pISSN 1738-2696 · eISSN 2212-5469
http://dx.doi.org/10.1007/s13770-016-9093-2
FEATURE ARTICLE

TERM

The Therapeutic Potential of Stem Cells and Progenitor Cells for the Treatment of Parkinson's Disease

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Parkinson's disease (PD) is the second most common neurodegenerative disorder. It is usually seen in those above 50 years old. Current medical treatments only provide symptomatic relief but cannot cure the disease. There are claims that PD can be cured by stem cell transplant. The present study is aimed to assess the clinical potency and safety of stem cell in treating PD. A total of eleven articles were included for analysis, with four randomised control trials (RCTs), five non-RCTs and 2 follow up studies. All the four non-RCTs showed improvement of Unified Parkinson's Disease Rating Scale with no adverse events. However, results from RCTs showed no significant differences in the rating score among the transplant group and the Sham surgery group. The secondary analysis of one study showed a significant improvement of the rating score in those patients aged 60 and younger. Transplant group also associated with an overall higher incidence of adverse events. In conclusion, the RCTs and non-RCTs produced opposite results. When the studies were performed as non-RCTs in small number of patients, they showed promising result in the patients. It could say that currently the use of stem cell/progenitor cells in treating PD need much research despite having the implanted stem cell to be able to survive and integrated. The survival of implanted dopamine neurons in the striatum, however, does not indicate a success in correcting PD symptoms. Further investigations will shed light on the application and mechanism of action of stem cells in treating PD. Tissue Eng Regen Med 2016;13(5):455-464

Key Words: Neurodegenerative disease; Cell therapy; Stem cell transplantation; Neuro-regeneration and neuroprotection

INTRODUCTION

Parkinson's disease (PD) is due to the loss or damage of dopaminergic neuronal cells in the substantia niagra. This leads to reduced production of neurotransmitter dopamine, which is responsible for motor symptoms in PD [1]. Pathologically, PD is characterized by the appearance of Lewy Bodies (eosinophilic inclusion bodies) in the remaining dopaminergic neurons in substantia nigra [2] and also presence of its motor symptoms which are due to the loss of dopamine. The symptoms include tremors, bradykinesia, rigidity and postural instability. It also has accompanied neuropsychiatric symptoms unrelated to dopamine loss, such as cognitive disorder, speech disorder, mood disorder, insomnia, reduced eye blink, dysphagia and sexual dysfunction [3].

Currently, there is no data available on the prevalence of PD in Malaysia. However a study published by neighboring country-Singapore in 2007 showed that the incidence rate was 32 per 100000 person for individuals aged 50 years and above [4]. Another study done in University Hospital, Kuala Lumpur by Chew et al. [5] in 1998 compared the incidence of PD among the three major races in Kuala Lumpur and Selangor. The study showed that the incidence of PD was highest among the Chinese (70.6%), followed by Indian (18.3%). The Malays had the least incidence which was only 9.9%. According to 2012 treatment guideline published by Malaysia Society of Neurosciences [6], medications used to treat PD are either by oral medication, for examples, levodopa, dopamine agonist, and amantadine, or by ablative surgery, or by deep brain stimulation.

The exact etiology of PD is unknown. However it is believed that it could be due to ageing, genetic predisposition, environmental toxin, oxidative stress or a combination of these [7]. About 15–25% of PD patients have family history of PD [8]. Up to year 2009, more than nine genes have been identified to be associated with an increased risk for PD [8]. Leucine-rich repeat kinase 2 gene mutation is the most gene associated with autosomal dominant PD [9]. The other genes that have been identified to be involved are duplication or triplication of alpha-

Received: October 7, 2015
Revised: November 29, 2015
Accepted: December 2, 2015
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synuclein gene, mutation of PARKIN gene, PINK-1 gene, and DJ-1 gene [8]. The mutation in these genes can lead to abnormal folding of protein and dysfunction of mitochondrial [3]. The possible environmental factors are like pesticides, herbicides and drinking well water [10]. Any combination of these factors could contribute to the development of PD by causing or accelerating nitrostriatal cell death.

Current options for the treatment of PD are either medical or surgical. approach. Different drug therapies are available for PD treatment. These drugs are used in combination as there is still no single effective treatment for PD. Examples of drugs available are levodopa, dopamine agonist, and selegiline. The aim of using the levodopa is to resupply the dopamine in the substantia nigra. Even though Levodopa is an effective drug in PD treatment, it is usually used in older patients, always advised to start at a lower dose, and used in patients with moderate to severe motor disability. There is no "Gold Standard" treatment for PD as yet and the choice of treatment usually is based on the patient's symptoms.

The limitation with the medication is that the patients will eventually face more fluctuation in motor symptoms and start to experience dyskinesia [11]. The motor fluctuation is described as "on" and "off" state. "ON" refers to improvement in the 'wearing off' symptoms after taking the treatment especially seen with Levodopa, and "OFF" refers to worsening of the PD symptoms before time for taking next dose of medication [12]. Dyskinesia refers to involuntary "wriggling" movement which usually occurs when a patient is in "ON" state. Once medical treatments are no longer effective, patients might have to consider surgical options like pallidotomy and deep brain stimulation [11].

Currently, stem cell therapy for PD is still under experimental stage, most of the studies were done in animals. The first clinical trial on PD patient was reported in 1989 by using aborted human fetal ventral midbrain tissue [13]. Since then, different clinical trials were conducted at different centers, using different sources of stem cells. However, the results produced were inconsistent, even for those patients treated in the same center and in the same study. Some of the results were promising and some didn't show any improvement. This review is conducted in order to assess the potential use and safety profile of stem cell therapy in PD. If the clinical efficacy could be established, it could serve as an initial step for more future clinical trials.

THE CLINICAL POTENCY AND SAFETY OF STEM CELL IN TREATING PARKINSON'S DISEASE

To determine the clinical potency and safety of stem cell in treating PD, a comprehensive analysis of reported clinical trials was conducted. A comprehensive search using the PubMed, Cochrane's Library, and Google Scholar was conducted in the English language from year 2000 to 2015. The keywords used were stem cell, embryonic stem cell, pluripotent stem cell, cell, Parkinson's disease, transplant and implant. The methodology employed in selecting clinical trials reported in journal articles and the quality assessment using JADAD score is described in details in Supplementary Material (in the online-only Data Supplement).

A total of 11 articles were included for analysis, with four randomised control trial (RCT), five non-RCT and 2 follow up studies. Periodic report summary from one ongoing multicenter open label clinical grafting trial sponsored by the European Union (TRANSEURO) was reviewed but has not been included in this study since details of patients and treatment protocol are not included in the report. The comparison of the results and side effects of the studies are presented in Table 1–7.

A total of 243 participants were included in these 11 selected studies with breakdown of 183 participants in RCT and 60 in non-RCT (Table 1). Different type of cells was either unilateral or bilateral were transplanted in PD patients via surgery (Table 2). In RCT studies, except study by Olanow et al. [14], which used placebo in control group, sham surgery was done in control group (Table 1). In both RCT and non-RCT studies the duration of follow up after transplant was between 12 to 36 months. Nine patients in follow up studies were monitored for the improvement as well as for any potential side effects between 5 to 18 years after transplant.

Four non-RCT showed improvement of Unified Parkinson's Disease Rating Scale (UPDRS) with no adverse events. Study by Xue et al. [15] shown the contralateral symptom improvement in 7 days, 1 month, and 3 months after transplantation. The ipsilateral symptom improvement was evaluated at 1 month and 3 months after transplantation.

Except studies by Trott et al. [16] in the other studies the primary end point was change between baseline and final visits in motor component of the Unified UPDRS in the practically defined off state (Table 3, 4, and 5). Trrot et al. [16] used neuropsychological tests to assess orientation, attention, language, verbal and visual memory, abstract reasoning, executive function, and visuospatial and construction abilities before and 1 year after surgery (Table 6).

In three RCT studies details of side effects were reported. The reported side effects were included death, dyskinesia, subdural hematoma, depression, hallucinations and falls (Table 7). There was no report of any serious adverse events in rest of studies.

Table 1. Clinical trials to treat Parkinson's disease using stem cells

No.	Author	Year	Title	Journal	Sample size	P	I	C	O	S	Quality assessment
1	Gross et al. [22]	2011	Intrastriatal transplantation of microcarrier-bound human retinal pigment epithelial cells versus sham surgery in patients with advanced Parkinson's disease: a double blind, randomised, cortrolled trial	Neurol	71	PD patient at least 5 years, responded to levodopa but insufficient control	Transplant with human RPE cells	Sham surgery	No benefit	RCT	JADAD SCORE 5
2	Trott et al. [16]	2003	Cognition following bilateral implants of embryonic dopamine neurons in PD: a double blind study	Neurol	39	PD at least 7 years	Transplant with embryonic dopamine neurons	Sham surgery	No benefit	RCT	JADAD SCORE 3
3	Freed et al. [17]	2001	Transplantation of embryonic dopamine neurons for Severe Parkinson's disease	N Engl J Med	39	PD at least 7 years	Transplant with embryonic dopamine neurons	Sham surgery	No difference	RCT	JADAD SCORE 3
4	Olanow et al. [14]	2003	A double-blind controlled trial of bilateral fetal niagral transplantation in Parkinson's disease	Ann Neurol	34	Advanced PD	Transplant with fetal nigra	Placebo procedure	No significant improvement, more adverse events	RCT	JADAD SCORE 5
5	Stover et al. [18]	2005	Intrastriatal implantation of human retinal pigment epithelial cells attached to microcarriers in advanced Parkinson's disease	Arch Neurol	6	Advanced PD (mean of 10.2 years)	Implantation of RPE cells on microcarriers	No control	UPDRS score improved by 48% at 12 months	Open-label pilot study	NOS 3 stars
6	Venkataramana et al. [19]	2010	Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease	Transl Res	7	PD patients (mean of 14.7 years)	Unilateral Transplantation of autologous BM-MSC	No control	Improvement in "on" and "off" UPDRS score	Open-label study	NOS 3 stars

Table 1. Clinical trials to treat Parkinson's disease using stem cells (continued)

No	Author	Year	Title	Journal	Sample size	P	I	C	O	S	Quality assessment
7	Venkataramana et al. [20]	2012	Bilateral transplantation of allogenic adult human bone marrow-derived mesenchymal stem into the subventricular zone of Parkinson's disease: a pilot clinical study	Stem Cells Int	12	PD patients (3–15 years)	Bilateral transplantation of allogenic BM-MSC	No control	Improvement in patients with early stage PD (less than 5 years), not in patients with late PD	Clinical study	NOS 6 stars
8	Yin et al. [21]	2012	Transplantation of human retinal pigment epithelium cells in the treatment for Parkinson's disease	CNS Neurosci Ther	11	PD patients	Transplantation of human RPE cells	No control	Improvement in UPDRS score	Clinical study	NOS 5 stars
9	Kefalopoulou et al. [27]	2014	Long-term clinical outcome of fetal cell transplantation for Parkinson disease: two case reports	JAMA Neurol	2	PD Patients who has undergone transplantation 15 years before	Intrastriatal transplantations of human fetal ventral mesencephalic tissue, rich in dopaminergic neuroblasts	No control	Improvement in UPDRS score	Follow up study	NA
10	Hallet et al. [28]	2014	Long-term health of dopaminergic neuron transplants in Parkinson's disease patients	Cell Rep	5	PD Patients who has undergone transplantation 5–14 years ago	Fetal midbrain dopamine cell suspension		Expression of dopamine transporters and mitochondrial morphology in fetal midbrain cellular transplants	Follow up study	NA
11	Xue et al. [15]	2013	Efficacy and safety of computer-assisted stereotactic transplantation of human retinal pigment epithelium cells in the treatment of Parkinson disease	J Comput Assist Tomogr	17	PD Patients for last 3 to 10 years	Fetal eyes, RPE-derived neural progenitor cells	No control	Contralateral and ipsilateral symptom improvement	Clinical study	NA

P: patient, I: intervention, C: comparator, O: outcome, S: study, NOS: New Castle Ottawa, PD: Parkinson's disease, RPE: retinal pigment epithelium, BM-MSC: bone marrow derived mesenchymal stem cell

DISCUSSION

Among the eleven articles listed in the Table 1, there are four RCTs, five non RCTs and 2 follow up studies. These studies used different source of stem cells for implantation such as embryonic stem cell (ESC), fetal niagral tissue, bone marrow derived mesenchymal stem cell (BM-MSC) and human retinal pigment epithelium (RPE) cells, as shown in Table 2. The cells were transplanted either bilaterally or unilaterally into the putamen. The articles published by Freed et al. [17] and Trott et al.

Table 2. Stem cell source, unilateral vs. bilateral transplantation in each study

No.	Author	Type of cell used	Method of transplantation/injection	Surgery-unilateral or Bilateral transplantation
1	Gross et al. [22]	Human RPE with microcarrier	Human RPE cells were isolated from the eye tissue of donors post mortem and expanded in culture media. During stereotactic transplantation around 325000 cells per side were injected into the post-commissural putamen	Bilateral
2	Stover et al. [18]	Human RPE with microcarrier	Human RPE cells were isolated from post-mortem human eyes obtained by accredited tissue banks after appropriate consent. The isolated cells were expanded. Stereotactic intrastriatal implantation of approximately 325000 RPE cells on microcarriers	Unilateral
3	Yin et al. [21]	Human RPE	hRPE cells in primary culture were isolated from human aborted fetal eyes. RPE-derived neural progenitor cells were obtained from culture. A total of 1×10^6 hRPE cells in 210 μL were deposited in the posterior putamen in one trace.	Unilateral
4	Trott et al. [16]	Embryonic dopamine neuron	Human embryonic mesencephalic tissue containing dopamineneurons was recovered from fragments of embryos aborted seven to eight weeks after conception. Tissue was transplanted up to four weeks after it had been obtained	Bilateral
5	Freed et al. [17]	Embryonic dopamine neuron	Cultured mesencephalic tissue from four embryos was implanted into the putamen	Bilateral
6	Olanow et al. [14]	Fetal nigral tissue	Fetal tissue was obtained from women undergoing elective abortions. Solid mesencephalic grafts derived from donor embryos were used for transplantation. Either one or four donors per side grafted stereotactically into the postcommissural putamen in two staged procedures separated by approximately 1 week.	Bilateral
7	Venkataramana et al. [19]	Bone-marrow-derived mesenchymal stem cell	60 mL of bone marrow was aseptically aspirated from the iliac crest. BM-MSCs were isolated and expanded before transplantation	Unilateral
8	Venkataramana et al. [20]	Bone-marrow-derived mesenchymal stem cell	60 mL of bone marrow was aspirated iliac crest from healthy donors. BM-MSCs were isolated.	Bilateral
9	Kefalopoulou et al. [27]	Fetal cell	Dissociated ventral mesencephalic tissue from 7 to 9 aborted human embryo (5 to 7 weeks) was implanted in each patient	Bilateral
10	Hallet et al. [28]	Fetal cell	Fetal ventral midbrain tissue (6 to 9 weeks) was collected from women undergoing elective abortion. A final cell concentration of approximately 80000/μL was used for each transplantation	Bilateral
11	Xue et al. [15]	hRPE	hRPE cells in primary culture were isolated from human aborted fetal eyes. RPE-derived neural progenitor cells were obtained from culture 4×10^6 hRPE cells into the putamina and lateral ventricles of PD cases by stereotactic surgery	Unilateral

RPE: retinal pigment epithelium, BM-MSCs: bone marrow derived mesenchymal stem cells

Table 3. Result of non randomised control trials

No.	Author	Title	Number of patients	Mean age	Mean duration of PD (years)	Duration of follow up	No. of patients lost to follow up	Mean UPDRS score (baseline off/on)	12 months off/on	% improvement (on or off)	*p* value
1	Stover et al. [18]	Intrastriatal implantation of human RPE cells attached to microcarriers in advanced Parkinson disease	6	52	10.2	24	0	118/NA	67.4/NA	42% (off)	0.3
2	Venkataramana et al. [19]	Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease	7	55	14.7	12–36	0	65/50.6	43.3/31.7	33% (off) 28% (on)	NA
3	Venkataramana et al. [20]	Bilateral transplantation of allogenic adult human bone marrow-derived mesenchymal stem cells into the subventricular zone of Parkinson's disease: a pilot clinical study	12	59	7.7	12	5	88.6/70.7	71/62.8	19.9% (off) 11.2% (on)	NA
4	Yin et al. [21]	Transplantation of human retinal pigment epitelium cells in the treatment for Parkinson's disease	11	66	6.4	12–36	0	93.6/64.8	NA/42.7	34% (on)	0.006

PD: Parkinson's disease, UPDRS: Unified Parkinson's Disease Rating Scale

Table 4. Changes in two randomised control trials after transplantation

No.	Author	Title	Number of patients	Age	Mean UPDRS score baseline off		12 months off		Changes (off)		*p* value
					Treatment group	Control/ sham	Treatment group	Control/ sham	Treatment group	Control/ sham	
1	Gross et al. [22]	Intrastriatal transplantation of microcarrier-bound human retinal pigment epithelial cells versus sham surgery in patients with advanced Parkinson's disease: a double blind, randomised control trial	71	Mean 55.9	48.8	48.8	38.3	38.7	-10.1	-10.1	0.94
2	Freed et al. [17]	Transplantation of embryonic dopamine neurons for severe Parkinson's disease	39	60 years old & younger	58	61	41	59	-17	-2	0.01
				Older than 60	59	71	59	70	0	-1	0.89

UPDRS: Unified Parkinson's Disease Rating Scale

Table 5. Changes in UPDSRS score seen in study by Olanow et al. [22]

No.	Author	Title	Number of patients	Placebo		One donor		Four donor		*p* values			
				UPDRS baseline	UPDRS 24 months	UPDRS baseline	UPDRS 24 months	UPDRS baseline	UPDRS 24 months	Overall	1 donor vs. placebo	4 donors vs. placebo	1 donor vs. 4 donors
1	Olanow et al. [14]	A double-blind controlled trial of bilateral fetal niagral transplantation in Parkinson's disease	34	51.5	59.9	47.9	52	48.6	44.4	0.244	0.334	0.096	0.479

UPDRS: Unified Parkinson's Disease Rating Scale

Table 6. Neuropsychological test (means and SD) for all patients in each treatment group at baseline and at one year follow up [14]

Test	Measure	Baseline		1 year follow-up	
		Real	Sham	Real	Sham
Mini-Mental State Examination (Orientation)	Total correct	9.4 (0.7)	9.6 (0.7)	9.2 (1.4)	9.4 (0.9)
Animal naming	Percentile	43 (33)	54 (26)	35 (31)	43 (30)
Boston Naming Test	Total correct	14.2 (1.4)	14.9 (0.3)	14.1 (1.7)	14.9 (0.4)
BVRT (matching)	Total correct	9.5 (1.2)	9.8 (0.6)	9.1 (1.9)	9.5 (0.4)
Rosen Drawing test (five items)	Total correct	3.2 (0.9)	3.5 (0.9)	2.6 (1.3)	3.2 (0.2)

Values are mean (SD). BVRT: Benton Visual Retention Test

Table 7. Summary of side effects observed in the studies

Author	Adverse events															
	Death		Dyskinesia		Subdural hematoma		Depression		Hallucinations		Falls		Any adverse event		Any serious adverse events	
	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Gross et al. [22]	20%	5.6%	2.9%	NA	NA	NA	14.3%	5.5%	22.8%	2.8%	NA	NA	100%	100%	39.0%	46.0%
Freed et al. [17]	NA	NA	17%	14.9%	1	0	5.7%	6.0%	5.0%	4.2%	2.1%	6.7%	48.7%	51.0%	40.0%	5.0%
Olanow et al. [14]	NA	NA	56.5%	18.2%	NA	NA	54.0%	26.0%	18.2%	30.4%	9.0%	13.0%	61.2%	39.0%	-	-

NA: no available data/or not mentioned in study, T: transplant group, C: control group

[16] were actually done on the same patients, but different outcomes were measured in the studies. The major improvement in PD patients was measured by Unified UPDRS, in both "on" and "off" state.

The main difference between the RCTs and non-RCTs is that they produced opposite results. When the studies were performed as non-RCTs in small number of patients, they showed promising result in the patients. Stover et al. [18] did a clinical study on 6 PD patients. The mean duration of PD in these patients was 10.2 years. In his study, human RPE attached to microcarrier was used. At 12th month follow up, he showed a 42% improvement in UPDRS score in "off" state. But this is a not significant result as the *p* value was 0.3. Venkataramana et al. [19] had conducted two different clinical studies. They first conducted a study on seven patients using the method of unilateral implantation of BM-MSC, at 12th month follow up, the improvement in UPDRS score during "off" state was 33% and during "on" state was 28%. They then conducted another clinical trial in 12 patients by doing bilateral transplantation of BM-MSC. This study also showed improvement in UPDRS score at 12 months in both "off" and "on" state [20].

Another clinical study was conducted by Yin et al. [21] using human RPE. This study was carried out in eleven patients, which managed to showed a significant increase of 34% (*p* value=0.006) in UPDRS score during "on" state at 12th month follow up. The positive finding in these non-RCTs could be due to the small number of patients involved in the study, as well as bias by the investigator and patient.

Gross et al. [22] conducted a double blinded RCT on 71 patients using human RPE bound to microcarrier. The mean age

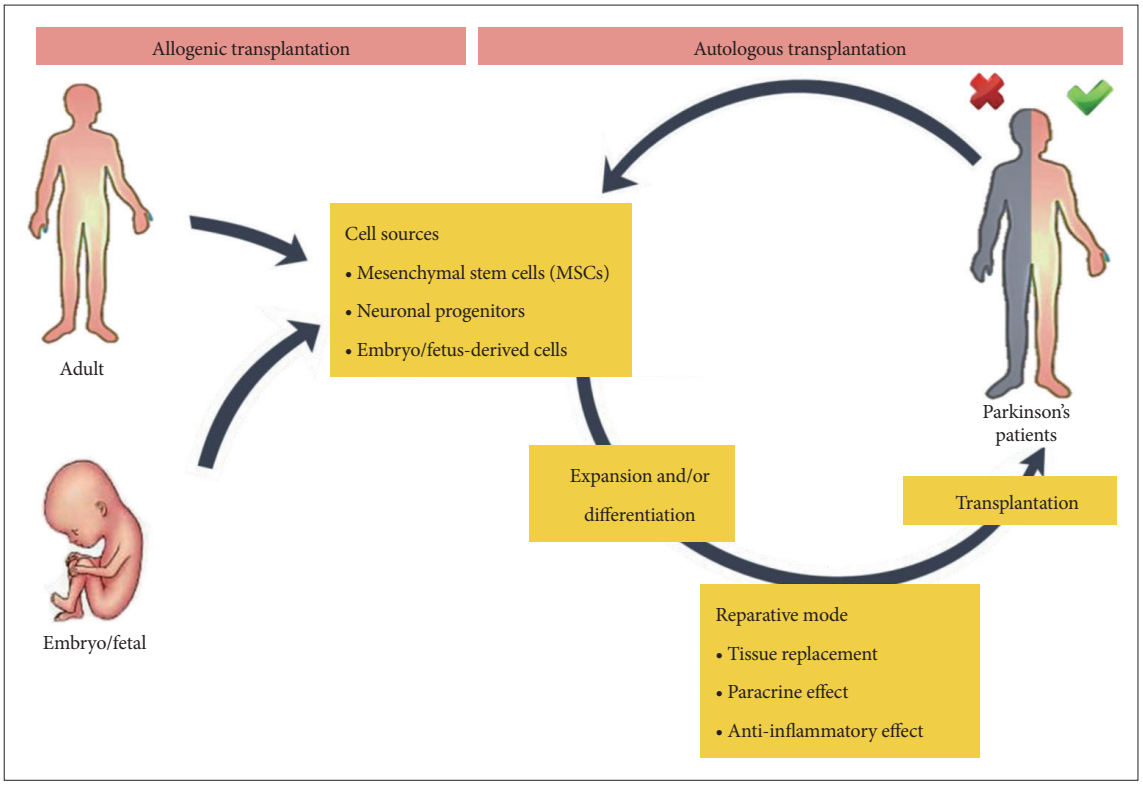

Figure 1. Flow of therapeitic stategy using allogeneic and autologous transplantation approach for treating Parkinson's patients.

of patients in his study was 55.9 years old. The follow up at 12 months post implantation showed slight improvement in UPDRS score during "off" state. When compared to the control group, which was Sham surgery, both procedures showed no significant difference in the scores of UPDRS.

Freed et al. [17] used embryonic dopamine neurons in the RCT. In this study, patients were randomly divided into two groups, one with bilateral implantation of embryonic dopamine neurons, and another group with Sham surgery. At 12th month follow up, the study failed to show any improvement in implant group, and there is no difference with the clinical outcome in those patients who had Sham surgery. However, secondary analysis of the study showed younger patients (60 years old and younger) had a significant improvement in UPDRS score (p=0.01), and the improvement in striatal 18F-fluorodopa uptake was confirmed by PET scan [17]. This showed that may be the brain plasticity of a younger patient is better. The neurological assessment carried out by Trott et al. [16] showed that there was no neurologic and cognitive improvement in the treatment group when assessed at 12th month.

In the RCT conducted by Olanow et al. [14], they divided 34 patients into three groups. One was Sham surgery as control, and the other two groups were given two different doses of fetal tissue (with one donor and four donors). The patients in this study were followed up and assessed. The assessment at 24 months failed to show any improvement in the motor symptoms by UPDRS score, regardless of the dosage of tissue used.

All the non-RCTs reported no significant side effects associated with the treatment. However, in the RCTs, it showed that the total percentage of side effects was higher in the transplant group when compared to Sham surgery group. The incidence of serious side effects was also seen with the transplant group, as showed in Table 7. One of the common complications of PD is dyskinesia; it had a higher incidence with the transplant group as shown in Table 7. This could be due to the extensive fiber outgrowth from the transplant, which leads to an excessive dopamine level [17,23].

In all the RCTs, even though patients had reported some mild improvement in the initial stage of treatment [19,20,22], none of these patients showed continuous improvement. In fact, deterioration of the symptoms was seen in some patients. Studies have shown that implanted stem cells are able to survive and reinnervate the striatum [23], however it has been proven that the grafted cells can developed PD-like pathology [24]. The great difference in the findings of non-RCTs and RCTs showed the importance of a proper double blinded RCT. So far there is still no proven RCT to support the use of stem cell in PD even though non RCTs support the use.

FUTURE PERSPECTIVES

In order to develop effective and efficient therapeutic strategies to cure neurodegenerative diseases like PD, having sourcing the therapeutic cellular resources and transplantation strategies are two major scopes of the cell therapy which are needed more attention (Fig. 1). Autologous and allogenic cellular resources such as mesenchymal stem cells, embryo/fetus derived progenitors/stem cells possess both advantages and challenges in their utilization for cell replacement therapy. Current research interest is focused on deriving these cellular resources and expand them *in vitro* culture in order to generate required cell mass for transplantation. Studies also address the strategies to characterize and differentiate these cells, if it required, to produce functional cells to restore the function and activity of the organ [25,26]. In general, the cell therapy is speculated to achieve the goal via 3 modes of therapeutic mechanisms: 1) Replacement of functional tissue/cells, 2) paracrine effect by producing neuro-protective and neuro-regenerative inducing factors, 3) anti-inflammatory effect of MSCs to protect the damage area from further undergoing neurodegeneration (Fig. 1). Emergence of cell-based therapies is needed to be coupled with therapeutic strategies in order to establish a defined and effective cell therapeutic procedure.

CONCLUSION

Based on the results and discussion, the use of stem cell in treating PD is requires a better insight in terms of their therapeutic contribution either through tissue replacement or paracrine effect. Even though implantation of stem cell is proven to be able to survive, the survival of implanted dopamine neurons in the striatum does not indicate a success in correcting PD symptoms. The role of dopamine neurons and the neurologic innervation in PD appear to be complex. Therefore, future studies are required to make the application of stem cell in this disease practical. Meanwhile, public education, strict rules and regulation should be available to protect the patients from being harmed.

Supplementary Materials

The online-only Data Supplement is available with this article at http://dx.doi.org/10.1007/s13770-016-9093-2.

Acknowledgements

The authors gratefully acknowledge University of Malaya through University Malaya Programme Grant (RP032-14HTM) for providing an opportunity to work on this review article.

Conflicts of Interest

The authors have no financial conflicts of interest.

Ethical Statement

The work have no ethical issues for human and animal right in the current study.

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