Anterior thalamic deep brain stimulation in epilepsy patients refractory to vagus nerve stimulation: A single center observational study

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ABSTRACT

Anterior thalamic deep brain stimulation (DBS) is a palliative treatment that may be considered in patients with drug resistant epilepsy (DRE) that fail treatment with vagus nerve stimulation (VNS). Combining VNS and DBS treatment is a therapeutic approach rarely reported. This single center observational study aims to describe response to DBS treatment in 11 epilepsy patients resistant to medications and VNS. Patients either had inactivated VNS (DBS only) or were treated with simultaneous DBS and VNS (DBS-VNS). Focal impaired awareness (FIA) and most disabling seizure rates were examined pre-DBS implantation, 3 months following implantation, and last follow up. Overall, a decrease in FIA (47.0 ± 30.7%, p = 0.02) and most disabling seizure rate (54.8 ± 34.2%, p = 0.03) was seen at last follow-up (average follow-up 28.5 ± 13.5 months). Eight of 11 patients were DBS responders (most disabling seizure rate reduction above 50%). No difference in seizure control was found between seven DBS only and four DBS-VNS patients. Our results argue that patients who have failed antiseizure medication and VNS therapies, could benefit from better seizure control if treated with adjunctive DBS. Larger prospective studies are needed to assess the efficacy and safety of combined neurostimulation treatments in DRE.

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1. Introduction

Nearly 30% of patients with epilepsy are resistant to antiseizure medications (ASMs) and suffer from drug resistant epilepsy (DRE) [1]. Surgical resection of the epileptic tissue is the most efficacious therapy for DRE, yet it requires a well-defined seizure onset zone that resides in a safely resectable brain region [2]. Amongst DRE patients undergoing pre-surgical evaluation, over 50% are eventually found not suitable for resective treatment [3]. These patients could benefit from palliative neuromodulatory treatments such as vagus nerve stimulation (VNS) or deep brain stimulation (DBS) of the anterior thalamic nuclei.

VNS treatment has been approved by regulatory agencies for over two decades with ample data supporting its clinical efficacy that increases with time, leading to long-term ≥50% seizure frequency reduction in 45–65% of patients [4]. Yet, it is estimated that a quarter of patients implanted with VNS do not benefit from better seizure control [5]. These VNS resistant patients are more likely to have failed multiple ASMs or surgical treatments [6–8]. For this highly resistant patient group, a different method of neurostimulation such as DBS could be considered. The question of efficacy of DBS treatment in VNS refractory patients remains open. The pivotal Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial included 110 patients implanted with DBS and required that VNS was removed prior to study inclusion. A 60% seizure rate reduction after five years of treatment was found regardless of whether patients had been previously treated with VNS, suggesting that DBS was effective in VNS refractory patients [9]. This conclusion has also been supported by smaller reports [10,11], most recently in a study that compared 12 patients with concomitant DBS and VNS, 12 patients with DBS and prior VNS use, and 9 patients treated by DBS with no history of VNS use, reporting similar efficacy of DBS treatment in all patient groups. This study, also reported, for the first time, that VNS and DBS may effectively function simultaneously [11]. On the other hand, a smaller study including 11 DRE patients with previous VNS treatment concluded that poor response to VNS is correlated with poor response to DBS treatment [12]. These contradictory data regarding the efficacy of DBS in VNS refractory patients, as well as the invasiveness of DBS treatment, might contribute to
under-utilization of DBS in DRE patients resistant to VNS. Furthermore, the question of whether simultaneous treatment of VNS and DBS is safe and whether it provides additional benefit compared to either treatment delivered alone, has been rarely and only recently reported. In this study, we aimed to describe the response to DBS treatment in patients resistant to medical and VNS treatments, and assess feasibility of simultaneous vagus nerve and anterior thalamic stimulation.

2. Materials and methods

In this retrospective observational study, we included all adult DRE patients refractory to VNS that were implanted with DBS at Tel-Aviv Sourasky Medical center (TLVMC), a nation-wide epilepsy surgery referral center in Israel, between January 2017 and January 2021. During the study period, other than DBS implantations, 80 epilepsy resections, 19 laser ablations and 68 VNS implantations were performed. All patients had a minimum of 6 months follow-up post DBS implantation.

Prior to VNS and DBS implantations, all patients underwent an extensive pre-surgical evaluation by a multi-disciplinary epilepsy team, consisting of neurologists, neurosurgeons, neuropsychologists and neuroimaging specialists. Patients who were found to be poor candidates for resective treatment, or have failed prior surgery, were offered VNS implantation. Patients that were VNS resistant (had <25 \% reduction in seizure rates compared to pre-VNS baseline, after a minimum of 18 months), were offered DBS therapy. Despite the lack of data supporting an additional benefit from combined VNS and DBS treatment, patients that have demonstrated any previous positive response to VNS (yet had <25 \% reduction in seizures) were encouraged to leave the VNS activated, yet this was left to patients’ preference. Patients treated solely with DBS were defined as the DBS only group, whereas patients that had simultaneous DBS and VNS treatments were defined as the DBS-VNS group.

We reviewed all patient charts and paper seizure diaries and conducted phone interviews with all patients and/or caregivers. All patients were treated by the same epileptologist prior to and after DBS implantation. For each patient, the frequency of focal impaired awareness seizures (FIAS), focal to bilateral tonic-clonic seizures (FBTCS) and atonic seizures leading to falls were collected at 3 months pre-DBS implantation baseline, 3 months post implantation and at last follow up. In patients with multiple seizure types, FBTCS and atonic seizures were considered the most disabling seizures, and were therefore considered in the analysis to determine DBS response, defined as over 50 \% reduction in most disabling seizure rate compared to pre-implantation baseline. In addition, we examined the acute post-operative complications, chronic adverse effects of therapy, number of post-implantation hospitalizations, and changes in ASMs and in stimulation parameters.

Previous VNS implantation (Aspire SR 106; Livanova Inc, Houston, Texas) were performed according to standard surgical procedure by applying helical electrodes around the left vagus nerve connected to an implantable pulse generator placed subcutaneously in the left upper chest wall [13]. DBS (ActivaTM PC model 3389; Medtronic Inc, Minneapolis, Minnesota) electrodes were stereotactically implanted under general anesthesia in the anterior thalamic nuclei bilaterally through trans- or extra-ventricular trajectories [14], and were connected to an internal pulse generator implanted subcutaneously in the right upper chest. Electrode contacts localization within the anterior thalamic nuclei were confirmed by post-op MRI. The active stimulating leads were selected according to anatomical localization in the inferior aspect of the anterior thalamic nuclei as well as impedance measurements between neighboring leads, with a minimum value of 600 \Omega set to ensure that contacts avoided CSF or the superficial area of the ATN [15]. DBS treatment was initiated a month after implantation, with initial stimulation parameters set to 5 V stimulation potential, 90 \mu s pulse width, 145 Hz, “ON” one minute and “OFF” five minutes. Patients were treated with high stimulation according to treatment protocol in the SANTE study, as well as evidence that high frequency stimulation results in greater activation in limbic networks compared to low frequency stimulation [16,17]. The impedances of the stimulating electrodes were measured immediately following implantation and in all outpatient visits and were within normal range in all patients. In all DBS-VNS patients, VNS was turned off prior to surgery and turned back on in the first outpatient clinical visit one month afterwards, with current being gradually titrated to the preoperative level. During follow-up period, changes in ASMs and stimulation parameters of all patients were performed by the same treating neurologist (FF), according to ongoing clinical assessment.

3. Results

3.1. Patient characteristics

A total of 11 patients (five males, age at DBS implantation 31.2 ± 8.6 years, seizure duration of 21.4 ± 7.8 years) were included in the study, with an average follow up of 28.7 ± 13.2 months (range 6–46 months). Patients have been previously treated with 8.5 ± 2.6 (4–12) ASMs, three patients underwent prior surgical resections. Demographic and clinical patient characteristics are summarized in Table 1. Seven patients were in the DBS only group (two males, age at DBS implantation 32.6 ± 8.1 years) and four were in the DBS-VNS group (three males, age at DBS implantation 29.0 ± 10.5 years). Among DBS only patients, VNS was turned off immediately prior to DBS surgery in four patients due to non-response to treatment, and in three patients VNS was deactivated one, two and three years prior to DBS implantation. There were no significant differences between DBS only and DBS-VNS patient groups with regard to demographic or clinical parameters including gender, age at implantation, epilepsy duration, number of ASMs, or follow up duration.

3.2. Overall efficacy of DBS treatment

Clinical outcomes and adverse effects related to treatment are presented in Table 2 and Fig. 1A. Two patients were DBS responders at three months, and eight patients were responders at last follow-up. Average FIAS rate reduction was 15.6 ± 36.3 \%(range 0 \% to 86 \%, p = .11) at three months and 47.0 ± 30.7 \%(range 0 \% to 93 \%, p = .02) at last follow up. Average most disabling seizure rate reduction was 18.3 ± 31.0 \%(range 0 \% to 85 \%, p = .3) at three months, and 54.8 ± 34.2 \%(0 to 100 \%, p = .03) at last follow up. Poor
responders had bilateral and extensive complex malformations of cortical development: patients #5 and #6 had subcortical band heterotopia, and patient #7 had bilateral perisylvian polymicrogyria.

3.3. DBS only and DBS-VNS subgroup analysis

In both the DBS only and DBS-VNS groups, one patient was a responder at three months (1 of 7 DBS only and 1 of 4 DBS-VNS patients, \( p = 0.7 \)) and four were DBS responders at last follow-up (4 of 7 DBS only compared to 4 of 4 DBS-VNS patients, \( p = 0.1 \)). There were no statistically significant differences in FIAS seizure reduction at three months (9.4 ± 38.5% DBS only compared to 32.8 ± 41.4% DBS-VNS seizure reduction, \( p = 0.5 \)), nor at last follow up (50.0 ± 40.1% DBS only compared to 48.8 ± 30.1% DBS-VNS, \( p = 0.9 \)). Likewise, no differences were found between the groups in most disabling seizure rate reductions at three months (16.6 ± 26.9% DBS only compared to 21.3 ± 36.8% DBS-VNS, \( p = 1 \)) or at last follow up (44.7 ± 38.9% DBS only compared to 72.5 ± 9.1% DBS-VNS, \( p = 0.2 \)).

Overall, the average change in DBS stimulation voltage during the follow-up period was 0.9 ± 0.9 mV (0.9 ± 0.9 DBS only compared to 0.9 ± 0.9 DBS-VNS, \( p = 0.8 \)). There were no significant differences between the groups regarding ASM changes and number of hospitalizations during the study period.

3.2. Adverse events

In the DBS only patient group, two patients had atonic seizures with traumatic injuries: patient #2 experienced a right frontal intracerebral parenchymal and subarachnoid hemorrhages at three months post implantation and required prolonged rehabilitation. Patient #1 suffered vertebral and rib fracture 12 months post implantation, and at 42 months suffered head trauma with damage to extra-cranial DBS lead necessitating electrodes removal and re-implantation. Additionally, two patients reported subjective memory deterioration, and two patients reported depressive symptoms during follow-up. In the DBS-VNS group, two patients had acute post-operative respiratory complications requiring intensive care unit (ICU) admission. Patient #8 had post-surgical pulmonary edema, and patient #9 experienced post-surgical lung atelectasis and bacterial pneumonia, requiring antibiotic treatment. Both patients required short term ventilatory assistance and subsequent rehabilitation treatment. Following treatment, both patients returned to their previous clinical baseline. DBS-VNS patient #8 experienced DBS battery depletion at 21 months post implantation, an event that triggered gradual worsening of seizure control followed by status epilepticus, requiring ICU admittance and urgent DBS neurostimulator replacement, after which the patient regained previous seizure control [18].

4. Discussion

In this observational study we describe a single center experience with DBS treatment in a cohort of DRE patients that have failed VNS treatment. We report an overall seizure rate reduction of approximately 50% at last follow up, both in FIAS as well as in most disabling seizures. Eight of 11 patients were DBS treatment responders. In light of the conflicting reports regarding DBS efficacy in VNS non-responders [9–12,16], our findings provide additional support for the use of DBS treatment in VNS refractory patients.

The potential therapeutic benefit from DBS in patients resistant to VNS could stem from vagal and anterior thalamic stimulations modulating different brain networks and therefore each exerting anti-epileptic effect in some patients but not in others. The precise mechanisms by which VNS and DBS therapies contribute to seizure control is complex and not fully understood. VNS neurostimulation is likely mediated via brainstem nuclei such as the nucleus coeruleus and dorsal raphe nuclei, which affect the noradrenergic and serotonergic tones in the thalami, prefrontal cortex, and limbic structures, thus influencing seizure susceptibility [19–21]. On the other hand, DBS of the anterior thalamic nuclei affects a key node in the Papez circuit, which has reciprocal connections with the hip-

Table 1

| Patient number | Age at DBS implantation (years) / Gender | Epilepsy duration at DBS implantation (years) | Epileptic syndrome (lesion) | Current treatment / Number of previous failed ASMs | Prior response to VNS treatment |
|----------------|----------------------------------------|---------------------------------------------|-----------------------------|-----------------------------------------------|--------------------------------|
| 1 | 34 / F | 19 | Bilateral fronto-central epilepsy (right temporal lobe polymicrogyria and cortical dysplasia) | CBZ, LTG, LCS, CLB | Non responder |
| 2 | 28 / M | 8 | Frontal epilepsy (unknown) | CBZ, TPM, LCS, BRV, CLB, Cannabis Oil | Non responder |
| 3 | 36 / M | 31 | Left fronto-temporal epilepsy (s/p left frontal resection revealing cortical gliosis) | LEC, LCS, CLB, Cannabis Oil | Non responder |
| 4 | 46 / F | 21 | Left temporal epilepsy (s/p left temporal lobectomy revealing left mesial temporal sclerosis) | OXC, CLB | Non responder |
| 5 | 34 / F | 29 | Bilateral frontal epilepsy (bilateral subcortical band heterotopia) | CBZ, TPM, CNZ | Non responder |
| 6 | 17 / F | 10 | Lennox Gastaut, Double cortex syndrome (complete band heterotopia) | LCS, PHB | Non responder |
| 7 | 33 / F | 24 | Bilateral perisylvian polymicrogyria | OXC, VPA, CLB | Non responder |
| 8 | 18 / M | 17 | Frontal epilepsy (bilateral frontal ependymoma due to peri-natal stroke) | CBZ, VPA, LEV, AZM | Poor responder |
| 9 | 38 / F | 32 | Bilateral fronto-temporal epilepsy (unknown) | CBZ, PHB, LEV, CLB | Poor responder |
| 10 | 38 / M | 26 | Right temporal epilepsy (right schizencephaly, right extensive fronto-parietal polymicrogyria, left frontal polymicrogyria and PNH) | LEC, OXC, LCS, CBZ, AZM | Poor responder |
| 11 | 22 / M | 19 | Right centro-parietal epilepsy (s/p right parietal resection revealing cortical dysplasia) | OXC, VPA, LTG, LCS, PER | Poor responder |

PNH – periventricular nodular heterotopia; ASM – anti seizure medication; CBZ – carbamazepine; LCS- lacosamide; CLB - clobazam; LTG – lamotrigine; TPM – topiramate; LEV – levetiracetam; BRV – brivaracetam; VPA – valproic acid; PHB – phenobarbital; OXC – oxcarbazepine; PER – perampanel; AZM – acetazolamide.
| Patient number | Treatment | Follow-up post DBS implantation (months) | Post-DBS implantation adverse events | Seizure type (most disabling in bold) | Post DBS implantation - seizures per month | Change in AEDs | Change in parameters |
|----------------|-----------|------------------------------------------|-------------------------------------|--------------------------------------|---------------------------------------------|---------------|----------------------|
| 1              | DBS only  | 42                                       | Fall with vertebral and rib fracture 12 months post implantation, fall with damage to electrodes require DBS explantation at 42 months. Memory disturbances. | AS, FIAS | 60 AS / 300 FIAS 60 AS / 300 FIAS 60 AS / 300 FIAS 60 AS / 300 FIAS 60 AS / 300 FIAS 21 AS / 30 FIAS 10 AS / 20 FIAS 10 AS / 20 FIAS 0 AS / 0 FIAS 0 AS / 0 FIAS 84 AS / 93 36 months | Add VPA + TPM, increase Cannabis | 6.5 V, 90 µs, 145 Hz, 1 m/3m |
| 2              | DBS only  | 44                                       | Atonic seizure resulting in fall and intracerebral bleeding 3 months post implantation. Memory disturbances, depression. | AS, FIAS | 30 AS / 50 FIAS 30 AS / 50 FIAS 30 AS / 50 FIAS 0 AS / 0 PS 0 AS / 20 FIAS 20 AS / 20 FIAS 20 AS / 20 FIAS 0 AS / 0 FIAS 0 AS / 0 FIAS 83 AS / 60 FIAS | 7.0 V, 90 µs, Add BRV, increase LCS | 145 Hz, 1 m/5m |
| 3              | DBS only  | 40                                       | None | FIAS | 40 FIAS 10 FIAS 12 FIAS 10 FIAS 4 FIAS 7 FIAS 10 FIAS 70 FIAS | 6.5 V, 90 µs, None | 145 Hz, 1 m/5m |
| 4              | DBS only  | 24                                       | None | FIAS | 28 FIAS 8 FIAS 15 FIAS 10 FIAS 8 FIAS 8 FIAS | 5.0 V, 90 µs, None | 145 Hz, 1 m/5m |
| 5              | DBS only  | 21                                       | Scalp sensory disturbances at implantation site, depression. | FIAS | 8 FIAS 7 FIAS 12 FIAS 8 FIAS 10 FIAS | 5.5 V, 90 µs, None | 145 Hz, 1 m/5m |
| 6              | DBS only  | 8                                        | None | AS, FIAS | 120 AS / 120 FIAS 120 AS / 120 FIAS 120 AS / 120 FIAS 120 AS / 120 FIAS 120 AS / 120 FIAS | Decrease LCS, switch LEV triggered by DBS battery depletion | 145 Hz, 1 m/5m |
| 7              | DBS only  | 6                                        | None | AS, FIAS | 20 AS / 20 FIAS 20 AS / 20 FIAS 20 AS / 20 FIAS 20 AS / 20 FIAS | 5.5 V, 90 µs, None | 145 Hz, 1 m/5m |
| 8              | DBS-VNS   | 46                                       | Acute post implantation respiratory failure requiring admittance to ICU, convulsive status epilepticus at 22 months triggered by DBS battery depletion | FBTCS, FIAS | 12 FBTCS/120 FIAS 12 FBTCS/120 FIAS 12 FBTCS/120 FIAS 12 FBTCS/120 FIAS | Add VPA, increase LCS, switch LEV to BRV | 145 Hz, 1 m/5m |
| 9              | DBS-VNS   | 33                                       | Acute post implantation respiratory failure requiring admittance to ICU | FIAS | 8 FIAS 8 FIAS 8 FIAS 8 FIAS 4 FIAS 4 FIAS | 5.5 V, 90 µs, Decrease CLB | 145 Hz, 1 m/5m |
| 10             | DBS-VNS   | 24                                       | None | AS, FIAS | 6 AS / 14 FIAS 6 AS / 14 FIAS 1 AS / 2 FIAS 2 AS / 3 FIAS 4 AS / 5 FIAS 1 AS / 5 FIAS | Decrease CNZ and AZM | 5.5 V, 90 µs, Decrease | 145 Hz, 1 m/5m |
| 11             | DBS-VNS   | 28                                       | None | FBTCS, FIAS | 8 FBTCS / 45 FIAS 10 FBTCS / 35 FIAS 8 FBTCS / 27 FIAS 4 FBTCS / 31 FIAS 5 FBTCS / 54 FIAS | Decrease PER | 5.5 V, 90 µs, Decrease | 145 Hz, 1 m/5m |

DBS only- patients treated with DBS only; DBS-VNS – patients treated with combined DBS and VNS treatment; FIAS – focal impaired awareness seizure; AS – atonic seizures; FBTCS – focal to bilateral tonic clonic seizures. Most disabling seizures are marked in bold; VPA – valproic acid; PER – perampanel; AZM – acetazolamide; CLB- clobazam; LCS- lacosamide; LEV – levetiracetam; BRV – brivaracetam; TPM – topiramate.
...pocampus and other cortical regions. Therefore, it is possible that the therapeutic effects of vagal and thalamic stimulations are exerted on different functional and epileptic networks with different anatomical distribution [22–24]. In our small cohort, patients that were non-responders had widespread and bilateral malformations of cortical development, raising the question if extensive developmental epileptic lesions are less likely to respond to DBS than other etiologies. Further and larger studies of clinical and laboratory biomarkers are needed to guide the clinician in tailoring a personalized neuromodulatory treatment to the specific epilepsy syndromes and etiologies.

It is yet unknown if simultaneous application of two neuromodulatory treatments with differing mechanisms of action can translate to better therapeutic results for patients. A very recent study that explored this question, reported equivalent seizure reduction rates in 12 patients with simultaneous VNS and DBS stimulation, compared to 21 patients treated by DBS only, either with or without a history of prior VNS treatment [11]. An additional recent study demonstrated feasibility of other dual stimulation approaches, namely VNS combined with either RNS or centromedian thalamic nucleus stimulation [25]. Although these studies are highly informative, additional reports are needed to assist in clinical decision making in this heterogeneous hard-to-treat patient population. Our study adds on to existing literature and provides additional support that dual stimulation approach is possible, however was underpowered to compare efficacy of dual vs DBS only stimulation.

Post-operative respiratory complications are rare in DBS implantation in epilepsy, and have been reported in only 0.4 % of patients treated with DBS for movement disorders [26,27]. In our cohort, two of four patients with DBS-VNS experienced postoperative respiratory complications requiring ICU admittance. However, considering that VNS was turned off a month prior to surgery, we attribute these complications to other comorbidities and lower baseline functional status, rather than to a direct effect of vagal stimulation, previously reported to increase perioperative risk for apnea and aspiration [28,29,30]. Nevertheless, clinicians should be aware of possible respiratory adverse effects, and future studies should look into respiratory complications in patients undergoing dual neuromodulatory treatment.

Our study has a few limitations: first, it included a small number of patients with clinically heterogeneous epileptic disorders and etiologies. Yet, the demonstration of a beneficial effect in the majority of this highly refractory patient population supports the validity of our findings. Second, the retrospective nature of the study could have biased the results, however, all patients were treated and seen regularly by the same neurologist, and records were examined and cross-checked by phone interviews, all of which aimed to reduce reporting bias. Third, in six patients ASMs were changed during the study period, possibly affecting seizure outcome. However, in three patients ASM doses were reduced due to better seizure control, and the remaining three patients were highly drug resistant, rendering it unlikely that dose increases could have significantly contributed to patient outcome. Lastly, follow-up periods for patients were variable, and although average follow up was 28 months, some of the patients had a follow-up of less than a year. Considering that the efficacy of neurostimulation is known to increase with time, longer follow-up could have resulted in even more favorable patient outcomes [9].

5. Conclusion

In our observational study, an additional beneficial effect of DBS treatment on seizure control in DRE patients refractory to previous VNS therapy was seen. Furthermore, we confirm the feasibility of a dual stimulation approach. Larger prospective studies are needed to assess the efficacy of combined neurostimulation treatments in controlling seizures and addressing side-effects and co-morbidities, in order to develop a more personalized approach to treating DRE patients.

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Author contributions

Conception and design: all authors. Acquisition of data: all authors. Drafting the article: Miron and Fahoum. Critically revising the article: Miron and Fahoum. Reviewed submitted version of the manuscript: all authors.
Ethics statement

The study was approved by the ethics committee of Tel-Aviv Sourasky Medical center.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Strauss has received speaker honoraria from Medtronic and Boston Scientific, and consultancy fees from INOMED on subjects unrelated to this manuscript. Dr. Fahoum has served on scientific advisory boards and received speaker honoraria from LivaNova, as well as speaker honoraria from Medtronic. Other authors have no conflicts of interest to declare.

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