Parkinson's disease (PD) is a progressive neurodegenerative disorder resulting from the depletion of dopaminergic neurons of the midbrain. The dopamine precursor levodopa (L-Dopa) is often prescribed as the first line of treatment to alleviate symptoms. Extended L-Dopa therapy is associated with significant side effects that impact quality of life. The search for a treatment that targets the etiology of PD has lead to clinical trials of cell transplant therapy aimed at regenerating a functional dopaminergic midbrain. The appropriate cell type to use for PD transplant therapy is under investigation. The optimal cell type will have a minimal risk of tumorogenicity and will not require the use of immunosuppressive agents, while having the potential to show significant benefits in motor functioning and quality of life. Clinical trials have shown cell transplant therapy to be a safe intervention that can be tolerated well by patients. Sham-surgery clinical trials demonstrate a significant placebo effect and show a need for more double-blind controlled clinical trials in this field.

INTRODUCTION

Parkinson’s Disease (PD) is a progressive neurodegenerative disease characterized by impairments in motor control. The disease is understood to result from the degeneration of the dopaminergic neurons of the substantia nigra pars compacta. The nigrostriatal tract projects from the substantia nigra to the striatum of the basal ganglia, and is involved in both motor and emotional processing within the limbic system. PD patients suffer difficulty in both executing motor tasks and controlling movement. Symptoms of PD include bradykinesia, rigidity, resting tremor and postural abnormality. Additional changes in emotion and cognitive functioning may present. PD is a progressive disease that is non-life threatening, although life expectancy may be shortened due to complications of the disease.

To date there is no cure that can halt the progression of PD. The standard treatment approach is to replace the loss of dopamine in the brain. Since dopamine cannot cross the blood-brain barrier, the dopamine precursor levodopa (L-Dopa) is prescribed orally. L-Dopa therapy can alleviate symptoms of PD most effectively in the early stages of the disease. Long-term use of L-Dopa therapy is associated with a wide range of side effects that may significantly impact quality of life. A particularly concerning side effect of L-Dopa is dyskinesia, a movement disorder characterized by the loss of voluntary movements and the presence of involuntary movements. Most common is peak-dose dyskinesia that occurs shortly after patients have taken a high dose of L-Dopa medication. Patients may also experience diphasic dyskinesia as the concentration of L-Dopa in the body changes.

The experience of these side effects causes the L-Dopa treatment regimen to be unsatisfactory for many patients. Dopamine agonists are also used as a first line treatment option, and show less dyskinesia but have a different side effect profile. Current research efforts focus on finding alternative treatments that target the PD etiology rather than symptomatology. Stem cell therapy is a possible treatment option under investigation. The goal of stem cell therapy for PD is to recreate a functional dopaminergic midbrain. In theory, pluripotent stem cells transplanted into the midbrain will become incorporated into the surrounding neural connections and will differentiate into dopaminergic neurons in response to environmental cues. The historical risk of any stem cell transplant is failure of the implanted cells to integrate into the host environment. These rapidly dividing
cells are then at risk of progressing into tumor growth. Another possible option in cell transplant therapy for PD is to transplant fully differentiated cells that are dopaminergic in nature. In this scenario the transplanted cells would have a much lower risk of developing into tumor growth. The ability of these cells to become functionally integrated is still under study.

Clinical trials to date have shown controversial results for both the safety and efficacy of stem cell treatment for PD. The typical surgical procedure is to deliver multiple injections of cells to the striatum trans-cortically via a stereotactically guided straight cannula. Possible complications of this procedure include intracranial hemorrhage and cortical damage. The standard approach to clinical trials has been to compare a treatment group, in which participants receive cell transplant surgery, to a control group in which participants undergo sham-surgery. Clinical outcomes following surgery are typically quantified by the Unified Parkinson’s Disease Rating Scale (UPDRS), which includes measures of motor functioning, mental functioning, mood, behavior, and activities of daily living. Clinical trial participants usually remain on their regular antiparkinsonian medications following the surgical procedure. Clinical outcomes are recorded in both “off-medication” and “on-medication” states. The off-medication state is defined as no less than 12 hours following a patient’s previous dose of L-Dopa. This is usually first in the morning before the patient takes their medication. The on-medication state is defined as a patient’s highest level of functioning during the daytime after they have taken their medication. In double-blind clinical trials, participants are typically followed by a physician who is blinded to their assigned treatment group. Medication adjustments are made as needed according to the patient’s functioning, and changes are recorded as tertiary clinical outcomes. Molecular outcomes following cell transplant can be measured by fluorodopa (F-Dopa) positron emission tomography (PET). This technique involves IV administration of F-Dopa, a radiolabelled dopamine precursor. F-Dopa crosses the blood-brain barrier and is converted to fluorodopamine by midbrain neurons. PET detection of increased F-Dopa uptake following cell transplant suggests an improved functional dopaminergic midbrain and success of the transplant at the molecular level.

The need to use immunosuppressive agents in neurological stem cell transplant remains undetermined. The brain is considered an immune privileged site that can typically withstand the introduction of antigens without eliciting an immune response. However, neural cell transplant research has found T lymphocytes and natural killer cells to be capable of targeting stem cells implanted in the brain. The possibility of rejection is a serious concern as it will diminish the possible benefits of cell transplant treatment. The risk of transplanted cells inducing graft-versus-host disease will depend on the cell type, but is less likely in immunologically immature cells such as human embryonic stem cells. Since the benefits of cell transplant therapy for PD may not outweigh the risks associated with systemic immunosuppression, the search for a cell type that will not require immunosuppression is critical if the treatment is to be introduced into clinical practice.

Embryonic and Fetal Stem Cell Transplant

Early PD stem cell experimentation involved the use of embryonic and fetal stem cells from human and animal sources. The first clinical trials began in the late 1980’s after promising evidence emerged from rodent and primate studies. Embryonic xenografts, stem cells from non-human species, have been trialed. In one study unilateral transplantation of embryonic ventral mesenteric porcine tissue was trialed in 12 PD patients. A local immunosuppression technique was used in this study in order to avoid systemic immunosuppression. The immunosuppressant cyclosporine was implanted in combination with the stem cells and also given pre- and post-operatively to 6 patients. Alternatively, in the other 6 patients the transplanted cells were treated with a monoclonal antibody directed against major histocompatibility complex I (MHC I). Surgery was tolerated well by all patients. Outcomes were measured by the UPDRS for 1 year post-surgery. A few patients showed notable improvement in functioning by 3 months following the intervention, while most patients showed little to no change in symptoms. Important to note is the lack of a control group in this pilot study. The patients showed only marginal improvements, which could be attributed to a placebo effect.

Extensive work has been done using human embryonic stem cell sources. One group of researchers has performed human embryonic stem cell transplants in more than 60 patients in total. In these clinical trials patients did not receive immunosuppressants. In the largest double-blind clinical trial performed by this research team, 40 patients were randomized to receive either cell transplant into the putamen or sham surgery. One year after surgery clinical improvement and an increase in putamen F-Dopa uptake was found compared to controls in patients who were younger than 60 years of age. The greatest improvement was seen in young male patients with less severe disease. After completion of the blinded study, 14 of 20 patients in the control group chose to undergo cell transplant. In a long-term study patients who received cell transplant were found to show continued improvement up to four years post-surgery. At this time the effect of age and sex was no longer significant. An additional increase in F-Dopa uptake was found at this time, indicating continual functional integration of transplanted cells in the putamen. Clinical outcomes were shown to correlate with F-Dopa uptake as detected by PET scanning. Pre-surgery neurotrophic factor treatment is recommended to increase the survival of implanted cells and maximize success. Through many years of work, the researchers have concluded that response to stem cell therapy correlates with an individual’s response to L-Dopa therapy prior to surgery. They have also concluded that transplant patients who show improvement in motor function have a tendency to develop dyskinesias after discontinuing L-Dopa medication.

In a long-term case study, two patients who received human mesencephalic embryonic stem cell transplantation were followed for eight years post-surgery. The patients’ response to treatment was monitored over time using single-photon emission computed tomography (SPECT) of radioligands for striatal dopamine transporters (DAT). This is an alternative method to measuring striatal uptake of F-Dopa with PET scanning. The patients showed clinically significant improvement in motor function over the eight...
years, correlating with increased DAT binding. However, both patients developed moderate-severe off-medication dyskinesia.

Another group of researchers has performed double-blind control trials using human fetal cell transplant. In one study 34 patients were randomized to receive bilateral fetal nigral cell transplant from one donor, bilateral transplant from four donors, or bilateral sham surgery. Outcomes were measured by PET detection of F-Dopa uptake and UPDRS for 2 years after the intervention. Patients were treated with the immunosuppressant cyclosporine and tolerated it well. PET detection showed an increase in putamen F-Dopa uptake in patients who received transplantation, the largest increase being in patients who received transplant from four donors. Adverse events occurred more commonly in subjects who underwent transplant than those who received sham surgery. The most common side effect was off-medication dyskinesia. Results showed that there was no overall significant benefit of receiving transplant compared to sham surgery. The patients who had the least severe symptoms prior to intervention showed a benefit compared to control patients, suggesting the intervention worked to slow disease progression but did not alleviate symptoms in patients with severe PD.

A common theme in the results of embryonic and fetal stem cell treatment for PD is the presence of off-medication dyskinesias in transplant recipients. This finding is very concerning to the future of stem cell therapies as dyskinesias can negatively and significantly impact quality of life. The 34 participants of a double-blind controlled study described above were assessed specifically for off-medication dyskinesias for up to two years following fetal nigral cell transplant. Video recordings were taken of the patients during on- and off-medication periods, and were analyzed by a movement disorders specialist who was blinded to the patient groups. The results showed 13 of the 23 transplant patients developed off-medication dyskinesias, whereas none of the patients in the placebo group showed this side effect. Patients who developed off-medication dyskinesia had been taking lower doses of L-Dopa than the transplant patients who did not. Interestingly, the patients who showed off-medication dyskinesia also showed greater improvement in UPDRS motor scores in the months following surgery. The researchers speculate these patients were more sensitive to both the benefits and side-effects of dopaminergic therapy.

In addition to the clinical findings of off-medication dyskinesias, other scientific and ethical issues inhibit the advancement of embryonic stem cell transplant for patients suffering from PD. Fetal and embryonic cells show more potential for tumorogenicity than other stem cell types. Animal studies that initially showed promising results from embryonic stem cell transplant later showed discouraging findings of tumor growth. The tumorogenicity of pluripotent embryonic stem cells is due to their potential to rapidly proliferate. Embryonic stem cells have a much greater capacity to divide and differentiate than adult-derived stem cells. Beyond the technical challenges of using embryonic stem cells are the ethical restrictions that limit the research possibilities in this area. Access to embryonic stem cell tissue for research purposes remains restricted and public support for the use of these tissues is limited. The use of adult-derived stem cells is much less controversial. For these reasons, researchers have been exploring the possibility of using stem cells from adult tissues in the treatment of PD.

Adult Cell Sources

Several adult cell sources have been trialed. Autologous transplant is ideal to eliminate the need to administer immunosuppressant therapy. Patient-derived induced pluripotent stem cells (iPSCs) held great promise in theory due to their capacity to divide and differentiate without any risk of rejection or inducing graft-versus-host disease. The technique involves culturing patient-derived somatic cells, such as skin cells, in vitro with growth and transcription factors that promote differentiation into dopaminergic neurons. Transplantation of iPSC-derived dopaminergic neurons have been tested in vivo using neurotoxin-induced parkinsonian animal models. An important finding was that iPSC-derived dopaminergic neurons from patients with familial PD show a parkinsonian phenotype. This renders the technique unsuitable for patients with familial PD, about 5% of the PD population. These cell lines are instead useful as a research tool to create a cellular model of PD.

Autologous transplant using other tissue types have been tested in clinical trials. Carotid body cells were transplanted into the striatum to treat PD in one study. The reasoning behind using this cell source is the nature of the glomus cells of the carotid bodies to release dopamine in response to low arterial oxygen concentration. These cells also grow and proliferate under hypoxic conditions, making them ideal for transplant into the cell-depleted PD striatum. In a pilot study, 6 patients received autologous cell transplant using glomus cells resected unilaterally from their own carotid body tissue. Participants tolerated the surgery well without serious adverse events. Improvement was shown in UPDRS scores 18 months post-surgery, but this was less significant for older patients. Histology studies of the carotid body tissue showed less glomus cells and more fibrous carotid body tissue in older patients, correlating with clinical outcomes. It is important to note that this pilot study was uncontrolled and may be susceptible to the placebo effect.

Autologous transplant of bone-marrow derived stem cells are another option under experimentation. In a pilot study 7 patients suffering from PD received unilateral transplantation of bone marrow-derived mesenchymal stem cells. Outcomes were measured using the UPDRS in on- and off-medication phases. Patients were also examined with MRI periodically following surgery, showing no notable changes and no evidence of tumor growth. No significant adverse events occurred. Patients showed marginal improvement in symptoms over a 2-year period and described a subjective improvement in well-being. There was no control group or blinding in this pilot study, and the results are therefore subject to the placebo effect.

A final cell type under consideration is human retinal pigment epithelial (RPE) tissue. These are potential candidates for PD treatment due to their characteristic secretion of L-Dopa. However, autologous transplant is not an option for this type of tissue. In a controlled clinical trial 35 patients suffering with PD received
intraparietal implantation of human postmortem RPE cells. The control group of 36 PD patients received sham surgeries. A large portion of the participants in this study experienced adverse events related to the surgical procedure, and these were more serious in the cell implantation group. Overall, patients that received RPE cell transplantation did not show a significantly greater improvement in their condition compared to the control group. A substantial placebo effect appeared to have occurred, emphasizing the need to continue double-blind studies in this field.

Human RPE cells have also been tested in a more recent pilot study. In an uncontrolled clinical trial 12 patients received unilateral cell transplantation from human postmortem RPE cells. Outcomes were measured intermittently for up to 3 years post-implantation using the UPDRS in on- and off-medication phases. PET scanning was used to detect DAT uptake pre and post-operatively, and showed increased DAT uptake 6 months after surgery in most patients. Participants did not experience any serious adverse events. Overall the patients showed improvement in their condition and a reduction in parkinsonian symptoms following surgery. Their improvements were greatest 12 months post-surgery and were less appreciative at 36 months. Since a control group was not used in this study, a placebo effect cannot be ruled out. Importantly, the results of this study indicate the procedure can be done safely.

Clinical Considerations

The limited number of randomized controlled trials of stem cell transplant for PD reflects the nature of the intervention and the challenges of conducting research in this area. Stem cell transplant surgery is risky and invasive, and recruiting participants for clinical trials can be difficult. A recent article addresses these challenges and makes recommendations for the process of selecting participants for first-in-human (FIH) stem cell trials, in which new cell types or surgical techniques are tested. In order for an intervention to be acceptable to enter FIH trials, a level of safety, efficacy, and competitiveness relative to existing treatments must be established based on results of laboratory and animal studies. The risk-benefit ratio of enrolling a patient in an FIH trial will depend on these factors and also on the severity of the patient’s disease. The authors argue that FIH trials for stem cell therapy may be too risky and invasive to be carried out in healthy individuals or even patients in early stages of PD. However, subjects at the final stages of their disease are unlikely to show promising results in response to the FIH intervention. The authors suggest selecting patients in order to minimize risk, maximize the ability to analyze results, and enhance the benefits to individual subjects and society.

The risks associated with stem cell transplant therapy will not be justifiable in clinical practice until the benefits are found to be substantially greater than current PD treatment options. To appreciate the benefits of therapy researchers must not only analyze changes in motor functioning but also the impact of treatment on overall quality of life. In a follow-up study of a double-blind controlled trial, 30 patients were assessed for one year following stem cell transplant for the impact of the intervention on their quality of life. Patients remained blinded to whether they received cell transplant surgery or sham surgery. Overall subjective quality of life did not differ between the treatment and control group. Interestingly, quality of life was measured as significantly higher for patients who believed they had received the cell transplant surgery. This highlights the influence of the placebo effect and the need for double-blind control studies in future research.

One aspect of quality of life that could be affected by cell transplant intervention is cognitive function. There is concern that the surgical procedure of stem cell transplant could damage the cortex and negatively impact cognitive functioning post-surgery. Cognitive function of embryonic stem cell transplant recipients have been assessed through neuropsychological evaluation using a battery of tests. The UPDRS and PET scanning were also used to allow interpretation of the cognitive test results. No significant difference in cognition pre- and post-surgery was found. This supports evidence that stem cell transplant can be safely performed.

CONCLUSIONS

The clinical studies discussed in this article outline important principles of cell transplant therapy for PD. The major risks of cell transplant therapy include tumor growth and the risks associated with immunosuppression. Additional risks include surgical complications such as intracranial hemorrhage and cortical damage. A feasible cell transplant treatment for PD would utilize a cell type that would not require immunosuppression and would be highly unlikely to cause tumor growth. Clinical trials seem to show that allograft embryonic stem cell transplant is possible without immunosuppression. The tumorigenicity of embryonic cells remains a concern from animal studies, although human clinical trials have not shown this adverse event. Ethical issues also restrict the use of embryonic stem cells in research. Finally, the clinical finding of off-medication dyskinesias drastically reduces the benefits of embryonic stem cell transplant compared with L-Dopa therapy.

Autologous cell transplant held great promise for the elimination of the need to administer immunosuppressants. The surgical procedures were well tolerated. However, improvements in clinical outcomes were not overly convincing. What has instead been convincing is the role of the placebo effect in clinical outcomes. The placebo effect has been a recurring theme in cell transplant studies for PD and a focus of this review article. Notably, the placebo effect is not unique to cell transplant therapy. Research in other treatment modalities for PD has also shown a role of the placebo effect. These include medical therapies, such as dopamine agonists, and surgical interventions including deep brain stimulation and subthalamic nucleus stimulation. The placebo effect of PD treatment is hypothesized to result from the effects of motivation and reward on dopamine action in the brain. The placebo effect has also been demonstrated in the treatment of other neurological disorders including multiple sclerosis and migraines. Increased medical attention that is associated with enrollment in a clinical trial may attribute to the placebo effect shared across multiple fields in neurological research. Surgical interventions have been found to show a more substantial placebo effect than medical
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therapies, illustrating the necessity of using double-blind clinical trials in surgical research. Recruiting participants for these studies is a challenge, however, and clinical trials often involve small numbers of patients. There is also a need to conduct long-term studies that will follow patients for many years after undergoing cell transplant surgery. If patients from previous clinical trials are followed up in the long-term, further improvements in their UPDRS scores might be found as the transplanted cells continue to be functionally integrated into the host midbrain.

It is important to note that the majority of clinical trials conducted to date included only PD patients who had responded well to L-Dopa therapy. This was decided to increase the likelihood of success of the clinical trials. If cell transplant were to be introduced into clinical practice, it would ideally be an option for patients who did not respond to other therapies. Future research will have to extend to include these patients in order to determine if this will be possible. Past trials have also shown that the best results were found in younger patients with mild disease. We hope that cell transplant therapy will one day be able to help patients with severe symptoms.

There remains to be many unknowns about stem cell therapy that prevent its introduction into clinical practice. Importantly, the clinical studies completed to date have shown cell transplant is an intervention that can be safely performed and well tolerated by patients. This is an achievement that opens the doors for continued work in this field to tap into the optimal cell type that can be used for therapeutic transplant.

References


Acknowledgements
Thanks to Dr. Qi Yuan of Memorial University of Newfoundland, Faculty of Medicine, for suggesting this project and reviewing the manuscript.