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Outcomes of vagal nerve stimulation in a pediatric population: A single center experience

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ABSTRACT

Objective: To evaluate the efficacy of vagus nerve stimulation (VNS) in pediatric patients with medically refractory epilepsy.
Method: We reviewed the medical records of 252 consecutive patients who underwent VNS implantation at a single center over a 5-year period. Patients with complete 6- and 12-month follow-up data were included. Analysis was also done across various subgroups including gender, age at implantation, seizure type, abnormal MRI findings pre-implantation, number of medications at baseline, history of SE, and duration of epilepsy.
Results: Complete follow-up data were available for 69 patients. Median seizure reduction for these patients was 50% (Q1: 0%; Q3: 73%) at 6 months and 40% (Q1: −25%; Q3: 75%) at 12 months. When stratified by baseline seizure frequency, there was a significant reduction from baseline of 61% at 6 months and 69% at 12 months for patients in the high-baseline frequency group. There were no significant reductions at month 6 or 12 months for the lower-baseline frequency group. Adverse events were reported in 40.6% (28 out of 69 patients). Six patients had the VNS removed for reasons including lack of efficacy and side effects and were excluded from the study group.
Conclusion: VNS provides significant seizure reduction, in particular in pediatric patients with a higher baseline seizure frequency.

1. Introduction

Vagus nerve stimulation (VNS) is an established adjunctive therapy for medically refractory epilepsy.[1,2] The therapy was approved in 1997 by the US Food and Drug Administration for use in adolescents and adults.[3] Combined analysis of these trials concluded that VNS therapy allowed 1/3 of treated patients to achieve a greater than 50% reduction in seizure frequency, a reduction which may continue even with long term use.[4] While the VNS is established for use in adults,[5–8] its potential value in the treatment of drug-resistant epilepsy in a pediatric population has not been conclusively established. Recently a small prospective study has been published suggesting that VNS may be effective in some children and adolescents, though not in others.[9,12,26] To date, few investigators have explored the efficacy and safety of VNS for refractory epilepsy in large pediatric populations over time.[10–13]

In this retrospective study, we aimed to expand the reported experience of VNS use in a pediatric population, with data from a single center. In addition, we also attempted to determine whether any specific clinical characteristics were associated with more favorable outcomes after VNS placement.

2. Methods

2.1. Patient selection

Prior to chart-review, institutional review board approval was obtained for this study. We reviewed the medical records of all

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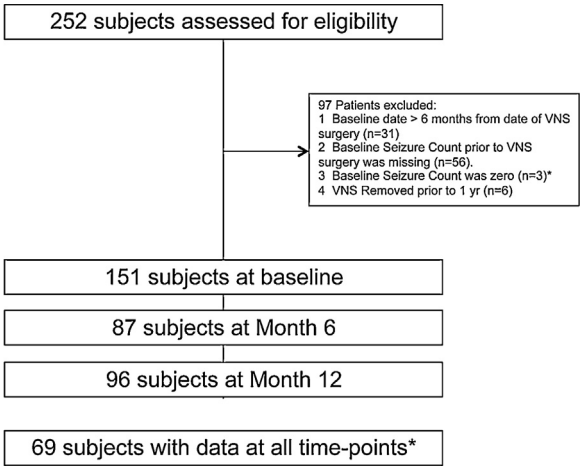

Fig. 1. Consort diagram. Only patients with complete data at baseline, month 6, and month 12 were included in statistical analysis. Sixty-nine patients were included. *Search using ICD-9 codes used returned some patients who did not undergo VNS implantations, but who underwent similar procedures for treatments in otolaryngology.

patients treated for epilepsy by VNS from December 1997 to March 2011 at Boston Children's Hospital. Patients were identified using the International Classification of Diseases, Ninth Revision codes 02.93, 89.15, 86.94, 86.95, 86.96, and 86.98. All medical records and reports of MRI findings were reviewed. Seizure outcome and VNS side effects were derived from the patient records and evaluated along with brain MRI findings, seizure type and localization, and previous seizure treatments.

2.2. VNS implantation

Implantation was performed by the same neurosurgeon following standard procedures (J.R.M.). Stimulation parameters were initially set at 0.25–0.5 mA current, 20–30 Hz frequency, 250–500 μs pulse width, 30 s on time and 5–10 min off time; the magnet current was generally set 0.25 mA higher with a stimulation duration of 60 s. Parameter adjustments were made at subsequent follow-ups by the patient's neurologist according to accepted adult guidelines.[14]

2.3. Follow-ups

Seizure frequency data was acquired at baseline (within 180 days prior to VNS implantation), at 6 month (±2 month window) and at 12 month (±3 month window) follow-up visits. Patients were required to have complete seizure data at all three of these time points to be included in the analysis.

Given the wide range of seizure frequencies at baseline, subjects were categorized by seizure frequency into a high-frequency group (those with a baseline frequency above the group median) and a low-frequency group (those with a baseline frequency below this median).

2.4. Statistical analysis

The primary outcome measure was the percentage change from baseline seizure frequency at the 6- and 12-month follow-ups. Differences in seizure percentage change were assessed using a Wilcoxon signed-rank test.

Subgroup comparisons were undertaken to assess if the median percentage change from baseline to 12 month follow-up was significantly different between the various groups stratified by demographic characteristics as specified in Table 3. P values <0.05 were considered statistically significant. All statistical analyses were performed using SAS, 9.3 (SAS, Cary, NC).

3. Results

3.1. Patient inclusion (Fig. 1)

Sixty-nine patients had complete data both at baseline and the two follow-up periods and formed the study group. Patients who had the VNS removed before 12 months were excluded from the analysis, though outcomes for this group are reported separately (Figs. 2 and 3.).

3.2. Population demographics

The median seizure frequency at baseline was 45 seizures/month (Q1: 10 seizures/month; Q3: 150 seizures/month). Patients were grouped according to the baseline median with Group 1 (low

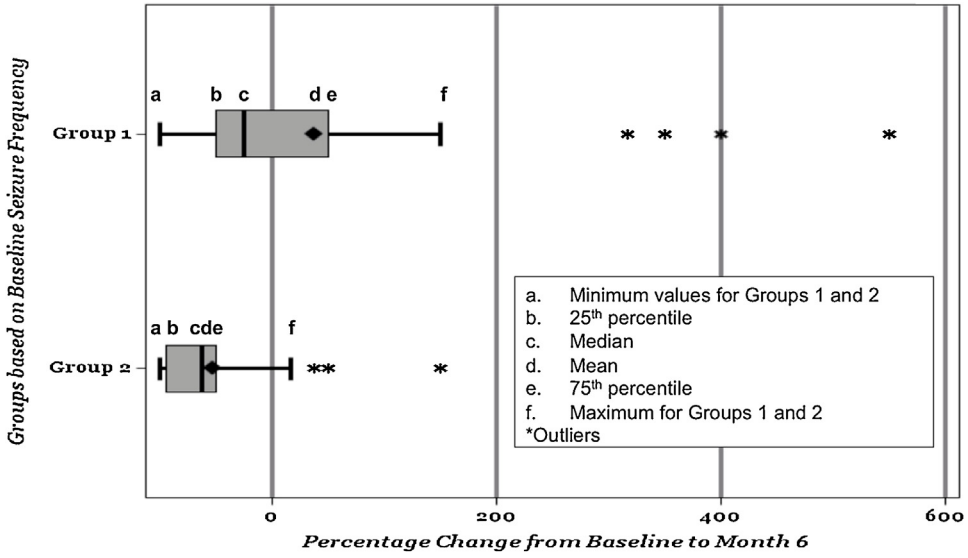

Fig. 2. Percentage change of seizures from baseline to 6 months. Patients in the low baseline group (Group 1) experienced a median seizure reduction of 25% (25% quartile, −50%; 75% quartiles, 50%) at 6 months ($p = 0.94$). Patients in the high baseline group (Group 2) experienced a median seizure reduction of 61% (25% quartile, −93%; 75% quartile, −50%) at 6 months ($p < 0.001$).

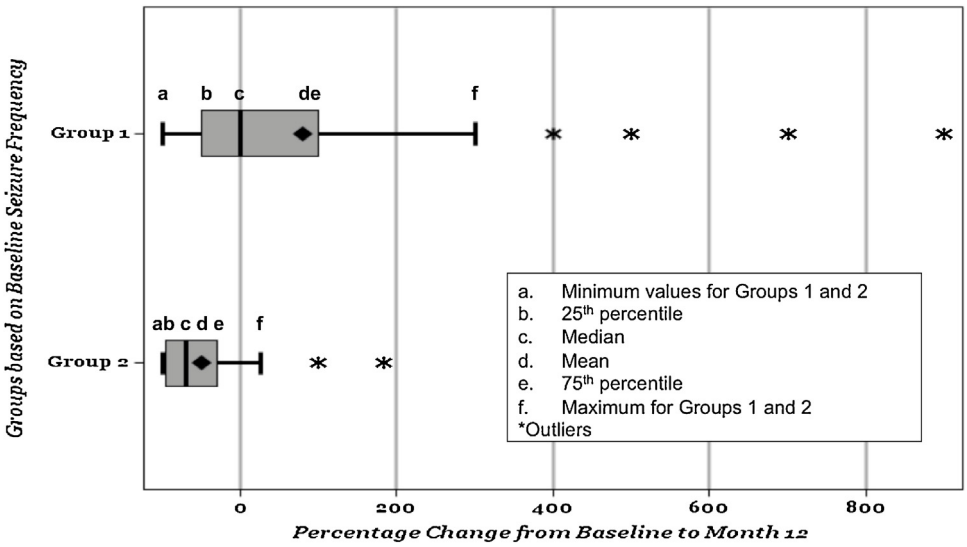

Fig. 3. Percentage change of seizures from baseline to 12 months. Patients in the low baseline group (Group1) experienced a median seizure reduction of 0% (25% quartile, −50%; 75% quartiles, 100%) at 12 months ($p = 0.39$). Patients in the high baseline group (Group 2) experienced a median seizure reduction of 69% (25% quartile, −96%; 75% quartile, −30%) at 12 months ($p < 0.001$).

baseline group, $n = 34$) experiencing ≤45 seizures/month and Group 2 (high baseline group, $n = 35$) experiencing >45 seizures/month. Demographic data for the population are outlined in Tables 1 and 2.

3.3. Results at six months (Table 3)

Thirty-seven (53.6%) out of 69 patients exhibited seizure reductions of ≥50% (achieved responder status) at six months. Seventeen patients (24.6%) achieved a 75% or greater reduction from baseline seizure frequency. Four patients (5.8%) achieved seizure freedom. Of the remaining 32 patients with less than 50% reduction (classified as non-responders), 17 (24.6%) experienced an increased number of seizures compared to baseline.

Compared to baseline, the overall population experienced a median reduction of 50% (Q1: 0%; Q3: 73%) at six months ($p = 0.005$). The high baseline group (>45 seizures/month at baseline) exhibited a median reduction from baseline of 61% (Q1: 50%; Q3: 93%) at 6 month follow-up ($p < 0.001$). The median seizure frequency at 6 months was significantly lower than at baseline. The low baseline seizure frequency group ($n = 35$) experienced a 25% median reduction in seizure frequency from baseline (Q1: −50%; Q3: 50%). The difference in median seizure frequency from baseline to month 12 was not statistically significant ($p = 0.94$).

3.4. Results at 12 months (Table 3)

At 12 months, 28 (40.6%) patients experienced seizure reductions ≥50%. Seventeen (24.6%) patients experienced a >75% reduction. Four patients (5.8%) were seizure free at 12 months. The remaining 41 (59.4%) patients had a less than 50% reduction in seizure frequency. Of these 41 patients, 20 had an exacerbation in seizure frequency compared to baseline.

At the 12 month follow-up, the overall population had a median reduction of 40% (Q1: −25%; Q3: 75%) from baseline frequency ($p = 0.058$). Analyzing the population with respect to high and low baseline groups, the high baseline group achieved significant reductions at 12 months follow-up, exhibiting a seizure reduction of 69% (Q1: 30%; Q3: 96%) from baseline ($p < 0.001$). The low baseline group did not show an overall reduction from baseline seizure frequency (median 0%, Q1: −50%; Q3: 50%) ($p = 0.39$).

3.5. Subgroup analysis

Among patients with the selected baseline characteristics we did not identify significant differences in outcome at 12 months follow-up (Table 3). Results suggested that in the low baseline group of patients, those younger than 10 years old at time of VNS implantation ($n = 20$) experienced a trend toward greater seizure reduction compared to those older than 10 years ($n = 15$) ($p = 0.06$). While numbers of patients with syndromes and epilepsy-related comorbidities were limited, outcomes in these groups are presented in supplemental Table 1.

3.6. VNS settings at 0, 6 and 12 months (supplemental Table 1)

Sixty-eight patients had an increase in current at 6 months and 61 had a further increase at 12 months. There was no significant difference in VNS settings including current, on-time or off-time between the low and high-frequency baseline groups at 6- and 12-month follow-ups (supplemental Table 2).

3.7. Discontinuation of VNS therapy

Six patients discontinued VNS treatment within the 12 month follow-up period. Reasons for discontinuation included infection requiring explantation of the device ($n = 3$), excessive nausea resulting in the VNS being turned off ($n = 1$), skin breakdown over the device leading to explantation ($n = 1$), and perceived lack of efficacy ($n = 1$).

3.8. Adverse effects of VNS therapy

Twenty-eight patients complained of adverse events that did not require discontinuation of therapy. The most frequently reported side-effect was seizure exacerbation of ≥50% from baseline ($n = 14$). Other side effects included voice changes ($n = 8$), coughing ($n = 6$), hoarseness ($n = 4$), throat tickle/paresthesias ($n = 3$), sleep apnea ($n = 1$), and nausea and vomiting ($n = 1$).

Table 1
Demographic data for the overall population at baseline.

Number of patients	69
Number of girls	29
Mean age (SD, range)	Mean 18.56yrs (SD = 6.81, Range 4-36yrs)
Past history of Status Epilepticus (SE)	16
Patients who developed SE after implant[a]	10
Age of seizure onset	28.63 months (SD = 34.32, Range birth-132 months)
Age at VNS implantation	11.07 yrs (SD = 5.31, Range 2-25yrs)
Seizure etiology	
Symptomatic	25
Idiopathic	36
Cryptogenic	8
Semiological characteristics	
Generalized	32.
Complex partial	6
Complex Partial with secondary generalization	28
Simple partial	1
Simple Partial with secondary generalization	2
EEG characteristics	
EEG available	63
Generalized and Focal	29
Multifocal	16
Generalized	7
Frontal	5
Temporal	5
Parietal	1
Lateralization	
Left	6
Right	8
No Lateralization	49
Imaging	
MRI Available	61
Normal MRI	21
Abnormal MRI	40
MRI findings	
Volume loss (unspecified)	13
Gliosis	11
Status post resection	8
Agenesis/Dysgenesis	8
Cortical Dysplasia	6
Encephalomalacia/Trauma	6
Cystic Lesions	4
Hydrocephalus	3
Polymicrogyria	2
Hemiatrophy	1
Tumor	1
MRI lesion lateralization	
Left	7
Right	5
Both	26
Unspecified	2
AEDs[a]	
Mean AEDs, baseline	2.73 (Range 1–5)
Mean AEDs at 6 months	2.58 (Range 1–5)
Mean AEDs at 12 months	2.72 (Range 1–6)
Resective surgery[a]	
Surgery pre implant	7
Surgery post implant	1

[a] Data such as development of SE after implantation, number of AED's and each follow-up, and additional epilepsy surgery were collected at subsequent follow-ups. *Abbreviations*: yrs., years; s/p, status post.

Table 2
Demographic data for study groups at baseline.

Characteristics	All subjects (*N* = 69)	GP1: low baseline ≤45 seizures[a] (*N* = 35)	GP2: high baseline >45 seizures[a] (*N* = 34)
Gender, No (%)			
Female	29 (42%)	17 (49%)	12 (35%)
Male	40 (58%)	18 (51%)	22 (65%)
Age at VNS			
N	*N* = 69	*N* = 35	*N* = 34
Median	10 years old	9 years old	11 years old
(Q1, Q3)	(5,14)	(5,15)	(5,14)
Number of medications			
<3	28 (41%)	16 (46%)	12 (35%)
≥3	41 (59%)	19 (54%)	22 (65%)
Seizures at baseline			
N	*N* = 69	*N* = 35	*N* = 34
Median	45	10	150
(Q1, Q3)	(10, 150)	(6, 30)	(90, 300)
Semiological characteristics, number (%)			
Simple	1(1%)	1(1%)	0
Complex	25 (36%)	13 (37%)	12 (35%)
Generalized	43 (62%)	21 (60%)	22 (65%)
Duration of epilepsy (years)			
N	*N* = 69	*N* = 35	*N* = 34
Median	8.3	8.1	8.5
(Q1, Q3)	(4.6,11.3)	(4.5,11.1)	(4.6,12.1)
Epilepsy syndromes/comorbidities			
N[b]	*N* = 14	*N* = 10	*N* = 4
Lennox Gastaut syndrome	*N* = 8	*N* = 2	*N* = 8
Cerebral Palsy	*N* = 5	*N* = 1	*N* = 4
Rett's syndrome	*N* = 2	*N* = 2	*N* = 0
Autism	*N* = 11	*N* = 8	*N* = 3

[a] Demographic data of the high and low baseline groups were similar to that of the overall population.
[b] A total of 14 patients were diagnosed. One patient had both Lennox Gastaut Syndrome and Cerebral Palsy.

4. Discussion

4.1. Summary

VNS may be effective in patients with high baseline seizure frequency. However, vagus nerve stimulation may lack long-term efficacy in pediatric patients with lower baseline seizure frequencies.

4.2. Seizure reduction at 6 months

Our study population experienced seizure reduction at the 6 month follow-up. Similar results were reported in a retrospective study of 125 patients indicating 51% seizure reduction at 6 months.[11] Findings are also consistent with another retrospective study with 46 children and adolescents.[13]

4.3. Seizure reduction at 12 months

Overall 40.6% patients continued to experience seizure reduction ≥50% after 12 months, and this was most prominent in patients with high baseline seizure frequency. Seizure frequency decrease in the low baseline seizure frequency group was not significant after 12 months. Another retrospective study noted that 31/69 pediatric patients had no worthwhile improvement in seizure frequency at a mean follow-up time of 3.9 years.[12] Additionally, 41 children and adolescents who received VNS therapy for a mean 2.6 years reported treatment failure in about 40%.[15] In a report of 96 pediatric patients treated for a mean of 2.7 years, 55% failed to respond to therapy.[10] A randomized controlled pediatric trial with 41 children and adolescents demonstrated similar findings, with the majority of patients (74%) failing to achieve significant seizure reduction after 39 weeks.[9] Furthermore, an international survey study indicated limited efficacy in 197 pediatric patients at one-year follow-up following VNS implantation.[16] However, while VNS may cause limited seizure reduction, it may nonetheless limit the severity of seizures. VNS in pediatric epilepsy lowered hospital admissions, emergency room visits, and events of status epilepticus and improved quality of life.[17] Our data now allow us to differentiate and interpret these results further and identify baseline seizure frequency, using a cut off of 45

Table 3
Change in seizure frequency across subgroups in high and low baseline groups.

		Total population ($n=69$)			Low baseline group ($n=35$)			High baseline group ($n=34$)		
		N	Median (Q1, Q3)	*P*	*N*	Median (Q1, Q3)	*P*	*N*	Median (Q1, Q3)	*P*
Duration of Epilepsy	≤8.3	34	40% (−10%, 72%)		18	13% (−100%, 50%)		16	58% (14%, 91%)	
	>8.3	35	40% (−33%, 92%)	0.8	17	−25% (−67%, 40%)	0.44	18	81% (38%, 97%)	0.29
Abnormal EEG findings	Absent	25	20% (−50%, 60%)		14	−18% (−150%, 50%)		11	54% (0%, 96%)	
	Present	38	41% (−89%, 0%)	0.26	19	17% (−110%, 50%)	0.66	31	73% (−13%, 96%)	0.47
No. of medications	<3	27	30% (−36%, 60%)	0.11	16	0% (−125%, 41%)		12	58% (15%, 73%)	
	≥3	51	45% (−10%, 92%)		19	10% (−67%, 58%)	0.46	22	90% (38%, 97%)	0.19
Prev. Episodes of S.E.	No	51	50% (−25%, 91%)		25	0% (−100%, 50%)		27	72% (38%, 96%)	
	Yes	16	34% (−77%, 66%)	0.65	10	13% (−36%, 45%)	0.61	6	55% (30%, 96%)	0.82
Gender	Female	29	38% (−36%, 73%)		17	−33% (−150%, 43%)		12	70% (−39%, 93%)	
	Males	40	43% (0%, 83%)	0.22	18	21% (−25%, 50%)	0.2	22	66% (−20%, 97%)	0.99
Age at VNS	<10yrs	35	43% (0%, 72%)		20	32% (−5%, 50%)		15	60% (8%, 92%)	
	≥10 yrs	34	38% (−36%, 91%)	0.72	15	−36% (−150%, 0%)	0.06	19	89% (38%, 96%)	0.54
Age at VNS	<12yrs	28	44% (−43%, 93%)		12	−43% (−168%, 13%)		16	91% (−37%, 96%)	
	≥12 yrs	41	40% (0%, 67%)	0.72	23	17% (−33%, 50%)	0.16	18	58% (−8%, 73%)	0.24
Seizure type[a]	Focal	25	50% (0%, 92%)		13	10% (−67%, 67%)		12	72% (33%, 96%)	
	Generalized	43	40% (−25%, 73%)	0.5	21	0% (−50%, 43%)	0.55	22	69% (20%, 92%)	0.86
Lateralization of lesion[b]	Unilateral	12	59% (−18%, 84%)							
	Bilateral	28	18 (−50%, 89%)	0.31						

[a] *Note*: Only 1 subject had a seizure type of simplex was excluded for comparison among groups due to small number of subjects in this category. Abbreviations: yrs., years.
[b] *Note*: Sample sizes of these subgroups were too small to divide further into high and low baseline groups. Seizure outcomes at 12 months were compared across multiple subgroups organized by baseline characteristics to determine which groups are most amenable to treatment. Although there were no significant differences in seizure outcome across these subgroups, patients in the low baseline group who were younger than 10 years of age experienced moderately better outcomes ($p=0.06$).

seizures per month at baseline, as prognostic indicator for good long-term response.

4.4. Efficacy of VNS according to seizure frequency

Patients in our series with initial higher seizure burdens at baseline responded more consistently to VNS. Similar findings were noted in a retrospective study with 50 adult patients.[18] Although seizure frequency may be a surrogate for epilepsy subtype in some patients, we did not observe significant differences in our analyses by epilepsy syndrome.

4.5. Comparison of VNS to alternative therapies

Outcomes of VNS in pediatric patients may be comparable to alternative treatment modalities for patients with refractory epilepsy. Treatment with two medications in patients with refractory epilepsy carries a 3% chance of seizure remission.[19] In children using the modified Atkins diet, 55% of patients had a favorable response (>50% seizure reduction).[20] In a randomized controlled trial investigating ketogenic and medium chain triglyceride diets, 17.8% of patients on the ketogenic diet and 22.2% on medium chain triglyceride diets had a favorable response.[21] Trials of anterior nucleus of thalamus stimulation for refractory epilepsy demonstrated that 54% of patients had a favorable response at 2 years.[22] In a study evaluating trigeminal nerve stimulation, thirty-eight percent of patients had a >50% response.[23] The present finding of 40.6% of patients having >50% seizure reductions suggests that VNS is comparable to these other treatments in the setting of refractory epilepsy.

4.6. Subgroup analyses

None of the baseline characteristics examined was associated with differences in VNS outcomes. In the low baseline seizure frequency group, younger patients showed moderately better outcomes. Other pediatric studies have similarly failed to identify differences in outcome based seizure type,[12,15,24–26] MRI abnormality,[25] pre-implantation number of medications,[27] and duration of epilepsy.[12,15,27,28] The responder rate of LGS patients in this series was similar to those reported in other studies and did not differ significantly from the group as a whole.[26,29,30]

4.7. Age

To date, several studies have evaluated the efficacy of VNS in children under 12 years.[10–13,15,25–28,30–34] Few have demonstrated that younger age at implantation lead to better outcomes.[13,25,34] Similar to the previously mentioned retrospective study of 46 patients,[13] trends related to age at implantation in our study only approached significance at 12 months. A study with 135 patients demonstrated that the pre-adolescent patients (0–12 years) had better clinical outcomes than older patients, with the youngest children (<6 years) experiencing superior outcomes.[34] A study in 43 patients <12 years of age reported that 51% experienced seizure reductions of >50%, and this is comparable to results in older children and adults.[26]

4.8. Challenges

Findings need to be interpreted in the setting of data acquisition and are subject to selection and information bias. The accuracy of seizure reporting depended primarily on patient and/or caregiver-reported information. There may be greater potential for seizure reduction in patients with higher seizure frequencies. Additionally, higher seizure frequency may make accurate seizure counts less accurate, but we believe that we might have missed more seizures at baseline than at follow up. While epilepsy subtype may have been a factor in seizure frequency, numbers of patients with epilepsy syndromes were too small in both groups to investigate this claim.

4.9. Conclusion

VNS has limited efficacy in pediatric epilepsy patients and in our series some patients even had seizure worsening. However, in selected patients with frequent seizures at baseline, VNS provides meaningful seizure reduction. Further data, either through larger comparative effectiveness or randomized controlled trials is needed to guide patient selection in the very young. A multi-center study may also be useful to determine if the same trends exist at other centers and if there are any correlations between these trends and various VNS stimulation parameters.

Conflicts of interest statement

The authors declare that they have no conflicts of interest.

Disclosures

This manuscript discusses off-label use of vagal nerve stimulation.

Camilla Yu, Sriram Ramgopal, Mark Libenson, Imane Abdelmoumen, Christine Powell, Kyle Remy, and Alexander Rotenberg have nothing to disclose.

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Tobias Loddenkemper serves on the Laboratory Accreditation Board for Long Term (Epilepsy and ICU) Monitoring (ABRET), performs Video EEG longterm monitoring, EEGs, and other electrophysiological studies at Children's Hospital Boston and bills for these procedures (20%), receives support from NIH/NINDS, is supported by a Career Development Fellowship Award from Harvard Medical School and Children's Hospital Boston, by the Program for Quality and Safety at Children's Hospital Boston, receives research funding from the Epilepsy Foundation of America, from the American Epilepsy Society, from the Center for Integration of Medicine & Innovative Technology (CIMIT), Cure, the Danny-Did Foundation, the Pediatric Epilepsy Research Foundation, and received investigator initiated research support from Lundbeck and Eisai Inc.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2013.10.002.

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