Is treatment with stem cells effective in Parkinson's disease?

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Abstract

Introduction

There are many patients with Parkinson's disease who have a limited response to conventional pharmacological treatment. The use of stem cells has been postulated as an alternative, although its effectiveness remains a matter of controversy.

Methods

To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified two systematic reviews including 21 studies overall, of which three were randomized trials. We concluded it is not clear whether stem cells have any effect on the symptoms of Parkinson's disease because the certainty of the available evidence is very low.

Problem

Parkinson's disease is a progressive and degenerative condition characterized by the destruction of dopaminergic neurons located in the substantia nigra, specifically in the nigrostriatal pathway, which leads to a progressive decrease in dopamine levels. As the disease advances there is also a loss in other neuronal groups (e.g. serotonergic, noradrenergic), which leads to a decrease in the number of functional dopaminergic and non-dopaminergic neurons, and the subsequent loss in the capacity to respond to treatment[1].

Despite improvements in pharmacological treatment which makes possible to control symptoms in a large proportion of patients, many patients remain symptomatic, or experience treatment-related complications, such as dyskinesias, akinesia and end-of-dose wearing off. In addition, Parkinson's disease also leads to non-motor manifestations such as cognitive impairment, which limits the therapeutic alternatives[2].

Consequently, new alternatives are actively investigated, such as the implantation of stem cells. Stem cells are precursor cells with the ability to self-renew and generate multiple mature cell types. Embryonic stem cells result from the isolation and culture of blastocyst cells, which are formed 5 days after fertilization, and are pluripotent, which means they can grow into any type of adult cellular lineage. Adult or somatic stem cells remain quiescent with limited self-renewal and differentiation capacity. Numerous types of precursor cells have been isolated from adult tissues, leading to the concept that all tissues have their own compartment of stem cells, responsible for replenishing cells that die within human organs. Mesenchymal cells, for instance, are stromal in origin and can be isolated virtually from any tissue in the body. The most obvious therapeutic potential of adult stem cells is to restore or replace tissues that have been damaged by disease or injury and to avoid the ethical problem of using embryonic derived cells. However, the actual efficacy of stem cells derived from non-hematological tissue remains a matter of debate[3].

Stem cell transplantation is a novel alternative in Parkinson's disease. Through implantation in the affected regions, it seeks to develop new synapses and restore the levels of dopamine in the nigrostriatal pathway. This technique requires stereotactic neurosurgery to graft them directly into required areas, which is not exempt of risks, generating controversy about the role of this intervention in Parkinson's disease.

Key messages

- It is not clear whether stem cells have any effect on the symptoms of Parkinson's disease because the certainty of the available evidence is very low, and on the other hand it is an intervention that carries risks and costs.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found two systematic reviews[1,4], including 21 primary studies[5-21,23-25] of which three correspond to randomized trials[5,7,19]. In one of the trials[19] the intervention was a fetal graft of porcine origin, so it was excluded from the analysis. This table and the summary in general are based on the other two trials[5],[7] since the observational studies did not increase the certainty of the existing evidence or provide additional relevant information.
What types of patients were included*	Both trials included participants with Parkinson's disease with at least two of the following symptoms: bradykinesia, rigidity, tremor at rest and stability in their medication.The age range was 34 to 75 years. One trial included patients with Parkinson's disease for more than 7 years (average duration of 14 years)[5], while the other trial included patients with advanced Parkinson's disease, but did not mention the duration of the disease[7]. Both trials excluded patients with previous neurosurgery or a history of psychiatric illness. One trial[5] excluded patients with Mini Mental Score (MMSE) below 24 points, hallucinations with levodopa, epilepsy or stroke, while the other trial[7] excluded atypical parkinsonism.
What types of interventions were included*	All trials compared grafting of mesencephalic tissue cells of embryonic origin by stereotactic surgery.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	Both trials compared against sham surgery without fetal cell grafting. No trial reported the dose of levodopa that was administered if necessary.
What types of outcomes were measured	All trials evaluated: • Severity of the disease assessed by total UPDRS (Unified Parkinson's Disease Rating Scale) and by Schawb and England Activities of the Daily Living Scale. • Need to use levodopa or other treatment • Non-severe adverse effects: dyskinesia One trial[5] reported outcomes at the first year after surgery, while the second[7] reported them at two years after the procedure.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information about the effects of stem cells for patients with Parkinson's disease is based on two randomized trials[5],[7], including 74 participants.

None of the systematic reviews presented a meta-analysis, or information that allows to reanalyse the trials, so the information presented below corresponds to a narrative synthesis of the information as reported by the reviews.

The summary of findings is as follows:

- It is not clear whether stem cells have any effect on the symptoms of Parkinson's disease because the certainty of the evidence is very low.
- It is not clear whether stem cells reduce the need for levodopa or other treatments because the certainty of the evidence is very low.
- It is not clear whether stem cells have adverse effects because the certainty of the evidence is very low.

Stem cells for Parkinson's disease		
Patients	Parkinson's disease	
Intervention	Stem cells	
Comparison	Placebo (sham surgery)	
Outcome	**Effects**	**Certainty of evidence (GRADE)**
Severity of the disease. Evaluated in Total UPDRS Scale* and Schwab and England Scale**	One trial[5] reported a significant change in the Schwab & England scale, but none reported improvement in the UPDRS scale[5,7].	⨁◯◯◯[1,2,3] Very low
Need for levodopa or other treatment	No trial reported changes in the doses of levodopa needed[5,7].	⨁◯◯◯[1,2,3] Very Low
Adverse effects Dyskinesia	One trial[7] reported 56% more dyskinesia in the group transplanted with fetal stem cells versus 18% in the placebo group.	⨁◯◯◯[1,2,3] Very Low

GRADE: Evidence grades of the GRADE Working Group (see later).

* Total UPDRS (Unified Parkinson's Disease Scale) is used to measure the severity of Parkinson's disease. A high value denotes larger deterioration.
** Schwab and England Scale evaluates functionality in a scale from 0% (vegetative state) to 100% (completely independent, able to perform all tasks without slowness, difficulty or impediment).

[1] We downgraded the certainty of evidence in one level because of risk of bias, since at least one trial had a very short follow-up.
[2] We downgraded the certainty of the evidence in one level for indirectness because it was not specified or differentiated the subtype of Parkinson's disease. In addition, it was not possible to generalize the procedure because it did not reflect the current practice (tissue storage, length of time before tissue transplantation, dose of levodopa used).
[3] We downgraded the certainty of the evidence in one level for imprecision, since at the extremes of the confidence interval the effects were opposite.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

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* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The results of this summary apply to people with Parkinson's disease of any age and . One trial[5] included a population with more than 7 years of disease, so the results could be extrapolated to people with long-term disease.

The limitations of existing evidence, both in the systematic reviews and in the primary studies, does not allow to establish if there is a subset of patients in whom there could be a different effect, such as subtypes of disease, or patients with cognitive compromise or other non-motor manifestation.

About the outcomes included in this summary

The outcomes presented in the summary of Findings table are those considered critical for decision-making by the authors of this article.

Eventually, there could be effects on other outcomes, however, they were not reported in the systematic reviews identified.

Balance between benefits and risks, and certainty of the evidence

Because the certainty of the evidence is very low, it cannot be ascertained whether the treatment with stem cells in Parkinson's disease has any benefit or serious adverse effect, so the risk/benefit balance of this intervention cannot be evaluated.

Although the evidence on adverse effects is limited, it is reasonable to estimate they should be larger in older patients with higher surgical risk.

Resource considerations

It is known that both storage and maintenance of stem cell storage centers are generally of high cost.

The cost associated with regulating production, good use and marketing is probably substantive.

The cost-benefit balance is not favorable, since it is a costly intervention for which it is not clear if there are any benefits and it is not free of risks.

What would patients and their doctors think about this intervention

Faced with the evidence presented in this summary, most patients and clinicians should lean against the use of stem cells in Parkinson's disease, since there are no proven benefits and it carries risks and costs.

Currently, there is a positive perception of the therapeutic effects of stem cells, both in the public and in many health professionals, which places additional difficulties in making decisions informed by evidence in this context.

Feasibility

Both trials mention that human embryonic cells were used from voluntary elective abortions, which implies a procedure that is not free of risks for mothers who make donations. No trials using other sources of embryonic cells were found. There are other methods for obtaining this type of tissues that are less invasive but have higher economic costs.

Differences between this summary and other sources

In general, the results of this summary are similar to the results presented by the systematic reviews identified.

The main clinical guidelines, such as the guideline of the Movement Disorders Society[26], Canadian Society[27], the NICE guideline[28] and the guideline of the European Federation of the Neurological Societies[29] do not mention the use of stem cells as a therapeutic option, neither mention that it is an alternative under study.

Currently there is no therapy based on stem cells approved by the U.S. Food and Drug Administration (FDA).

Could this evidence change in the future?

The probability of future evidence changing the conclusions of this summary is very high, because of the high level of uncertainty.

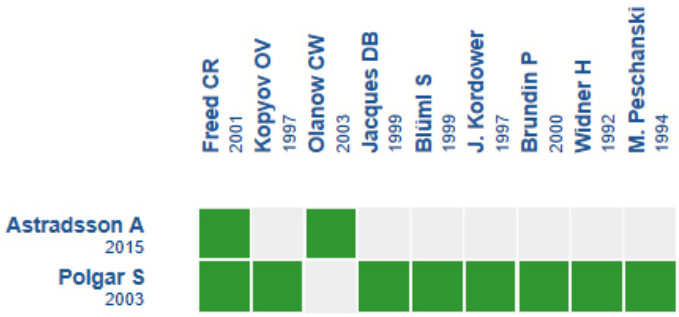
There are currently four published trials[30-33], not included in the identified reviews, which evaluate into stem cell transplantation in Parkinson's patients and their clinical effects, and at least three trials in progress[34-36] according to the International Clinical Trials Registry Platform of the World Health Organization.

There are foundations like the Michael J. Fox Foundation that are actively investigating on the use of stem cells in people with Parkinson's disease.

New systematic reviews including the new trials are key to shed light on this topic. Currently there is a systematic review in progress according to the International prospective register of systematic review PROSPERO[37].

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Acupuncture for Parkinson's disease

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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