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The cell repair research for Parkinson's disease: A systematic review

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REVIEW ARTICLE

The cell repair research for Parkinson's disease: A systematic review

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ABSTRACT

Background and Objective: Parkinson's disease (PD) is a common neurodegenerative disease. Previous studies have demonstrated the effect of cell-based therapies, but their clinical efficacy and safety have not been evaluated. This review protocol aimed to systematically evaluate the effect of stem cell therapy in patients with PD and to develop an evidence base for guiding policy and practice.

Methods: PubMed, Embase, MedlinePlus, *The Lancet* and *Brain* were searched over the period January 2001 to October 2019. The keywords used for searching were "Parkinson's disease" and "cell therapy" and "mesenchymal stem cells" and "embryonic stem cells" and "brain-derived neural stem cells" and "neural progenitor cells". The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and a measurement tool, Assessment of Multiple Systematic Reviews (AMSTAR), to assess systematic reviews were used to assess the reporting quality and methodological quality. Data extracted included study details, participant details, intervention details and outcome.

Results: Nine valid research papers were screened out by systematic analysis. These nine studies were carried out in different countries, with different populations and cell types. According to evaluation methods used, all of the transplantation therapies reported can improve the symptoms of PD patients.

Conclusions: Cell transplantation is a potential treatment option for PD. More studies with strict study design, larger sample sizes, and longer follow-up are needed in the future.

1 Introduction

Parkinson's disease (PD) is a prevalent neuro-

degenerative disease which affects 1%–3% of the population over 60 years of age. The main pathological characteristic of PD is the dysfunc-

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tion or loss of dopamine (DA) neurons in the substantia nigra, which leads to a motor disorder, such as tremor, rigidity, bradykinesia, or postural instability [1, 2]. Treatment strategies for PD patients include traditional treatments, such as dopamine medication or surgical procedures, and novel methods, such as alternative therapies, Chinese medicine, optogenetics and cell transplantation.

The traditional treatments enhance dopamine levels by using levodopa, a dopamine precursor, to increase dopamine production or carbidopa to reduce dopamine degradation in the peripheral blood. Long-term treatment with levodopa or carbidopa can be accompanied by the development of both behavioral and motor complications, such as dyskinesia [3]. Surgical procedures include deep brain stimulation (DBS) and pallidotomy, which involves small destruction of the subthalamic nucleus to stimulate the dysfunctional neurons [4]. All of these strategies are available for the symptomatic treatment of PD, but cannot prevent progression of the disease.

Chinese medicine can effectively relieve the symptoms of PD. In particular, acupuncture is widely used in PD treatment [5]. Optogenetics has provided the opportunity to modulate specific target neurons. Since optogenetics can individually control specific neurons in freely moving animals, it could be proposed to restore neural circuit function to PD [6]. Recently cell-based therapies have gained prominence, as promising treatments to replace the missing dopamine neurons and restore the motor function of PD patients [7–9]. Open clinical trials have demonstrated that mesenchymal stromal cells and embryonic stem cells (ESCs) may reduce neuronal cell loss and benefit PD patients [10]. The Unified Parkinson's Disease Rating Scale (UPDRS) has shown a steady improvement in patients and their symptoms, including facial expression, gait, and freezing

episodes. No tumor formation, transplantation complication, severe hemorrhage, infection or severe immune rejection was reported, suggesting the efficacy and safety of human stem cells. One study reported that grafted nigral neurons were found to have Lewy body-like inclusions 14 years after transplantation, which suggests that PD can affect grafted cells in the striatum [7], and the clinical benefits induced by grafts were gradually lost following transplantation [11]. All of these studies suggest that the effect and safety of cell therapies should be evaluated, whilst monitoring the long-term and side effects.

Cell-based therapies have gained attention in recent years; however, their clinical safety, feasibility and efficacy are still unknown as only a few relevant case studies have been reported. Therefore, a systematic review is needed. In this review, we systematically evaluate the efficacy of cell transplantations in PD treatment. A comprehensive and systematic understanding may help to develop the evidence base for PD therapies to guide policy and benefit patients in clinical practice.

2 Methods

2.1 Study inclusion and exclusion criteria

The inclusion criteria were (1) formal published studies; and (2) human study. No restrictions on language or publication status were applied. The exclusion criteria were (1) article types including conference abstract, review, case, editorial, and letter; (2) repeated publications; and (3) studies with inadequate data and unavailability of full-text articles, and ongoing trials.

2.2 Data sources and search strategy

We searched the references systematically in several major meta-databases. Pubmed, Embase and MedlinePlus were searched over the period from January 2001 to October 2019. Other

resources, including unpublished grey literature and published literature from the journals *The Lancet* and *Bain*, were also searched by screening reference lists. The keywords used for searching were “Parkinson’s disease” and “cell therapy” and “mesenchymal stem cells” and “embryonic stem cells” and “brain-derived neural stem cells” and “neural progenitor cells”. Our search terms for Pubmed were (“Parkinson disease” [Mesh]) OR (idiopathic Parkinson's disease [Title/Abstract]) OR (Lewy body Parkinson's disease [Title/Abstract]) OR (paralysis agitans [Title/Abstract]) AND (“stem cells” [Mesh]) OR (progenitor cells [Title/Abstract]). In addition, we did a round of manual search of the references from the included studies.

2.3 Data extraction and management

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and a measurement tool, Assessment of Multiple Systematic Reviews (AMSTAR), were used to assess the reporting quality and

methodological quality. The data extracted included study details (publication year, country), participant details (demographics, stem cell species), intervention details (such as indicators, diagnostic tools), and outcome.

2.4 Selection of studies

Two investigators carried out the database search independently, based on the same criteria. Two investigators further worked independently to assess each study for inclusion based on the criteria. Disagreements were resolved by discussion between the investigators. The study flow diagram is shown in Fig. 1.

3 Results

Through systematic analysis, we summarized the effectiveness of cell therapy in nine studies. Table 1 shows that a total of 139 patients with PD were investigated over the 9 studies, including 2 groups from China, 2 groups from

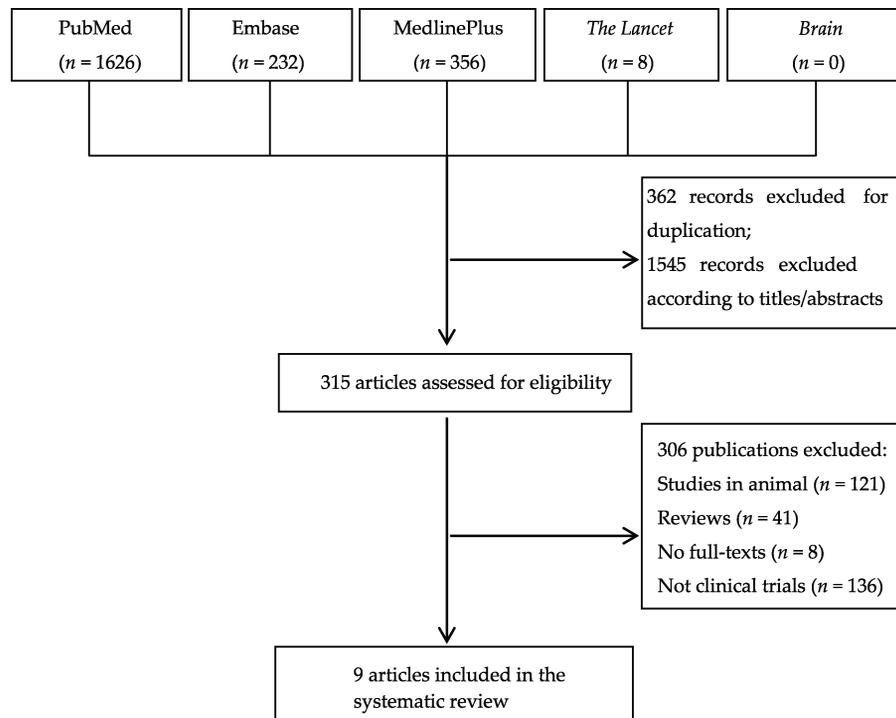


Fig. 1 Flow diagram of literature and screen strategy.

Table 1 Overall information of the studies.

Study	Country	PD patients				Type of study; follow-up time (months)	Study design
		N	Mean age/Age range (years)	Female (%)	Mean duration time (years)		
Leng et al. [12]	China	21	57.33/42–79	28.57	–	case series; 7–57	a prospective, single-dose, uncontrolled, pilot study
Brazzini et al. [13]	Peru	50	62.5/38–81	28.0	9.3	case series; mean 7.4 ± 4.5, range 1–18	a prospective, single-dose, uncontrolled, pilot study
Yin et al. [14]	China	12	66/52–88	58.33	6.4	case series; 12–36	a prospective, single-dose, uncontrolled, pilot study
Canesi et al. [8]	Italy	5	64.8/60–68	80.0	–	case series; 1–12	Clinical Trials (NCT 01824121)
Venkataramana et al. [9]	India	7	55.4/22–62	0	14.7 ± 7.56	case series; 12–36	a prospective, single-dose, uncontrolled, pilot study
Freed et al. [10]	USA	40	57/34–75	47.5	14	case series; 36	a prospective, single-dose, randomized controlled, pilot study
Li et al. [11]	Sweden	1	86	0	10	case report; 288	a prospective, uncontrolled, pilot study
Kefalopoulou et al. [15]	England	2	68/67–69	0	11	Case series; 180/216	a prospective, uncontrolled, pilot study
Kordower et al. [7]	USA	1	61	100	22	Case report; 168	a prospective, uncontrolled, pilot study

America, 1 group from Peru, 1 group from Italy, 1 group from India, 1 group from Sweden and 1 group from England, i.e., these studies were distributed throughout Asia, Europe, North America and South America. The ages of the PD patients ranged from 22 to 88 years old, and the mean age distribution was 50–70 years old. Overall, there are fewer female patients than males, and many of these patients had an average disease duration of > 10 years. Study type and study design of each study and the follow-up time are also shown in Table 1.

Table 2 shows the PD treatment options investigated in the 9 articles, including transplantation of neural precursor cells, autologous bone marrow stem cells, retinal pigment

epithelium (RPE) cells, mesenchymal stem cells (MSCs), embryonic dopaminergic neurons, and fetal cells to PD patients. To evaluate the effects of transplantation, such as tumor formation, immune rejection, graft-induced side effects, etc., these 9 articles used diagnostic and measurement tools including magnetic resonance imaging (MRI), positron emission computed tomography (PET) and immunohistochemistry.

Several indicators were used to evaluate efficacy (Table 3). Eight of the studies used the UPDRS as an effective indicator to evaluate PD patients. By analyzing the differences in UPDRS scores before and after transplantation, most of the articles reported significant reduction in UPDRS

Table 2 Treatment and diagnostic tools.

Study	Stem cell species	Treatment	Diagnostic and measurement tools	Results
Leng et al. [12]	neural precursor cells	local injection	MRI, PET-CT	an increase in dopamine release during the first 6 months
Brazzini et al. [13]	autologous bone marrow stem cells	super selective intra-arterial autologous stem cell implants	MRI, MRS	mean improvements in NAA/Cr ratio in both basal ganglia
Yin et al. [14]	RPE cells	surgical procedure	PET	an increase in dopamine release during the first 6 months
Canesi et al. [8]	MSCs	venous implants	SPECT, PET, FP-CIT, β -CIT	significant positive changes during the first 6 months
Venkataramana et al. [9]	BM-MSCs	surgical procedure	MRI	no significant changes at 12 months
Freed et al. [10]	nerve cells	surgical procedure	PET	an increase in ^{18}F -dopa uptake at 12 months
Li et al. [11]	embryonic dopaminergic neurons	transplantation into the putamen	Immunohistochemistry, imaging, quantification	survival of dopaminergic neurons in the grafts and complete reinnervation of grafted putamen
Kefalopoulou et al. [15]	fetal cells	transplantation into the putamen	PET	an increase in ^{18}F -dopa uptake
Kordower et al. [7]	dopaminergic neurons	transplantation into the putamen	Immunohistochemistry	Lewy body-like pathology in long-term nigral grafts

RPE, retinal pigment epithelium; MSC, mesenchymal stem cell; BM-MSC, bone marrow MSC; MRI, magnetic resonance imaging; PET, positron emission computed tomography; PET-CT, PET-computed tomography; MRS, magnetic resonance spectroscopy; SPECT, single photon emission computed tomography; NAA/Cr, N-acetylaspartate/creatine.

scores after transplantation: Leng et al. reported from baseline score of 80.71 ± 15.48 to 72.76 ± 13.31 , 7–57 months after transplantation [12];

Brazzini et al. reported from baseline score of 68 and quartile deviations (QD) of 25 to 34 (QD 20), with a mean follow-up of 7.4 ± 4.5 months [13]; Yin et al. reported from baseline score of $58.8 \pm 27.7/82.9 \pm 28.7$ to $43.8 \pm 23.3/64.0 \pm 32.1$, 36 months after transplantation with/without medication [14];

Venkataramana et al. reported from baseline score of $50.6 \pm 15.9/65 \pm 22.1$ to $31.7/43.3$, 12–36 months after transplantation with/without medication [9].

Four of the articles used Hoehn-Yahr(HY) scores

to evaluate the patients; similarly, the scores decreased following transplantation:

Leng et al. reported, from baseline score of 3.71 ± 0.94 to 2.86 ± 1.05 , 7–57 months after transplantation [12];

Brazzini et al. reported from baseline score of 3.0 (QD 1.0) to 2.0 (QD 0.5), with a mean follow-up of 7.4 ± 4.5 months [13];

Venkataramana et al. reported from baseline score of 2.785 ± 1.1 to 2.5, 12–36 months after transplantation [9].

In addition, the Parkinson's Disease Questionnaire (PDQ-39), the Schwab and England Activities of Daily Living Scale (SE-ADL), Northwestern University Disability Scale (NUDS),

Table 3 Indicators used to evaluate efficacy of transplantation.

Study	Indicators					
	UPDRS	HY	PDQ-39	SE-ADL	NUDS	PSP
Leng et al. [12] (sores pre-first surgery/pre-second surgery, 7–57months, on medication)	80.71 ± 15.48/ 72.76 ± 13.31	3.71 ± 0.94/ 2.86 ± 1.05	110.62 ± 17.62/ 104.90 ± 17.60	37.14 ± 13.47/ 52.38 ± 14.11	–	–
Brazzini et al. [13] (baseline/7.4 ± 4.5 months, on medication)	68(QD 25)/34(QD 20)	3.0(QD 1.0)/ 2.0 (QD 0.5)	–	70(QD 20)/ 80(QD 10)	16.5(QD 9.25)/7.0 (QD 7.25)	–
Yin et al. [14] (baseline/36 months)	58.8 ± 27.7/43.8 ± 23.3 (on medication) 82.9 ± 28.7/64.0 ± 32.1 (off medication)	–	–	–	–	–
Canesi et al. [8] (baseline/12 months, medication not mentioned)	38/44	0.8/0.8	–	–	–	42/52
Venkataramana et al. [9] (baseline/12–36 months)	50.6 ± 15.9/31.7 (on medication) 65 ± 22.1/43.3 (off medication)	2.785 ± 1.1/2.5 (medication not mentioned)	–	14% improvement (12–36 months, medication not mentioned)	–	–
Freed et al. [10] (12 months)	19.5 ± 8.5 (on medication) 58.5 ± 20 (off medication)	–	–	–	–	–
Li et al. [11]	–	–	–	–	–	–
Kefalopoulou et al. [15]	38/22 (baseline/216 months, off medication) 23/18 (baseline/180 months, off medication)	–	–	–	–	–
Kordower et al. [7]	No on medication score, an increase in off medication score	–	–	–	–	–

UPDRS, Unified Parkinson's Disease Rating Scale; HY, Hoehn-Yahr scores; SE-SDL, Schwab and England Activities of Daily Living Scale; NUDES, Northwestern University Disability Scale; PSP, Progressive Supranuclear Palsy Rating Scale.

and Progressive Supranuclear Palsy (PSP) Rating Scale were also used in some of the studies to evaluate the efficacy. PDQ-39 and NUDES scores decreased slightly following transplantation, while SE-ADL scores increased. Details of the assessment of the safety of the transplantation in each study are provided in Table 4. The assessment of tumor formation, immune rejection, use of immunosuppressants,

graft or delivery induced side effects, illnesses, sequelae, and death are included. In the 9 investigated studies, no serious adverse events associated with cell implantation or surgical procedure developed. One group reported the sudden death of a patient from a heart attack 4 days after cell implantation, but they have ruled out the direct relationship with the implant or implantation procedure [4]. Another

Table 4 Safety evaluation of the procedures.

Study	Projects					
	Tumor formation	Immune rejection and use of immunosuppressant	Graft or delivery induced side effects	Illnesses or incidents that required medical treatment	Sequelae	Death
Leng et al. [12]	0	0	0	–	–	–
Brazzini et al. [13]	–	–	0	0	–	1 (sudden heart attack)
Yin et al. [14]	–	–	–	0	0	0
Canesi et al. [8]	–	–	–	–	–	–
Venkataramana et al. [9]	–	–	–	–	–	–
Freed et al. [10]	–	–	–	1 (subdural hematoma)	0	0
Li et al. [11]	–	–	–	–	–	–
Kefalopoulou et al. [15]	–	–	–	–	–	–
Kordower et al. [7]	–	–	–	–	–	–

group described the development of a subdural hematoma in one of their patients, which was detected about 6 weeks after surgery and was “possibly” related to the procedure [5]. In summary, the transplantation would induce side effects, but no serious events occurred in the 9 studies that we investigated.

4 Discussion and conclusions

The literature results were obtained by systematic analysis of 9 valid research papers, which aimed to evaluate the clinical safety, feasibility and efficacy of cell transplantation in the treatment of PD. These studies were carried out in different countries and regions, and the populations of the studies also varied. The researchers used different stem cell types to treat PD. Leng et al. reported a trial to evaluate the clinical safety and effectiveness of transplantation of neural precursor cells in the treatment for PD [12]. Brazzini et al. evaluated the feasibility, safety, and effectiveness of intra-arterial autologous implantation of adult stem cells for PD [13]. Yin et al. assessed the clinical effect of transplantation of human RPE cells into the unilateral post-commissural

putamen for treatment of PD [14]. Canesi et al. [8] and Venkataramana et al. [9] reported the prospective and pilot study of autologous bone marrow MSCs (BM-MSCs) unilaterally transplanted in patients with PD. Li et al. [11], Kefalopoulou et al. [15] and Kordower et al. [7] reported the long-term clinical outcomes of transplantation of fetal cells or embryonic dopaminergic neurons in patients with PD.

Across the world, the prevalence of PD steadily increases with age [6, 16, 17]. Some researchers suggest a peak around the age of 70 years, with a gradual reduction in prevalence with increasing age [16]. In this systematic review, we found that the average age of patients with PD, who used cell transplantation as a treatment method, was 50–70 years; the majority was in their 60s, which is consistent with previous studies. Many of the patients had experienced disease durations of > 10 years. Freed et al. suggested that the transplantation was beneficial to patients at 60 years old or younger, but not to older patients [10]. Regardless of the possible interpretation, all age-related data must be interpreted. In the given studies, the population of elderly patients was commonly small; therefore a few reported

cases may have a significant influence on the results. The analysis of geographical variations in prevalence is easily confused with demographic differences between populations [1]. Our systematic review aimed to investigate the effects of demographic differences through age-specific analysis. By comparing age groups across regions, we found that fewer PD patients at the ages of 50–59 years were cured by cell transplantation in Asia than in North America, and the number of cured 60–69-year-olds in North America was significantly lower than in Europe, Asia, and South America.

Based on the 9 articles, we were able to divide the transplanted stem cells into three categories: ESCs, MSCs, and brain-derived neural progenitor cells (NPCs), which all have the potential to differentiate into dopaminergic cells. Different cell types have different transplantation methods, but the transplantation method does not affect the clinical effect of patient. Eight of the articles used the UDPRS score to evaluate the patients before and after transplantation, to determine any improvement in their symptoms. The results concluded from the 9 studies suggest that the stem cell transplantation is effective for the treatment of PD. Since the survival of DA-rich cells in the grafted tissue is likely to be a key factor, and the grafting protocol differs in several important respects among those clinical transplantation programs [18], it is difficult to speculate which of the three types of stem cells is the most effective. Stem-cell derived cell therapy requires more studies to investigate the safety of stem cell transplantation for PD due to difficulties in controlling differentiation of multipotent stem cell and concerns over tumorigenicity. The diagnostic and post-transplant examination tools mainly used included MRI, magnetic resonance spectroscopy (MRS), single photon emission computed tomography (SPECT), PET, immunohistoche-

mistry, imaging, and quantification. MRI was the main diagnostic tool, used in 5 of the 9 articles. MRI can be used to visually determine whether a patient's brain tissue is abnormal, and combining with the UPDRS score, it is effective to diagnose PD.

By evaluating with UPDRS, HY scores, PDQ-39 and SE-ADL, Leng et al. found that the symptoms of patients improved after transplantation [12]. According to the UPDRS, HY scores, SE-ADL and NUDS scores, significant differences were found between baseline and follow-up evaluations in the Brazzini group's study [13]. Yin et al. found improvement in the primary outcome measure at 3 months post-treatment, particularly the UPDRS-M score in the off medication [14]. Canesi et al. used UPDRS and HY scores to assess motor function in patients 12 months after MSC infusion, and found mild improvements [8]. Venkataramana et al. found that patients subjectively reported marginal improvement in symptoms [9]. Kefalopoulou et al. found that ON periods were prolonged and the patients' self-reported frequency and severity of motor fluctuations diminished [15]. Kordower et al. observed that initially the patient experienced an improvement in functioning, including UPDRS motor OFF scores, but that this was followed by progressive worsening of symptoms [7]. However, Freed et al. found that the UPDRS scores of younger patients in the transplantation group had greater improvement than those in the sham-surgery group [10]. In summary, transplantation therapy can improve PD symptoms; however, comparisons between the traditional and transplant treatments is relatively insufficient.

At present, cell therapy for PD is still in its infancy, and its safety has been questioned. In our systematic review, none of the 9 articles included showed significant side effects

following transplantation. Leng et al. examined tumor formation, immune rejection, graft-induced side effects, and delivery-related side effects following transplantation, and found all patients behaved normally after transplantation [12]. In the study reported by Brazzini et al., several patients suffered varying degrees of problem, which were not related to transplantation, and one died from heart attack [13]. Freed et al. reported a subdural hematoma was detected about 6 weeks after surgery, which was thought to be “possibly” related to the surgery, as the MRI had been normal on the day after surgery [10]. Kefalopoulou et al. reported two patients with graft-induced side effects, but the influence was insignificant when compared to the effectiveness of the transplant [15]. Li et al. reported that post-mortem autopsy of a PD patient implanted with dopamine neurons 24 years ago revealed that positive inclusion of ubiquitin and α -synuclein was observed in 11%–12% of implanted dopaminergic neurons. And the clinical benefits induced by transplantation in this patient were gradually lost 14 years after transplantation [11]. Kordower et al. also reported a similar phenomenon [7]. Cell transplantation performed by these two groups could only improve PD symptoms in a short term, which was probably because that implanted cells lost their efficacy during major degenerative changes and widespread α -synucleinopathy development in host brains. In summary, stem cell therapy for PD is safe, and the possible graft-induced side effects are slight and the advantages outweigh the disadvantages.

Cell transplantation is a potential treatment option for patients with PD, because of its satisfactory efficacy and safety. To date, studies in this field are limited; therefore, more studies with strict study design, larger sample sizes, and longer follow-up are needed to further investigate the efficacy and safety.

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Conflict of interests

Haitao Xie is the general manager and technical director of Guangdong Xiankangda Biotechnology Co., Ltd. in Dongguan, Guangdong, China.

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