and leading to a social isolation of such persons.

Probability of MFs appearance depends not only on the terms and the nature of PD in the patient. Duration of therapy using the preparations of levodopa and daily dose maintaining are of great significance. The patient's age when primary disease began is also important. For instance, the patients until the age of 50 can significantly quickly and much often develop movement disorders; however, after 6 years from PD beginning such manifestations are characteristic for almost all patients in this age group [6]. The main factor of MFs occurrence is an inevitable nigrostriatal degeneration of the neurons in PD patients, which results in loss of "buffer" ability of the striatum; provoking changes in a functional state of dopaminergic receptors and activating such striatal neurons because of intermittent stimulation caused by l-DOPA use. Against the background of levodopa therapy, higher frequency of MFs and movement disorders first of all, might be explained by D1-/D2-receptors stimulation, and fluctuation of levodopa stable concentration in blood, simultaneously. On the other hand, dyskinesia may rarely happen in PD patients along with administration of dopamine receptor agonists which selectively influence D2-receptors and maintain much stable concentrations of drugs in blood. In development of dyskinesia, dysfunctions of non-dopaminergic systems may be also of certain importance. This is proved by an effectiveness of amantadine in dyskinesia cases which can influence the glutamatergic system throughout the NMDA-receptors block [7].

Therefore, efficient strategy for prevention of MFs consists in prescribing l-DOPA for the patient as late as possible, together with all attempts for mobility support in PD cases by prescribing the other antiparkinsonian agents (e.g., monoaminoxidase inhibitors, dopamine receptor agonists, or amantadine drugs) [8]. However, since beginning of treatment with l-DOPA, such patients develop the realization cascades with the MFs. Over a longer timeframe, frequency and expressiveness of MFs may become equal both in the PD patients who began therapy with levodopa preparations and in persons who received therapy by another medicine [9].

For the recent decades, scientists all over the world have been investigating a positive influence of stem cells and possibility of their clinical use in therapy for PD patients [10-12]. A number of studies devoted to fetal stem cells administration emphasize certain therapeutic effectiveness in cases of PD treatment [13-15]. Nowadays, the International Association of Neurorestoratology (IANR) has established and introduced "The Clinical Cell Therapy Guidelines for Neurorestoration (IANR/CANR 2017)". In addition, the US FDA classified the cell therapy products into stem cell-derived cell therapy products and mature/functionally differentiated cell-derived cell therapy products (in conformity with the Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products) [16].

Analysis of the results of the studies on human stem cells administration, which had been made from the end of 80s and till the beginning of 2000s, accumulated all the data which allowed us to take some valuable conclusions. For instance, clinical improvements had been gradually developing in the treated patients with PD (from 6 to 24 months after treatment beginning), which is an explanation of the slower growth, differentiation and specialization of donor dopaminergic neurons into existing system of innervation within brain structures of the recipient [15,16]. Engraftment and multi-year functioning of donated dopaminergic neurons of fetal origin had been also confirmed owing to the system of inter-neuronal connections (decreased clinical manifestation of disease) [17]. Based on the findings of Positron Effusion Tomography (PET), the researchers proved that administered fetal stem cells were completely integrated [18].

Along with the positive results, scientists also observed some difficulties in therapy. For example, in about 15%-50% of patients undergoing replacement therapy with fetal stem cells, the authors revealed "transplant-induced dyskinesia" which usually appeared when patients discontinued or suddenly reduced their levodopa doses; or if tapering the dose of the other antiparkinsonian drugs was initiated by the patient. Its appearance can be explained by the mosaic re-innervation at the sites of transplantation and most probably associated with an excessive secretion of dopamine by the donor cells [19,20].

For efficient clinical use, stem cells must show regulated dopamine releasing, as well as properties which would be similar by their effectiveness to neurons of "Substantia Nigra". Those stem cells should possess ability of regenerating dopaminergic system within a striatum, including functional links with extra-striatum neuronal connections in the host. In addition, stem cells shall eradicate motor deficits and helping with long-lasting symptomatic improvements in PD patients, stem cell suspensions must not have side effects, no chance to cause tumor or graft-versus-host disease [21].

The *in vitro* generation of SC-derived cells which owe DA-ergic properties from fetal brain, Embryonic SCs (ESCs) and from bone marrow derived cells had already been described by the scientists. Despite of capacity of such cells to restore functional state in the patients with PD by means of DA-ergic neuron replacement had been clearly demonstrated with hfVM tissue, we are focusing now on production of much standardized DA-ergic neuroblasts from stem cells for transplantation. Specifically, ESCs and iPSCs seem to remain the simplest for clinical manipulation towards a DA-ergic area and for production of great numbers of DA-ergic neurons *in vitro*. Nevertheless, Neuronal Stem Cells (NSCs) of fetal brain

might be also useful for clinical application [21].

The objective of our study was dynamic evaluation of the MFs patterns in the patients with PD after complex treatment using intrathecal (endolumbar) fetal stem cell administration with inclusion of cryopreserved stem cells of 7-11 weeks fetal brain and treatment by means of classical methods for the patients with strict following all recommendations on the standard therapy.

## MATERIAL AND METHODS

Our study was conducted with inclusion of 68 patients who had confirmed diagnosis of PD first time and undergoing treatment by use of levodopa. All treated patients had been under observation by the specialists of Cell Therapy Center EmCell for at least 5 years.

All treated patients had been divided into 2 groups who were comparable by sex and the age, the features of MFs and the PD stage. Authors assessed the next symptoms of MFs: dyskinesia and specific phenomena which manifested in the patient by fluctuation of motor activity during the day (Figure 1).

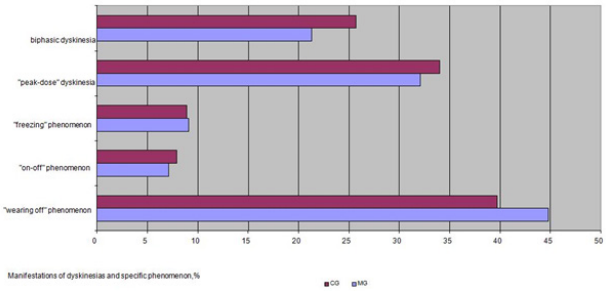


**Figure 1:** Motor fluctuations in PD patients of the MG and the CG.

In view of this, the MG constituted 38 patients with their mean age of 51.6 ± 6.7 yrs., including 71.2% of men, and 27.8% of women, with average degree of PD severity by the modified Hoehn and Yahr scale which made up 3.1 ± 0.7 and disease duration in the patients was 7-15 (9.7 ± 2.9) years. The CG included 30 patients whose mean age was 48.4 ± 5.1 yrs. (men-63.3%, and women-36.6% among them), whereas average degree of PD severity in the patients of the CG constituted 2.9 ± 0.6 (Hoehn and Yahr scale) and having disease duration for about 6-17 (10.9 ± 2.1) years. Both the MG and the CG patients included a majority of persons suffering from the mixed type of Parkinson's disease (51% and 56%, respectively, p>0.05).

No single case of infection, malignancy or psychic disease was recorded in the treated patients of the MG and the CG. Absence of cognitive deficits and emotional instability was evaluated by means of Mini–Mental State Examination (MMSE), whereas the Beck Depression Inventory (BDI) was used for assessment of depressive disorders in the PD patients [22,23] (Table 1).

**Table 1:** Indexes of mental and emotional evaluation of patients before stem cell treatment.

| Scale/scores | Patients of the MG | Patients of the CG | P value |
|---|---|---|---|
| Mini–mental state examination (MMSE) | 28.01 ± 0.24 | 28.70 ± 0.16 | p>0.05 |
| Beck depression inventory (BDI) | 21.16 ± 2.06 | 20.48 ± 1.76 | p>0.05 |

All patients under study received therapy in accordance with the standard treatment protocol (dopamine receptor agonists, central anticholinergic drugs, MAO inhibitors type B, and drugs of l-DOPA in various combinations). Calculation of levodopa dose in preparations administered to the patients was the next: range of the assay constituted from 300 to 1200 mg/daily. Thus, a mean drug dose with l-DOPA for the MG patients made up: 611.35 ± 24.41 mg/day, whereas CG patients received 750 ± 23.51 mg/day (p>0.05) (Figure 2).

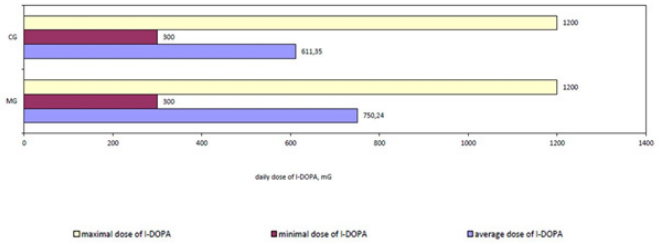


**Figure 2:** Level of l-DOPA daily dose in the patients of the MG and the CG.

The mean treatment duration among the MG patients who were receiving l-DOPA made up 7.2 ± 2.1 yrs., whereas the same index among the patients of the CG constituted 6.5 ± 1.9 yrs. (p>0.05).

The patients in both groups underwent routine therapy by medicines in conformity with the contemporary protocol for PD patients and all of them underwent therapy by means of levodopa, in particular [22,24]. During the whole period of observation, patients did not change their drug regimens. The MG patients, together with the standard treatment had been administered intrathecal (endolumbar) injection using a preparation of cryopreserved stem cells harvested from 7-11 weeks gestation fetal brain. Fetal stem cells were prepared from the human fetuses without any developmental pathology or infection. The fetuses were obtained according to the Ukrainian legislation as a result of artificial pregnancy termination by healthy women, who had been previously examined for viral and hemic infections.

Intrathecal administration of fetal stem cells was performed in accordance with the requirements for aseptic and antiseptic after performing local analgesia with 2.0 mL Sol. lidocaini 0.5%, in the area between the 3rd and the 4th spinous processes, or injected into the site between the 2nd and the 3rd acanthi. Manipulation was done in a sitting or lateral decubital position the patient. After the procedure with intrathecal (endolumbar) injection, aseptic dressing was placed onto the area of puncture. During the next 2 hrs after injection the patient remained in a horizontal position on the back. Treatment program included 3 intrathecal administrations with the assigned intervals of 3-4 days. The volume of stem cell preparation was not less than 5.0 mL and the number of nucleated cells made up at least 0.1 x $10^8$/mL per 1 injection. Amount of viable stem cells in the suspension constituted 91.0% ± 10.0%.

Diagnosis of PD had been verified on the background of inclusion and exclusion criteria, in accordance with the treatment protocol for the patients: "Parkinson's disease (G20) – clinical recommendations" [20].

Assessment of PD severity was made by means of the Hoehn and Yahr scale (1967). Evaluation of dyskinesia and specific phenomena severity was carried out in accordance with the Abnormal Involuntary Movement Scale (AIMS), Fahn-Marsden

rating scale (F-M) (Fahn., 1985), and the Section IV of the Unified Parkinson's Disease Rating Scale (UPDRS) [24-26]. Patient's life quality evaluation was performed by use of the 36-Item Short Form Survey (SF-36) and Schwab and England Activities of Daily Living scale (ADL) [27,28]. Analysis of the results was conducted prior to treatment, over 3 and 6 months post-therapy. Statistic processing for the findings had been performed by means of Statistika v.6.0 software package with calculation of the mean value and standard errors. Student's t-criterion was applied for determining statistical significance.

## RESULTS AND DISCUSSION

By no means, patients treated in the MG reported any complication as graft-versus-host disease. In addition, in such patients we recorded a satisfactory tolerability of intrathecal injection containing 7-11 weeks stem cells derived from human fetal brain. In 2 persons after intrathecal administration moderate headache was determined, which resolved spontaneously during 1 hrs? In any single case, we did not observe development of allergy reaction or psychomotor excitation among the treated patients.

Even though our clinical observation continued relatively short period of time (during 6 months) following intrathecal fetal stem cells injecting, we did not notice any side effects of therapy that might negatively influence the functions of brain, cardiovascular or the other systems. All patients completed the course of treatment as it had been scheduled.

Positive results in treated patients who showed decreased manifestation of MFs were demonstrable in 83,7% of individuals in the MG, some insignificant increase in MFs was noticed in 4,8% of the patients in the MG, whereas CG patients had stabilization of process in 5.6% of cases, and the rest of them had much intense MFs of various degree. In addition, significant decrease of MFs was observed in the patients of the MG over 3 months after fetal stem cell treatment on the base of standard PD protocol (due to the results of the AIMS scale, Section IV of the UPDRS scale and evaluation of dystonia severity by Fahn-Marsden rating scale) ($p<0.05$). In the patients included to the CG, over 3 months after treatment the same results had defined somewhat slow negative dynamics, which was significant over 6 months ($p<0.05$). Stabilization of MFs manifestations in the patients of the MG was established over 6 months after stem cell therapy ($p<0.05$) (Table 2).

As a result, the patients of the MG noticed significant decrease in manifestation of MFs by the AMIS, Section IV of UPDRS and by Fahn-Marsden rating scale for dystonia severity over 3 and 6 months after treatment. This can prove that intrathecal administration of stem cells harvested from fetal brain has positive influence on manifestation of MFs already at the early stages of combined therapy

Positive clinical influence of reduced MFs manifestations on daily activity and functional independence of the patients has been established by comparing the results of life quality in both groups under study. Corresponding scores are shown in the Figure 3, which suggests the acquired results in accordance with SF-36 scale for evaluation of life quality as it has been determined in the patients over 6 months after treatment beginning (Figure 3).

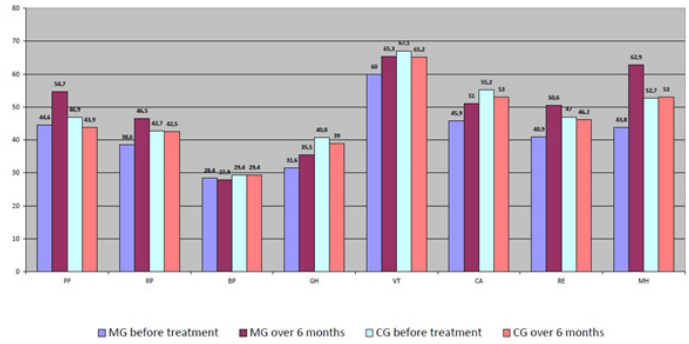


**Figure 3:** Index of life quality evaluation in patients of the MG and the CG during the whole period of observation.

Plenty of studies well established that dopaminergic fetal neurons may survive and grow following intra-striatum transplantation to the PD patient's brain. PET scan detected increase of enhancement of f-DOPA within the transplanted putamen, whereas histopathology study results shown survival of implanted dopaminergic neurons and re-innervation of striatum of brain [29]. The principal issue in this therapy direction is surgery method, that creates additional risks of complications related to the process of transplantation itself. However, our method of intrathecal administration is much safe in view of probability of technical difficulties and complications just after injection of stem cell suspensions.

Moreover, if targeted use of stem cells to cerebral tissue, there is a proved risk of developing "transplant-induced dyskinesia". As reported by the studies including 3 patients who were administered

**Table 2:** Dynamic changes of motor fluctuations in PD patients of the MG and the CG.

| Scales | Motor fluctuations, scores (M ± m) | | | | | |
|---|---|---|---|---|---|---|
| | Before treatment | | Over 3 months after treatment | | Over 6 months after treatment | |
| | MG | CG | MG | CG | MG | CG |
| AIMS scale | 17.82 ± 0.73 | 16.60 ± 0.61 | 15.01 ± 0.61 | 17.82 ± 0.40 | 14.17 ± 0.84 | 18.61 ± 0.37 |
| Fahn-Marsden rating scale (F-M) | 28.62 ± 0.90 | 27.01 ± 0.81 | 24.30 ± 1.20 | 28.90 ± 0.69 | 24.67 ± 1.01 | 29.60 ± 0.52 |
| Section IV of UPDRS | 7.6 ± 0.41 | 6.1 ± 0.39 | 5.6 ± 0.52 | 7.4 ± 0.54 | 5.56 ± 0.55 | 7.9 ± 0.51 |

fetal mesencephalic transplants about 13-16 years earlier, researchers established good clinical results in treated patients, which remained overtime even in absence of any treatment by use of l-DOPA drugs, or agonists. In some period of time, they noticed moderate severity of episodes with "transplant-induced dyskinesia" [30].

In summary, this study demands new methods or routes for prevention of such a complication, whereas the above method under study might be rather encouraging.

Therefore, among the patients with diagnosed PD undergoing fetal stem cells treatment along with standard therapy, a decrease of MFs manifestations both by objective and subjective parameters had been identified. Nevertheless, we realize that informative base of our observations is not sufficient for a broad clinical application of this method of therapy. Use of cryopreserved stem cells of fetal brain is safe and effective treatment which requires further ongoing observation for a longer period of time.

## CONCLUSION

Intrathecal administration of neural progenitor stem cells in the patients with manifested motor fluctuation on the background of standard therapy over 3 and 6 months demonstrates significant decrease of MFs expressiveness in most of the patients, whereas life quality in treated patients had been significantly improved already over 6 months.

Neural progenitor stem cells when used intrathecally is safe and effective method of treatment to be administered as a complex therapy for the patients suffering from PD with movement abnormality.

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