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Photobiomodulation Therapy and Cell Therapy Improved Parkinson's Diseases by Neuro-regeneration and Tremor Inhibition

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Abstract

Introduction: Parkinson's disease (PD) is a progressive and severe neurodegenerative disorder of the central nervous system (CNS). The most prominent features of this disease are cell reduction in the substantia nigra and accumulation of α-synuclein, especially in the brainstem, spinal cord, and cortical areas. In addition to drug-based treatment, other therapies such as surgery, cell therapy, and laser therapy can be considered. In this study, articles on cell therapy and laser therapy for PD have been collected to evaluate the improvement of motor function, cell differentiation, and dopaminergic cell proliferation.

Methods: Articles were collected from four electronic databases: PubMed, Scopus, Google Scholar, and Web of Science from 2010 to 2022. The keywords were "photobiomodulation", "low-level light therapy", "Low-level laser therapy", "near-infrared light", "Parkinson's disease", "Parkinsonism", and "stem cell therapy". About 100 related articles were included in the study.

Results: The results of the studies showed that cell therapy and laser therapy are useful in the treatment of PD, and despite their limitations, they can be useful in improving PD.

Conclusion: Concomitant use of cell therapy and photobiomodulation therapy can improve the symptoms of PD.

Keywords: Parkinson's disease; Near-infrared light; Laser therapy; Stem cell therapy

Introduction

The adult central nervous system (CNS) includes a large number of neurons with distinct functional characteristics that regulate up to 100 trillion synapses. The adult brain contains at least 10 types of dopaminergic neurons and glial cells can regenerate CNS in neurological disease.[1] Parkinson's disease (PD) is a major neurological disease that occurs all over the world and in both women and men. PD is the second most common neurodegenerative disease in people after Alzheimer's disease. The onset of PD can be familial or individual, primary or delayed, and with or without symptoms.[2] It is associated with clinical symptoms such as dyskinesia, muscle rigidity, resting tremor, and postural reflex disorder. The pathological background is the loss of dopaminergic neurons in the nigrostriatal system and α-synuclein positive inclusions in cell bodies and neurites (Lewy bodies) of nigral and olfactory bulb (OB) neurons.[3] In addition to dopaminergic neurons, other neuronal populations may be affected which include parts of the locus coeruleus (noradrenergic), raphe nucleus (serotonergic), Meynert nucleus, and dorsal motor nucleus of the vagus nerve, Cingulate cortex, entorhinal cortex, olfactory bulb, and sympathetic and parasympathetic ganglia in the intestine. This disease is caused by an imbalance between stimulation and inhibition of the regulatory ganglia due to dopamine inhibition of the putamen. As a result, the inhibitory output of putamen to the outer part of the globus pallidus increases, leading to a decrease in the inhibitory output of the external globus pallidus. This, in turn, increases the stimulation of the inner globus pallidus which causes an increase in the inhibition of the putamen,

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decreases the excitatory output from the thalamus, and finally decreases the motility.[4] Studies show that the primary demonstration of PD occurs outside of the CNS. Non-motor manifestations can be constipation, rapid eye movement, sleep behavior disorder, anxiety, olfactory disorders, depression, and anemia.[5] Factors involved in PD lead to mitochondrial dysfunction, oxidative stress, and activation of apoptotic pathways, which ultimately lead to the destruction of dopaminergic neurons. These factors include aging, environmental factors, and genetic factors.[6] In affected individuals, dopamine levels and the number of receptors within the meninges decrease with age, and PD occurs.[7] Most cases of PD are not inherited and the cause remains largely unclear. Epidemiological studies have shown that environmental factors play an important role in neurodegenerative damage. The MPTP toxin selectively causes the death of neurons in the substantia nigra in humans and laboratory models.[8] About 5% to 10% of cases of PD, which are caused by mutations in a series of specific genes, are inherited. Some involved genes include PARK1 to PARK16.[9] Although PD is one of the most common neurodegenerative diseases in the world, it is still considered an incurable disease. Many therapeutic approaches have been suggested so far, and they include various drugs, surgical procedures, stem cell therapy, and LED light therapy.[10] Prescribing drugs only helps to improve the quality of life and increase the functional capacity of these patients. Medications can help manage walking problems, movements, and tremors and increase dopamine stores in the brain. These drugs in people with PD need to be changed over time, and the dosage of drugs and their timing need to be adjusted.[11] In most people with PD, Levodopa is used as the first line of treatment for the first 5 years. Motor symptoms initially improve by 20% to 70% in these individuals. Within 2 to 3 weeks after drug treatment, the feeling of fatigue decreases. Slowness in movement, stiffness, and continuous walking improves over 3 months, but the response of tremors varies in different individuals and may be short-lived. Speech disorders, swallowing, and instability improve at the beginning of treatment, but the central symptoms generally do not respond to the drug. Other side effects of this drug include marked tremors.[12] Surgical procedures are deep brain stimulation in the subthalamic nucleus and globus pallidus through implanted electrodes and thalamotomy. The inadequacy of effective drug therapies for motor neuron diseases, and all neurological disorders in general, has increased the potential use of stem cells and LED.[13]

Cell Therapy for Parkinson's Disease

Induced Pluripotent Stem Cell-Derived Dopaminergic Progenitor

A pre-clinical study shows that the use of induced pluripotent stem cell-derived dopaminergic progenitor cells is not associated with tumorigenesis or cell toxicity. The injection of dopaminergic progenitors into the striatum (6-OHDA-lesioned rats) shows behavioral improvement. But studies also show that transplantation of pluripotent cells and neuro-progenitors leads to the imbalance of neurotransmitters and abnormalities in neural connections that lead to seizures, inhibition, or overactivity of pre-existing neural circuits with an effect on cognition and behavior.[14]

Neural Stem Cell

There are pluripotent stem cells that are extracted from embryonic and adult nerve tissues and have the ability to self-renew and self-regenerate, as well as the ability to differentiate into specialized neurons and glial cells for post-injury repair.[15] In a study of overexpression of Wnt5a in neuronal stem cells derived from embryonic ventral mesencephalon of transgenic mice, neurospheres were obtained and transplanted into the mouse striatum, which is functionally integrated with the striatum. The results showed the establishment of action potentials, the presence of postsynaptic currents, and functional expression of the DA D2 auto-receptor. A study suggests that the secretome of human neural progenitor cells can show more functional improvement and reduction of movement defects compared to the Parkinson's groups and the human neural progenitor cells treatment group.[16]

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) do not express HLA-class II stem cells and suppress immune system activity. The ability of self-renewal, differentiation, and suppression of the immune system in MSC can make them a good candidate for several disorders such as neurological diseases. The immunomodulatory property of MSC is useful in cell therapy protocols for neurovascular and chronic neurodegenerative diseases. Marcia showed that intracerebral administration of human umbilical cord-derived MSC (HUC-MSC) in the Parkinson's model (induced by neurotoxin-MPTP in rats) could improve motor defects including hypokinesia, catalepsy, and bradykinesia. Furthermore, this study showed that the administration of fibroblasts without stem cells was very harmful and could cause significant neurodegeneration and impaired motor function. Co-transplantation of UC-MSC with fibroblasts has adverse effects and exacerbates neurodegeneration and motor impairment.[14] A study has proposed a method that could be a new cell therapy application in PD. This study showed that the use of differentiated UC-MSC to dopaminergic phenotype is better than undifferentiated cells MSC and the expression levels of tyrosine hydroxylase and Nurr1 are higher compared to differentiated bone marrow MSC (BMMSC).[17] Another study showed that using Wharton's jelly-derived MSCs in PD rats could improve,

dopaminergic neurons, and motor activity.[18] Evidence suggests that the role of transplanted cells is more in the production and release of protective factors than in cell replacement.[19] Human umbilical cord blood (HUCB (cells is currently the largest source of stem cells available for human biomedical research and clinical development. It was shown that intracerebroventricular administration of HUCB delays disease progression by releasing cytokines, chemokines, and anti-inflammatory properties in two mouse models of motor neuron degeneration. One of the causes of neurological diseases is a decrease in neurotrophic factors such as vascular endothelial growth factor (VEGF). A study showed that the combination of VEGF expression and HUC-MSC therapy was able to reduce the lack of dopaminergic neurons. This study showed that it differentiates into dopaminergic neurons.[20] A study showed that human umbilical cord-derived MSC-derived supernatants activated with curcumin increased proliferation, expression of tyrosine hydroxylase, and microtubule-associated protein-2 and decreased nitric oxide (NO).[21] Injection of BMMSC into substantia nigra in mice with PD increased TH-positive cells (tyrosine hydroxylase) and TH-positive fibers in the striatum. This study showed that MSC cells can survive and migrate in the brain and differentiate into GFAP-positive cells and nestin cells.[3] One of the phenotypic markers of dopaminergic neurons in region A9 in substantia nigra is the coexpression of tyrosine hydroxylase and GIRK2. A study showed that in Parkinson's model in rats, intranasal injection of endometrial MSCs improved behavioral parameters and increased dopaminergic neurons.[22] In PD, in addition to motor disease, lower urinary tract disorders are seen. The nigrostriatal lesion caused bladder dysfunction. A study showed that the use of human amniotic fluid stem cells and BMMSC temporarily ameliorated bladder dysfunction in the rat PD model.[23] Another study showed that in the PD model in rats, intranasal injection of endometrial MSCs improved behavioral parameters and increased dopaminergic neurons. Because the in vivo survival and differentiation of BMMSC are relatively low, BMMSC-derived neurotrophic factors such as glial cell line-derived neurotrophic factor (GDNF) increase the survival and differentiation of MSC into neuronal and glial-like cells and increase dopaminergic contents in the striatum.[24] A study showed that retinoic acid (RA) and Creatine response element-binding protein (CREB) in MSC could increase the differentiation of MSC into neurons.[25]

In one study, the in vivo use of BMMSCs in the PD model of rats showed an increase in tyrosine hydroxylase, positive fibers in the striatum, and TH-positive neurons in substantia nigra pars compacta. This in vitro study showed that the effect of SDF-1α increased dopaminergic neurons and also reduced cell death.[26] Neuroinflammation plays an important role in the pathogenesis of PD. A study showed that only intravenous injection of allogeneic BMMSCs in Parkinson's patients was tolerable and could be used as an immunomodulatory therapy.[27] Adipose MSCs are derived from adipose tissue and are capable of autologous transplantation and are also able to differentiate into neurons. A study showed that the use of MSCs increased tyrosine hydroxylase and decreased TGF-β and MCP-l in the Parkinson's model in rats.[28] PD causes structural and functional changes in mitochondria. A-synuclein, parkin, DJ-1, PINK1 genes are directly or indirectly involved in mitochondrial function. Another study showed that in the Parkinson's model in mice, the use of adipose MSCs reduced structure-modified mitochondria and preserved mitochondrial complex I.[29] One of the limitations of MSC transport in the brain is the blood-brain barrier. The use of magnetic nanoparticles can act as potential delivery vehicles to improve the function of MSCs.[30] Magnetic nanoparticles can cross the blood-brain barrier and can be widely used in the diagnosis and treatment of diseases. A study showed that using human adipose-derived stem cells using magnetic nanoparticles improved behavioral and motor functions in the (6-OHDA)-induced PD mouse model.[31] The cell delivery method is very important in cell-based therapy in neurological disorders. The delivery method is effective in transplant survival, adequate enrichment of therapeutic cells in the brain, and their distribution in peripheral organs. A study showed that intranasal delivery in MSCs increased tyrosine hydroxylase levels in the ipsilateral striatum and substantia nigra.[32] The main effect of MSCs in regenerative medicine is due to the secretion of biologically active molecules, which is called the scrotum. In a study, the injection of human MSC secretome to substantia nigra and striatum was able to partially revert the motor phenotype and the neuronal structure in the rat model of PD.[33] Considering that hyposmia and loss of memory function are two major nonmotor symptoms of PD, a study showed that ADMSC increased neurogenesis in hippocampal and subventricular regions and protected dopamine levels and upregulated peripheral anti-inflammatory cytokines.[34] Another study showed that the injection of human MSCs into the striatum was dose-dependent, which maintained the survival of the striatal/nigral dopaminergic terminus, and increased neurogenesis in the subventricular region, as well as the proliferation of proliferating cells, and the migration of neuroblasts was observed in the damaged striatum.[35] In another study, it was shown that the use of Olfactory ectomesenchymal stem cells (OE-MSCs) in the magnetically targeted cell delivery approach increased dopaminergic neuron cells by the expression of Nurr1, dopamine transporter (DAT), and paired-like homeodomain transcription factor 3 (TH) in the rat models of PD.[36] Also, a study showed that the use of OE-MSCs increased the expression of DA markers, namely dopamine transporter (DAT), tyrosine hydroxylase (TH), and nuclear receptor related-1 (Nurr1) and improved

motor coordination, muscle activity, and locomotor performance in the model of PD.[37] Alternatively, intrastriatal grafting is more efficient with higher cell retention both in the substantia nigra compacta and in the striatum leading to improved behavior. A study shows that the use of MSC helps maintain their differentiation into neuronal cells. MSC protect neurons from the toxic effects of 6-OHDA.[38]

Induced Pluripotent Stem Cell (iPS)-Derived Dopaminergic Neurons

There is a possibility of tumorigenesis in iPS-derived donor cells. A preclinical study in Parkinson's model in primate PD models shows that the use of iPS cell-derived dopaminergic progenitors can propagate dense neurites in mature dopaminergic neurons to the host striatum.[39] A study showed that in PD, differentiation of human ES cells and IPS into midbrain neurons was possible with FGF8a, WNT, and low-dose retinoic acid, SHH.[40] By providing isogenic cells, iPS cells create the conditions for suppressing the patient's immune response to transplant neurons.[41] Epidemiology studies indicate that exposure to pesticides, metals, polychlorinated biphenyl, some solvents, and some other substances increase the risk of developing PD. Environmental factors are harmful by three mechanisms: (1) Induction of ROS production - Cycle change, (2) Changes in mitochondrial metabolism, and (3) Reduction in oxidation, which creates oxidative stress.[8] Due to the limited access to embryonic tissue, the use of human embryonic stem cells in the treatment of PD is considered optional.[42] A study showed that the use of efficient protocols to differentiate DA neurons from human ES/iPS cells and non-human primate iPSCs to intrastriatal to SD rats was very effective and the use of non-human primate iPSCs was more effective for neuronal differentiation and more valuable for preclinical evaluation.[43] iPSC-derived donor cells have tumorigenic properties and cell sorting using antibodies CORIN to remove unwanted cells. CORIN is specifically expressed in the floor plate where dopaminergic (DA) neuron progenitor cells are located. A study showed that sorted CORIN + cells expressed dopaminergic precursor markers in the midbrain, including FOXA2 and LMX1A, generated from human induced pluripotent stem cells could enrich midbrain DA progenitor cells that can improve the behavior of 6-OHDA-lesioned rats.[44] LRTM1 is specifically expressed in mouse fetal ventral midbrain, and human iPSC-derived LRTM1+ cells survive and differentiate into midbrain dopaminergic neurons, resulting in a significant improvement in motor behavior without tumor formation.[45]

Other Cells

Parthenogenetic stem cells are used to produce an unlimited number of nerve cells because they are made from unfertilized oocytes. A study showed that the use of parthenogenetic stem cell-derived neural stem cells to the striatum and substantia nigra in monkeys increased survival, dopamine levels, striatal DA concentration, fiber innervation without dyskinesia, tumor, and the formation of safe ectopic tissue in the PD model.[46]

Photobiomodulation

Studies have shown that the use of Photobiomodulation therapy will reduce oxidative stress and increase growth factors, cell proliferation and reduce inflammation in different tissues.[47] Photobiomodulation (PBM) is one of the simplest strategies to reduce brain diseases or improve brain function. Light penetrates externally (for example, through the skull), with sufficient intensity at the right dose to the scalp and skull. The results of studies using transcranial PBM showed that it could improve nerve function. However, the transfer of energy throughout the scalp and skull in the transcranial method is limited. A study showed that photobiomodulation (808-nm near-infrared light) reduced movement disorders and increased dopaminergic neuronal, in a rat genetic model of PD. These effects persisted for at least 6 weeks after treatment.[48] A study showed that PBM was a safe treatment for a wide range of clinical signs and symptoms of PD in patients. The results showed improvement of the disease up to one year, and mobility, cognition, dynamic balance, and fine motor skill significantly improved.[49] In a study, neuroprotection of NIr in mice treated with MPTP was dose-dependent, and when high concentrations of MPTP were used, the dose of NIr needed to be increased to protect cells and reduce astrogliosis.[50] This study also showed that the use of PBM (10 mW) in monkey models of PD increased the expression of tyrosine hydroxylase and GDNF.[51] Another study also showed that the use of NIr (670 nm at 40 mW/cm^2 for 90 seconds once/day for 4 days) in mice treated with MPTP increased TH + cell and dopaminergic cells in substantia nigra pars compacta.[52] With similar results, a study showed that NIr was not effective in the incerta-hypothalamus zone.[53] Lipopolysaccharide, a component of gram-negative bacterial cells, releases cytokines, resulting in the activity of immune cells and inflammation, thereby causing cellular stress, ROS production, and dopaminergic cell death. A research study used lipopolysaccharide to induce PD. The results of transcranial PBM radiation showed that it could reduce inflammation.[54] Therefore, the intracranial method is one of the alternative methods of photobiomodulation, which is the implantation of optical fiber in the lateral ventricle without any behavioral defects or tissue necrosis. Rather, it can induce astrogliosis in the midbrain and striatum and reduce microglial morphological changes (670 nm at 5.3 mW/cm^2 given as follows: 90 s twice/day for 2 days).[55] Furthermore, a study showed that in mice receiving

MPTP and treated with NIr, it could improve greater locomotor activity (~40%) and increased the number of dopaminergic cells (~20%).[56] A study showed that PBM (670 nm, 0.16 mW) in the acute MPTP mouse model protected dopaminergic cells when used intracranially and intermittently, and when PBM (4 × 90 seconds over 2 days) was used intermittently, stronger protection was achieved.[57] A study also showed that using PBM (810 nm, 160 μW, 90 s twice a day for 2 days) to the midline of the midbrain improved dopaminergic cells.[58] This study also showed that a higher dose of NIr (125 J) had no toxic effect on cells in the midbrain implantation in the monkey model of PD. The intra-cranial laser implant (670 nm, 10 Mw in cycles of 5s on/60 s off delivered: Over 5 days) showed an increased neural cell in substantia nigra pars compacta.[59] Also, external LED (670 nm at 50 mW/cm^2 for 90 seconds once/day for 2, 5, or 10 days at back or hindlimbs) in Acute MPTP mouse mode led to the mitigation of neurotoxic effects of MPTP.[60] A study showed that PBM (940 ± 10 nm, 6.0 mW/cm^2 ± 10% with a 56.7-mA) + H2 therapy in 18 patients (age 30–80 years) with PD for 2 weeks could reduce disease severity and increase the Unified Parkinson Disease Rating Scale. Light is designed to be placed on the posterior aspect of the neck midline, pointing to the midbrain.[61]

Conclusion

The results of this study showed that the use of cell therapy improves the symptoms of PD and that the rate of recovery depends on various factors, including cell type, injection rate, frequency of injections and disease progression. The best type of injectable cell is the MSC. Regarding the effect of a laser on treatment, studies prove that radiation at a specific dose with the right wavelength and time has an important effect on improving the symptoms of PD.

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Conflict of Interests

The authors declare that there is no conflict of interest.

Ethical Considerations

The Ethics Committee of Shahid Beheshti University of Medical Sciences (SBMU) has legal the procedures on this; take a look at (IR.SBMU.RETECH.REC.1400.007).

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