EVALUATION OF RURAL PEDIATRIC PATIENTS WITH INTRACTABLE EPILEPSY FOR VAGAL NERVE STIMULATION: A TELEHEALTH EDUCATION BASED MODEL

A thesis submitted to the University of Arizona College of Medicine – Phoenix

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Abstract

Vagal Nerve Stimulation (VNS) has been a treatment of choice for pediatric patients with medically refractory epilepsy for over 20 years since FDA approval in 1997. It is relatively minimally-invasive to other surgical interventions, has few complications, and has a significant impact on decreasing the frequency, severity, and duration of seizures. This project sought to answer three main questions. What are the epidemiologic factors that are significant for pediatric medically refractory epilepsy? What are the best outcome predictors for VNS implantation? And finally, is there a way to improve rural physicians' decision making abilities when referring patients for evaluation of VNS implantation?

We evaluated a single-institution's outcomes with VNS implantation and analyzed national data through the KID database with regards to cost disparities between rural and urban areas. At Phoenix Children's Hospital, we found that of the 41 patients who had VNS implantation and met inclusion over a 6 year period, over 70% of patients achieved greater than 50% seizure frequency reduction. Other predictors of improved outcomes are device output current settings, as well as race. Of the national database, we have found that a disparity does exists, with rural patients on average waiting one year longer than urban patients to get the implantation. Other differences were found, such as length of stay. Rural patients had more neurologic comorbidities, and stayed on average 2 days less than urban patients. An educational webinar presentation was created, aimed at informing primary care physicians about the indications for VNS implantation. Ultimately we predict that with the webinar, more patients with intractable epilepsy will be evaluated earlier and eventually have implantation of the VNS device. Future work will use the webinar presentation to reduce the rural and non-rural healthcare practice disparities that exist.

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Introduction

Epilepsy is a common pediatric problem, affecting 1% of the population with approximately 30% of children with epilepsy refractory to standard anticonvulsant medications[1]. When appropriate, surgery offers these children a chance for seizure freedom and medication withdrawal, or seizure frequency and intensity reduction with medication reduction, along with an improved quality of life. Over the last 15 years, the field has advanced technologically, made epilepsy surgery more readily available, and expanded the patient population that might potentially benefit. Numerous surgical options are available to patients for cure including focal resection, lesionectomy, and hemispherectomy. When cure is not possible, neuromodulation using vagus nerve stimulation (VNS) has been available for over 20 years[2]. It is necessary to review our results from these epilepsy surgeries for continued growth in our understanding of the disease and further improvements in recommending therapeutic interventions. It is also important to share our results with the larger medical community to reinforce this option as a successful treatment for medically refractory epilepsy. Without surgery as an option, most of these children will continue to have frequent seizures which will impact their quality of life and options for the future.

Epilepsy surgery is felt by many in the medical community to be a last resort option and only used when every other treatment option has failed. We have learned in the last 10 years that surgery is safe and effective and should be offered sooner. Children who have surgery earlier recover more quickly and have improved development and cognitive function. We have also learned that patients who fail to achieve seizure control on the first two anticonvulsant medications prescribed have less than a 10% chance of achieving seizure freedom with the next medication. Surgery offers a 50 – 80% chance of seizure freedom, depending on the procedure, with low complication rates. One way to improve care for children with epilepsy is to review our data and share with the medical community to educate that surgery is a safe and effective option that should be offered sooner in the child's treatment algorithm.

There has not been a considerable amount of research done regarding perioperative care for pediatric patients with drug-resistant epilepsy (medically refractory seizures). There also is no standard of care when it comes to follow up for these patients post-op. Finally, there needs to be an acceptable manner in which a complete standard of care is available and disseminated to patients in a rural setting. It is necessary to understand all of the possible complications post-operatively, as well as the necessity to evaluate specific ways in which the seizures/epilepsy is being affected by the VNS (how the severity/frequency/hospital visits changes with respect to pre and post VNS implant, as well as adjustments that are made to the stimulating device). Surgical complications regarding VNS implantation are common, and should be further understood to increase the education of both physicians and patients. Vocal stridor, for example, is known to vary based on the coil diameter, and it is also understood that adjustments need to be made on an individual basis[18]. Also, while current studies show that VNS implantation does not reduce risk of premature death from Sudden Unexpected Death due to Epilepsy (SUDEP) as a result of the intractable epilepsy overall, improved outcomes with new technology such as with newer models of generators and closed loop systems, may have a different impact[19].

Besides improvements in our understanding of intractable epilepsy and its treatment, we need to consider the unique issues affecting rural populations. Strides have already been made to evaluate telehealth as an acceptable alternative to track epileptic patients, and thus we can try to see a large need to generate a standard protocol for evaluating rural pediatric VNS patients through a telehealth network[3]. Access to medical care in rural Arizona is an issue that affects pediatric epileptic patients. Rural isolation has been linked to a reason for the above average healthcare disparities observed for epileptic patients. Arizona falls below the USA average number of neurologists per 1000 patients with epilepsy (USA avg: 6.1, AZ avg: 5.8)[4]. With over 12% of the AZ population living in rural residence, a tele-presence alternative should be sought for rural VNS patients. Additionally, there is not a solid literature base that describes the epidemiology of intractable epilepsy or pediatric patients' responses to VNS implantation, and some foundational work to understand the population dynamics will be helpful in determining prospective patients to focus enrollment on. Cost utility studies have been done in developing countries such as Jordan, and researchers have concluded that VNS implantation was favorable

and lead to improvement in quality of life[20]. This notion should be applied to rural areas within Arizona, and thus can have similar expectations.

In order to address the healthcare disparities within rural areas, continuing medical education programs have been developed which can be accessed online. Webinar style programs have been identified as having a significant influence on how surgeons and radiologists behave after participation in the program[5]. These webinars approach the large issue of reaching many individuals where access to such education is difficult due to location/distance. Projects such as this current one will address previously described needs to enhance community awareness within rural Arizona[16].

With regards to the VNS implants themselves, a majority of the physician and patient education is done through the producer of the implant[7]. Currently, physicians have to request education material, and if they are unaware of any developments or changes, there is the possibility that they will stay uninformed. Providing this information to rural physicians through a webinar has the possibility to increase awareness of up to date technology and indications for referring patients for evaluation for epilepsy surgery and the potential benefit of the VNS.

Materials and Methods

Phase I: Retrospective

Inclusion criteria were as follows: subjects were pediatric patients (all children ages birth to 21 years) who had undergone VNS implantation surgery at Phoenix Children's Hospital for the treatment of intractable epilepsy, between January 1, 2009 and November 30, 2015 and had follow-up at least for 6 months with documented device adjustments. Patients were excluded on the following basis: if their surgery was a re-implantation of a VNS or revision surgery, if there was not a complete clinical record, if they did not follow up for the minimum of 6 months, or if they had any other epilepsy surgeries performed after the VNS implantation. Rural patients were further identified by sorting the subject database by zip code and excluding all zip codes within the Phoenix and Tucson metropolitan areas. Table 1 lists inclusion and exclusion criteria.

Data analyzed included where the subjects were referred from, pre-surgical work-up, surgical procedures performed, and outcomes including number of post-surgical seizures, neuropsychological results, and complications. Subject data was also looked at to analyze if anyone was lost to follow-up. The post-operative follow-up appointments were examined to determine what aspects of this care can be delivered through a telehealth model, in order to reduce potential "lost to follow-up" patients.

A secondary database was examined to identify patients using the same subject criteria above, but applied to the entire country. We examined the following data elements of the KID national database in the years 2003, 2006, and 2009 to further understand the disparities between rural and urban patients: Age, gender, race, primary payer, hospital metrics, and patient location, length of stay, total charges, and presence of neurologic comorbidities.

Phase I data retrieval through Phoenix Children's Hospital as well as the national KID database, was accomplished with patient selection using CPT codes 64568 (Insertion of new cranial nerve stimulator and electrodes), Procedure Codes: 04.92, and 86.94, ICD 9 Codes: 345.01, 345.11, 345.41, 345.51, 345.61, 345.71, 345.81, and 345.91, and ICD 10 codes: G40.019, G40.119, G40.219, G40.319, G40.419, G40.804, G40.919, and G40.B19. These numbers were retrieved

from cms.gov/medicare-coverage-database, and listed codes that contained the keywords "epilepsy, intractable, not status epilepticus".

In order to adequately and effectively evaluate the outcomes for the subjects, we created a modified Engel Outcome Scale (mEOS). This scale aimed to take into account subjective and objective reporting, and was reported on a scale from 1-12. Table 2 outlines the data elements that go into calculating the mEOS.

Phase II: Prospective

Information about the retrospective study provided a basis for generating a webinar based educational tool for physicians and potential patients. The webinar incorporated best practices, best outcome predictors from the retrospective phase, as well as the well accepted literature regarding VNS implantation, and present the information in a narrative PowerPoint presentation with audio recording. Figure 1 demonstrates one example slide of the PowerPoint presentation. The entire presentation can be found in the supplemental figures section.

Data Analysis

For outcomes including changes in seizure frequency and duration and the EOS, we used the point bi-serial correlation and spearman correlation depending on the characteristics of variables. For example the values with seizure frequency change is considered an ordinal variable. Any ordinal variables was correlated using spearman. Any binary or nominal data was correlated using the point bi-serial. The outcomes defined by mEOS were more continuous thus we used simple linear regression to ascertain trends.

Regarding the KID database data, a linear regression was performed to compare continuous variables. Fisher's Exact Test was used to compare categorical variables.

Inclusion Criteria	Exclusion Criteria
Age: 1 - 21 years old	Incomplete clinical record
AND	*OR*
Diagnosed with intractable epilepsy (failed use of > 2 anti-epileptic drugs indicated for their seizure	Surgery was a reimplantation or VNS revision
AND	*OR*
Had VNS implantation between Jan 1, 2009 - November 30, 2015	Other epilepsy surgeries were performed after VNS implantation
AND	*OR*
Had follow-up for minimum 6 months	Did not follow-up for minimum of 6 months

Table 1. Inclusion and exclusion criteria for patient selection for retrospective analysis.

Grading Scale	*Engel Outcome Scale*	*Seizure frequency change from baseline*	*Seizure duration change from baseline*
0	-	>90% decrease	>90% decrease
1	Free from disabling seizures with some nondisabling seizures	>50% decrease	>50% decrease
2	Rare debilitating seizures since surgery	>10% decrease	>10% decrease
3	Worthwhile seizure reduction	no change	no change
4	No appreciable change	increase	increase

Table 2. Modified Engel Outcome Scale (mEOS). The mEOS is calculated using qualitative and quantitative data, including the Engel Outcome Scale (EOS), as well as changes in seizure frequency and duration. Adding up each column from 0-4 will yield a mEOS score ranging from 0-12.

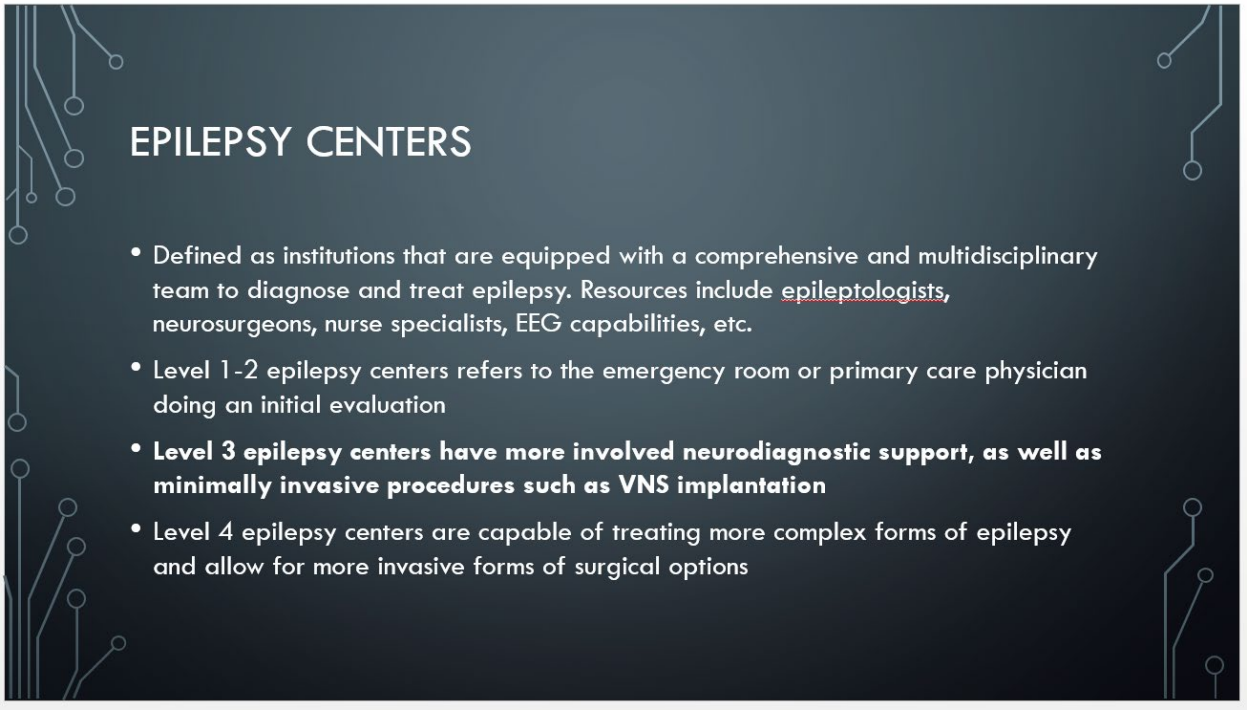

Figure 1. PowerPoint presentation example.

Results

Outcomes from Phoenix Children's Hospital (PCH) Data

To elucidate the effects of VNS surgery, we sought to examine the outcomes at Phoenix Children's Hospital. Eighty-one patients were initially identified having met inclusion criteria, and forty were excluded based on the exclusion criteria. Of the reasons patients were excluded, most common was not enough records or no follow-up documentation beyond 6 months (23 patients), incorrect timing of VNS placement (16 patients), or concurrent epilepsy surgery (1 patient with corpus callosotomy performed within the same hospitalization as VNS implantation). Patients were relatively evenly split between male and female, with 18 male and 23 female patients. The most predominant race was White (31 patients), followed by Hispanic (7 patients), Native American (2 patients), and Black (1 patient).

The average age at seizure onset was 4.1 years (standard deviation ±4.8 years), and the average age at implantation was 10.02 years (standard deviation ±5.7 years), with a total average time of 5.92 years from diagnosis until implantation. Twenty-five patients had some form of congenital neurodevelopmental delay, the most common being autism (7 patients) and cerebral palsy (5 patients), followed by rare congenital disorders such as Aicardi Syndrome, Tuberous sclerosis, and Lennox-Gastaut Syndrome. Seizure types were broken down into 3 categories: non-focal, focal, and both. In total, 31 patients experienced only non-focal seizure types, 5 patients experienced only focal seizures, and 5 with both. Only one patient had their seizure type change after VNS implantation, when a patient started out with only focal seizures, and then went on to develop non-focal seizures after implantation.

On average, patients were tried on 5.1 (standard deviation ±1.9 AEDs) anti-epileptic drugs (AEDs), with 5 being the most common. After VNS implantation, the average AED use dropped down to 3.0 (standard deviation ±1.5 AEDs), with 3 being the most common ($p < 0.05$). Complications included cough (2.4%), device infection (4.9%), and changes to voice (7.3%). The average length of follow-up was 3.7 years (standard deviation ±1.7 years), and the average number of follow-up visits documented in that time was 13.5 (standard deviation ±9.5 visits). The average Engel

Outcome Score was 2.8 (standard deviation ±1.15). The average modified Engel Outcome Score (mEOS) was 7.15 (standard deviation ±3.49). With regards to change in seizure frequency, 39 patients had documented changes. Greater than 90% seizure frequency reduction was achieved in 17 (43.6%) patients, 12 (30.8%) patients achieved greater than 50% seizure frequency reduction, 3 (7.7%) patients achieved greater than 10% decrease, and 7 (17.9%) experienced no appreciable change in seizure frequency. Seizure duration change was only documented in 29 patients. Six patients (20.7%) achieved greater than 90% reduction in seizure duration, 8 (27.6%) patients achieved greater than 50% reduction in seizure duration, 3 (10.3%) patients achieved greater than 10% reduction in seizure duration, 10 (34.5%) patients achieved no change in seizure duration, and 2 (6.9%) patients had an increase in the duration of their seizures.

Predictors of Improved Outcomes

Many variables were examined in this study, ranging from demographics, to seizure and epilepsy characteristics, to device settings. Female gender was associated with improved outcomes defined by the EOS ($p < 0.05$). Race had a near significant relationship with outcomes defined by the mEOS, with Whites having better outcomes than Hispanics, and Hispanics having better outcomes compared to Native Americans ($p = 0.059$). Device output current was associated with a decrease in the seizure frequency ($p = 0.0008$), with 1.75 mA being associated with the lowest mEOS score. An increase in the device pulse width was associated with improved mEOS scores ($p = 0.011$). Other settings such as on and off time, signal frequency, and magnet settings did not alter outcomes in any statistically significant manner.

Disparities in Healthcare Delivery

We first examined patient demographic data from the PCH database. We were only able to find two patients out of forty-one that lived outside of urban zip-codes. Figure 2 shows a map of Arizona and includes where the patients' zip codes are.

Next, we examined the KID national database over the years 2003, 2006, and 2009, and extracted patient data from 1,015 patients with similar selection criteria as explained in the methods section above. The distribution of patients across the 3 years was relatively equal, each between

30-35% of the 1,015 patients. Gender was roughly split evenly, with 50.1% of the sample being female. Age at time of procedure was 10.2 years on average. Patients were majority Caucasian, approximately 70%, followed by 15.9% Hispanic, and 6.4% African American. Primary payer for the majority of patients was private insurance, at 54.3%, followed by Medicaid 40.6%. Most hospitals that performed the VNS implantation had urban designation; 98.6% of procedures done were done in urban hospitals, and 1.4% done at rural centers. Most patients lived in areas with population greater than 50,000 people, with only 9.7% of patients living in areas that had less than 50,000 people.

After comparing the rural and urban hospitals, we obtained the following data. Between the 1,015 patients over the 3 years, only 26 patients had their VNS implantation done at rural hospitals. The age of patients who had received VNS implantation at rural centers compared to urban was on average 1.1 years older, 11.4 compared to 10.3 years at rural and urban hospitals, respectively ($p = 0.003$). Medicaid was the majority primary payer for the rural patients, at approximately 71.9%, compared to only being primary payer for 39.1% of patients at urban hospitals ($p = 0.10$). Length of stay were lower in the rural hospitals, with patients staying a total of 1.36 days compared to urban hospitals of 3.82 days ($p < 0.001$). Total charges had a similar relationship, with rural hospitals charging $31,886.50 compared to $47,592.80 at urban hospitals ($p < 0.001$).

Phoenix Children's Hospital Patient Characteristics	
Variables	**Values**
Total # of patients included in data	41
Age at seizure onset, years (mean, standard deviation)	4.1, ±4.8
Age at VNS implantation, years (mean, standard deviation)	10.0, ±5.17
Gender (# of female)	23
Race	
White (#, %)	31, 75.6%
Black (#, %)	1, 2.4%
Hispanic (#, %)	7, 17.1%
Native American (#, %)	2, 4.9%
Neurocognitive comorbidites	
Autism (#, %)	7, 17.1%
Cerebral Palsy (#,%)	5, 12.2%
Congenital Disorders (#, %)	7, 17.1%
Seizure Type	
Non-Focal (#, %)	31, 75.6%
Focal (#, %)	5, 12.2%
Both (#, %)	5, 12.2%

Table 3. Phoenix Children's Hospital Patient Characteristics.
Eighty-one patients met the inclusion criteria, and 40 patients were excluded.

Phoenix Children's Hospital Patient Data	
Variables	**Values**
AED use pre-VNS implantation (mean, std dev)	5.1, ±1.9
AED use post-VNS implantation (mean, std dev)	3.0, ±1.5
Engel Outcome Score (mean, std dev)	2.8, ±1.2
Modified Engel Outcome Score (mean, std. dev)	7.2, ±3.5
Seizure Frequency Change	
> 90% decrease (#, %)	17, 43.6%
> 50% decrease (#, %)	12, 30.8%
> 10% decrease (#, %)	3, 7.7%
No appreciable change (#, %)	7, 17.9%
Seizure Duration Change	
> 90% decrease (#, %)	6, 20.7%
> 50% decrease (#, %)	8, 27.6%
> 10% decrease (#, %)	3, 10.3%
No appreciable change (#, %)	10, 34.5%
Increase (#, %)	2, 6.9%
Surgical Complications	
Cough (#, %)	1, 2.4%
Voice changes (#, %)	3, 7.3%
Device infection (#, %)	2, 4.8%
Other (#, %)	4, 9.8%
None (#, %)	31, 75.6%
Follow-up length (years, std dev)	3.7 ±1.7
Follow-up visits (# of visits, std dev)	13.5, ±9.5

Table 4. Phoenix Children's Hospital Patient Data.

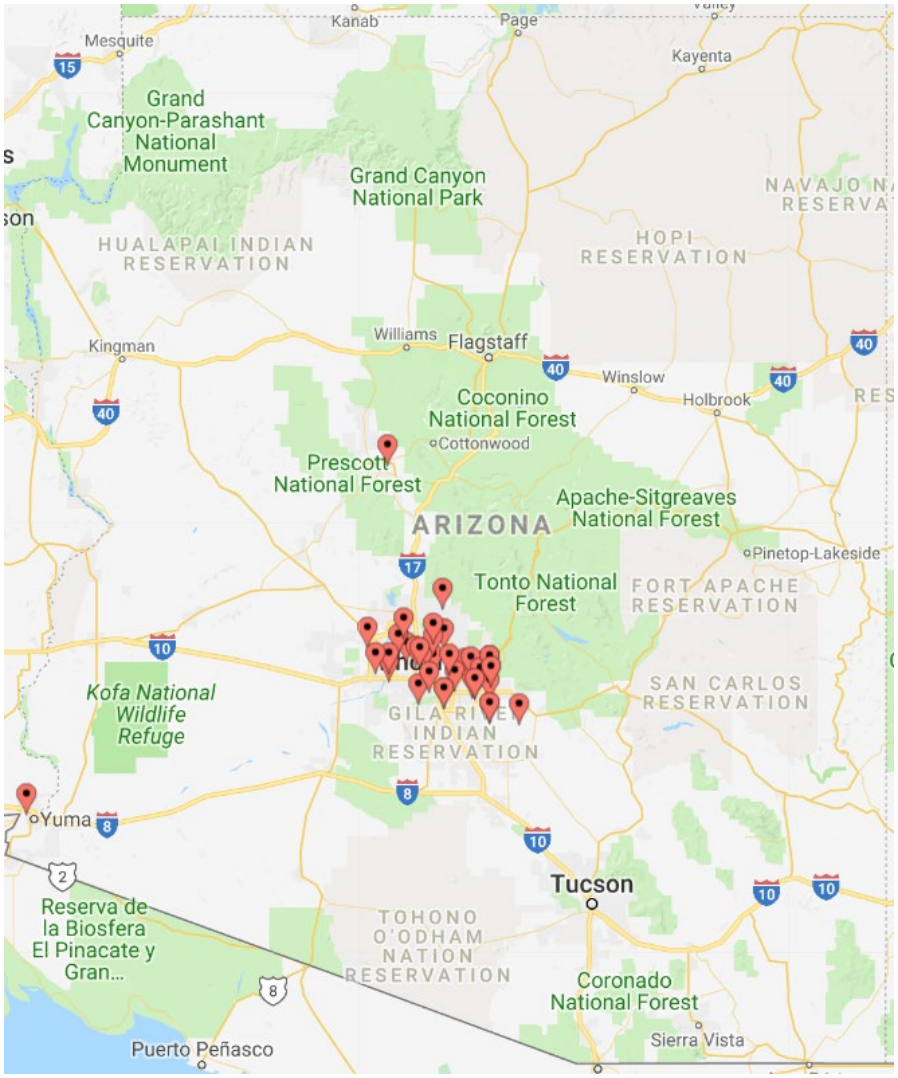

Figure 2. Map of Arizona including patient distribution. Patient "pins" on the map are determined by zip-code. Two out of forty-one zip codes were classified as rural.

Variables	Values N=1015
Age, years (mean, 95% CI)	10.2 (9.60, 10.7)
Gender (Female %, 95% CI)	50.1 (45.7, 54.5)
Race (%, 95% CI)	
Caucasian	70.0 (64.1, 75.4)
African American	6.36 (3.91, 10.2)
Hispanic	15.9 (11.7, 21.5)
Asian/Pacific Islander	0.26 (0.04, 1.93)
Native American	0.30 (0.05, 2.00)
Other	7.04 (4.14, 11.7)
Primary Payer (%, 95% CI)	
Medicare	0.16 (0.02, 1.14)
Medicaid	40.6 (35.1, 46.3)
Private	54.3 (48.7, 59.7)
Self-pay	0.41 (0.009, 1.68)
No Charge	0.15 (0.002, 1.10)
Other	4.41 (2.92, 6.58)
Hospital Location (%, 95% CI)	
Rural	1.36 (0.22, 7.82)
Urban	98.6 (92.2, 99.7)
Patient Location (%, 95% CI)	
Central (pop ≥1mil)	38.5 (32.6, 44.7)
Fringe (pop ≥1mil)	25.6 (21.8, 29.9)
Pop 250,000-999,999	16.7 (13.3, 20.7)
Pop 50,000-249,999	9.41 (7.25, 12.1)
Micropolitan	5.69 (3.64, 8.78)
Non-core counties	4.04 (2.31, 6.97)
Hospital Region (%, 95% CI)	
Northeast	15.1 (8.72, 24.9)
Midwest	20.9 (13.1, 31.6)
South	39.8 (26.7, 54.5)
West	21.4 (14.237.8)
Length of Stay (mean, 95% CI)	3.73 (2.86, 4.59)
Total Charges (mean, 95% CI)	46803.3 (41993.6, 51613.5)
Chronic Lung Disease (yes %, 95% CI)	8.30 (5.92, 11.5)
Chronic Neurological Disease (yes %, 95% CI)	2.42 (1.35, 4.32)
Chronic Obesity (yes %, 95% CI)	1.33 (0.67, 2.58)
Chronic Pulmonary Disease (yes %, 95% CI)	0 (0.0)
Mortality (%, 95% CI)	0 (0.0)

Table 5. Characteristics of patient data from KID Database. Patient data obtained over multiple years (2003, 2006, 2009). Demographically, patients are majority Caucasian, and live in populations over 50,000 people.

Variables	Hospital Location		
	Rural N=26	Urban N=989	P-value
Age, years (mean, 95% CI)	11.4 (7.20, 15.6)	10.3 (9.70, 10.8)	0.003
Gender (Female %, 95% CI)	64.1 (3.05, 99.0)	50.0 (45.7, 54.5)	0.45
Race (%, 95% CI)			0.84
Caucasian	100.0	68.9 (63.0, 74.3)	
African American		6.66 (4.11, 10.6)	
Hispanic		16.7 (12.2, 22.5)	
Asian/Pacific Islander		0.27 (0.004, 2.02)	
Native American		0.31 (0.005, 2.09)	
Other		7.07 (4.09, 11.9)	
Primary Payer (%, 95% CI)			0.10
Medicare		1.16 (0.02, 1.23)	
Medicaid	71.9 (0.02, 99.9)	39.1 (34.0, 44.4)	
Private	10.2 (1.04e-12, 1.0)	55.8 (50.5, 60.9)	
Self-pay		0.44 (0.11, 1.80)	
No Charge		0.16 (0.02, 1.19)	
Other	17.9 (0.92, 83.6)	4.34 (2.84, 6.57)	
Hospital Bed Size (%, 95% CI)			0.43
Small		13.3 (7.19, 23.2)	
Medium		20.8 (12.8, 31.9)	
Large	100.0	65.9 (53.5, 76.5)	
Patient Location (%, 95% CI)			0.074
Central (pop ≥1mil)		40.1 (34.2, 46.3)	
Fringe (pop <1mil)	35.9 (0.98, 96.9)	25.6 (21.2, 30.1)	
Pop 250,000-999,999	35.9 (0.98, 96.9)	16.1 (12.6, 20.4)	
Pop 50,000-249,999	28.1 (0.004, 99.9)	8.93 (6.74, 11.7)	
Micropolitan		5.31 (3.21, 8.66)	
Non-core counties		3.84 (2.12, 6.84)	
Length of Stay (mean, 95% CI)	1.36 (0.43, 2.28)	3.82 (2.88, 4.75)	<0.001
Total Charges (mean, 95% CI)	31886.5 (24223.5, 39549.5)	47592.8 (42556.5, 52629.1)	<0.001
Chronic Neurological Disease (yes %, 95% CI)	17.9 (0.92, 83.7)	2.36 (1.28, 4.32)	0.14
Mortality (%, 95% CI)	0 (0.0)	0 (0.0)	N/A

Table 6. Comparison of variables between rural and urban patients. On average, patients with VNS implantation at rural hospitals were 1.1 years older than patients at urban hospitals. Patients at rural hospitals had shorter length of stays and decreased total charges compared to urban hospital patients.

Discussion

After performing a retrospective single-institution validation review of the efficacy of vagal nerve stimulation for pediatric medically refractory epilepsy, we have confirmed that this is a safe, minimally invasive, and effective method to reduce the seizure burden. Race seemed to play a role in the outcomes, with White patients having lower modified Engel Outcome Scores compared to Hispanics, and Hispanics having lower modified Engel Outcome Scores when compared to Native Americans. While this arm of the study did not look into the socioeconomic status with relation to these patients, it could play a role into the reasoning for the difference in outcomes. Genetics may also play a role in the race disparity.

Vagal nerve stimulation in general is indicated in generalized and non-focal epilepsy, and 30/41 patients had only non-focal seizure types, with 5 patients who had only focal seizures, and 5 patients who had both focal and non-focal seizures. This is a self-selecting group, as most patients being referred for implantation were from non-rural areas, and referred by specialists such as child neurologists. We anticipate that one of the reasons for a decrease in the rural referral base is due to the lack of knowledge regarding the indications for referral.

The safety of the surgery is also well documented, prior to this study. Our data conclude that the complications associated with implantation were rare, and only included minor complications such as temporary cough, or surgical site infections. Many of these complications were transient, and physicians were able to mitigate symptoms by reducing the amplitude of stimulation from the device. The device implantation also did not alter the pathology of the seizures in harmful ways, with only one patient developing a new seizure type after the surgery.

We created a useful tool in the evaluation of seizure activity before and after epilepsy surgery. The Engel Outcome Scale (EOS) has been widely used, however it is largely subjective and has the potential of creating low inter-rater reliability. The modified Engel Outcome scale (mEOS) that was utilized for this study incorporate both the subjective nature of the original EOS, as well as more objective measures such as changes in seizure frequency and duration. We anticipate

scoring methods such as the mEOS can be used to obtain a more holistic understanding of the impact epilepsy surgery has on patients.

Follow up after VNS implantation is critical, as the device is not immediately therapeutic in the post-operative period. Multiple follow-up appointments are required to increase the dose of stimulation current, as well as other settings that need to be fine-tuned to suit the needs of the patient. We found that the most common device setting associated with improved outcomes was a device output current of 1.75 mA, which can be used to inform future providers when making adjustments to the VNS. While our study did not conclude what the effects of other settings are, such as pulse width, on and off time, signal frequency, and magnet settings, it is important to further examine the relationship between these settings in a higher power study. Having a greater understanding of the electrophysiologic interplay between the stimulator settings and the effects on seizure activity can assist with troubleshooting as well as potentially reducing the amount of follow-up appointments. Further study into the electrophysiology is required to understand the mechanisms of specific device settings with regards to epilepsy.

When assessing the disparities between rural and urban patients, the Phoenix Children's Hospital data was deemed to be insufficient, as only 2 patients were located in "rural" zip-codes, as defined by the Centers for Medicare and Medicaid Services[21].

It is useful to take a small tangent and discuss the difficulty with studying disparities between rural and non-rural patients. There is currently no agreed-upon definition for any location to get the "rural" designation. For the purposes of this paper, we have chosen to cite the United States Census Bureau, which defines an urbanized areas as 50,000 or more people, and "whatever is not urban is considered rural."[22] When applicable, zip-codes have rural and urban designations as defined by CMS, which was also a definition that was taken into consideration for this paper.

A healthcare disparity exists between rural and urban pediatric patients who are suffering from medically refractory epilepsy. The first disparity is a simple comparison between the ratios of patients in our sample who are rural and of all rural persons in the United States. Only roughly 9% of patients in the data can be categorized as living in rural locations, compared to the 19.3%

of persons in the United States who live in rural areas[23]. Given no epidemiologic studies that show any differences in the rate of medically refractory epilepsy with relation to geographic location, the rates of rural patients who receive VNS implantation should be close to 19.3%. Possible explanations for this could be that patients are simply not being referred enough for escalation of therapy by their rural primary care pediatricians. Other contributing factors also come from the difficulties associated with traveling to tertiary care centers, which can potentially be hours away from the patients' homes.

A second glaring disparity exists between these patients. On average, patients who received the VNS implantation at rural centers were over 1 year older than patients at urban hospitals. While, older age at VNS implantation does not portend worse outcomes, it can be inferred that rural patients on average had to deal with the consequences of medically refractory epilepsy longer than urban patients[24]. Such consequences for example can be suffering from debilitating seizures.

One last and surprising disparity was found between rural and urban hospitals. Patients at rural hospitals stayed on average 2 days less than patients at urban hospitals. This seems to be a standard and well reported finding, with all rural hospitals having length of stays on average about 2 days less than urban hospitals[25]. It must be mentioned that VNS implantation is done as an outpatient surgery, with most patients at large epilepsy centers going home within the same day as their implantation. We must then infer that patients that have protracted hospital stays longer than one day are due to patients who are already in the hospital for evaluation and then go straight to VNS implantation as an inpatient. Finally, we must further examine the data as to why rural hospitals are performing VNS implantation in the first place, where it is usually done in larger urban epilepsy centers.

Future Directions

This project has established the well-known efficacy of vagal nerve stimulation for use in pediatric patients with medically refractory epilepsy. With the creation of the modified Engel Outcome Scale, we anticipate wider use of this scoring system, as it incorporates both qualitative and quantitative information. Lastly, we hope to further the study of the telemedicine presentations as a model to disseminate information and reduce healthcare disparities in rural areas.

Conclusions

This study aimed to answer 3 main questions regarding vagal nerve stimulation for use in pediatric patients with medically refractory epilepsy. We performed a retrospective single institution validation study to confirm the efficacy of pediatric VNS, and found that at Phoenix Children's Hospital, the majority of patients experienced significant and worthwhile reduction in seizure quality, duration, and frequency. We found variables that are associated with improved outcomes, including race, as well as device settings. Lastly, we found a disparity that exists between rural and non-rural patients in regards to VNS implantation. Such disparities include rural patients likely not being referred for VNS evaluation, as well as waiting longer to get the procedure done. We developed steps to address this disparity through a prototype telemedicine educational presentation aimed at informing rural primary care physicians about the indications for VNS referral. Our study paves the way for further understanding of the predictors for improved outcomes after VNS implantation, along with attempts at reducing healthcare disparities in rural areas.

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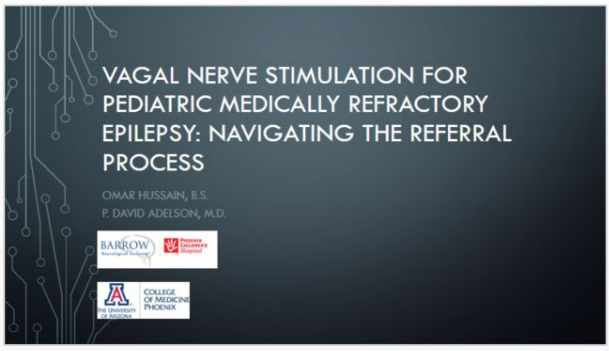
Supplemental Figure 1. Educational PowerPoint Presentation.



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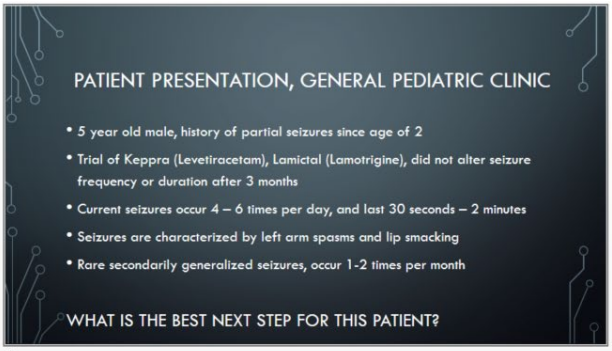

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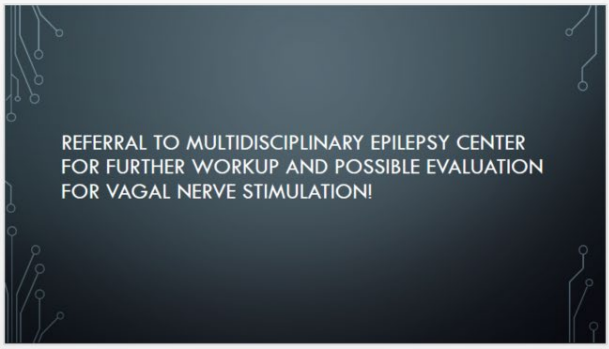

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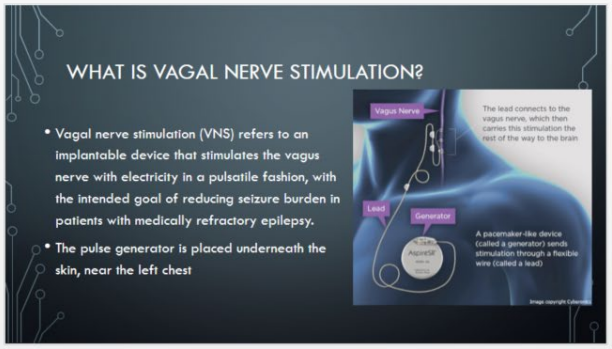

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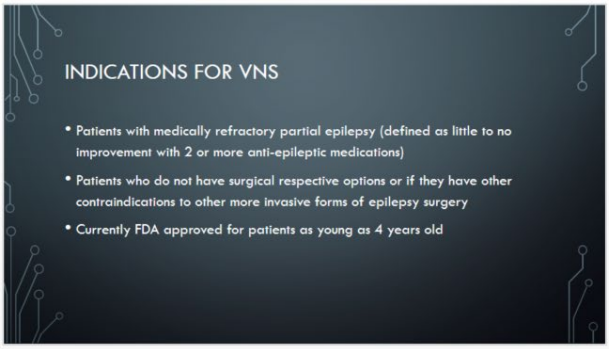

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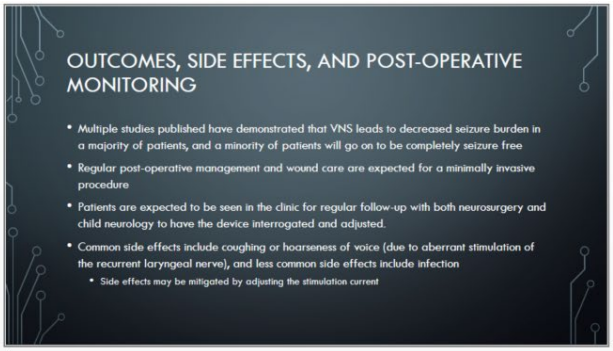

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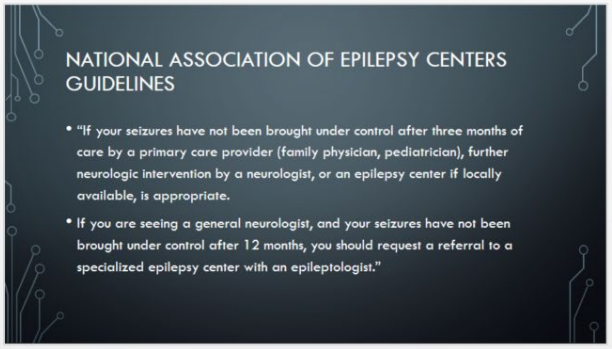

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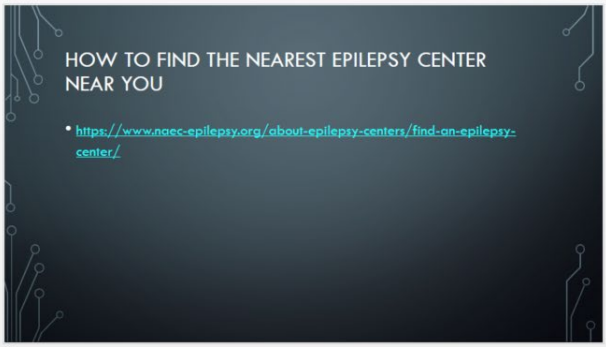
HOW TO FIND THE NEAREST EPILEPSY CENTER NEAR YOU
• https://www.naec-epilepsy.org/about-epilepsy-centers/find-an-epilepsy-center/

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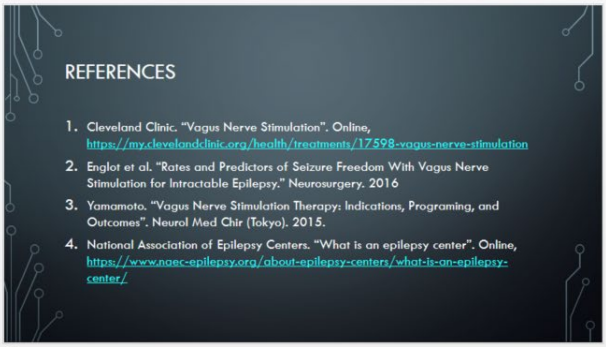
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