Bilateral Fornix Deep Brain Stimulation for Alzheimer's Disease: Surgical Safety in the ADvance Trial

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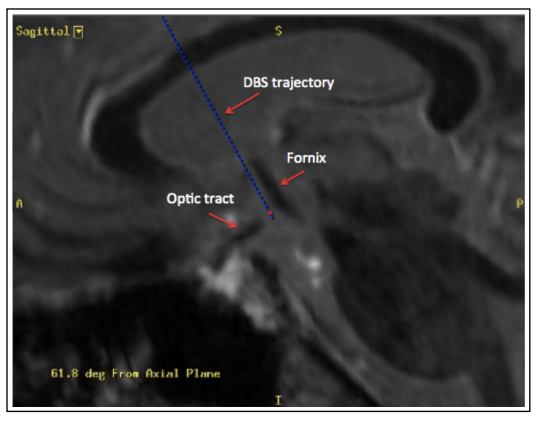
Introduction

This report describes the stereotactic technique, hospitalization, and 90-day perioperative safety in patients who underwent bilateral deep brain stimulation (DBS) of the fornix for the treatment of mild probable Alzheimer's disease.

Methods

The ADvance Trial is a multicenter, 12 -month, double-blind, randomized, controlled, feasibility study being conducted to evaluate the safety, efficacy, and tolerability of DBS of the fornix in patients with mild probable Alzheimer's disease (Figure 1). Intraoperative and perioperative data were collected prospectively. All patients underwent postoperative magnetic resonance imaging (MRI). Stereotactic analyses were performed in a blinded fashion by a single surgeon. Adverse events (AEs) were reported to an independent clinical events committee and adjudicated to determine relationship between the AE and the study procedure.



Results

Between June 1, 2012 and April 30, 2014, 42 patients with mild probable Alzheimer's disease were treated with bilateral fornix DBS (mean age 68.2 ± 7.8 [range 48.0 – 79.7], 19 male and 23 female). The mean planned target coordinates were x = 5.2 ± 1.0 mm (range 3.0 – 7.9), y = 9.6 ± 0.9 mm (range 8.0 – 11.6), z = -7.5 ± 1.2 mm (range -5.4 – -10.0), and the mean postoperative stereotactic radial error on MRI was 1.5 ± 1.0 mm (range 0.2 – 4.0). Mean length of hospitalization was 1.4 ± 0.8 days (Table 1). Twenty-six (61.9%) patients experienced 64 adverse events related to the study procedure, of which 7 were serious adverse events experienced by 5 patients (11.9%) (Table 2). Four (9.5%) patients required return to surgery: 2 for explantation due to infection, 1 for lead repositioning, and 1 for chronic subdural hematoma. No patients experienced neurological deficits as a result of the study and no mortalities were reported.

Factor	Trial Site UT	BAI	Brown	UF	JH	BSHRI	Penn	Total
no. of patients	12	9	6	5	4	4	2	42
sex (no of patients)								
female	5	4	2	3	2	1	2	19
male	7	5	4	5	2	3	0	23
age in yrs**	68.7 ± 6.8 (52.9, 77.1)	71.1 ± 3.0 (66.7, 74.9)	75.3 ± 3.2 (71.6, 79.7)	62.7 ± 6.7 (57.1, 72.9)	60.3 ± 10.2 (48.0, 72.7)	64.8 ± 12.1 (51.1, 78.0)	66.1 ± 10.6 (58.6, 73.6)	68.2±7.8 (48-79.7)
duration of surgery	4.6 ± 1.7	2.7 ± 0.6	4.5 ± 0.3	6.4 ± 1.	4.5 ± 0.7	2.6 ± 0.5	3.3 ± 0.4	4.1 ± 1.6
duration of hospitalization	1.3 ± 0.6	1.0 ± 0.0	1.2 ± 0.4	1.2 ± 0.4	3.3 ± 0.5	1.0 ± 0.0	2.0 ± 0.0	1.4 ± 0.8
interval from diagnosis**	2.6 ± 1.2 (0.7, 4.4)	0.9 ± 0.8 (0.0, 2.8)	4.1 ± 1.5 (1.5, 5.9)	2.6 ± 2.1 (0.4, 5.6)	2.6 ± 2.5 (0.3, 5.9)	1.6 ± 1.5 (0.4, 3.8)	2.1 ± 2.0 (0.6, 3.5)	2.3 ± 1.7 (0.0, 5.9)
AE	8	17	20	1	6	2	9	63
SAE	2	1	1	0	2	0	0	6

*UT = University of Toronto, BAI = Banner Alzheimer's Institute, UF = University of Florida, JH = Johns Hopkins University, BSHRI = Banner Sun Health Research Institute, Penn = University of Pennsylvania
** Data are presented as the mean ± SD with the range in parentheses.

Conclusions

Accurate targeting of DBS to the fornix without direct injury to it is feasible across surgeons and centers. At 90 days after surgery, bilateral fornix DBS was well tolerated by patients with mild probable Alzheimer's disease.

Adverse Event	Number of Patients
Dermatalogic	
Bruising, left forehead and cheek	1
Contact dermatitis	1
Rash	1
Fatigue	
Fatigue	5
Increased fatigue	1
Gastrointestinal	
Nausea	2
Nausea	1
Nausea and vomiting	1
Vomiting	2
Genitourinary	
Urinary retention	3
Headache or Other Pain	
Headache	11
Headache, nausea & vomiting	1
Left mastoid pain	1
Left neck discomfort	1
Neck / shoulder pain	1
Major Surgical Site	
Bilateral subacute and chronic subdural hematoma	1
Chest abscess	1
IPG infection	2
Left electrode lead misplacement	1

Adverse Event	Number of Patients
Mental Status Change	
Confusion	2
Delirium	2
Depressed mood	1
Minor Surgical Site	
Fluid collection	1
Neck discomfort due to pulling of	1
Redness of left frontal incision without drainage or swelling	1
Right periorbital edema	2
Small pustule at the right chest near the surgical scar	1
Surgical site pain in the right chest	1
Swelling at suture behind right ear with	1
Swelling of left eyelid	1
Bilateral eyelid swelling	1
Extra-axial collection	1
Inflammation at IPG site	1
Left cerebral convexity subdural	1
Pink skin behind right ear	1
Pinkish discharge	1
Possible infection at surgical site	1
Rash on right chest around incision	1
Small intracerebral hemorrhage, right	1
Surgical pain	1
Swelling and redness	1
Trauma	
Fall	1

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the surgical technique used for DBS-f 2) Discuss patient selection criteria for the ADvance Trial 3) Comment on safety of DBS-f