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Vagus nerve stimulation with tachycardia detection provides additional seizure reduction compared to traditional vagus nerve stimulation

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ABSTRACT

Purpose: This study investigates the clinical and cost effectiveness of switching from traditional vagus nerve stimulation (VNS) to responsive VNS (rVNS), which has an additional ictal tachycardia detection and stimulation (AutoStim) mode.
Methods: Retrospective chart review was used to collect data from patients with medically refractory epilepsy who underwent generator replacements. Patients with confounding factors such as medication changes were excluded. Vagus nerve stimulation parameters, seizure frequency, and healthcare costs were collected for the 1-year period following generator replacement with the rVNS device.
Results: Documented seizure frequency was available for twenty-five patients. After implant with rVNS, 28% of patients had an additional ≥50% seizure reduction. There was a significant decrease in the average monthly seizure count ($p = 0.039$). In patients who were not already free of disabling seizures ($n = 17$), 41.2% had ≥50% additional seizure reduction. There was no difference in healthcare costs during the 1-year follow-up after the rVNS implant compared with one year prior.
Conclusions: Ictal tachycardia detection and stimulation provided a significant clinical benefit in patients who were not free of disabling seizures with treatment from traditional VNS. There was no additional increase in healthcare costs during the first year after device replacement.

1. Introduction

Vagus nerve stimulation (VNS) therapy is one of the few Food and Drug Administration (FDA)-approved neurostimulation treatment options for medically refractory epilepsy. Vagus nerve stimulation therapy has been shown to be safe, with half to two-thirds of patients achieving >50% seizure reduction [1–5] and is associated with improvement in various quality of life metrics as subjectively rated by physicians [6]. Long-term follow-up of patients treated with VNS therapy has also shown an age-adjusted decrease in Sudden unexpected death in epilepsy (SUDEP) risk [7]. The new responsive VNS (rVNS) devices have a closed loop feature, AutoStim, which can detect ictal tachycardia and use this sudden increase in heart rate as a surrogate marker for seizure detection to deliver an additional preset stimulation. While the rVNS device is also well-tolerated and associated with seizure reduction from baseline [8,9], there are limited studies that have evaluated whether it provides any additional clinical benefit. Additional reductions in seizure frequency have been reported in 36% to 71% of patients [10,11] treated with VNS who were reimplanted with the rVNS device, highlighting the need for further studies.

Traditional VNS therapy has demonstrated overall cost savings in patients by decreasing clinical resource utilization and epilepsy-related clinical events, resulting in a net cost savings after 1.5 years [12]. In pediatric populations, VNS has shown total healthcare cost reductions, in part due to reduction of major clinical events (such as status epilepticus) and improvement in overall quality of life measures [13]. The cost effectiveness of the newer rVNS device compared with traditional VNS therapy is not known.

The aim of this study was to evaluate the clinical and cost effectiveness of rVNS compared with traditional VNS therapy.

2. Methods

2.1. Data collection

Retrospective chart review and analysis was conducted with approval of the Institutional Review Board at the University of Nebraska

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Medical Center. Data were collected using the EPIC® electronic medical record system. Patients who underwent VNS therapy generator replacement (elective or patients who required battery replacement) with the rVNS (VNS model 106 or AspireSR) between 7/2015 and 11/2016 and had at least 1 year of follow-up were eligible for inclusion in the study. Clinical data, average monthly frequency of disabling seizures (seizures with impaired awareness/complex partial seizures, convulsions), VNS therapy parameters, number of emergency room (ER) visits, hospitalizations, intensive care unit (ICU) admissions, and epilepsy clinic visits pertaining to seizure or seizure-related complications were obtained from chart review. Telephone encounters made by the epilepsy case managers and epilepsy clinic nurses were identified. Data were collected in 3-month blocks for the period between 12 months prior to VNS therapy replacement with rVNS and 12 months after the implantation date to give quarterly data.

Of the 43 patients that met the inclusion criteria (Fig. 1), those with a prior explanted VNS therapy generator (n = 4) or a VNS therapy generator with a nonactive battery of unknown duration (n = 2) were excluded. Patients with any new antiepileptic drug (n = 7) added or a second neurostimulator (RNS system) placed (n = 1) during the 1-year follow-up period were also excluded. Review of rVNS therapy parameters showed that 3 patients did not have the AutoStim feature activated; two of these patients had a duty cycle of 58%. After excluding patients with these possible confounders, a total of 26 patients were included in the study.

2.2. Data analysis

The comparison of average monthly seizure activity before and after rVNS device implant was done using the Wilcoxon signed rank test. Because of the highly skewed nature of the data and the relatively small sample size, a nonparametric test was more appropriate than a paired t-test. Regression analyses were performed using SAS 9.4; plots and Wilcoxon tests were performed using R version 2.2.1. A Poisson generalized estimating equation was used to compare the rate of usage by quarter of the emergency room, telephone consult service, clinic visits, hospital, and ICU between the year before and after rVNS implant. A random subject effect was used to account for the correlation between multiple observations in the same subject, and the interaction term, between period and quarter was used to test if the effect of time was statistically distinguishable between the pre- and post-rVNS device periods.

3. Results

3.1. Patient demographics and VNS therapy parameters

Patient characteristics are shown in Table 1. The average age of patients in our cohort was 37 ± 11.9 years. Of the patients, 42% were male and 58% were female. All patients were non-VNS therapy naïve and had at least one year of prior VNS therapy (average was 4.6 ± 3.4 years, range: 1–12 years). Most patients had focal epilepsy (73%).

Table 1
Patient demographic and VNS parameters.

Age[a]	37.1 ± 11.85 years
Gender	Male = 11, female = 15
Duration of prior VNS therapy [a]	4.6 ± 3.4 years
Type of epilepsy	Focal = 19, generalized = 7
Pre-rVNS output current [b]	1.6 mA (1–2.25 mA)
Post-rVNS output current [b]	1.6 mA (1–2.25 mA)
Pre-rVNS duty cycle [b]	25% (10–58%)
Post-rVNS duty cycle [b]	16% (10–51%)
AutoStim threshold (n = 20) [b]	40% (20–70%)

[a] Expressed in mean ± std. dev.
[b] VNS settings are expressed as median and range.

The output current prior to the rVNS device implant ranged from 1 to 2.25 mA, and the duty cycle ranged from 10% to 58%. One year after the rVNS device implant, 65% of patients had no changes made to their output current. Among the patients where changes in currents were made, 2 patients had their currents increased (by 0.25 mA and 0.5 mA, respectively) and 7 had their output currents decreased (none by greater than 0.75 mA). One year after the rVNS device implant, 50% of patients had modifications in their duty cycles. Four patients had their duty cycle increased, and nine had their duty cycles decreased. Of these, only one patient had more than an 11% change in their duty cycle. For that one patient, the duty cycle was lowered from 58% to 15% after the rVNS device implant. The AutoStim parameter was active in all included patients. The AutoStim threshold was only documented in 20 patients. The average AutoStim threshold was 40% (range: 20%–70%).

3.2. Clinical comparison of traditional VNS with rVNS

Twenty-six patients were included in the study. None of these patients had any change in antiepileptic medications during the 1-year follow-up period. One patient did not have seizure frequency documented. In the remaining 25 patients, the average monthly seizure frequency was variable. Overall, the mean seizure frequency was reduced from 6.29 seizures/month (range: 0–30) prior to rVNS implant to 3.78 seizures/month (range: from 0 to 30) following rVNS implant. Further clinical details including epilepsy type and average seizure frequency are available in Supplemental data Table 1.

We used the McHugh scale [14] to classify average monthly seizure reduction, 1 year after the rVNS device implant. Sixteen percent of patients were Class I (had additional 80–100% reduction), 12% were Class II (additional 50–79% reduction), 8% were Class III (additional <50% reduction), and 64% had no additional reduction in seizures. Data on seizure reduction from magnet use only (McHugh Class IV) were not documented.

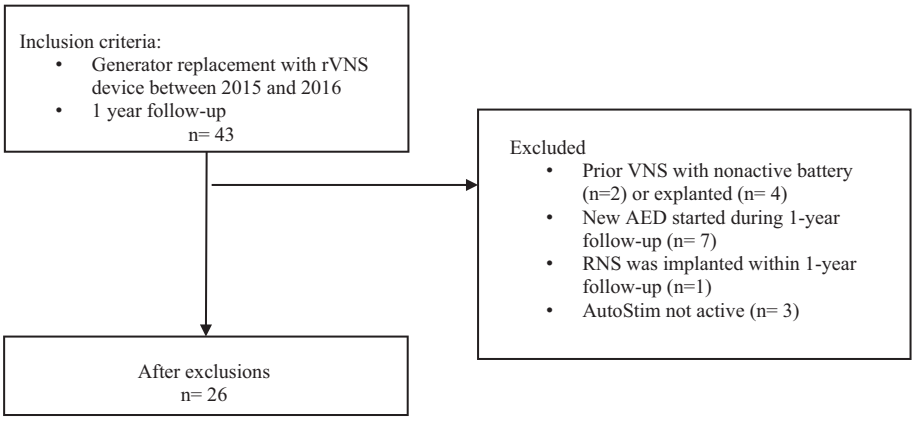

Fig. 1. Study protocol overview.

Of the patients who had no additional seizure benefit, half of them were already seizure-free prior to the rVNS device implant. We further analyzed the cohort of patients who were not already seizure-free (n = 17). Of these patients, 47.1% had no additional improvement in seizure frequency, 11.8% had less than 50% additional reduction in seizure frequency, 17.7% had 50–79% additional reduction in seizure frequency, and 23.5% had additional 80–100% reduction in seizure frequency. Overall, 41.2% had a >50% additional reduction in seizure frequency (Fig. 2).

We compared the pre- with post-rVNS device average monthly seizure activity in each patient using the Wilcoxon signed rank test. This was statistically significant at a p-value of 0.0039.

3.3. Cost effectiveness comparison of traditional VNS with rVNS

Healthcare cost was estimated based on the number of visits for ER, clinic, hospital, and ICU admissions and the Medicare reimbursement rates for each type of visit. Emergency room cost, clinic cost, and hospital costs were estimated based on a rate of $525, $673.5, and $6200 per visit, respectively. Intensive care unit cost was estimated based on a rate of $11,500 per visit. When estimating costs for telephone support provided to these patients, a cost of $4 per phone call was used based on an annual nurse salary of $100,000 and an average call length of 5 min.

Regardless of the outcome and period considered, the effect of time was not statistically different from 0 (p-values all >0.05). Further, there were no detectable differences between the effect of time in the prereplacement period compared with the postreplacement period. As only a single subject utilized the ICU, the ICU outcome could not be modeled.

As shown in Supplemental Data Table 2, the Wilcoxon test results suggested that costs related to phone consultation with the patients were lower in the postreplacement period than in the prereplacement period ($p < 0.01$). However, there were no detectable differences between the ER costs, clinic costs, hospital costs, ICU costs, and total costs in the prereplacement period compared with the postreplacement period.

4. Discussion

4.1. rVNS with AutoStim feature provides additional seizure reduction

In patients who were not already seizure-free with traditional VNS, rVNS with AutoStim was associated with an additional ≥50% seizure reduction in 41.2% of patients. This was directly attributable to the AutoStim feature, as there were no changes in antiepileptic drugs and no significant changes in the output currents and duty cycles before and after rVNS implant (Table 1). Previous studies have reported 71% of patients with a >50% reduction [11], where they evaluated a longer follow-up period (21 months) and noted that concurrent medication changes in the follow-up period were not considered. A more recent study reports that 36% of the patients who had a low response to traditional VNS models achieved >50% seizure reduction with rVNS [10]. Further studies to evaluate whether patients with known ictal tachycardia are more responsive to the AutoStim feature of the rVNS device would be of interest. Our results support the clinical decision that in patients undergoing battery replacement, rVNS devices with the AutoStim feature should be considered.

4.2. rVNS with AutoStim feature does not increase healthcare cost burden

There was no statistically significant difference in the total healthcare cost (hospital, clinic, ER, and telephone support) in the 1-year after implantation with the newer rVNS device. One potential explanation is that the 1-year time period may have been too short to fully evaluate any cost-saving benefits with the rVNS device. Previous studies have reported an overall cost savings in patients after 1.5 years [12].

4.3. Limitations

Our study was based on retrospective data collection and analysis and is limited by patient recall bias and imperfections of documentation in clinic notes. Seizure frequencies were patient or caregiver reported and may be a source of bias. While our sample size was small, one of the strengths of our study was meticulous exclusion of any confounders including effects of antiepileptic drug changes. We also reviewed the VNS parameters to confirm that no large changes in output currents or duty cycles were made in the postimplant period to isolate the effects of the AutoStim feature.

Vagus nerve stimulation therapy is FDA-approved for patients with focal epilepsy, and our cohort was comprised of patients with both focal and generalized epilepsy. Multiple studies have shown that VNS is also effective in patients with generalized epilepsy [15,16]. Our study is, therefore, a representation of the real-world population treated with VNS therapy.

5. Conclusion

In this single center retrospective study, we attempted to evaluate whether there was any additional benefit with the AutoStim feature in non-VNS therapy naïve patients. We show that in patients who were not already free of disabling seizures with prior VNS therapy, 41.2% of patients had an additional ≥50% reduction of seizure frequency in the 1-year following generator replacement with the rVNS device with AutoStim feature. There was no increase in total healthcare costs in

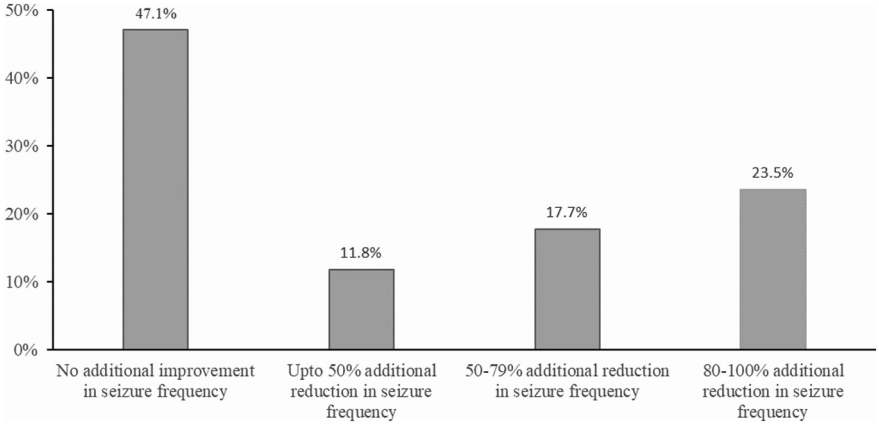

Fig. 2. Additional reduction in seizure frequency following replacement with rVNS in patients who were not seizure-free (n = 17); 41.2% of patients had an additional ≥50% reduction in seizure frequency.

the follow-up period. Overall, this study supports the clinical decision of considering a rVNS therapy device that includes the AutoStim feature in patients who require VNS battery/generator replacement.

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Author contributions

P.D. and D.M. contributed to the study concept and design. K.G., K.S. and P.D. contributed to acquisition of data. P.D., K.G., C.W., H.W. and D. M. contributed to analysis and interpretation of the data. P.D., K.G. K.S. contributed to drafting the manuscript.

Declaration of competing interest

Deepak Madhavan is a consultant for Neuropace and a speaker for Greenwich Pharmaceuticals. The remaining authors have no conflicts of interest.

K.G.'s current address is Cleveland Clinic; K. S's current address is Thomas Jefferson University.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107280.

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