Research Paper

A study of novel bilateral thermal capsulotomy with focused ultrasound for treatment-refractory obsessive–compulsive disorder: 2-year follow-up

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Background: Recently, a new thermal lesioning approach using magnetic resonance–guided focused ultrasound (MRgFUS) was introduced for the treatment of neurologic disorders. However, only 2 studies have used this approach for treatment-refractory obsessive–compulsive disorder (OCD), and follow-up was short-term. We investigated the efficacy and safety of bilateral thermal lesioning of the anterior limb of the internal capsule using MRgFUS in patients with treatment-refractory OCD and followed them for 2 years. **Methods:** Eleven patients with treatment-refractory OCD were included in the study. Clinical outcomes were evaluated using the Yale–Brown Obsessive Compulsive Scale, the Clinical Global Impression scale (including improvement and severity), the Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A) at 1 week and 1, 3, 6, 12 and 24 months following MRgFUS. Neuropsychological functioning, Global Assessment of Functioning and adverse events were also assessed. **Results:** After MRgFUS, Yale–Brown Obsessive Compulsive Scale scores decreased significantly across the 24-month follow-up period (mean ± standard deviation, 34.4 ± 2.3 at baseline v. 21.3 ± 6.2 at 24 months, $p < 0.001$). Scores on the Hamilton rating scales for depression and anxiety also significantly decreased from baseline to 24 months (HAM-D, 19.0 ± 5.3 v. 7.6 ± 5.3, $p < 0.001$; HAM-A, 22.4 ± 5.9 v. 7.9 ± 3.9, $p < 0.001$). Global Assessment of Functioning scores improved significantly (35.8 ± 4.9 at baseline v. 56.0 ± 10.3 at 24 months, $p < 0.001$) and Memory Quotient significantly improved, but other neuropsychological functions were unchanged. The side effects of MRgFUS included headache and vestibular symptoms, but these were mild and transient. **Limitations:** The main limitations of this study were the small sample size and the open-label design. **Conclusion:** Bilateral thermal lesioning of the anterior limb of the internal capsule using MRgFUS may improve obsessive–compulsive, depressive and anxiety symptoms in patients with treatment-refractory OCD, without serious adverse effects.

Introduction

Obsessive–compulsive disorder (OCD) tends to run a chronic course and cause severe distress. Patients with OCD usually show impaired social, academic and occupational functioning.[1] The standard initial treatment for OCD consists of cognitive behavioural therapy and pharmacotherapy with serotonin reuptake inhibitors. However, many people with OCD do not respond adequately to standard treatment[2] and some fail to respond, even after all of the best available treatments have been attempted. For people with treatment-refractory OCD, an alternative approach using neurosurgical interventions — including deep brain stimulation and ablative neurosurgery — has been applied with varying outcomes.[3]

Recently, a new thermal lesioning approach using magnetic resonance–guided focused ultrasound (MRgFUS) has been introduced for the treatment of neurologic disorders.[4] Compared to other neurosurgical approaches, MRgFUS is a minimally invasive procedure involving non–cranium opening surgery, and it has no adverse radiation effects. In addition, closed-loop monitoring in real time allows for confirmation of lesion size and location during every stage of lesioning, as well as accurate thermocoagulation.[5] We previously described a proof-of-concept study of bilateral thermal lesioning of the anterior limb of the internal capsule (ALIC) using MRgFUS in 4 patients with treatment-refractory OCD and following patients for 6 months.[6] Here, we report the 2-year follow-up results for 11 patients with treatment-refractory OCD (including the

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4 described in our previous report), who underwent bilateral thermal capsulotomy using MRgFUS. We evaluated efficacy in terms of the severity of obsessive–compulsive, depressive and anxiety symptoms, and we assessed whether MRgFUS caused any physical or cognitive adverse effects.

Methods

Participants

All 11 patients had treatment-refractory OCD and were recruited from a patient pool at Severance Hospital, Yonsei University Health System, a tertiary hospital in South Korea. The inclusion criteria were as follows: a primary diagnosis of OCD according to the Structured Clinical Interview for DSM-IV[7]; at least a 3-year history of OCD symptoms with psychosocial dysfunction (determined by a Global Assessment of Functioning [GAF] score of ≤ 50)[8]; a minimum score of 28 on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS)[9]; and treatment-refractory status — that is, nonresponsive to pharmacological treatment (more than 2 types of serotonin reuptake inhibitor at the maximum tolerated dose for more than 12 weeks) and cognitive behavioural therapy (a minimum of 20 sessions of primarily therapist-guided Exposure and Response Prevention [ERP]). Full inclusion and exclusion criteria can be found at www.clinicaltrials.gov/ct2/show/NCT01986296?term=OCD001&rank=2.

We initially recruited participants with more refractory characteristics than described in the inclusion criteria; the number of characteristics and duration of treatment exceeded the entry criteria for all patients. All patients had failed to respond to more than 3 serotonin reuptake inhibitors, including clomipramine, and more than 1 antipsychotic drug augmentation strategy (≥ 3 serotonin reuptake inhibitors and ≥ 1 antipsychotic) and had had symptoms of OCD with psychosocial impairment for at least 5 years. Patients who had a current or previous psychotic disorder, bipolar disorder or significant cognitive impairment (based on a Mini Mental State Examination,[10] score ≤ 24) were excluded from the study. All patients continued to take their previous medication, using the same regimen and the same dosage, over the entire 2-year study period. After the first week following MRgFUS, patients were encouraged to continue using the cognitive behavioural skills they had learned previously; we did not deliver regular, formal cognitive behavioural therapy sessions after the surgery. The CONSORT flow chart can be found in Appendix 1, Figure S1, available at jpn.ca/170188-a1.

This study was approved by the Institutional Review Board of Severance Hospital. All participants gave written informed consent. This trial is registered with ClinicalTrials.gov, number NCT01986296 (www.clinicaltrials.gov/ct2/show/NCT01986296?term=OCD001&rank=2).

Outcomes

We measured the severity of obsessive–compulsive symptoms using the Y-BOCS.[9] We also assessed Clinical Global Impression (CGI) scores, including improvement (CGI-I) and severity (CGI-S). Patients were classified as responders, partial responders or nonresponders based on the criteria for treatment response and remission of obsessive–compulsive symptoms listed in Table 1.[11] We assessed depressive and anxiety symptoms using the 17-item Hamilton Rating Scale for Depression (HAM-D)[12] and the Hamilton Rating Scale for Anxiety (HAM-A),[13] respectively. The criteria for treatment response and remission of depressive and anxiety symptoms[14] are also listed in Table 1. We assessed Y-BOCS, CGI, HAM-D and HAM-A at baseline, 1 week, and 1, 3, 6, 12 and 24 months.

We conducted comprehensive neuropsychological tests at baseline and 6, 12 and 24 months, including the Korean version of the Wechsler Adult Intelligence Scale (K-WAIS, intellectual function),[15] the Memory Quotients (visual and verbal memory ability) of the Rey-Kim Memory Test,[16] the Controlled Oral Word Association Test (COWAT, executive function),[17] the Korean Colour Word Stroop Test (Stroop, executive function)[18] and the Digit Span test (forward, attention).[19]

We assessed global psychosocial and occupational functioning using the GAF[8] test at baseline and 3, 6, 12 and 24 months.

Adverse events or changes in a patient's physical and behavioural condition were evaluated during the surgical

Table 1: Classification of treatment response for obsessive–compulsive, depressive and anxiety symptoms

Treatment response	Definition
Obsessive-compulsive	
Responder	Y-BOCS reduction ≥ 35% relative to the baseline score + CGI-I 1 (very much improved) or 2 (much improved)
Partial responder	Y-BOCS reduction 25%–35% + CGI-I ≥ 3 (minimally improved)
Remission	Y-BOCS ≤ 12 + CGI-S 1 (normal, not at all ill) or 2 (borderline mentally ill) ≥ 1 week
Depressive	
Responder	HAM-A reduction ≥ 50% relative to the baseline score
Remission	HAM-A ≤ 7
Anxiety	
Responder	HAM-D reduction ≥ 50% relative to the baseline score
Remission	HAM-D ≤ 7

CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; Y-BOCS = Yale–Brown Obsessive Compulsive Scale.

procedure and at each follow-up visit by both an experienced neurosurgeon and psychiatrist, who questioned in general terms. Physical adverse events were also assessed using a physical examination checklist, and psychiatric adverse events were evaluated using mental status examinations and psychiatric interviews. All changes in physical and behavioural condition reported by patients and caregivers were considered to be adverse events.

Primary outcome measures were Y-BOCS and CGI. Secondary outcome measures were depression and anxiety symptoms (HAM-D, HAM-A), neuropsychological tests, global functioning (GAF) and adverse events associated with the procedure.

Focused ultrasound capsulotomy

The details of the focused ultrasound capsulotomy procedure have been decribed previously.[6] In brief, MRgFUS sonications were performed using a 3-T MR (GE Medical Systems) and the ExAblate 4000 (InSightec) systems. The bilateral ALIC was targeted along the bicommisural line, 7 mm in front of the anterior margin of the anterior commissure. With stepwise increases in acoustic power and energy, high-power sonications were applied to achieve a peak temperature of 51°C to 56°C for more than 3 s. The goal was to create a 10 mm elliptical lesion along the internal capsule on coronal imaging by adjusting the target centre. Before and after every sonication, the patient was clinically assessed by both a neurosurgeon and a psychiatrist to identify physical or psychological adverse events. All patients were fully awake and responsive throughout the procedure, after which they were monitored for approximately 24 h as inpatients. The number, temperature and total duration of the sonications and the skull density ratio of the patients are listed in Appendix 1, Table S1. Brain MRI was evaluated immediately and at 1 week, 1 month and 6 months after MRgFUS to detect the lesions and any other complications related to the sonications (Appendix 1, Figure S2).

Statistical analysis

We analyzed changes in clinical symptoms (Y-BOCS, CGI-S, CGI-I, HAM-D, HAM-A), neuropsychological function (K-WAIS, Memory Quotient, COWAT, Stroop, Digit Span), global functioning (GAF) and body weight using linear mixed models for repeated measures, nonrestrictively assuming an unstructured covariance matrix. A post hoc analysis with Bonferroni correction examined changes from baseline for each variable. Statistical analyses were performed using SPSS version 23.0 (SPSS Inc.). Statistical significance was set at $p < 0.05$ (2-tailed).

Results

Participants

Participant demographic and clinical characteristics are presented in Table 2.

Clinical outcomes

Table 3 shows detailed preoperative and postoperative clinical data for each patient. Mean Y-BOCS, HAM-D and HAM-A scores decreased significantly across the 24-month follow-up period (Y-BOCS, $F_{6,10.0} = 18.6$, $p < 0.001$; HAM-D, $F_{6,10.0} = 13.4$, $p < 0.001$; HAM-A, $F_{6,10.0} = 85.4$, $p < 0.001$; Table 3 and Fig. 1A to C). Post hoc analyses indicated that obsessive–compulsive, depressive and anxiety symptoms began to significantly improve as early as 1 week after MRgFUS (Y-BOCS, $p = 0.035$; HAM-D, $p = 0.001$; HAM-A, $p = 0.002$, after Bonferroni corrections) and the improvements continued throughout the 24-month follow-up period (all $p < 0.05$ after Bonferroni corrections). The Y-BOCS, HAM-D and HAM-A graphs for individual patients are presented in Appendix 1, Figure S3A to S3C. The mean CGI-S and CGI-I scores also decreased significantly over the 24-month follow-up period (CGI-S, $F_{6,10.0} = 11.3$, $p = 0.001$; CGI-I, $F_{5,10.0} = 13.3$, $p < 0.001$).

For Y-BOCS, the mean ± standard deviation (SD) score of 34.4 ± 2.3 at baseline decreased to 23.6 ± 4.5, 21.8 ± 4.8 and 21.3 ± 6.2 at 6, 12 and 24 months, respectively. At 12 months, 6 (54.5%) patients were responders and 3 (27.3%) patients were partial responders. At 24 months, 6 patients were responders, 2 (18.1%) were partial responders and 1 had achieved full remission. For HAM-D, the mean ± SD score of 19.0 ± 5.3 at baseline decreased to 9.0 ± 3.5, 8.9 ± 5.4 and 7.6 ± 5.3 at 6, 12 and 24 months, respectively. At 12 months, 6 patients were in remission and all were responders. At 24 months, 7 (63.6%) patients were responders and 6 were in remission. For HAM-A, the mean ± SD score of 22.4 ± 5.9 at baseline decreased to 8.5 ± 4.6, 8.5 ± 4.9 and 7.9 ± 3.9 at 6, 12 and 24 months, respectively. At 12 months, 8 (72.7%) patients were responders and 6 were in remission. At 24 months, 8 patients were responders and 7 were in remission.

The mean GAF score increased significantly across the 24-month follow-up period ($F_{4,10.0} = 25.2$, $p < 0.001$; Table 3 and Fig. 1D). The mean GAF score showed significant improvement as early as 3 months after MRgFUS (the first follow-up on GAF; $p < 0.001$ after Bonferroni correction). The GAF graphs for individual patients are presented in Appendix 1, Figure S3D.

Neuropsychological function

Detailed neuropsychological function data for individual patients are shown in Table 4, Table 5 and Table 6. The mean Memory Quotient score improved significantly across the 24-month follow-up period ($F_{3,6.5} = 236.3$, $p < 0.001$). We observed no significant changes in K-WAIS, COWAT, Stroop or Digit Span scores.

Adverse events

All patients tolerated the MRgFUS procedure well. The most common adverse event during the procedure was headache. Seven patients (63.6%) had several short, periodic headaches during sonication at temperatures > 50°C. These symptoms were mild and resolved spontaneously or with a

Table 2: Participant demographic and clinical characteristics at baseline

Pt. no.	Sex/age, yr	Primary OCD symptoms	Psychiatric comorbidity	Illness duration/ treatment duration, yr	Current medications	Previously failed medications
1	M/24	Contamination fear, washing, counting	Major depressive disorder	11/5	Escitalopram 40 mg, valproic acid 250 mg, alprazolam 0.25 mg	Fluoxetine 60 mg, paroxetine 60 mg, clomipramine 100 mg, risperidone 3 mg
2	M/29	Contamination fear, washing	Obsessive-compulsive personality traits	17/11	Fluoxetine 80 mg, escitalopram 30 mg, buspirone 20 mg	Fluoxetine 80 mg, sertraline 200 mg, quetiapine 300 mg, aripiprazole 15 mg, escitalopram 40 mg, clomipramine 150 mg
3	M/22	Aggressive obsession, washing, counting	Major depressive disorder	13/8	Sertraline 200 mg, clomipramine 100 mg, aripiprazole 15 mg, risperidone 10 mg, olanzapine 5 mg	Escitalopram 20 mg, sertraline 300 mg, fluoxetine 80 mg, venlafaxine XR 150 mg, quetiapine 800 mg, risperidone 4 mg, aripiprazole 15 mg, palliperidone 9 mg
4	F/44	Pathologic doubt, checking	Major depressive disorder	24/19	Fluoxetine 80 mg, olanzapine 10 mg	Clomipramine 125 mg, paroxetine 40 mg, fluoxetine 80 mg, escitalopram 30 mg, aripiprazole 15 mg, olanzapine 20 mg
5	F/37	Contamination fear, washing	Minor depression	10/8	Fluvoxamine 150 mg, venlafaxine XR 75 mg, chlorpromazine 50 mg, clonazepam 0.5 mg	Fluoxetine 80 mg, clomipramine 100 mg, fluvoxamine 300 mg, venlafaxine XR 112.5 mg, aripiprazole 10 mg
6	M/34	Sexual obsession, pathologic doubt, checking, reassurance seeking	None	15/13	Fluoxetine 180 mg, sertraline 100 mg, risperidone 7 mg, aripiprazole 10 mg, alprazolam 0.75 mg, clonazepam 0.5 mg, propranolol 40 mg, trihexine 4 mg	Sertraline 300 mg, fluoxetine, 80 mg, clomipramine 125 mg, olanzapine 10 mg
7	M/37	Obsession with need for symmetry or exactness, intrusive nonviolent thought and image, obsession about mistakes, repeating, checking, ordering, counting	Schizotypal personality traits	16/8	Escitalopram 70 mg, risperidone 5 mg, lorazepam 1 mg, clonazepam 1 mg, alprazolam 0.25 mg, benztropine 2 mg, propranolol 60 mg, diazepam 4 mg	Fluoxetine 80 mg, paroxetine 60 mg, sertraline 300 mg, venlafaxine XR 150 mg, clomipramine 150 mg, haloperidol 10 mg, risperidone 6 mg
8	F/26	Contamination fear, obsession about certain numbers, washing, counting, checking	None	13/10	Escitalopram 30 mg, sertraline 100 mg, risperidone 4 mg, imipramine 50 mg, clonazepam 0.5 mg, trihexine 2 mg	Clomipramine 100 mg, escitalopram 60 mg, venlafaxine XR 225 mg, risperidone 4 mg, aripiprazole 15 mg
9	F/40	Aggressive obsession, obsession about responsibility, contamination fear, undoing, repeating, washing	None	22/20	Escitalopram 40 mg, fluoxetine 80 mg, aripiprazole 5 mg, clonazepam 0.5 mg	Fluoxetine 80 mg, escitalopram 50 mg, clomipramine 125 mg, sertraline 200 mg, olanzapine 20 mg, bronanserin 4 mg
10	F/42	Contamination fear, obsession about mistakes, washing, checking	None	11/10	Sertraline 300 mg, escitalopram 10 mg, clomipramine 100 mg, risperidone 4 mg	Clomipramine 100 mg, fluoxetine 80 mg ziprasidone 100 mg, sertraline 200 mg
11	F/23	Contamination fear, washing	Major depressive disorder	9/6	Sertraline 200 mg, escitalopram 20 mg, risperidone 4 mg, procyclidine 5 mg	Paroxetine 60 mg, sertraline 200 mg, risperidone 3 mg, clomipramine 100 mg

F = female; M = male; OCD = obsessive–compulsive disorder; pt. = patient.

single dose of analgesic medication. Five patients (45.5%) had increased vestibular symptoms, such as nausea, vomiting or dizziness, which continued until the end of the procedure. These symptoms resolved spontaneously or after a single dose of an antiemetic drug. Three patients (27.3%) felt increased anxiety, which subsided after a single benzodiazepine dose. Two patients (18.2%) complained of stomach upset and were given a single dose of an H_2 blocker. One patient (9.1%) experienced a transient warm sensation in the brain during sonication at higher temperatures. No significant physical adverse events (such as fatigue, urinary incontinence or seizure) or behavioural changes (such as hypomania, personality changes, emotional blunting, indifference or carelessness), which were reported in previous capsulotomy studies,[20,21] occurred during the 24-month follow-up period. We observed no significant changes in weight during the 24-month follow-up period (mean ± SD; 66.3 ± 11.5 kg at baseline, 67.2 ± 11.7 kg at 6 months, 66.0 ± 10.6 kg at 12 months, and 66.2 ± 11.8 kg at 24 months; $F_{3,10.0}$ = 0.3, p = 0.812). No significant psychiatric or behavioural

Table 3: Individual clinical symptom measures after MRgFUS, 24-month follow-up (part 1 of 2)

Measure	Pt. no.	BL	1 wk	1 mo	3 mo	6 mo	12 mo	24 mo	IR at 6 mo, %	IR at 12 mo, %	IR at 24 mo, %
Y-BOCS*	1	38	36	35	32	29	18	21	23.7	52.6	44.7
	2	34	32	27	18	18	22	27	47.1	35.3	20.6
	3	35	31	32	28	26	15	14	25.7	57.1	60.0
	4	34	28	22	22	21	22	19	38.2	35.3	44.1
	5	37	35	29	28	27	28	30	27.0	24.3	18.9
	6	35	28	29	24	23	20	14	34.3	42.9	60.0
	7	34	20	18	21	16	23	21	52.9	32.4	38.2
	8	36	33	30	28	29	27	26	19.4	25.0	27.8
	9	30	30	28	27	27	21	21	10.0	30.0	30.0
	10	34	30	30	27	19	15	12	44.1	55.9	64.7
	11	31	30	30	30	25	29	29	19.4	6.5	6.5
	Mean ± SD	34.4 ± 2.3	30.3 ± 4.3	28.2 ± 4.6	25.9 ± 4.2	23.6 ± 4.5	21.8 ± 4.8	21.3 ± 6.2	31.1 ± 13.3	36.1 ± 15.3	37.8 ± 18.9
HAM-D†	1	27	7	5	7	4	4	7	85.2	85.2	74.1
	2	18	15	8	11	11	21	15	38.9	–16.7	16.7
	3	25	11	13	12	11	6	3	56.0	76.0	88.0
	4	20	10	6	10	9	6	5	55.0	70.0	75.0
	5	24	10	5	9	15	14	15	37.5	41.7	37.5
	6	19	11	10	11	9	5	2	52.6	73.7	89.5
	7	17	9	5	10	11	13	14	35.3	23.5	17.6
	8	13	10	8	6	8	10	1	38.5	23.1	92.3
	9	16	8	10	11	9	3	9	43.8	81.3	43.8
	10	9	6	9	6	2	6	3	77.8	33.3	66.7
	11	21	13	12	16	10	10	10	52.4	52.4	52.4
	Mean ± SD	19.0 ± 5.3	10.0 ± 2.6	8.3 ± 2.8	9.9 ± 2.9	9.0 ± 3.5	8.9 ± 5.4	7.6 ± 5.3	52.1 ± 16.4	49.4 ± 31.8	59.4 ± 27.7
HAM-A‡	1	34	5	6	6	4	4	7	88.2	88.2	79.4
	2	17	14	7	7	7	19	15	58.8	–11.8	11.8
	3	31	13	16	15	17	6	7	45.2	80.6	77.4
	4	26	9	7	8	5	4	5	80.8	84.6	80.8
	5	19	10	8	8	5	15	14	73.7	21.1	26.3
	6	21	9	11	12	13	6	2	38.1	71.4	90.5
	7	17	10	9	14	8	12	10	52.9	29.4	41.2
	8	20	8	10	14	8	9	7	60.0	55.0	65.0
	9	20	9	19	18	8	5	7	60.0	75.0	65.0
	10	16	7	11	6	3	5	4	81.3	68.8	75.0
	11	25	20	22	21	15	9	9	40.0	64.0	64.0
	Mean ± SD	22.4 ± 5.9	10.4 ± 4.1	11.5 ± 5.3	11.3 ± 5.1	8.5 ± 4.6	8.6 ± 4.9	7.9 ± 3.9	61.7 ± 17.3	56.9 ± 31.3	61.5 ± 24.7

Table 3: Individual clinical symptom measures after MRgFUS, 24-month follow-up (part 2 of 2)

Measure	Pt. no.	BL	1 wk	1 mo	3 mo	6 mo	12 mo	24 mo	IR at 6 mo, %	IR at 12 mo, %	IR at 24 mo, %
GAF§	1	30	—	—	40	40	53	55	33.3	76.7	83.3
	2	35	—	—	45	45	36	42	28.6	2.9	20.0
	3	30	—	—	40	43	69	69	43.3	130.0	130.0
	4	33	—	—	43	51	55	55	54.6	66.7	66.7
	5	32	—	—	40	40	37	40	25.0	15.6	25.0
	6	33	—	—	45	45	60	65	36.4	81.8	97.0
	7	42	—	—	48	58	55	55	38.1	31.0	31.0
	8	39	—	—	43	43	48	50	10.3	23.1	28.2
	9	43	—	—	51	55	65	65	27.9	51.2	51.2
	10	35	—	—	47	60	65	70	71.4	85.7	100.0
	11	42	—	—	45	48	50	50	14.3	19.0	19.0
	Mean ± SD	35.8 ± 4.9	—	—	44.3 ± 3.6	48.0 ± 7.1	53.9 ± 10.8	56.0 ± 10.3	34.8 ± 17.4	53.1 ± 38.8	59.2 ± 38.6
CGI-S¶	1	7	7	7	5	5	4	4	—	—	—
	2	6	6	5	4	4	4	5	—	—	—
	3	6	6	6	5	4	3	3	—	—	—
	4	6	5	4	4	4	4	4	—	—	—
	5	7	7	6	5	5	5	5	—	—	—
	6	6	5	5	4	4	4	3	—	—	—
	7	7	5	4	4	4	4	4	—	—	—
	8	6	6	6	5	5	4	4	—	—	—
	9	5	5	5	4	4	4	4	—	—	—
	10	6	5	6	4	4	3	2	—	—	—
	11	5	5	5	5	5	5	5	—	—	—
	Mean ± SD	6.1 ± 0.2	5.6 ± 0.2	5.4 ± 0.3	4.5 ± 0.2	4.4 ± 0.2	4.0 ± 0.2	3.9 ± 0.3	—	—	—
CGI-I**	1	—	4	4	3	3	1	2	—	—	—
	2	—	4	3	2	2	2	3	—	—	—
	3	—	3	4	2	2	1	1	—	—	—
	4	—	3	2	2	2	2	2	—	—	—
	5	—	4	3	3	3	3	3	—	—	—
	6	—	3	3	2	2	2	1	—	—	—
	7	—	2	1	2	1	2	2	—	—	—
	8	—	4	4	3	3	2	2	—	—	—
	9	—	4	4	4	3	2	2	—	—	—
	10	—	2	3	3	2	1	1	—	—	—
	11	—	4	4	4	4	4	4	—	—	—
	Mean ± SD	—	3.4 ± 0.2	3.2 ± 0.3	2.7 ± 0.2	2.5 ± 0.2	2.0 ± 0.3	2.1 ± 0.3	—	—	—

BL = baseline; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; IR = improvement rate; MRgFUS, magnetic resonance–guided focused ultrasound; SD = standard deviation; Y-BOCS = Yale–Brown Obsessive Compulsive Disorder Scale.

*Mean Y-BOCS scores decreased significantly across the 24-month follow-up period (linear mixed model; $F_{6,10.0} = 18.6$, $p < 0.001$).

†Mean HAM-D scores decreased significantly across the 24-month follow-up period (linear mixed model; $F_{6,10.0} = 13.4$, $p < 0.001$).

‡Mean HAM-A scores decreased significantly across the 24-month follow-up period (linear mixed model; $F_{6,10.0} = 85.4$, $p < 0.001$).

§Mean GAF scores increased significantly across the 24-month follow-up period (linear mixed model; $F_{4,10.0} = 25.2$, $p < 0.001$).

¶Mean CGI-S scores decreased significantly across the 24-month follow-up period (linear mixed model; $F_{6,10.0} = 11.3$, $p = 0.001$).

**Mean CGI-I scores decreased significantly across the 24-month follow-up period (linear mixed model; $F_{5,10.0} = 13.3$, $p < 0.001$).

adverse events, such as changes of personality, mania/hypomania, impulsivity or alcohol consumption, were declared by patients or caregivers or observed by psychiatrists (SJK and CHK) during the 2-year follow-up period.

Discussion

In this study of bilateral thermal lesioning of the ALIC using MRgFUS in patients with treatment-refractory OCD, we found significant improvement of obsessive–compulsive, depressive and anxiety symptoms, with only a few transient and acceptable adverse events over 24 months of follow-up.

At 24 months, 54.6% of patients (6/11) were responders, 18.1% (2/11) were partial responders and 9.1% (1/11) were in remission. Our findings are compatible with those of previous studies of capsulotomy in people with OCD, which showed a full response in approximately 50% (25% to 80%) of patients and a partial response in approximately 20% (0% to 33%).[14,22–24] A recent systemic review of observational studies of capsulotomy for OCD reported that after 12-month follow-up, the mean reduction in Y-BOCS score and full response rate were 37% and 41%, respectively.[21] A meta-analysis of deep brain stimulation including 31 studies that involved 116 participants and targeted the striatal area (ALIC, ventral capsule, ventral striatum, nucleus accumbens and ventral caudate), subthalamic nucleus or inferior thalamic peduncle reported a global reduction of 45.1% in Y-BOCS score and a global responder percentage of 60.0%.[25] The results of our study on obsessive–compulsive symptoms confirm that bilateral thermal lesioning of the ALIC with MRgFUS appears to have an efficacy comparable to that reported in other capsulotomy, cingulotomy or deep brain stimulation studies.

Of the 7 patients (including 3 partial responders) who did not show a full response at 6 months, 3 improved further and qualified as full responders at 12 and 24 months. These results imply that 6 months may not be long enough to draw

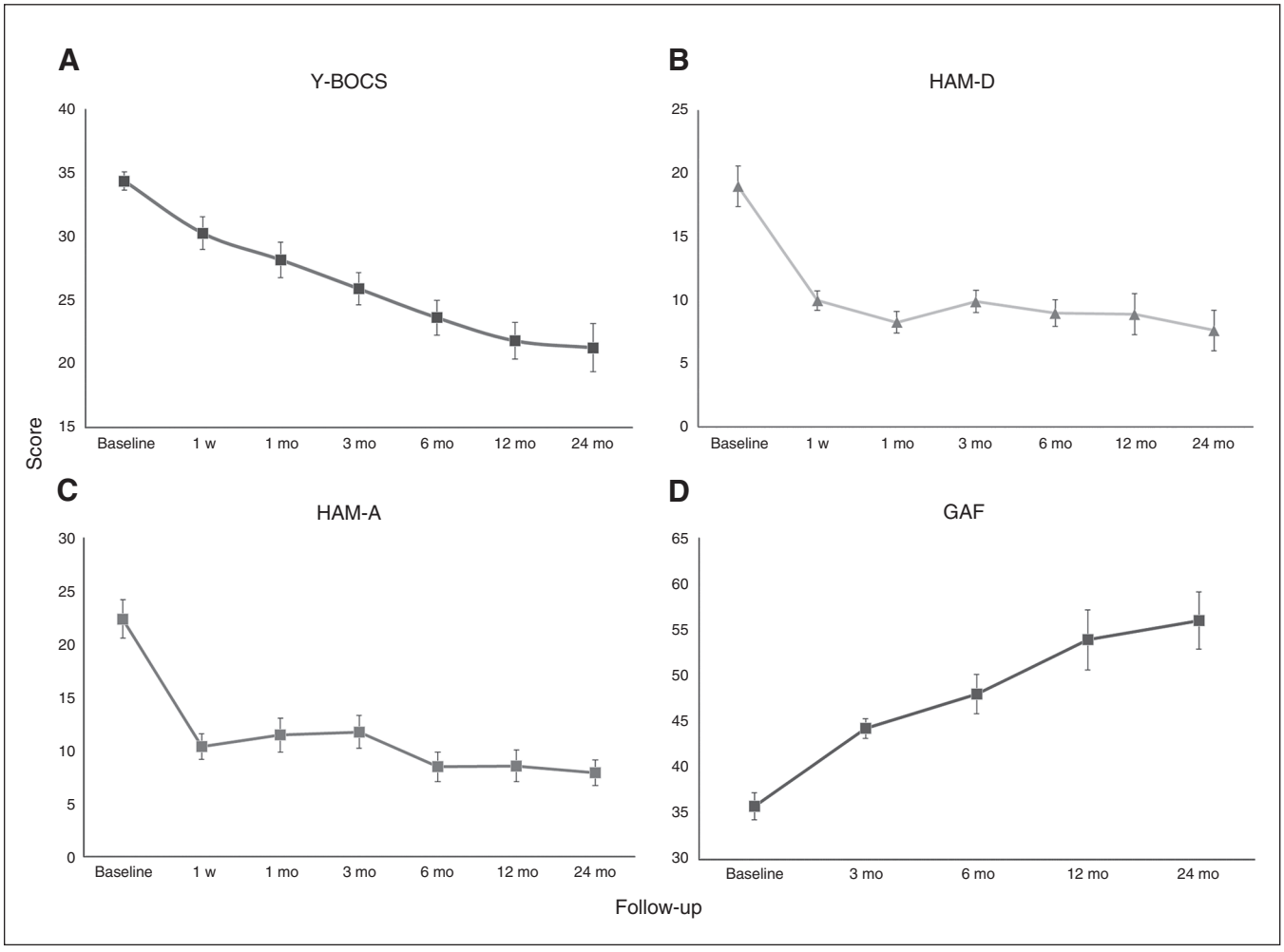

Fig. 1: Improvement in clinical outcomes and global functioning. Data appear as mean ± standard error. Panels show the changes in mean (**A**) Y-BOCS, (**B**) HAM-D, (**C**) HAM-A and (**D**) GAF scores during the 24-month follow-up period after MRgFUS. Higher scores on Y-BOCS, HAM-D and HAM-A indicate more severe symptoms. Higher scores on GAF indicate better global psychosocial and occupational functioning. GAF = Global Assessment of Functioning; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; MRgFUS = magnetic resonance–guided focused ultrasound; Y-BOCS = Yale–Brown Obsessive Compulsive Scale.

conclusions about the effects of MRgFUS. Although still speculative, it may be necessary to inform the patients and caregivers about this potential lag in response before surgery.

In terms of time course and efficacy, we found that obsessive–compulsive symptoms began to significantly improve as early as 1 week after MRgFUS and continued to improve after 6 months. Some studies also found early onset of improvement (2 weeks to 3 months)[14,22,23] and a delay in improvement (after 12 months) after capsulotomy[22,24] or cingulotomy.[26,27] Taken together, the previous and current findings suggest that the therapeutic effects of neurosurgical interventions are related to functional brain interruption and reorganization after lesioning.[22,27]

Moreover, we observed significant improvement in depressive and anxiety symptoms after MRgFUS. The rates of improvement of depression and anxiety in this study were in line with those reported by previous studies (44.7% to 68.1% for HAM-D and 48.4% to 77.0% for HAM-A).[28–30] Interestingly, we observed significant improvements in depression and anxiety symptoms as early as 1 week after MRgFUS. Another recent study reported a significant reduction in HAM-D and HAM-A scores as early as 2 weeks after bilateral capsulotomy.[14] A study using deep brain stimulation of the nucleus accumbens for refractory OCD also reported significant decreases in HAM-D and HAM-A scores, and the effects of deep brain stimulation on anxiety and depression were

Table 4: K-WAIS and Memory Quotient tests after MRgFUS, 24-month follow-up

	K-WAIS				Memory Quotient (Rey-Kim Memory Test)*			
Pt. no.	BL	6 mo	12 mo	24 mo	BL	6 mo	12 mo	24 mo
1	118	124	130	124	106	119	121	127
2	115	119	—	98	99	111	—	98
3	80	80	89	92	94	97	115	117
4	78	81	—	88	100	97	—	98
5	107	110	—	107	100	107	—	116
6	98	90	101	105	89	93	99	114
7	71	74	73	83	59	75	92	81
8	59	71	72	75	84	109	104	102
9	92	99	96	96	110	122	134	125
10	77	71	86	87	103	109	116	123
11	105	109	120	—	91	97	101	—
Mean ± SD†	90.9 ± 19.3	93.5 ± 19.7	95.9 ± 20.7	95.5 ± 14.0	94.1 ± 13.9	103.3 ± 13.3	110.3 ± 13.7	110.1 ± 14.8

BL = baseline; K-WAIS = Wechsler Adult Intelligence Scale, Korean version; MRgFUS = magnetic resonance–guided focused ultrasound; pt. = patient; SD = standard deviation.
*Mean Memory Quotient scores increased significantly across the 24-month follow-up period (linear mixed model; $F_{3,65} = 236.3$, $p < 0.001$).
†Mean values at 12 months were from 8 patients (data for patients 2, 4 and 5 were missing). Mean values at 24 months were from 10 patients (data for patient 11 were missing).

Table 5: COWAT after MRgFUS, 24-month follow-up

	COWAT							
	Semantic				Phonemic			
Pt. no.	BL	6 mo	12 mo	24 mo	BL	6 mo	12 mo	24 mo
1	28	20	25	24	61	58	57	49
2	21	16	—	16	47	41	—	33
3	15	21	20	18	30	28	35	46
4	13	14	—	14	24	21	—	31
5	24	20	—	21	40	46	—	39
6	17	19	17	22	39	27	35	38
7	19	14	16	16	19	21	32	34
8	11	12	9	14	23	38	31	29
9	18	13	16	12	27	30	35	28
10	16	19	14	17	21	21	34	39
11	32	33	30	—	59	89	70	—
Mean ± SD*	19.5 ± 6.4	18.3 ± 5.8	18.3 ± 6.6	17.4 ± 3.9	35.5 ± 15.0	38.2 ± 20.6	41.1 ± 14.3	36.6 ± 7.0

BL = baseline; COWAT = Controlled Oral Word Association Test; MRgFUS = magnetic resonance–guided focused ultrasound; pt. = patient; SD = standard deviation.
*Mean values at 12 months were from 8 patients (data for patients 2, 4 and 5 were missing). Mean values at 24 months were from 10 patients (data for patient 11 were missing).

Table 6: Stroop and Digit Span tests after MRgFUS, 24-month follow-up

	Stroop*				Digit Span (forward)			
Pt. no	BL	6 mo	12 mo	24 mo	BL	6 mo	12 mo	24 mo
1	0.70	0.79	0.75	0.75	8	13	10	10
2	1.45	1.44	—	1.75	14	13	—	14
3	1.46	1.40	1.17	0.95	9	10	14	10
4	1.42	1.01	—	1.13	9	10	—	14
5	0.98	1.07	—	1.11	12	13	—	13
6	1.53	2.08	2.04	1.10	12	11	14	14
7	1.56	1.59	1.53	1.47	13	10	11	11
8	1.25	1.16	1.16	1.13	9	7	7	11
9	0.96	0.89	1.02	1.01	7	6	12	8
10	1.57	2.11	1.45	1.23	8	7	8	9
11	0.84	0.74	0.68	—	11	11	14	—
Mean ± SD†	1.25 ± 0.32	1.30 ± 0.48	1.22 ± 0.45	1.16 ± 0.28	10.2 ± 2.3	10.1 ± 2.5	11.3 ± 2.8	11.4 ± 2.2

BL = baseline; pt. = patient; MRgFUS = magnetic resonance–guided focused ultrasound; SD = standard deviation; Stroop = Colour Word Stroop Test, Korean version.
*Mean reaction time for correct trials (s).
†Mean values at 12 months were from 8 patients (data for patients 2, 4 and 5 were missing). Mean values at 24 months were from 10 patients (data for patient 11 were missing).

more robust and immediate than those on obsessive–compulsive symptoms,[31] consistent with our results. These findings suggest the possibility of using neurosurgical procedures such as MRgFUS or deep brain stimulation to treat major depressive or anxiety disorders in addition to OCD. The improvement in obsessive–compulsive, depressive and anxiety symptoms noted within a week of the procedures could have been placebo effects rather than true therapeutic effects. However, this is less likely because the improvements continued throughout the 24-month follow-up period, and OCD is known to be associated with a reduced placebo response.[32]

One of the most fascinating results of this study was the lack of major adverse events. Only mild and transient complications, such as headache, vestibular symptoms, anxiety and a hot sensation in the brain, were reported, and all of these resolved immediately after the procedure.

More importantly, overall neuropsychological function was unchanged or improved over time. Memory Quotient scores significantly improved, and K-WAIS, COWAT, Stroop and Digit Span scores were unchanged. Similar to our results, other studies have reported improved visuospatial memory.[33] Our results suggest that bilateral thermal lesioning of the ALIC with MRgFUS does not negatively affect various domains of neuropsychological function, including intelligence, memory, attention, learning ability and executive function. The positive effect on memory function may be explained by several mechanisms, such as amelioration of symptoms or interruption of abnormal circuits.[33] However, improvements in Memory Quotient should be interpreted with caution, because they could have been due to learning effects through repeated examinations.

To date, most stereotactic ALIC ablative procedures have been performed using radiofrequency thermal ablation or gamma knife. Because of the nature of the radiofrequency ablation technique, lesion size can be quite variable and can injure adjacent areas, resulting in substantial risk of complications.[20] Gamma knife is a noninvasive technique and appears to have fewer risks, but still has serious adverse effects, including radiation-induced complications.[3]

Rates of transient adverse outcomes of capsulotomy, including asymptomatic hemorrhage, seizure and hallucinations via radiofrequency thermal ablation and gamma knife, have been reported to be 0% to 220% and 0% to 260% across studies, respectively.[21] Rates of serious or permanent adverse outcomes, including intracranial hemorrhage, brain edema with permanent sequela, hemiparesis, personality change, cognitive impairment, weight gain, recurrent seizures and more, have been reported to be 11.2% to 40% and 0% to 40%, respectively.[21] It is difficult to compare these rates of adverse events, especially transient ones, because criteria varied across studies, and the studies had relatively small sample sizes. However, in our study, we found no serious or permanent sequelae, suggesting more favourable outcomes with respect to adverse events. Although a recent randomized trial of capsulotomy in refractory OCD with gamma knife suggested that smaller lesions would be expected to come with fewer serious adverse events, development of delayed brain cyst and manic episodes were reported in that study.[24]

Currently, deep brain stimulation is considered an alternative to stereotactic ablation neurosurgery for OCD.[3,31] It has the advantages of adjustability, less destructiveness and reversibility. However, it is also an invasive procedure with the placement of leads in the brain, which can increase vulnerability to hemorrhage or infection. It also comes with a risk of device failure and requires repeated surgery to exchange the battery.

Bilateral thermal lesioning of the ALIC with MRgFUS has obvious advantages over conventional neurosurgical procedures. It is an incisionless, nonradiation ablation method. The ablation temperature and the lesion size and location can be verified in real time with magnetic resonance thermography and sequential magnetic resonance images, enabling neurosurgeons to make adjustments and reposition immediately in case of need.[34] Thermal lesions created by MRgFUS are precise and can be confined to the ALIC without extensive tissue

damage beyond the target, minimizing complications without losing efficacy.[20] In the present study, no serious perilesional edemas were found.

Limitations

Several limitations in this study should be addressed. First, this study was an open-label design, and assessments were not performed by independent, blinded raters. This may have resulted in a bias in favour of improved symptoms for both the patients and the raters. In addition, open, uncontrolled psychosurgery studies tend to show inflated effect sizes. Lopes and colleagues[35] reported a response rate of 60% (3/5) after 48 months following gamma capsulotomy in their open, uncontrolled pilot study,but in their subsequent double-blind, placebo-controlled, randomized clinical trial, the response rate was 25% at 12 months.[24] Therefore, randomized controlled trials should follow this study to validate the effects of MRgFUS on OCD.

Second, we did not use systematic assessment tools to evaluate psychiatric adverse events, such as mood instability or personality changes, which have been reported in previous deep brain stimulation or ablative intervention studies.[20,21] Although the patients were evaluated by experienced psychiatrists using mental status examinations and unstructured psychiatric interviews at each visit, we cannot rule out the possibility that subtle psychiatric adverse effects were overlooked. Further studies using formal systematic assessments of psychiatric or behavioural changes, such as personality, mania/hypomania, impulsivity, alcohol consumption and more, are warranted.

Third, neuropsychological evaluations were conducted using the same versions in each assessment. It is possible that learning effects could have affected the results, although the intervals between the assessments were not short (6 or 12 months).

Fourth, no patients received regular formal cognitive behavioural therapy sessions after surgery, although they were encouraged at each follow-up visit to continue with the ERP they learned before surgery. Patients 1, 3, 6, 9 and 10 practised ERP continuously after surgery and were able to stand the procedure much better than before. In turn, their obsessions and especially compulsions decreased further. Patients 4, 7 and 8 practised ERP irregularly, but also were able to stand the procedure better than before. Patients 2, 5 and 11 could not stand ERP and seldom practised it.

Fifth, no patients in this study had used higher doses of clomipramine, because they had used it as an augmentation to selective serotonin reuptake inhibitors. Although we ensured that all participants were treatment-refractory, because they did not respond to more than 2 selective serotonin reuptake inhibitors at maximum tolerable doses and a submaximal dose of clomipramine, we could not rule out the possibility of some patients responding to a higher maximal dose of clomipramine.

Finally, functional neuroimaging studies, such as PET or fMRI, to elucidate underlying neural mechanisms for the effects of MRgFUS on obsessive–compulsive, depressive and anxiety symptoms were not included in this study. Further studies using functional neuroimaging are needed.

Conclusion

The results of this study indicate that bilateral thermal lesioning of the ALIC with MRgFUS may be an effective and safe approach for improving obsessive–compulsive, depressive and anxiety symptoms in patients with treatment-refractory OCD. The side effects of MRgFUS capsulotomy seem to be mild and transient. In addition, it may not negatively affect neuropsychological function. However, the small sample size and 2-year follow-up period of this study were not enough, especially to detect adverse events. Larger randomized controlled trials with sham controls and long-term follow-up are needed to validate these promising results.

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