Seizure: European Journal of Epilepsy 94 (2022) 74–81

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Comparison of traditional and closed loop vagus nerve stimulation for treatment of pediatric drug-resistant epilepsy: A propensity-matched retrospective cohort study

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ARTICLE INFO

Keywords:
VNS
Refractory
Child
Seizure
Neurosurgery

ABSTRACT

Objective: For epilepsy patients with drug-resistant, unresectable epilepsy, vagus nerve stimulation (VNS) is an option for seizure control. Approximately 40–70% of patients will achieve ≥50% seizure reduction with VNS. New closed loop VNS models detect ictal tachycardia and responsively stimulate the vagus nerve. The effectiveness of closed loop VNS compared to traditional VNS for pediatric epilepsy is unknown.

Methods: An 11-year retrospective electronic medical record review at Children's Hospital of Pittsburgh was performed. Patients with drug-resistant epilepsy who underwent VNS implantation were included. Patients were divided into groups based on VNS model: *traditional* versus *closed loop*. Those who transitioned from traditional to closed loop VNS were excluded. Given potential for selection bias, propensity scores matching was utilized to compare traditional to closed loop VNS patients. Patients with focal versus generalized epilepsy were also separately analyzed. The primary outcome was "VNS response", defined as at least 50% seizure frequency reduction from baseline.

Results: A total of 320 patients were included in this sample. The percentage of matched patients (total $n = 220$: $n = 179$ traditional VNS, $n = 41$ closed loop VNS) who responded to VNS after one year of therapy was 43% for traditional VNS and 39% for closed loop VNS ($p = 0.64$). After two years of therapy, a higher proportion of closed loop VNS patients than traditional VNS patients responded to VNS among all subgroups, though no differences were statistically significant ($p>0.05$). Notably, for those with generalized epilepsy, 73% of closed loop patients responded to VNS compared to only 46% of traditional patients ($p = 0.10$). After two years of VNS therapy, patients were taking approximately the same quantity of antiseizure medications as baseline (change of +0.074 +/- 0.90) with no difference between VNS models ($p = 0.87$).

Significance: Among pediatric patients with drug-resistant epilepsy, closed loop VNS trends towards a higher rate of VNS response after two years of treatment, especially among generalized epilepsy patients. Neither model of VNS allows patients to reduce antiseizure medication quantity after two years.

1. Introduction

In the United States, approximately 0.6% children between the ages of 0 and 17 have active epilepsy [1,2]. Of these patients, 30% will have antiseizure medication (ASM)-resistant epilepsy [3]. For patients with drug-resistant epilepsy and seizure foci which cannot be surgically resected, vagus nerve stimulation (VNS) is a viable palliative option for seizure control [4–8]. Estimates of VNS response among pediatric patients vary, though evidence suggests that 40–70% will achieve ≥50% seizure frequency reduction at two years with VNS [9–11].

The mechanism of action of VNS for epilepsy treatment is not yet fully understood, though it is likely multifactorial. Stimulation of the

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https://doi.org/10.1016/j.seizure.2021.11.016
Received 13 September 2021; Received in revised form 8 November 2021; Accepted 23 November 2021
Available online 29 November 2021
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vagus nerve is primarily thought to: 1) prevent seizure initiation in regions of the brain susceptible to excitability, 2) modulate midbrain and hindbrain structures thereby promoting seizure suppression, and 3) moderate the release of norepinephrine and serotonin (both thought to have antiseizure roles) at the level of the locus coeruleus and raphe nuclei, respectively [12–14]. Traditional VNS models are "open-loop", meaning that they stimulate the vagus nerve in fixed "on/off" cycles. More recently, heart-rate responsive VNS models have been developed. These "closed loop" models contain an algorithm to detect changes in heart rate, effectively serving to both screen for ictal tachycardia and proactively stimulate the vagus nerve if tachycardia develops. In other words, closed loop VNS models selectively stimulate the vagus nerve when seizures are expected to occur.

Recent analyses of closed loop VNS have been promising, albeit limited by small sample sizes [4,15-17]. The effectiveness of closed loop VNS compared to traditional models remains unclear, especially among pediatric patients with epilepsy. To assess the relative clinical effectiveness of closed loop VNS, we performed an 11-year retrospective analysis of pediatric patients who received VNS at UPMC Children's Hospital of Pittsburgh. We assessed the effectiveness of closed loop VNS in reducing seizure frequency when compared to traditional VNS. Given the selectivity of vagus nerve stimulation offered by closed loop models, we hypothesized that closed loop VNS would be more effective than traditional VNS.

2. Methods

A retrospective electronic medical record review of UPMC Children's Hospital of Pittsburgh between January 1st, 2009 and January 1st, 2020 was performed (see Fig. 1). Patients were included if they had drug-resistant epilepsy and underwent implantation of VNS between the ages of 0 and 21. Per the International League Against Epilepsy (ILAE) definition, we defined drug-resistant epilepsy as the "failure of adequate trials of two tolerated, appropriately chosen and used ASMs schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[18] Patients' primary neurologists and/or neurosurgeons determined whether his/her epilepsy was "drug-resistant" per these guidelines and whether they were suitable candidates for VNS. At our institution, two models of closed loop VNS are utilized: the SenTiva™ (model 1000) and the AspireSR® (model 106). Therefore, patients whose first VNS was a model 1000 or model 106 were included in the closed loop VNS group and patients with models 101–105 (All Pulse™ Model 102, Pulse Duo™ Model 102R, Demipulse® Model 103, DemiPulse Duo™ Model 104, and AspireHC® Model 105) were included in the traditional VNS group. This study was approved by the University of Pittsburgh Institutional Review Board.

The primary outcome for this analysis was the proportion of patients achieving at least 50% seizure frequency reduction. Complication rates and changes in quantity of ASMs were secondary outcomes.

2.1. Measures

Patients were categorized as having metabolic, structural, genetic, or uncategorized etiologies of epilepsy [19]. Patients were considered to have a metabolic etiology of epilepsy if they had an enzyme deficiency leading to epilepsy, mitochondrial disorder, peroxisomal disorder, glucose transporter deficiency, or cerebral folate deficiency [20]. Those with structural etiologies of epilepsy had abnormalities on MRI in the absence of a known genetic condition, including trauma/injury, lissencephaly, and static encephalopathy. Patients were considered to have genetic etiologies of epilepsy if they had a known genetic condition confirmed by genetic analysis or strong family history in the absence of genetic testing, with the most common genetic causes in our sample being Aicardi syndrome, tuberous sclerosis, and neurofibromatosis. All patients with epilepsy that did not fit into these etiology categories had uncategorized epilepsy.

The duration of a patient's epilepsy before VNS implantation was considered to be the time from their initial diagnosis until their first VNS surgery. Patients' epilepsy was characterized based on focality of epilepsy using pre-VNS electroencephalogram (EEG). Patients with focal discharges on pre-VNS EEG were considered to have focal epilepsy, while patients with generalized discharges or numerous multifocal discharges on pre-VNS EEG were considered to have generalized epilepsy. Patients with focal discharges that secondarily generalized were

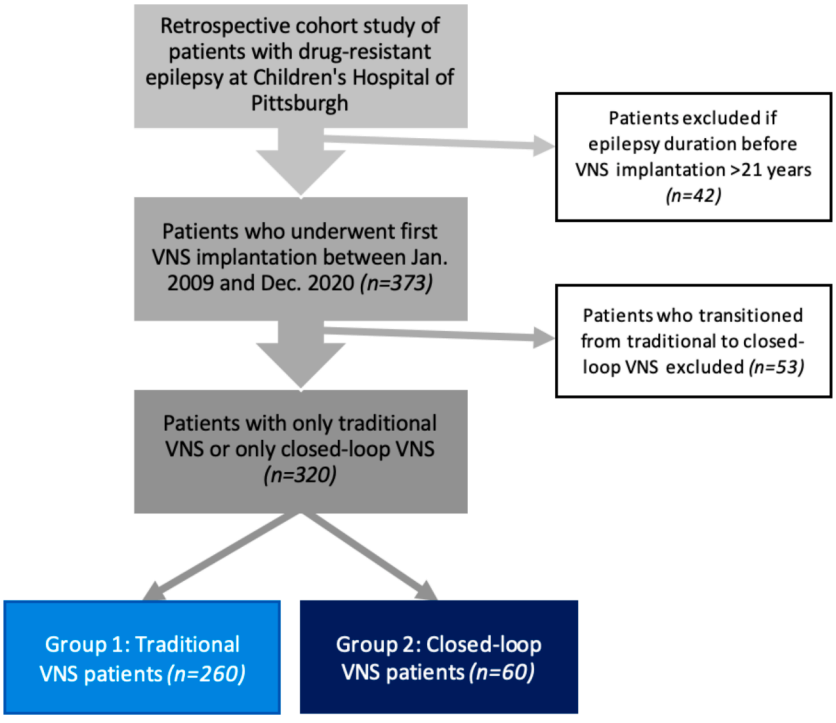

Fig. 1. A flowchart depicting the methodological inclusion and exclusion criteria for this analysis.

considered to have focal epilepsy for the sake of simplicity and to optimize subgroup sample sizes.

All outcomes were determined by electronic medical record review of neurology and neurosurgery notes at three time points: 1) the most recent encounter before VNS implantation, with the encounter occurring no longer than six months before VNS surgery, 2) one year after VNS implantation, and 3) two years after VNS implantation. Total seizure frequency was determined based on clinical notes, which typically reflect both parental observation of the patient's seizures and neurologist/neurosurgeon expertise. Total seizure frequency reduction after VNS implantation at each follow up time point was categorized as "at least 50% seizure frequency reduction" or "less than 50% seizure frequency reduction" relative to the patient's seizure frequency before VNS. If adequate documentation was not available within a three-month time interval of a given follow up point, data for that timepoint was considered missing.

Quantity of ASMs were recorded from electronic medical records at all three time points. Given that a random selection of patients did not follow up at each outcome time point, we examined ASM quantity at one year or two years, whichever time point was later. Complications were recorded based on neurology and neurosurgery clinic visits from patients' initial VNS implantation until their latest follow-up as of the year 2020. Minor complications included coughing with VNS activation, gagging with VNS activation, vocal changes, and neck pain. Infections related to VNS implantation, fractured lead wires, any permanent anatomic damage related to VNS implantation, and any complication requiring reoperation were considered major complications.

2.2. Statistical analyses

All statistical analyses were performed using Stata software for Mac, Version 17.0 (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.). All statistical testing was done with a type I error rate of 5% and all p-values were two-sided. Basic demographics and epilepsy characteristics were compared between groups.

The model of VNS patients received was not determined randomly, so there were differences between the closed loop and traditional VNS groups at baseline. Further, the retrospective nature of the study design introduces additional biases. Therefore, we utilized propensity score matching to minimize bias and create similar groups of patients who underwent traditional and closed loop VNS. Logistic regression was used to model the propensity of selection into the closed loop VNS group as a function of patient sex, duration of epilepsy before VNS implantation, number of preoperative ASMs, and the duration of time since a patient's first VNS implantation (which served as a proxy for the year of the patient's surgery). We created a matched set of traditional to closed loop VNS patients and assessed between-group propensity score balance with matched variance ratios and boxplots (*see supplemental Fig. 1*). Descriptive statistics, including sample proportions, means, and standard deviations were assessed with chi-square tests and independent sample t-tests. Fisher exact tests were used when expected cell counts were <5 and Wilcoxon rank-sum tests were used when continuous dependent variables were not normally distributed.

Due to missing data one and two years after VNS implantation, we performed two sensitivity analyses. The first sensitivity analysis assumed that all patients with missing data did not achieve VNS response, while the second assumed that all patients with missing data did achieve VNS response. With these respective assumptions, parametric chi-squared tests were again performed to assess differences in the proportion of patients achieving at least 50% seizure frequency reduction at one and two years after VNS.

3. Results

3.1. Demographics

A total of 373 patients underwent VNS between 2009 and 2020. Patients who transitioned from traditional to closed loop VNS ($n = 53$) were excluded from this analysis. Therefore, the final sample consisted of 320 patients with either only traditional VNS or only closed loop VNS. All patients had VNS implanted on the left side of their neck to stimulate the left vagus nerve. There were 260 patients in the "traditional VNS" group and 60 patients in the "closed loop VNS" group. There were no significant differences between traditional and closed VNS groups with regards to sex, etiology of epilepsy, death, age of epilepsy onset, or duration of epilepsy prior to VNS surgery (Table 1). Prior to propensity score matching, patients with traditional VNS versus closed loop VNS had significantly more epilepsy surgeries (2.1 versus 1.4, respectively; $p<0.001$) and VNS surgeries (1.9 versus 1.2, respectively; $p <0.001$). Patients with traditional VNS also took fewer ASMs before VNS implantation than those with closed VNS (2.2 ASMs versus 2.4 ASMs; $p = 0.02$). After using propensity score matching to create a comparable cohort of 179 patients with traditional VNS and 41 patients with closed loop VNS, demographics and pre-VNS epilepsy characteristics were similar between groups (Table 1). The balance of propensity scores was further validated by balanced box plots between the matched cohort *(see supplemental Fig. 1)*.

3.2. VNS response

Fig. 2 shows the proportion of patients achieving VNS response—at least 50% seizure frequency reduction—at one year after VNS (Fig. 2a) and at two years after VNS (Fig. 2b). There was no significant difference between traditional and closed loop VNS groups with regards to VNS response at one year (43% versus 39%, respectively; $p = 0.64$) or two years (48% versus 62%, respectively; $p = 0.19$) (Table 2).

3.3. Patients with focal epilepsy versus those with generalized epilepsy

Before propensity score matching, 134 patients were classified as having focal epilepsy and 115 patients as having generalized epilepsy. There were no significant differences in VNS response at any time point between the traditional and closed loop VNS groups among those with either focal epilepsy or generalized epilepsy (Fig. 2). Interestingly, after two years of VNS therapy, 72.7% (8 patients) of the closed loop VNS group achieved VNS response, while only 45.7% (27 patients) of the traditional VNS group achieved VNS response ($p = 0.10$).

3.4. Change in ASMs

The right-hand side of Table 3 shows the propensity-score matched changes in ASMs from baseline to patients' latest follow-up. At their latest follow-up after VNS therapy, a total of 55 patients (25%) in the matched sample (25% of patients with traditional VNS; 24% of patients with closed loop VNS) were able to reduce their quantity of ASMs by at least one, while 103 patients (47%) maintained the same number of ASMs (46% of patients with traditional VNS; 51% of patients with closed loop VNS), and 61 (29%) increased their quantity of ASMs by at least one (29% of patients with traditional VNS; 24% of patients with closed loop VNS). There was no significant change in ASMs from baseline between groups ($p = 0.87$). On average, after both traditional and closed loop VNS, patients took approximately the same number of ASMs as they did pre-VNS ($p = 0.87$).

3.5. Complications

There were a total of 20 minor complications (9.1%) among and 23 major complications (10.5%) all VNS surgeries in our matched sample.

Table 1
Demographics and pre-vagus nerve stimulator (VNS) epilepsy characteristics of the study sample, split by whether patients received traditional VNS or closed-loop VNS.

	Before Propensity Score Matching			After Propensity Score Matching		
	Traditional VNS ($n = 260$) n (%)	Closed loop VNS ($n = 60$) n (%)	p-value	Traditional VNS ($n = 179$) n (%)	Closed loop VNS ($n = 41$) n (%)	p-value
Sex (F)	127 (48.9%)	28 (46.7%)	0.76	92 (51.1%)	17 (41.4%)	0.25
Etiology of epilepsy			0.41			0.08
Metabolic	34 (17.0%)	3 (6.9%)		31 (19.8%)	2 (5.7%)	
Structural	64 (32.0%)	16 (37.2%)		36 (23.1%)	13 (37.1%)	
Genetic	75 (37.5%)	17 (39.5%)		69 (44.2%)	13 (37.1%)	
Other	27 (13.5%)	7 (16.3%)		20 (12.8%)	7 (20.0%)	
Epilepsy type			0.22			0.27
Focal	112 (55.7%)	22 (54.2%)		89 (56.0%)	17 (45.0%)	
Generalized	89 (44.3%)	26 (45.8%)		70 (44.0%)	20 (54.0%)	
Patient deceased	9 (3.4%)	4 (6.6%)	0.28[F]	9 (5.1%)	2 (4.9%)	0.66[F]
Age at seizure onset (years)	3 ± 4.4	3 ± 3.9	0.32[W]	3 ± 4.3	3 ± 2.6	0.80[W]
Epilepsy duration pre-VNS (years)	9.4 ± 4.9	9.8 ± 5.1	0.53	8.4 ± 4.9	9.9 ± 4.8	0.06[W]
Total number of epilepsy surgeries	2 ± 1	1 ± 0.74	**<0.001**[W]	2 ± 1	1 ± 0.83	**<0.001**[W]
Total number of VNS surgeries	2 ± 0.97	1 ± 0.56	**<0.001**[W]	2 ± 0.98	1 ± 0.56	**<0.001**[W]
Quantity of pre-VNS AEDs	2 ± 0.76	2 ± 0.83	**0.02**	2 ± 0.76	2 ± 0.82	0.34

[F] Fisher's exact test.
[W] Wilcoxon rank-sum test
All tests were either χ^2 tests or independent sample t-tests assuming equal variances unless otherwise noted. Non-parametric tests were used when appropriate; $p<0.05$ was considered significant.

In the matched sample, a total of 14 minor complications occurred in patients with traditional VNS (7.8%) and 6 minor complications in patients with closed loop VNS (12.2%). Similarly, 21 major complications occurred in patients with traditional VNS (11.7%) and 2 major complications occurred in patients with closed loop VNS (4.9%). There were no differences in minor complications ($p = 0.245$) or major complications ($p = 0.264$) between patients with traditional and closed loop VNS (Table 3).

4. Discussion

In this study, we present the largest retrospective analysis comparing traditional VNS to closed loop VNS among pediatric patients with drug-resistant epilepsy. Our results revealed that closed loop VNS is as effective as traditional VNS for pediatric patients with drug-resistant epilepsy. Furthermore, our analysis suggests that after two years of VNS therapy, closed loop VNS trends toward having a higher 50% seizure frequency reduction rate, especially for patients with generalized epilepsy ($p = 0.10$).

It is important to note that the effects we report are after propensity score matching and that our propensity score included the time since the patients' surgery. At our institution, closed loop VNS was introduced in late 2015. Therefore, almost all VNS surgeries performed after October of 2015 utilized closed loop models. Conversely, all patients who received traditional VNS in our sample were implanted before October of 2015. We considered that medical management of epilepsy could have improved over time, meaning that patients in the closed loop sample could have simply had better outcomes independent of the effects of the VNS. Furthermore, neurologists and neurosurgeons at our institution changed over the time span of the study, which introduced further potential for bias. By calculating propensity scores utilizing the time since surgery (as a proxy for the year of surgery), we were able to minimize the selection bias posed by the arbitrary introduction of closed loop VNS models at our institution.

Our demographics reflect standard demographics for pediatric patients who receive VNS, and our analysis revealed that patients with traditional VNS had significantly more epilepsy surgeries and VNS surgeries than the closed loop VNS group. Given that patients with traditional models were implanted with VNS before 2016, they have had VNS for longer than the closed loop group. Therefore, it is not surprising that they have underwent more surgeries (i.e., pulse generator revisions) than those who received closed loop VNS.

With regards to the effects of VNS in improving patients' seizure burden, one of the first randomized control trials comparing the efficacy of various stimulation parameters VNS for patients with focal epilepsy demonstrated that 33% of patients (8 out of 24) with low frequency stimulation achieved >50% seizure frequency reduction by 16–18 months of VNS stimulation, whereas 65% of the patients (17 out of 26) in the high-frequency stimulation group achieved VNS response [21]. Another early randomized control trial revealed that 31% of patients receiving therapeutic dose stimulation responded to VNS, versus 13% of patients receiving subtherapeutic stimulation [22]. Since these landmark trials in the 1990s, several subsequent analyses have examined the efficacy of VNS. The resulting evidence demonstrates wide variability in response rate to VNS [4,6,7,9,10,21,23-39]. Few of these analyses independently examine the pediatric population [6,7,9,23,26,32,34-37]. Orosz et al., in their sample of 347 pediatric patients, found that 43.8% of their sample responded to VNS after two years[36], while Rossingol et al., in their sample of 28 patients, found this rate to be 68% at two years [37]. Furthermore, existing literature suggests that seizure frequency burden tends to decrease with longer duration of VNS therapy [36,40]. Our analysis is consistent with the state of existing literature: 42% of our total sample responded to VNS after one year of implantation and 50% responded after two years. In other words, as time progressed, a larger proportion of our sample responded to VNS stimulation, just as expected.

Comparing effect sizes among the overall patients in our sample, the proportion who achieved VNS response after closed loop VNS was similar to that of those who received traditional VNS after one year of therapy. After two years of therapy, our results appear to show that closed loop VNS allowed a larger proportion of patients to achieve treatment response, though these results were not "statistically significant." Over last two decades, predictive factors for VNS response have been sought, though none have consistently demonstrated to predict across multiple studies. In a meta-analysis by Englot, Chang, and Auguste (2011), results revealed that patients younger than six years of age and those with primarily generalized epilepsy syndromes exhibited a more dramatic decrease in seizure frequency than older patients and those with primarily focal epilepsy, respectively [30]. Thus, while the differences in VNS response were "statistically insignificant" in our analysis, p values do vary considerably from study to study. It is possible that our study simply did not detect our observed group differences.

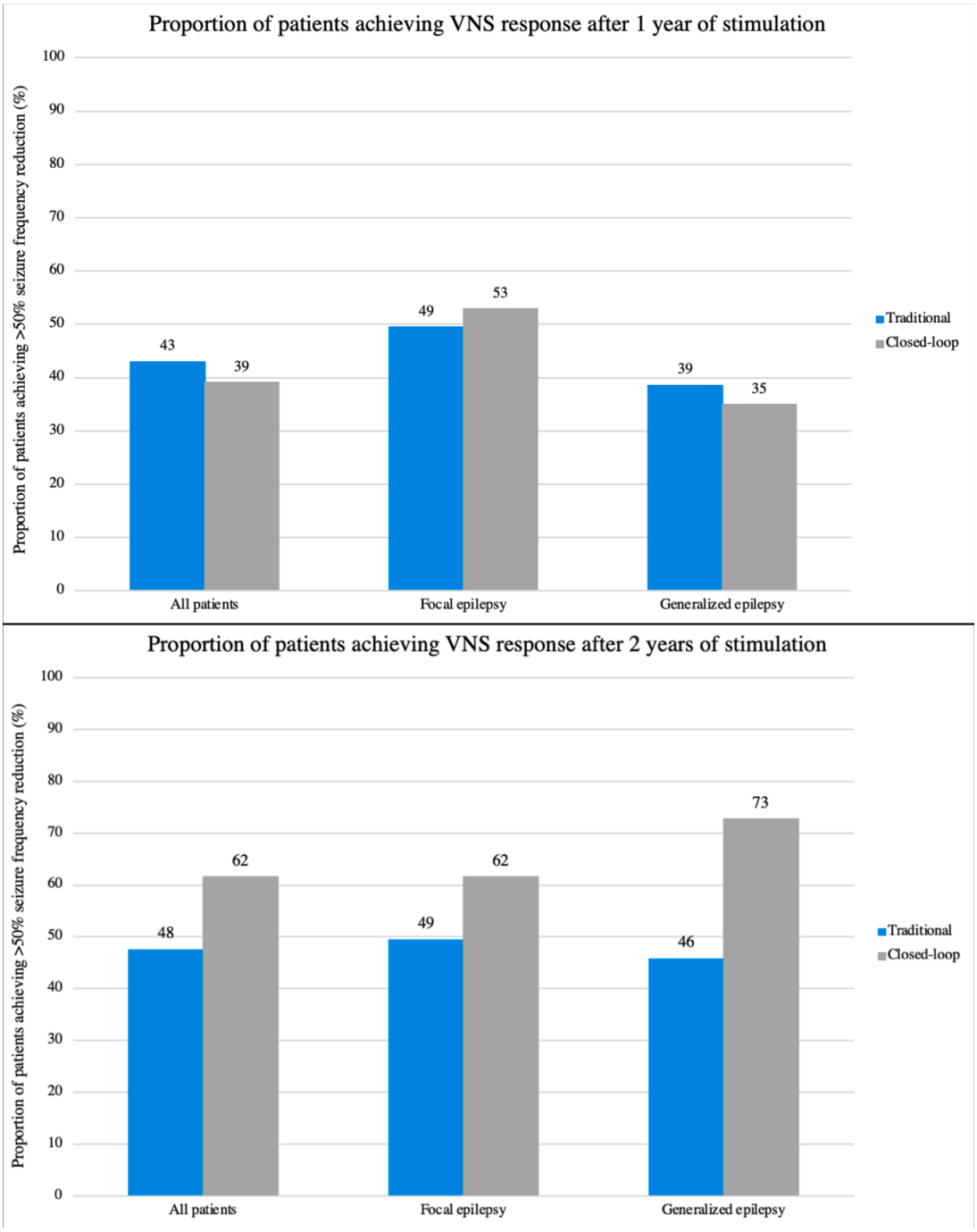

Fig. 2. The proportion of propensity-score matched patients achieving at least 50% seizure frequency reduction after a) 1 year of stimulation and b) 2 years of stimulation, split by those who received traditional VNS versus closed loop VNS. χ^2 tests were performed to assess differences in proportions; $p<0.05$ was considered significant. Absolute percentage of patients achieving VNS response are reported above each corresponding bar in the figure.

Another interesting consideration is that early brain plasticity may have attenuated potentially observable differences between our subgroups. Evidence suggests that seizures are implicated in structural changes in the brain[41] and can influence neural circuitry [42]. Especially for patients with early-onset seizures or long duration of epilepsy before VNS, seizure-induced brain stimulation could have caused enough changes to brain structure and circuitry that response to VNS becomes improbable for both focal- and generalized epilepsy patients.

Furthermore, our results are interesting to consider in the context of underlying closed loop VNS physiology. A 2014 study by Eggleston, Olin, and Fisher suggested that a similar proportion of patients with generalized seizures and focal seizures experience significant changes in ictal heart rate [29]. Extrapolating these results, one may expect patients with focal and generalized onset seizures to respond similarly to closed loop VNS. However, a more recent study by Hirsch et al. demonstrated that ictal tachycardia was an early predictor of seizure activity, especially among seizures originating in the mesial temporal and in right temporal area [43]. Based on the results of this study, it would be expected that patients with seizures originating from or implicating the mesial temporal lobe would be more likely to respond to closed loop VNS than traditional VNS. Other studies have suggested that patients with generalized epilepsy are more likely than those with focal epilepsy to experience ictal tachycardia [44,45]. Therefore, with the advent of closed loop VNS, which stimulates the vagus nerve in response to ictal

Table 2
Comparison of the proportion of VNS responders* at 1 year and 2 years after VNS implantation among those with traditional VNS and those with closed loop VNS.

		Before propensity matching				After propensity matching		
	n(%) of VNS responders* after 1 year of therapy	Complete data	Sensitivity analysis		n(%) of VNS responders * after 2 years of therapy	Complete data	Sensitivity analysis	
			Assuming all non-responders	Assuming all responders			Assuming all non-responders	Assuming all responders
Traditional VNS	180 (43%)	179 (43%)	260 (29%)	260 (60%)	161 (48%)	160 (48%)	260 (29%)	260 (83%)
Closed loop VNS	41 (39%)	41 (39%)	60 (27%)	60 (58%)	26 (62%)	26 (62%)	60 (27%)	60 (68%)
p-value	0.66	0.64	0.65	0.77	0.19	0.18	0.69	**0.02**

* VNS responder: patients achieving ≥50% seizure frequency reduction
All tests were χ^2 tests given that no cells had expected values <5; $p<0.05$ was considered significant.

Table 3
Secondary outcomes, including the mean change in antiepileptic drugs (AEDs) from pre-VNS to the patients' latest follow-up and complication rates, split by traditional VNS and closed loop VNS.

	Before propensity score matching			After propensity score matching		
	Traditional VNS ($n = 260$) n (%)	Closed loop VNS ($n = 60$) n (%)	p-value	Traditional VNS ($n = 179$) n (%)	Closed loop VNS ($n = 41$) n (%)	p-value
Change in quantity of AEDs	+0.10 ± 0.94	−0.04 ± 0.75	0.32	+0.05 ± 0.96	+0.02 ± 0.76	0.87
Complication rate for VNS surgeries						
Minor*	18 (6.9%)	6 (0.1%)	0.56[F]	14 (7.8%)	6 (14.6%)	0.25[F]
Major**	33 (12.7%)	2 (3.3%)	0.14[F]	21 (11.7%)	2 (4.9%)	0.26[F]

* Minor complications included vocal changes with VNS activation, coughing with VNS activation, gagging with VNS activation, and pain at surgical site.
** Major complications included fractured lead wires, device-related infections, any surgery- or device-related complication resulting in permanent anatomic damage, and any complication requiring reoperation.
[F] Fisher's exact test
All tests were independent sample t-tests assuming equal variances, χ^2 tests, or Fisher's exact tests when expected cell counts<5; $p<0.05$ was considered significant.

tachycardia, there has been anticipation as to whether these models would be particularly effective for patients with generalized seizures or known ictal tachycardia. Concrete data have yet to demonstrate such findings.

Our analysis offers a piece of evidence to support the physiological foundation of closed loop VNS. In a recent study by Lo et al. (2021), the authors found in a small cohort that after changing from traditional to closed loop VNS models, seizure frequency reduction significantly increased from 60% to 83% [46]. In their sample, an additional 20% of patients achieved McHugh class I or II. These findings mirror those of Datta et al. Lo et al.'s results may help elucidate the physiology of tachycardia-responsive VNS. All patients in Lo et al.'s sample had intellectual disability, which could indicate that these patients had some element of generalized seizure activity. Given that generalized seizures may have a predilection for ictal tachycardia, perhaps the patients in Lo et al.'s sample were more likely to have ictal tachycardia and therefore responded better to closed loop VNS. That said, it is also known that VNS response tends to improve over time. In our cohort of patients with generalized epilepsy, a notably higher proportion of those who receive closed loop VNS responded to VNS at two years than those with traditional VNS – 73% versus 46%. As aforementioned, while our results were not statistically significant, the effect size is relatively large, especially given the perspective that only 40–70% of patients with ASM-resistant epilepsy are expected to achieve at least 50% seizure frequency reduction with VNS at all. Moreover, after two years of stimulation, a higher proportion of patients with closed loop VNS achieved VNS response than those with traditional VNS among all subgroups we examined, further suggesting that closed loop VNS may be more effective than traditional VNS in the long-term.

4.1. Limitations

This analysis has several limitations which must be considered. Firstly, many patients in this sample developed new seizure semiologies at subsequent follow-up points. The pediatric population of epilepsy patients is traditionally challenging to study, as their epilepsy phenotype changes as the brain develops [47]. To minimize the effect of changes in semiology over time, outcomes were recorded at one year and two years, rather than longer-term follow up time points. Secondly, our primary outcome data are based on parents' self-report from neurology office visits. It is possible that patients' seizures were not quantifiable (i.e., clusters of absence seizures or myoclonic jerks), went unnoticed, occurred nocturnally, or were forgotten. Thus, our data may reflect fewer seizures than occurred for each patient. At the same time, parents may have reported events which they felt were seizures but were not captured and confirmed to be seizures on EEG; therefore, our data could reflect some events which were not seizures at all. To address this issue, our data collection process was rigorous and explicit. Only known seizures captured on EEG or events felt to be seizures by the patient's primary neurologist/neurosurgeon were included as part of our "total seizure frequency" count. Our data inclusion allows us to optimize this study's internal validity at the cost of its external validity. Because of our rigorous data inclusion criteria, we also had relatively small sample sizes at the two-year outcome time point, where our effect sizes were largest between groups. Our power to detect differences in these effect sizes at the alpha=0.05 level was <50%; therefore, the lack of statistical significance demonstrated by this analysis could reflect low power. Replicating this study with larger samples will be crucial to understanding the true impact of closed loop versus traditional VNS, especially in the long term. Another limitation of this analysis is that closed loop VNS was only available at our institution around 2015. Therefore, the availability of closed loop VNS may have introduced spurious biases which influenced our results, as suggested by the results of our sensitivity analysis. We addressed this issue by including a proxy for the year of surgery in our propensity score calculation. Finally, the results of this analysis are not a reflection of the effects of VNS in isolation. The healthcare team adjusted

ASMs and VNS stimulation parameters as clinically indicated. In this sense, our analyses cannot distinguish the effects of VNS, medical management, and natural disease progression. With that said, we utilized propensity score matching to compare patients with similar quantities of ASMs before VNS and to compare patients treated in similar years so as to balance the effects of medical management on treatment response.

4.2. Future work

This analysis utilized data from patients with traditional VNS versus those with closed loop VNS models only. It intentionally excluded patients who transitioned between VNS models. A recent analysis by Datta et al. (2020) revealed that 28% of patients who transitioned to closed loop VNS had an additional 50% decrease in seizure frequency at one year of therapy, without increase in healthcare costs [15]. However, this study was limited by a sample size of 25 patients. The state of current evidence suggests transitioning from a non-heart rate-based (i.e., traditional) model to one that selectively detects ictal tachycardia and stimulates the vagus nerve (i.e., closed loop) may be beneficial for patients. Thus, future analyses should seek to replicate Datta et al.'s methodology in a larger sample. Furthermore, this analysis primarily examined response to VNS rather than seizure freedom rates after VNS therapy. It would intuitively appear that similar variables would predict VNS response and seizure freedom following VNS, though a recent analysis by Englot and Rolston (2016) revealed that patients older than 12 years of age were more likely to achieve seizure freedom after VNS [48], while Englot et al. (2011) found that younger pediatric patients were more likely to respond to VNS therapy [30]. This suggests that differences exist between predictors of VNS response and seizure freedom after VNS therapy. Englot and Rolston performed their study at the time when closed loop VNS models were first being implemented in clinical practice. Therefore, future studies can assess whether the ictal tachycardia detection offered by closed loop models is predictive of seizure freedom following VNS therapy. Further, an intriguing extension of our study is to examine the effectiveness of traditional VNS versus closed loop VNS after adjusting for the number and timing (i.e., nocturnal versus awake) of ictal events. In our sample, it is plausible that patients with generalized epilepsies may simply have had a higher frequency of ictal events than those with focal epilepsies. Therefore, our observed effect size between traditional- and closed loop VNS for patients with generalized epilepsies may be secondary to ictal VNS activation itself. Another avenue for future work derives from a recent analysis by de Vos et al.: their team demonstrated that quantification of pre-VNS EEG symmetry may potentially be utilized to predict response to VNS [27]. Thus, three additional extensions of our analysis are to assess 1) whether closed loop VNS alters interictal EEG symmetry after two years of therapy and 2) if such alterations exist, then whether they produce a favorable EEG profile for VNS response, and 3) if patients with known ictal tachycardia truly are more likely to respond to closed loop VNS models.

5. Conclusions

Among pediatric patients with drug-resistant, unresectable epilepsy, closed loop VNS appears to allow a greater proportion of patients to achieve $\geq$50% seizure frequency reduction in the long-term, especially among patients with generalized epilepsy. However, larger samples are needed to replicate and support this finding. The complication profile between traditional and closed loop VNS is similar. Closed loop VNS does not allow patients to decrease their quantity of ASMs when compared to traditional VNS.

Declaration of Competing Interest

Dr. Taylor Abel is a consultant and receives research funding from the Monteris Corporation, which is not related to the content of this study. None of the other authors has any conflict of interest to disclose.

Acknowledgements

None

Sources of funding

Dr. Taylor Abel receives funding from NIH R21 DC019217 and NIH R01 DC013315.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.11.016.

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