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Stem Cell Therapy for Parkinson's disease: Are Double-Blind Randomized Control Trials the Best Design for Quantifying Therapy Outcomes?

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Abstract

Randomized controlled trials [RCTs] are recognized as the most rigorous method for evaluating the safety and efficacy of novel interventions. The fact that a series of RCTs evaluating cellular therapies for Parkinson's disease [PD] resulted in negative outcomes has delayed the translation of stem cell research into viable treatments for people with brain damage. At present, there are a variety of strategies being followed to improve outcomes for cellular therapies, including reassessment of the theory and methodology guiding the research program. In this position paper we present an argument based on empirical and theoretical grounds that the use of double-blind, placebo controlled trials are not the best approach for testing the efficacy of cellular therapies for PD.

Evidence includes the highly variable effects of neural grafts found in double blind RCTs in comparison to the much larger benefits in open-label trials for people with PD in double-blind RCT. We suggest that the ambiguity and confusion created about the actual nature of the treatment in the context of a double-blind trial compromises the efforts of participants and their Carers to make the best therapeutic use of the grafted cells. The theoretical grounds for rejecting the use of double-bind RCTs is based on the Composite Brain Theory, which postulates that to insure optimal therapeutic outcomes it is essential to integrate the intracerebral grafting of cells with an active program of neurorehabilitation.

We are recommending the use of pragmatic RCTs which involve the comparison of cellular transplantation and rehabilitation with best practice pharmacotherapy or Deep Brain Stimulation as comparison groups. Using a pragmatic trial design will ensure optimal outcomes for each of the treatment groups and produce evidence applicable for identifying best available treatments for people with PD.

Keywords: Stem cells; Parkinson's; RCT; Pragmatic trial; Sham surgery; Cellular therapies; Physiotherapy

Introduction

The prevalence of brain disorders, in particular Parkinson's disease [PD], stroke, and Alzheimer's disease [AD] is expected to rise considerably associated with the increasing age of the populations of developed countries [1]. Therefore, it is essential to develop innovative and effective interventions which can be implemented to contain the burden of disease associated with brain disorders [2]. Progress in stem cell research and the successful translation of these discoveries into viable cellular therapies may be key to achieving this objective [3-5].

Stem cell research is a massive, international research program, looking at numerous cell lines which may be applied in various therapeutic ways, such as the replacement of lost cells, neuroprotection, triggering neurogenesis, and releasing trophic factors [6]. The problem is that the discoveries of pre-clinical laboratory research have not always been translated into viable treatments which can be implemented consistently with the current principles of evidence-based practice [7,8]. In the present paper we will focus on research pertaining to developing cell therapies for PD, as a research program where a sufficient number of trials have been completed and published to enable the critical discussion of methodological and conceptual issues.

Positive results for stem cell therapy have been reported for pre-clinical studies using animal models and also significant and clinically meaningful improvements in many patients participating in "open-label, before-after" studies. These results indicated potential benefits of cellular therapies for the treatment of PD [9-12]. The problem which has emerged over the previous decade is that the results of double-blind randomized controlled trials [RCTs] have not always produced results confirming the anticipated level of efficacy for intracerebral grafting. Further, the emergence of severe adverse outcomes such as late onset of drug independent dyskinesias associated with the trials has resulted in a temporary cessation of some RCTs [13]. The reconstruction of the human brain was a far more challenging project than it was optimistically imagined thirty years ago [14,3]. Regardless of the well known challenges of reconstructing the human brain, many research groups are currently working to advance the safety and efficiency of cellular therapies [15,16]. Several lines of research are being pursued; developing cell-lines for transplantation, identifying the optimal parameters for surgically implanting cells and formulating protocols for the rigorous evaluation treatment safety and efficacy [6,5]. The question being addressed in the present commentary is: What is the optimal design for evaluating the efficacy of reconstructive cellular therapies for people living with idiopathic PD?

The aims of this position paper are to: [i] critically examine the strengths and limitations of trials designs for evaluating the effects of stem cell therapy for people with Parkinson's disease, and to [ii] propose a paradigm for conducting a pragmatic and ethical RCT for evaluating in the clinical efficacy of stem cell therapy.

Randomized Controlled Trials: Their Contribution

Stem cell therapies, neural grafting and other forms of brain tissue replacement have been trialed for more than 20 years [12]. Despite the growing number of positive reports on their effects, there is an arguable risk to people living with Parkinson's disease and the community that the multitude of cell lines currently being developed may be grafted prematurely as clinical treatments without sufficient evaluation of their safety and efficacy [17]. The methodological rules and administrative regulations which define the criteria for the safe introduction of treatments such as new pharmaceutical products, needs also to apply to surgical procedures, including the grafting of cells [18,19].

Beginning in the mid 1990s, practicing neurosurgeons and researchers expressed concerns regarding the inadequate methodological standards employed to assess the efficacy of novel surgical methods, including reconstructive neurosurgery [17,18,20]. It is generally accepted that the improvement seen in the signs and symptoms of a group of patients following uncontrolled interventions may be due to bias or the confounding influences of extraneous variables [21,22]. Estimates of the efficacy of intracerebral grafts based on the results of "open-label, before-after" designs are probably inaccurate, as it is unclear to what extent improvements are caused by the grafts, rather than extraneous factors such as placebo responses or observed bias [23,20].

Randomized controlled trials [RCTs also refer to as randomized clinical trials] are experimental designs used for evaluating the efficacy of clinical interventions. RCTs have been referred to as "gold standard designs" for producing the most credible level of evidence for demonstrating the efficacy of a given treatment. By controlling for sources of bias and confounding extraneous variables RCTs ensure the internal validity of the evaluation process [21]. The ideal design for conducting an RCT is the double-blind, placebo controlled, prospective trial where neither the recipients of the therapy, primary carers nor the assessors of the outcomes were aware of the exposure of the participants to the active or the control treatment [24-26].

The implementation of double-blind surgical trials generally requires the creation of placebo-controlled groups. In the context of surgical evaluation, placebo or *sham* surgery is conducted in a way that imitates the apparent components of a surgical procedure, but whilst withholding active components responsible for the clinical benefits [27]. The averaged scores of the sham operated control groups are subtracted from those of the actively treated group, enabling the researchers to identify what is assumed to be the true, unbiased effect of the surgical intervention. With an increased recognition of the need for evidence based surgery, numerous researchers and bioethicists argued for the adoption of placebo or sham surgery for conducting RCTs [20,27-29]. This has been the case for stem cell, therapies and neural grafting in PD, where several double-blind trials therapy have been reported [14,30-32].

Bioethicists, including Macklin [1999] [33], Kim, de Vellis [2003] [34] and Leeds [2003] [35] pointed out that placebo brain surgery involves active interventions including cutting into the human body and administrating of drugs including analgesics and potent but ineffective immunosuppressants. These interventions, in the context of a deontological ethical framework, are regarded as unacceptable ways of treating patients. In particular, it needs to be taken into account that people with advanced Parkinson's disease are already disabled by having a serious and progressive neurological condition for which medications often fluctuate in their effectiveness. The fact that patients provided 'informed consent' to participate and that no deaths or serious health consequences have been reported placebo surgery [36], does not necessarily make sham surgery ethically acceptable [37].

Sham-surgery has been justified in the context of a utilitarian ethical framework [27] on the grounds that the methodological and clinical benefits of implementing double-blind RCTs outweigh the associated risks/harms to the participants [20]. The difficulty with this position it is not sufficient to assume that this design is methodologically advantageous but rather, the postulated benefits need to be confirmed by the published results. If these benefits are not evident, then there is no justification for the necessity of using sham surgery for creating control groups [38,39].

Analyses of the results of RCTs for PD, published in peer-review journals and employing sham operated controls did not indicate the expected large and consistent placebo effects [37,39]. Large placebo effects were not evident in the sham operated groups in comparison to their baseline scores. Therefore, there is little convincing evidence that the performances of sham operated groups are significantly different to an equivalent patient with PD receiving standard L-Dopa based pharmacological treatments[37,39].

It was suggested that the double-blind RCTs for PD failed to show statistical or clinical significance due to the poor effect sizes, evident in all the groups receiving grafted neurons [24]. The poor efficacy of the cellular therapies was demonstrated compared to baselines scores, thus the presence of the sham-operated controls were not relevant to protect against false positive decisions [39]. Overall, the evidence indicates that at this stage of the research program of cellular therapies for PD, clinically meaningful improvements in the treatment groups in double-blind RCTs are highly variable and cannot be reliably reproduced [24].

Alterman et al. [2011] [24] analyzed the results of published RCTs and concluded that the differences between the outcomes of the open-label and double-blind trials were mainly due to observer bias. While inflation of the benefits through observer bias cannot be ruled out, clearly the concealment of the intervention creates an ambiguous confusing context for the participants, their families and primary care givers. The uncertainty regarding whether or not they actually received the transplant cells, may limit the actions of the effective development and integration of the grafted neurons into neural networks. Therefore, the level of activity by patients may be reduced, failing to ensure optimal functional recovery. Therefore, the outcomes of double-blind RCTs do not appear to support the notion that the use of placebo control groups is the best possible method for evaluating the benefits of cellular therapies for PD.

Theoretical Background

The Composite Brain Model [CBM] [26] was formulated as an alternative conceptual approach to the currently dominant understanding of the recovery process following neural grafts. The CBM postulates that intracerebral transplantation does not restore impaired brains to their premorbid states, but rather creates a new kind of "composite" structure, with the grafted cells enhancing the overall neural plasticity of the impaired host brain [40]. That is, the new cells create the potential for the functional reorganisation of the compromised neural networks and for the subsequent behavioural

recovery. The CBM proposes a hierarchically organised, open system which explicitly includes the patient as a person living in an actual physical and social environment. There are reciprocal interactions among the constituent elements of the hypothesised system [26] as indicated in the diagram below.

Graft ↔ Host Brain ↔ Person with Graft ↔ Environment

It is hypothesised that each level of the neuraxis the circuitry of the host brain is shaped by interacting influences from both the graft and the environment through both direct and polysynaptic pathways [26]. Evidence from pre-clinical studies indicates that the host system as a whole and the cells constituting the graft respond to environmental stimuli, and have been shown to participate in learning processes [41-43]. It follows from this position that researchers addressing the safety and efficacy of cellular therapies need to take into optimise the psychosocial context for the recovery process following the grafting of the cells [43].

It follows from the Composite Brain Model that the practice of neural reconstruction is seen as a two stage process; first, the grafting of immature cells into the host brain, and second, the provision of personal support and environmental stimulation for the graft recipients. The second, psychosocial stage ensures: [i] the adaptive integration of the cells with the host brain and [ii] the functional recovery of the patients in their social and physical environments. That is, it is not enough to replace the impaired dopaminergic cells and then to leave recovery to intrinsic biological mechanisms. Rather, the application of the model requires strategy for ensuring that the patients are actively included in the process of integrating the grafted cells into neural networks and learn, over time how to make best use of their reorganised brains. By combining both biological and psychosocial dimensions we will be in a position to develop and implement best practice cellular therapies for patients with brain disorders. Ultimately, the key requirement is to devise effective rehabilitation programs that target the needs of people adapting to their new intracerebral grafts [40,41].

We argue that optimal neurorehabilitation provides an enriched environment to support neural grafting and other stem cell therapies. The term "neurorehabilitation" refers to "… the clinical subspecialty that is devoted to the restoration and maximization of functions that have been lost due to impairments caused by an injury or disease to the nervous system" [44]. This involves physical, social and cognitive elements and aims to assist people to achieve their goals through practice of daily tasks in contexts that support recovery. Thus, rather than simply grafting cells into the human brain, rehabilitation provides the added benefits of an enriched environment with the potential to improve therapy outcomes and optimise results.

The Case for Pragmatic RCTs

The double-blind RCTs discussed earlier are referred to as *explanatory* trials aiming to demonstrate the causal effects of a treatment. *Pragmatic* trials are where researches aim to replicate, as closely as possible, the accepted features of practices for producing best possible therapeutic outcomes [45,46]. Applying the Composite Brain Model to designing clinical trials requires that the transplantation of cells should be followed by the active inclusion of the patients and their carers into the recovery process that is offering rehabilitation. Therefore, as discussed previously, the use of highly controlled, double-blind explanatory trials are not the optimal way to evaluate the efficacy of reconstructive cellular therapies as these designs minimise the contributions of the participants and their carers to recovery.

Also the placebo controlled groups reduces the external validity that is the clinical applicability of the data produced by the RCTs [37]. Sham surgery is a methodological artefact, as it does not produce outcomes directly relevant to making every day clinical judgments. There are several existing and developing treatments for PD, appropriate for setting the criteria for safety and efficacy for determining best practice.

It has been suggested previously that the most effective way of conducting cellular therapies for PD is by combining transplantation for PD with neurorehabilitation. It follows that a pragmatic RCT will be best implemented after effective rehabilitation programs are developed and successfully integrated with neural transplantation [43]. Further, to improve the internal validity of the trial, we need to identify acceptable rehabilitating programs for all the treatment groups [DBS and pharmacotherapy].

A clinically relevant design for a pragmatic trial could include three groups of patients with PD with the participants randomly allocated to one of the following:

- Cellular transplantation and rehabilitation

- DBS and rehabilitation

- Pharmacotherapy and rehabilitation [standard treatment]

"Control groups other than placebo groups are commonly used for implementing RCTs when double-blind evaluations are difficult, unrealistic or ethically unacceptable to implement. For example, where the active involvement of the participants is essential for ensuring the efficacy of a treatment, such as is the case for conducting neurological rehabilitation" [47].

Implementation of A Pragmatic Trial

The following methodological issues are relevant to designing a pragmatic trial for evaluating the safety and efficacy of cellular therapies for PD. IT is assumed that the CONSORT statement will be used to guide the design and reporting of the proposed trial [24-25].

Population and sample

A realistic goal for neural reconstruction is not to cure the disease but to provide "best practice" treatment for defined subgroups of people with PD. Given that the variables such as age and duration of the disease may influence the clinical outcomes [48], it follows that some patients with PD might not benefit significantly from either of the two surgical interventions. There are various inclusion and exclusion criteria for selecting participants for DBS and cellular therapy trials [48,49]. It is essential to select a sample of patients who can be randomly assigned to any one of the three treatment groups. However, it is an inevitable that the selection process will restrict the external validity of the pragmatic trial by limiting the population of patients with PD to whom the results can be generalised.

Sample size

Power represents the probability of detecting a significant effect when it is, in fact, true for the population. Institutional review committees favour a power efficiency of 0.8 or more before giving the go ahead for a trial [21]. In other words, the researchers must provide evidence that there is an 80% probability that the sample is large enough to demonstrate statistically significant outcomes [50].

If the differences between DBS and cell therapies are likely to be small, large sample sizes are required for identifying differences on specified outcome measures. A large sample size will also enable the

conduct of post-hoc test for the best treatment for various subgroups with PD.

Implementation of the treatments

The details for implementing the three different treatments will be determined by the multi-disciplinary team responsible for the trial. The feature common to all the three interventions is that they will be followed by an appropriate movement, exercise and cognitive rehabilitation program [51,52].

The neurorehabilitation literature reflects a rapidly growing evidence base underpinning goal directed rehabilitation as a foundation for optimal recovery in brain lesions. There is now strong evidence in animal studies that synaptic plasticity occurs at a cellular level and the brain can learn new ways to perform functions that have been disrupted with surgery, disability and brain injury [53]. This appears to be enhanced by enabling animals and people to practice in enriched environments that afford therapy experts, equipment, environmental conditions, rewards and a supportive atmosphere that maximizes positive recovery [26,43]. Functional connectivity following brain damage, brain surgery or stem cell therapy could be promoted through goal directed practice, gait retraining, hand rehabilitation and progressive resistance strength training and other "exercises" and by structuring the environment and the tasks they perform. According to Olver et al. [2013] [54] adaptive learning could possibly be enhanced through … "participation in rehabilitation programs that promote positive neural changes through the processes of learning and practice. Research exploring adaptive, goal directed motor learning strategies for advancing neural grafting and stem cell therapy which have not to date adequately embraced rehabilitation as an adjunct to care and to optimize therapy outcomes".

Assessment of outcomes

Biological and functional changes in PD patients are assessed using variety of brain imaging techniques and standardized test. A battery of tests, referred to as the CAPIT protocol [Core Assessment Program for Intracerebral Transplantations] has been adapted by numerous research groups, although in modified forms. More recently, modified assessment protocols, such as CAPIT-PD [49] also include tests for cognitive functioning and quality of life [QOL] evaluations for producing evidence of psychological changes in patients.

It is anticipated that the currently available reliable and valid clinometric tests for PD will be used to assess changes in the patients participating in the proposed pragmatic RCTs. There are now many validated assessment tools commonly used in quantifying therapy outcomes in Parkinson's disease. The most commonly used ones are the modified Unified Parkinson's disease Rating Scale [MDS-UPDRS] [55], Hoehn and Yahr [1967] [56], Profile PD [57], 6 minute walk test [58], Dyskinesia Rating Scale [55] and Freezing of Gait Questionnaire [59]. These are reviewed and critically evaluated in the context of clinical decision making algorithms in McGinley and Danoudis [2013] [60]. In addition, the inclusion of rehabilitation will require identifying and negotiating with the participants' specific functional improvements which are realistic. For example, a PD patient may have lost the ability to drive a car; it could be a realistic objective to re-learn to drive safely following transplantation. The extent to which patients can achieve a set of realistic objectives would be part of the battery of tests relevant to evaluating changes following the different interventions for PD.

It is evident that not all of the outcomes for the three different treatments [pharmacological, DBS and transplantation] can be directly compared. For example, ^{18}Flurodopa PET scans are used for assessing improvements in striatal dopamine turnover; and are essential for assessing transplanted patients. However, these brain imaging results may not be directly relevant to DBS and pharmacologically treated groups. However, there are sufficient [overlapping] assessments available for devising a protocol for comparing the risks and benefits of the treatments [Table 1].

A useful outcome measure is the overall reactivity at the end point of the trial for determining whether or not the interventions resulted in clinically meaningful, life changing benefits. Table 1 shows some of commonly used clinical outcome measures for evaluating changes [60]. For a positive indication of overall recovery, it would be expected that a patient would improve on most of the measures as determined by the multi-disciplinary team. The proportion of patients showing positive reactivity in each of the treatment groups [PT, DBS, TR] would be meaningful indicators of effect size, and analyzed as odds ratios [ORs]. Table 1 is simply an illustration, the clinical team designing and implementing the pragmatic RCT will select ultimately the outcome measures and identifying the degree of improvements representing a meaningful change. Neurorehabilitation providers, in particular, will identify outcome measures which are sensitive to the spectrum of varied activity limitations characterizing a group of PD patients.

Also it will be essential to use single-blind techniques for data collection with such standardized scales. These are commonly used techniques for concealing the treatment status of the patients from independent assessors [24].

Analysis and interpretation

The results of the pragmatic trail will provide evidence for answering two important practice related questions:

- How much improvement is likely with the three treatments from baseline to end point?

- What are the differences between the results of the three groups?

The analyses of changes in body structures [dopaminergic system] and functions using standardized imaging techniques or tests could be conducted using a variety of descriptive and inferential statistics. These statistics, such as t-tests, ANOVA, post-hoc tests are generally used to analyze parametric data produced in RCTs [e.g. 30]. However, analyses relevant to current evidence-based practice need to determine effect sizes, combined with 95% confidence intervals [61]. Where non-parametric analyses are required, such as with the 'Reactivity' measure

Measures	Criterion for recovery
1. Unified Parkinson's disease rating scale (MDS-UPDRS)	A clinically meaningful reduction in signs and symptoms
2. Changes in medication	A meaningful reduction in L-DOPA and other medications aiming to up regulate the dopaminergic system
3. Response to medication	Increases in 'on time'; decreases in 'off-time' and drug induced dyskinesias
4. Activities of Daily Living (ADL)	Meaningful improvements in the execution of personally and socially relevant tasks
5. Self assessed global change in disease impact	Improvement in condition in comparison to baseline
6. Quality of Life (QAL)	Self perceived, meaningful increases in health, physical and emotional wellbeing

Table 1: Outcome Measures for Overall Reactivity at end point.

illustrated in Table 1, effect size measures such as percent changes and or ORs are the relevant statistics.

Comparative efficacy, as discussed above, is only one aspect of evaluating the results and determining best-practice [21]. Additionally, the data produced by the proposed RCT would be analyzed for additional outcomes [22], including estimates of the costs and comparative cost effectiveness of the three treatment modalities.

Conclusion

Research for producing viable cellular therapies for the treatment of PD has progressed to the point where several double-blind RCTs were completed and published. In the context of evidence based health care, RCTs are recognized as the most rigorous approaches to evaluating the efficacy of treatments. Accordingly, the negative findings of these RCTs resulted in cellular therapies not being adopted for the treatment of patients with PD. This was a valid decision, regardless of previous evidence for the benefits of intracerebral grafting found in 'open' or 'before-after' evaluations. However, there is continuing research into stem cells and the process of translating of research outcomes. We suggested that one of the reasons for the poor efficacy shown in double-blind RCTs may have been due to the uncertainty and ambiguity for the participants regarding the best course of action following the grafting of the cells.

We argued on both empirical and theoretical grounds that double-blind RCTs were not the best way for conducting evaluation of cellular therapies. The evidence provided by the double-blind RCTs indicated very modest and highly variable placebo effects and there was a large reduction in the outcomes for the transplanted groups, in comparison to the significant benefits previously found in open label studies.

A pragmatic trial comparing the benefits of cell transplantation with standard pharmacotherapy and DBS, would allow the integration of each treatment with a relevant rehabilitation program. This approach would provide evidence regarding the actual clinical efficacy of each treatment and enable the building of a database suited for making decisions relevant to the selection of the most suitable treatments for patients with PD. We provided a rather broad outline for the rationale and implementation of pragmatic trials for evaluating reconstructive cellular therapies. There are many questions left unanswered such as, how to insure the internal validity of the trials, or how to determine best outcomes for each treatment or how to devise and deliver rehabilitation to patients having different biological treatments for PD.

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