Therapeutic Potential of Pluripotent Stem Cell-derived Dopaminergic Progenitors in Parkinson's Disease: A Systematic Review Protocol

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Protocol

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Abstract

Background: Parkinson's disease (PD) is the second most common age-dependent neurodegenerative disease that causes motor and cognitive disabilities. This disease is associated with a loss of dopamine content within the putamen, which stems from the degeneration of dopaminergic (DA) neurons in the Substantia Nigra pars Compacta (SNc). Several approved drugs are available that can effectively treat symptoms of PD. However, long-term medical management is often complicated and does not delay or halt disease progression. Alternatively, cell replacement strategies can address these shortcomings and provide dopamine where it is needed. Although using human pluripotent stem cells (hPSCs) for treatment of PD is a promising alternative, no consensus in the literature pertains to efficacy concerns of hPSC-based therapy for PD. This systematic review aims to investigate the efficacy of hPSC-derived DA progenitor transplantation to treat PD in preclinical animal models.

Methods: This is a systematic review of preclinical studies in animal models of PD. We intend to use the following databases as article sources: MEDLINE (via PubMed), Web of Science, and SCOPUS without any restrictions on language or publication status for all related articles published until the end of 2019. Rescue of motor deficits is defined as the primary outcome, while histological and imaging data comprise the secondary outcomes. Two independent reviewers will select the titles and abstracts, extract data from qualifying studies, and assess the risk of bias by using the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool and the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) checklist. The standardized mean difference (SMD) will be calculated to determine the efficacy of the treatment, with 95% confidence intervals (95% CI). The heterogeneity between studies will be calculated by "I^2 inconsistency of values and Cochran's Q statistical test", where I2 > 50% and/or p < 0.10 suggest high heterogeneity. Meta-analyses of random effects will be run when appropriate.

Discussion: This study will present an overview of preclinical research on hPSCs and their therapeutic effects in PD animal models. This systematic review will point out the strengths and limitations of studies in the current literature while encouraging the funding of new studies by public health managers and governmental bodies.

Background

Parkinson's disease (PD) impacts one percent of the population above 60 years old; this presents an enormous economic and societal burden due to the global increase in aging. PD is a chronic neurodegenerative disease clinically diagnosed by tremor, rigidity, bradykinesia, cognitive disabilities, and other signs and symptoms that currently have no cure. Our understanding of the pathogenesis of PD suggests that inflammation, oxidative stress, excitotoxicity, mitochondrial dysfunction, and degeneration of dopaminergic (DA) neurons in the Substantia Nigra pars compacta (SNc) are to blame. The hallmark of the disease is the accumulation of Lewy bodies, which are inclusions of cytoplasmic proteins, mostly comprised of misfolded α-synuclein [1].

Treating PD is a challenge for clinicians. Surgical and pharmaceutical interventions are common, although they only temporarily mitigate the symptoms [2-5]. Pharmaceutical interventions mostly consist of DA medications (e.g., Levodopa). However, long-term use of these medications causes significant adverse effects that include exacerbations of dyskinesia and drug resistance [3]. Deep brain stimulation (DBS) is the most common surgery used to treat PD. This treatment involves stimulation via implanted electrodes in the subthalamic nucleus and globus pallidus [5]. Immunotherapy is another approach where antibodies against α-synuclein are administered. However, immunotherapy raises the concern that reducing α-synuclein levels can halt normal protein function that leads to neurotoxicity [4]. Gene therapy has been considered in the treatment of PD. Specifically, trials have been conducted with AAV2-GAD gene therapy for advanced PD, but this approach seems to only be useful in genetic forms of PD [6-8].

The revolution in stem cell biology in the early 1980s opened up new avenues for many researchers and clinicians. Different types of pluripotent/multipotent cells are potentially used in preclinical and clinical studies. Pluripotent stem cells (PSCs), including embryonic stem cells (ESC), obtained from the inner cell mass of blastocysts and induced pluripotent stem cells (iPSC) derived by reprogramming somatic cells can differentiate to different cell types of interest, including DA neurons. These DA neurons have been used extensively in animal models of PD that were established using neurotoxins or pesticides. Such Parkinsonism has been successfully treated with fetal midbrain grafts and ESC-derived DA cells [9,10].

As mentioned, the most recent developing treatment for PD is cell replacement therapy with a prospective long-term relief of disease symptoms. Many preclinical studies have investigated the therapeutic effects of PSC-DA neurons on PD animal models. The most widely used and well-established PD animal models are created by the administration of 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Transplantation of human neural progenitor cells (NPCs) extracted from the midbrain of 14-week-old fetuses restored motor dysfunction and in rats injected with 6-OHDA [3, 11]. Other cell sources for this purpose that proceeded to clinical trials in humans had poor clinical outcomes. These include medullary tissue, retinal pigmented epithelium cells, carotid body cells, and mesenchymal stem cells [4].

In contrast, promising clinical trials have been conducted that involved the implantation of midbrain DA progenitors from the human fetal brain to individuals with PD. However, the use of fetal tissue poses several problems - low availability, high variability, and ethical concerns that differ (are different) between countries. Researchers and clinicians have searched for alternate cell sources. iPSCs or ESCs-derived DA progenitor cells appear to be the most suitable alternative to generate ventral mesencephalic DA progenitors and for transplantation in PD [12].

Existing systematic reviews of stem cell therapy in PD focused on mesenchymal stem cells, which have the disadvantages of modest clinical outcomes and insufficient sources of embryonic tissues [5, 13]. Therefore, in this systematic review, we intend to comprehensively examine the therapeutic effects of human and non-human primate PSC-derived DA progenitors in rats, mice, and monkeys with PD. Treatment outcomes will be evaluated by obtaining data from the various behavioral tests performed. We

aim to examine the efficacy of primate PSC-derived DA progenitor transplantation for treating PD in preclinical studies as an outlook for launching clinical trials.

Methods

The protocol of this systematic review will adhere to the desired anecdote matters for systematic reviews and meta-analyses for protocols (PRISMA-P), recommendations for reporting of systematic reviews and meta-analyses of animal experiments [15-17]. This protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO—CRD42020168304) at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=168304.

Eligibility criteria

Types of studies

All animal intervention studies that included a control group will be enrolled in this systematic review, which evaluates human and non-human primate PSC-derived DA progenitor transplantation in preclinical animal models of PD. Only published studies published in English without any date restrictions will be assessed.

Types of animal models

All studies that used animal models of experimental PD (6-OHDA or MPTP) in which the animals developed characteristic motor deficits will be considered in this systematic review.

Types of comparators

The comparison group includes animal models of PD that did not receive cells.

Types of intervention

The intervention group includes animals that received human and non-human primate PSC-derived DA progenitors, and have been investigated for the treatment of PD.

Only studies that used iPSCs and ESCs of a primate origin to derive DA progenitors, neural stem cells (NSCs), or NPCs following the establishment of the PD model will be included in the study.

Exclusion criteria

Non-intervention studies such as case reports, congress abstracts, letters to the editor, human studies, and studies that include in vitro experiments will be excluded. Studies that do not evaluate behavior as an outcome will be excluded, in addition to studies that included PSCs from a non-primate source.

Types of outcome measures

Primary

The rescued motor deficits are defined as the primary outcome. They will be measured by the apomorphine-induced rotation test (APO-IR), amphetamine-induced rotation test (AMP-IR), stepping test, spontaneous forelimb use test, cylinder test, neurological scores, spontaneous movement, spontaneous rotation, time in movement, or rotarod test.

Secondary

Secondary outcomes include histological and neuroimaging data obtained before and after cell injections.

Searching methods for identification of studies

Electronic searches

Electronic databases used by MEDLINE via PubMed, Web of Science and SCOPUS from their foundation until the end of December 2019 without any search filters and restrictions of language, date of publication, or publication status are utilized.

Search strategy

The main terms are: "pluripotent stem cell" OR "dopaminergic progenitor" OR "DA progenitor" OR "neural stem cell" OR NSC OR "neural progenitor" OR NPC OR "embryonic stem cell" OR ESC OR "induced pluripotent stem cell" OR iPSC OR "pluripotent stem cell" OR PSC) AND (Parkinson's). Supplement 1 lists the details of search strategies to be used in the electronic databases.

Data collection and analysis

Selection of studies

All studies are imported into Covidence, which is a not-for-profit service established in 2013, and run by a team in Melbourne, Australia [18]. At first, duplicate studies will be removed by Covidence. Then, two reviewers (AAK and ZS) will independently screen titles and abstracts. Any conflicts between reviewers will be solved by agreement or by a third reviewer (HB). After screening the titles and abstracts, the same reviewers will independently evaluate the full text of the studies by using a standardized form that contains the inclusion and exclusion criteria.

Data extraction

Two reviewers (ZS and ME) will independently extract all available sources in the text and graphs of each article. If only graphical data are available, values for mean and standard deviation or standard error will be obtained by using GraphClick (Arizona Software, Phoenix, AZ, USA) under high magnification. The

calibration exercises will be conducted to ensure consistency between reviewers before starting data extraction.

The data will be extracted using standardized extraction forms: 1) study characteristics (author, year of publication); 2) features of the included animals and animal models (animal species, PD model, age, gender, farming situations, numbers of animals in intervention, and comparison group); 3) interventions (time and description of preparation); and 4) outcomes of interest.

Risk Assessment of bias (Assessment of bias risk)

Two reviewers (ZS and ME) will independently use the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool to evaluate the quality of the studies and risk of any bias. The SYRCLE risk of bias tool includes ten defined criteria assessment domains related to biases of selection, performance, identification, attrition, and reporting. For each included study, all domains will be scored as low, high, or unclear risk of bias [19].

The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) checklist will be used to evaluate the selected studies. This checklist evaluates publication in a peer-reviewed journal, recording of temperature control, randomized treatment allotment, blinded evaluation of results, reporting of blinding of the operator, suitable animal models, reporting of a sample size calculation, agreement with animal wellbeing principles, statement of potential conflict of interest, and a comprehensive follow-up [20, 21].

Assessment of the treatment efficacy

The calculations for all included variables are as follows: standardized mean difference (SMD), odds ratio (OR), and related 95% confidence interval (CI) for each result using Cohen's method to normalize the different animal species. Binary data will be calculated as the risk ratio (RR) with 95% CI.

Assessment of heterogeneity and data synthesis

The heterogeneity between studies will be estimated by calculating “I^2 inconsistency values and Cochran’s Q statistical test”, where $I^2 > 50\%$ and/or $p < 0.10$ recommend high heterogeneity. Heterogeneity will be defined according to the I^2 range: 0% -40% (minor heterogeneity), 40% -60% (moderate heterogeneity), 60% -90% (substantial heterogeneity), and >90% (significant heterogeneity) [22].

The analyses will be performed using Review Manager 5.3 [23]. In cases where the Review Manager statistical software is not sufficient, data analyses will be performed by STATA® statistical software, version 14.2 (Stata Corp., College Station, TX, USA) [24].

Assessment of publication bias

A graphical funnel plot will be used where at least ten studies contribute to a pooled analysis to investigate the publication bias, which will be presented in the studies [25].

Discussion

This study will provide clinicians and researchers with evidence of preclinical research and relevant evidence that pertains to the therapeutic potential of PSC-derived DA progenitor transplantation for PD. This study intends to show the strengths and limitations of the previous studies to suggest future outlooks in this field. Although numerous experimental studies about the effects of PSC-based therapy for PD have been published, there is no consensus in the literature. Therefore, a systematic analysis of existing experimental studies is essential as a perspective for launching clinical trials.

Abbreviations

PD: Parkinson's disease

DA: Dopaminergic

hPSCs: human pluripotent stem cells

PSCs: Pluripotent stem cells

ESC: Embryonic Stem Cells

iPSC: Induced Pluripotent Stem Cells

NSCs: Neural Stem Cells

95% CI: 95% Confidence Intervals

CAMARADES: Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies

MeSH: Medical Subject Headings

OR: Odds ratio

PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols

PROSPERO: International Prospective Register of Systematic Reviews

RR: Risk ratio

SMD: Standardized mean difference

SYRCLE: SYstematic Review Center for Laboratory animal Experimentation

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Aliasghar Karimi: conception and study design, data collection and analysis, manuscript drafting

Zahra Shiri: conception and study design, data collection

Mitra Elmi: data collection, manuscript drafting

Hossein Baharvand: conception and study design, data collection and analysis, manuscript drafting, supervision

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