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Review article

Effects of intracerebral neurotrophic factor application on motor symptoms in Parkinson's disease: A systematic review and meta-analysis

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ABSTRACT

Introduction: Neurotrophic factors (NTFs) have been evaluated for neuroprotective effects in Parkinson's disease (PD). However, clinical trials examining the efficacy of intracerebral administration of NTFs on motor symptoms in PD have produced mixed results, and are thus inconclusive. The objective of this systematic review and meta-analysis was to determine the effects of intracerebral NTF application on motor symptoms in people with PD.

Methods: We searched PubMed, MEDLINE, EMBASE, and Cochrane from inception through to March 31 2016 for open-label trials and randomized controlled trials (RCTs) which intracerebrally administered NTFs to PD patients, and which performed motor examination using the Unified Parkinson's Disease Rating Scale.

Results: Eight studies with a total of 223 participants were included. Fixed effects analysis revealed that NTF treatment did not significantly reduce motor symptoms in PD patients compared to placebo controls ($P = 0.98$). Combining open-label and RCT data, both treatment with NTFs ($P < 0.001$) and treatment with placebo ($P < 0.05$) significantly improved motor function in PD patients when compared to predicted symptoms in untreated PD controls. Finally, random effects analysis revealed that NTF-treated PD patients were not significantly likely to improve following intracerebral NTF administration ($P = 0.25$).

Conclusion: In conclusion, intracerebral NTF administration does not improve motor symptoms in PD patients, when compared to placebo-treated controls. These findings may guide therapeutic decisions and inform future research on NTFs and their application in PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, in which nigrostriatal dopaminergic (DA) neurons progressively degenerate to cause debilitating motor symptoms [1–5]. Despite decades of research, there is no disease-modifying therapy for PD [4–6]. Current symptomatic treatments improve quality of life and functional capacity, however their efficacy wears off over time and they cause disabling side-effects [6,7]. Thus, there is an urgent need to develop new therapies that halt/reverse the neurodegeneration in PD.

Neurotrophic factors (NTFs) are endogenous proteins critical for the development and maintenance of neurons [8]. Several NTFs promote the survival and growth of midbrain DA neurons *in vitro* and *in vivo*, while glial cell line-derived neurotrophic factor (GDNF) and neurturin (NTN) have been used in PD clinical trials [8–10]. These NTFs have been delivered to the PD brain via various delivery methods, to distinct target region(s), in small- and larger-scale clinical trials. While initial open-label trials have demonstrated the feasibility and potential efficacy of NTFs in improving motor symptoms in PD patients, more recent clinical trials have had limited success. Despite this, in principle NTF therapy is still a promising disease-modifying therapy for PD, and remains an area of intense scientific research. To date however, a systematic review of the NTF trials in PD patients has not been published. Thus, the aim of this study was to conduct a systematic review and meta-

Abbreviations: CI, confidence interval; DA, dopaminergic/dopamine; GDNF, glial cell line-derived neurotrophic factor; NTF, neurotrophic factor; NTN, neurturin; PD, Parkinson's disease; RCT, randomized controlled trial; RR, risk ratio; UPDRS, Unified Parkinson's Disease Rating Scale.

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analysis to quantitatively evaluate the effectiveness of intracranial NTF application in clinical trials on the motor symptoms of people with PD, in comparison to PD patients who did not receive NTF treatment.

2. Methods

2.1. Study design and registration

The present systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [11], and is registered with PROSPERO (registration number CRD42016033889).

2.2. Selection criteria for studies

2.2.1. Study designs

Eligible studies included open-label trials and randomized controlled trials (RCTs) which were published in the English language.

2.2.2. Participants

We included studies which examined people with PD. We did not make exclusions based on PD disease stage, age, gender or medication.

2.2.3. Interventions

We included clinical trial studies in which PD patients received intracranial administration of NTFs. We included studies which administered NTFs to the brain (any region(s)), brain parenchyma and/or ventricular system. Studies administering NTFs peripherally, outside of the central nervous system, were not included as NTFs do not cross the blood-brain barrier. We did not exclude studies based on the method chosen to administer NTFs. We defined NTFs as proteins that are critical for the development and maintenance of neurons in the developing and adult brain, and we excluded any studies which administered molecules, compounds or proteins that did not meet this definition.

2.2.4. Comparators

Given the selective, yet broad, nature of participants chosen for this review, and the single therapeutic intervention of interest, we solely compared PD patients which had received intracranial NTF administration to control PD patients which did not receive intracranial NTF administration. We did not exclude studies based on the nature of the control treatment.

2.2.5. Outcomes

The primary outcome measure for this systematic review was the assessment of motor symptoms of PD patients through motor examination using the Unified Parkinson's Disease Rating Scale (UPDRS), in which a decrease in UPDRS score is indicative of improved PD symptoms. Studies which did not assess motor symptoms by use of the UPDRS score were excluded. All response rates were calculated as the mean response of all randomised patients. Improved or disimproved motor symptoms (lower or higher UPDRS score, respectively) served as a dichotomous outcome. When studies reported UPDRS scores at various-time points during a trial, we recorded the mean of those multiple values. Adverse effects that resulted in death at any point during or after the trial, as a direct result of the treatment intervention, were also recorded. Studies were not selected for inclusion or exclusion based on the length of follow-up of outcomes. No secondary outcomes were recorded.

2.3. Search strategy

We searched PubMed, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception through to March 31, 2016 using a combination of the following MeSH search terms: Parkinson disease AND nerve growth factors AND clinical trial. To ensure literature saturation, we scanned the reference lists of included studies or relevant reviews identified through the search. We also searched the authors' personal literature databases to make sure that all relevant material was captured. The literature search was limited to studies in the English language.

2.4. Data collection and analysis

2.4.1. Selection of studies

Two review authors (SH/GO'K) independently screened titles and abstracts of all studies identified through database searches in the citation library. Irrelevant studies were excluded. For the remaining studies which appeared to meet the inclusion criteria, the full text article was uploaded to the citation library, and two authors (SH/GO'K) independently applied the predefined selection criteria. We resolved any disagreement through discussion, and consultation with a third author (AS) when necessary. We recorded the reasons for exclusion.

2.4.2. Data extraction and management

A form for standardised data extraction was designed and tested before two review authors (DL/AS) independently extracted data, which was subsequently verified by another independent reviewer (SH) to reduce errors and bias in data extraction. Data abstracted included all information of interest e.g. participant details, methodology, intervention details, and relevant patient outcomes. Reviewers resolved any disagreements by discussion, and one arbitrator (SH) adjudicated any unresolved disagreements. One review author (SH) collated and entered all data into Review Manager 5.3 (ReviewManager version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

2.4.3. Assessment of risk of bias in included studies

Two review authors (DL/AS) assessed the risk of bias using the Cochrane risk of bias assessment tool outlined in chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions, which classifies studies as having low, high, or unclear risk of bias in the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and carryover effect. Any disagreements were resolved first by discussion and then by consultation with a third author for arbitration (SH). One author (SH) computed graphic representations of potential bias within and across studies using Review Manager 5.3.

2.4.4. Measures of treatment effect

The treatment effect for the primary outcome data was expressed as a pooled risk ratio (RR) with 95% confidence interval (CI). Studies with multiple treatment groups were combined into a single group, while missing data was sought from original authors if deemed necessary. The primary analysis was per individual randomised.

2.4.5. Assessment of heterogeneity

Clinical heterogeneity was assessed by considering the variability in participant factors between trials (e.g. age) and trial factors (e.g. randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions). We discussed clinical homogeneity, and based on this discussion, we decided whether pooling of data was appropriate. Statistical

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