Peripheral nerve graft implants into the substantia nigra of subjects with Parkinson's disease undergoing deep brain stimulation surgery: a safety study

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1. Introduction

In Parkinson's disease (PD), the substantia nigra undergoes a loss of dopaminergic cells and cellular function. Previous studies have shown that neurotrophic factors including GDNF, BDNF, and NT-3 can promote dopaminergic function. We have begun a Phase I clinical trial to examine the safety and feasibility of implanting an autologous peripheral nerve graft into the substantia nigra of PD patients undergoing deep brain stimulation (DBS) surgery. The Schwann cells in the graft may serve as an alternative source of the growth factors GDNF, NGF, BDNF, and NT-3.

2. Goal

- Examine safety and side effect profile from implanting peripheral nerve tissue into the substantia nigra during DBS surgery.
- Test potential clinical response.

3. Methods

Participant profile:

- Average age = 59.5
- 4 males, 1 female.
- Progressive Idiopathic PD >5 yrs
- Medication responsive with motor fluctuations
- Cognitively intact
- Met criteria for DBS surgery

Baseline evaluations:

- Unified Parkinson Disease Rating Scale (UPDRS) on and off medication,
- Quality of life rating (PDQ-8),
- Formal neuropsychological evaluation
- Treat to best patient response

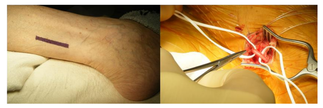
1, 3, 6, 9, 12 months:

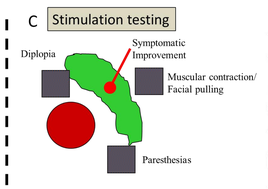
- UPDRS evaluations on/off stimulation

4. DBS surgery provides an avenue for delivering peripheral nerve graft to substantia nigra

Reversed two stage procedure to implant DBS system

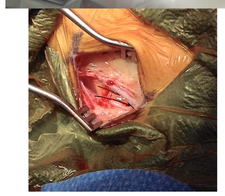
Stage I Implantation of DBS hardware and sural nerve preparation.

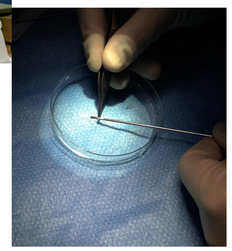


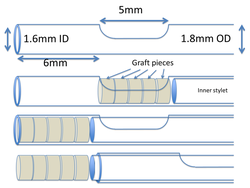


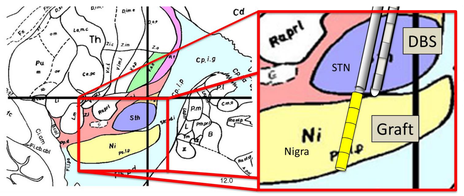
Stage II **A)** Awake, CRW Frame based surgery **B)** Microelectrode recordings **C)** Test stimulations **D)** Implantation of stimulating electrodes.

Graft harvesting, loading and implantation of graft during Stage II









Harvesting of sural nerve tissue

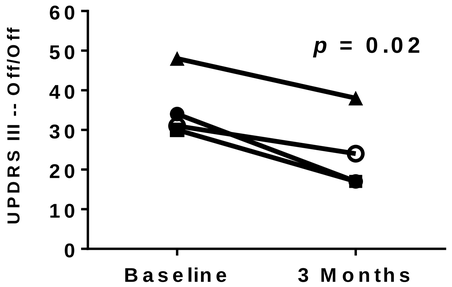
Implantation of graft

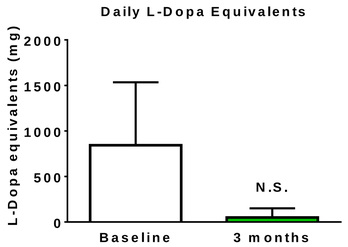
Target: substantia nigra, 1-6mm below base of subthalamic nucleus

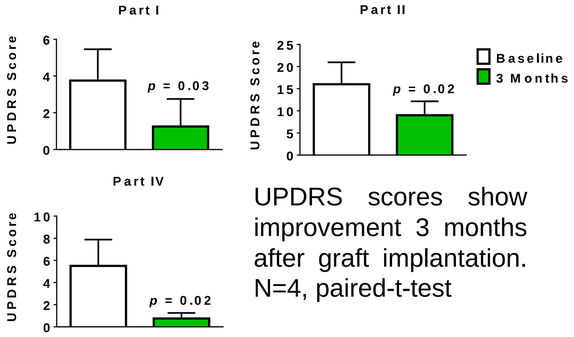
Trajectory: 3mm posterolateral to DBS based on visual targeting

5. Off-treatment motor scores improving three months after graft implant

Individual motor scores

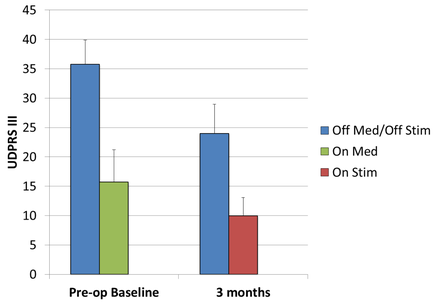


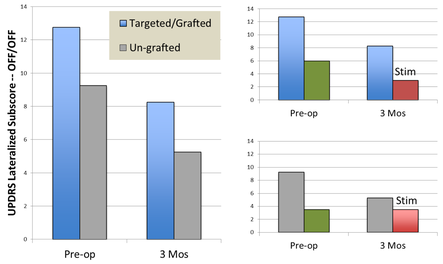




UPDRS scores show improvement 3 months after graft implantation. N=4, paired-t-test

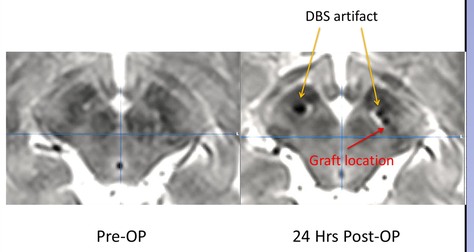
Motor Exam On and Off Medication and Stimulation





Motor scores were compared Off stimulation/Off medication and On stimulation and On medication. Additionally, lateralized scores on UPDRS Part III were compared.

6. Imaging results



DBS electrode and graft placement evaluated with 1.5T MRI.

7. Adverse Effects

Subject No.	Adverse Event	Status	Relatedness
1	Urinary retention	Resolved	procedure
2	hypomania	Resolved	Stimulation
3	none	N/A	N/A
4	Superficial cellulitis	Resolved	procedure
5	Cough headache	Resolved Resolved	Not related DBS surgery

8. Summary

- Peripheral nerve graft surgery successfully completed in 5 of 5 participants.
- Adverse events comparable to reported effects with DBS surgery.
- Average medication levels decreased after 3 months.
- Motor scores OFF medication and OFF stimulation improved after 3 months.

9. Future Work

- Examine safety and feasibility of bilateral nerve graft implants to the substantia nigra.
- Examine efficacy of nerve graft implant on motor and non-motor symptoms.

10. Acknowledgements

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