Use of vagal nerve stimulation as a treatment for refractory epilepsy in dogs

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Objective—To evaluate safety and efficacy of vagal nerve stimulation in dogs with refractory epilepsy.

Design—Placebo-controlled, double-masked, crossover study.

Animals—10 dogs with poorly controlled seizures.

Procedure—A programmable pacemaker-like device designed to deliver intermittent stimulation to the left cervical trunk of the vagus was surgically implanted in each dog. Dogs were assigned randomly to two 13-week test periods, 1 with nerve stimulation and 1 without nerve stimulation. Owners recorded data on seizure frequency, duration, and intensity, as well as adverse effects.

Results—No significant difference in seizure frequency, duration, or severity was detected between overall 13-week treatment and control periods. During the final 4 weeks of the treatment period, a significant decrease in mean seizure frequency (34.4%) was detected, compared with the control period. Complications included transient bradycardia, asystole, and apnea during intraoperative device testing, and seroma formation, subcutaneous migration of the generator, and transient Horner's syndrome during the 14-day period between surgery and suture removal. No adverse effects of stimulation were detected, and most owners were satisfied with the treatment.

Conclusions and Clinical Relevance—Vagal nerve stimulation is a potentially safe approach to seizure control that appears to be efficacious in certain dogs and should be considered a possible treatment option when antiepileptic medications are ineffective. (*J Am Vet Med Assoc* 2002;221:977–983)

Epilepsy is a common neurologic disorder of dogs and has been reported to account for 2 to 3% of all dogs evaluated at veterinary referral hospitals.[1,2] The mainstay of treatment for canine epilepsy is antiepileptic medication, yet drug treatment alone fails to effectively treat epilepsy in a proportion of dogs. As many as 30% of epileptic dogs have medically refractory seizures, and satisfactory seizure control is never attained despite treatment with 1 or more antiepileptic drugs administered at putative therapeutic serum concentrations.[3-5] Furthermore, medical seizure management is frequently associated with considerable adverse effects, such that less than half of all dogs with epilepsy remain seizure-free without adverse effects from the medication.[6] These adverse effects range from sedation and ataxia to more serious complications such as hepatotoxicosis and bone marrow suppression.

Similar difficulties are encountered in the treatment of humans with epilepsy. In an attempt to more effectively manage patients with these refractory seizures, research has recently expanded into development and use of alternative methods of seizure control. Among these alternative modalities, **vagal nerve stimulation (VNS)** has emerged as a promising form of treatment for humans.

The initial rationale for the use of VNS as a potential treatment for seizures was supported by extensive physiologic and anatomic data. Approximately 80 to 90% of the vagus nerve consists of afferent fibers originating in the viscera, which terminate primarily in the nucleus of the solitary tract. They synapse with axons that project diffusely to multiple cortical and subcortical sites of the brain, where they exert widespread effects on neuronal excitability.[7] Investigators in the 1930s initially determined that stimulation of the cervical portion of the vagus nerve in cats changed cortical EEG activity.[8] In subsequent studies,[9,10] electrical stimulation of the vagus nerve at high frequencies and intensities caused desynchronization of the EEG recorded from cortical neurons. These observations led to the hypothesis that epileptic discharges, attributable to spontaneous synchronous activity of cortical neurons, could be interrupted or prevented by stimulating the vagus nerve. Studies in dogs,[11] rats,[12] and monkeys[13] revealed that intermittent stimulation of the left cervical vagus trunk could effectively prevent experimentally induced seizures. This finding subsequently led to the development of an implantable pacemaker device[a] that delivers repetitive stimulation to the left cervical vagus nerve, as an alternative treatment for seizures in humans.[14] On the basis of results from initial controlled studies in humans,[15,16] in 1997 the FDA approved the use of the device as an adjunctive treatment in reducing the frequency of seizures in adults and adolescents > 12 years of age with partial-onset seizures, which are refractory to antiepileptic medications.

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Presently, more than 10,000 people have received the implanted device. The device has a degree of effectiveness in approximately two-thirds of individuals, and one-third report a decrease in seizure frequency of at least 50%.[17] The complication rate associated with the implant procedure is low, and adverse effects during stimulation of the nerve are typically considered minor and well tolerated by patients.[16-18] Consequently, VNS is now recommended for patients 12 years of age or older with medically intractable partial seizures, who are not candidates for surgical treatments such as focal cortical resection or temporal lobectomy.[19]

The purpose of the study reported here was to evaluate the efficacy of VNS in controlling medically refractory seizures and determine the potential safety and tolerability of the surgically implanted VNS device in epileptic dogs.

Materials and Methods

Patient selection—Selection criteria for the study included onset of seizures between 1 and 5 years of age with a 1-year documented history of seizures; a historical seizure frequency of at least 5 seizures/mo and a seizure-free period of no longer than 2 weeks, or cluster seizures occurring at least once per month; current treatment with therapeutic serum concentrations of orally administered antiepileptic medications; and minimum weight of 15 kg (33 lb), because of the size of the device. Dogs that met all selection criteria were considered candidates for the study. Owners were required to provide informed consent prior to the study. Dogs that met initial eligibility criteria underwent further testing to rule out any underlying cause for the seizures, including hemogram, serum biochemical profile, urinalysis, bile acid concentrations determined after withholding of food and after eating, CSF analysis, canine distemper virus titers in serum and CSF, and computerized tomographic scan of the brain. If any abnormalities were identified that could account for the seizure disorder, the dog was disqualified from further participation in the study. Ten dogs that met all selection criteria were enrolled in the study.

The implantable device—The nerve stimulating system includes a subcutaneously implanted pulse generator, bipolar stimulating coil electrodes that are applied to the left cervical vagus nerve trunk, a unified lead that connects the electrode to the generator, and software through which the system is activated and adjusted.[14] The pulse generator[b] is powered by a single lithium thionyl chloride battery and is housed in a hermetically sealed titanium case. The generator case, which looks similar to a cardiac pacemaker, is 55 mm in diameter, 13.2 mm thick, and weighs 65 grams. The stimulating electrode[c] is made of flexible and biocompatible platinum ribbon embedded in a silicone helix. The helical shape allows the electrodes to be self-sizing and conform to the shape of the nerve, thereby minimizing mechanical trauma to the nerve during placement and permitting the platinum ribbon to maintain optimum mechanical contact with the nerve. The device is programmed with a personal computer by use of programming system software and a programming wand.[d] The software allows noninvasive communication with the pulse generator after it is implanted in the patient, such that the device can be turned on or off and stimulus parameters can be adjusted.

Surgery—The device was surgically implanted via general anesthesia by use of a similar technique to that initially described in experimental dogs[11] and later modified for use in humans.[20] Cardiovascular monitoring during the surgical procedure included continuous lead-II ECG monitoring and indirect blood pressure measurements taken at 5-minute intervals. The dog was placed in right lateral recumbency with the head and neck rotated approximately 45° clockwise. The skin was surgically prepared over the entire aspect of the left cervical region, extending past the dorsal and ventral midlines. The caudodorsal portion of the prepared area was extended past the left scapula. A 15-cm linear skin incision was made approximately 1 cm dorsal and parallel to the jugular furrow. The subcutaneous tissues were incised, and dissection was extended through the sternocephalicus muscle at the level at which the dorsal sternooccipitalis and ventral sternomastoideus portions of the muscle join. The trachea was gently reflected ventrally to expose the left carotid sheath. The carotid sheath was opened, and the vagosympathetic trunk was freed from the adjacent connective tissue and isolated with vessel loops. A 10-cm linear skin incision was made approximately 1 cm from dorsal midline, with the caudal extent of the incision located just cranial to the left scapula. A subcutaneous pocket was made in the area by bluntly elevating the subcutaneous tissues from the underlying muscles to allow the pulse generator to fit snugly in the pocket. A shunt-passing tool was used to tunnel subcutaneously from the ventral cervical incision to the pocket in the dorsal cervical region, and the electrode leads were passed through the tunnel. Returning to the ventral cervical incision, the spiral electrodes and tethering lead were wrapped around the isolated nerve. Silicone tie-downs were used to anchor the leads in place and provide strain relief and were fastened to the underlying fascia with nonabsorbable suture. The leads were connected to the generator, and the system was tested to ensure that the device was operational. The generator was placed in the subcutaneous pocket in the dorsal cervical region and anchored to the underlying fascia with nonabsorbable suture. The wounds were flushed with cefazolin[e] and closed routinely. After fully recovering from anesthesia, usually 1 day after surgery, a second device test was performed during which a lead-II ECG was evaluated during a 15-minute period to monitor for any change in heart rate or rhythm. Aside from this testing of the device, the system was maintained at 0 current during surgery and for 2 weeks after surgery.

Study design—The clinical trial was designed as a double-masked crossover study with each dog undergoing a treatment period during which the device was active and a control period in which the device was inactive. The study protocol was approved by the North Carolina State University Institutional Animal Care and Use Committee. Prior to surgical implantation of the device, baseline data were collected for a minimum of 8 weeks, during which owners began recording seizure frequency, duration, and severity on standard forms designed for the study.[f] Baseline data were compiled to determine a monthly seizure frequency prior to the surgical intervention, as well as to measure owner compliance regarding data collection. For dogs that had cluster seizures, owners were instructed to count each individual seizure episode as a separate seizure. Following a 2-week postoperative recovery period, dogs were randomly assigned to 1 of 2 groups on the basis of the order of the treatment and control periods. Randomization was performed by a statistician not otherwise involved in the study. Treatment and control periods were 13 weeks in duration and were separated by a 4-week washout period. Owners were instructed to continue to collect all data initiated during baseline in addition to noting any adverse effects. Antiepileptic drug dosage was not altered throughout the study. Dogs were monitored at 4-week intervals; records of seizure activity and adverse effects were reviewed by an investigator who was unaware of treatment group, and serum drug concentrations were measured at

each visit. A different investigator was responsible for checking the device's function and turning the device on and off as needed. Stimulation parameters included frequency of 30 Hz, pulse width of 500 µs, on-time of 30 seconds, and off-time of 5 minutes. These parameters were the same as those used in human clinical trials. The current delivered by the device during the treatment period was set on the basis of each individual dog's tolerance to the stimulation. When the current was increased beyond the tolerance point, the dog began to cough during the 30-second cycle in which the device was stimulating the nerve. To keep the study masked, the optimal current was determined to be the highest curent for which no cough was elicited. The current was kept at this established optimal strength throughout the treatment phase of the study.

At the end of each dog's participation in the study, the order of the test periods was revealed and owners were given the options of having the device removed, kept in place but turned off, or turned on. Owners were contacted at the termination of the study and asked to respond to a questionnaire. Owners were asked to rate their overall experience with the use of VNS in their dog and their satisfaction with the incidence of postoperative complications and adverse effects associated with the device, using a scale of 1 to 5 (1 = extremely dissatisfied, 2 = somewhat dissatisfied, 3 = neutral, 4 = somewhat satisfied, 5 = extremely satisfied). Owners were asked to assess their dog's overall quality of life after VNS, compared with that before the implant, on the basis of a scale of 1 to 5 (1 = marked decrease, 2 = decrease, 3 = no change, 4 = increase, 5 = marked increase).

Statistical analysis—Seizure frequency during each 13-week test period was determined for each dog. Mean seizure frequencies during the treatment and control periods were compared by use of a paired Student *t* test. Statistical analysis was based on a null hypothesis that there was no change in seizure frequency during stimulation, compared with the control period. In addition, the percentage difference in seizure frequency between treatment and control periods was calculated for each dog and analyzed for the study population by use of a 1-sample *t* test against a hypothetical mean of zero. Mean seizure duration and mean seizure severity were calculated for each dog during the two 13-week test periods. Mean seizure severity was determined from responses provided by the owner on the standardized seizure forms, such that each seizure was assigned a numeric score from 3 to 18, with a higher number corresponding to a more intense seizure. For the population of dogs, mean seizure duration and mean seizure severity during the treatment and control periods were compared by use of a paired Student *t* test, on the basis of the null hypothesis that there was no change in seizure duration or intensity during the stimulation period, compared with the control period. A Wilcoxon signed-rank test was planned in the event that any data were not normally distributed. Median serum antiepileptic drug concentrations were compared between treatment and control periods by use of a Wilcoxon signed-rank test. To assess any lag in efficacy or increased effectiveness over time, analyses of mean seizure frequency, percentage difference in seizure frequency, mean seizure duration, and mean seizure severity were repeated for data obtained only during the final 4 weeks of each test period. All statistical analyses were performed with a commercially available software package.[g] A value of $P < 0.05$ was considered significant for all comparisons.

Results

Ten dogs that met eligibility criteria were enrolled in the study. All dogs that underwent implantation of the device subsequently completed the study. Age of the dogs at enrollment ranged from 2 to 6 years (median, 4.5 years). There were 6 neutered males, 1 sexually intact male, and 3 neutered females. Breeds included 3 Border Collies, 3 mixed-breed dogs (2 Labrador Retriever crosses and 1 Brittany Spaniel cross), and 1 each of German Shepherd Dog, Golden Retriever, Labrador Retriever, and Boxer. Duration of seizures prior to enrollment in the study ranged from 1 to 5 years (mean ± SD, 2.2 ± 1.4 years). Nine of the dogs were being treated with phenobarbital and potassium bromide, and 1 dog was receiving combination treatment with potassium bromide and felbamate. Antiepileptic drug concentrations were within established therapeutic ranges. Duration of antiepileptic drug treatment ranged from 8 to 54 months (median, 19 months), and dogs had been treated with the current combination of medications for 4 to 41 months (median, 13.5 months). Seizures occurred in clusters in all dogs, with a frequency ranging from 2 to 3 times/wk to once monthly. Four of the dogs were reported to have primary generalized seizures, whereas the other 6 dogs had partial seizures with secondary generalization. Two dogs in the latter group occasionally had complex partial seizures that did not generalize, and another dog also had generalized atonic seizures. There was no statistical difference in seizure frequency between the baseline and control period for the group of dogs.

Efficacy—Comparison of seizure frequency during the 2 test periods was performed for 9 of the 10 dogs. One dog had a drastic change in its home situation and was cared for by several different people during 3 months of the study and was excluded from efficacy analysis because of concerns regarding the accuracy of collected data. Seizure frequency during the 13-week treatment period relative to the 13-week control period decreased in 4 dogs, remained unchanged in 2 dogs, and increased in 3 dogs. Mean ± SEM difference in seizure frequency between the control and treatment periods (–0.89 ± 1.81 seizures) was not significant. Mean percentage decrease in seizure frequency between the control period and the treatment period was 5.1% and was not significant. There were no significant differences in mean seizure duration or mean seizure intensity between the treatment and control periods.

Analysis of data from the final 4 weeks of each test period revealed that 5 dogs had a reduction in seizures during the treatment period relative to the control period, 3 dogs had no change in seizure number, and 1 dog had an increase in seizure number with 1 additional seizure. A significant ($P = 0.028$) mean difference in seizure frequency between these 4-week control and treatment periods was identified (mean ± SEM, –1.44 ± 0.65 seizures). Mean percentage decrease in seizure frequency between the control and treatment periods was 34.4% ($P = 0.047$). No differences in mean seizure duration or mean seizure intensity were identified.

Safety and tolerability—Data on safety and tolerability were compiled from all 10 dogs. Surgical complications were encountered during intraoperative device testing, including transient bradycardia in 3

dogs and transient apnea in 1 dog. Two of the dogs that had bradycardia developed asystole during the test period, and 1 dog's heart rate decreased from 80 to 40 beats/min during the test. The cardiac and respiratory effects lasted < 30 seconds and ceased after the stimulator was inactivated at the end of the test, and consequently required no intervention. Electrocardiography performed during the postoperative test with the dogs in an awake state did not detect a change in heart rate or rhythm in any of the dogs.

Postoperative complications that were encountered included Horner's syndrome, seroma formation, and migration of the generator. Two dogs developed Horner's syndrome in the left eye that was first observed approximately 24 hours after surgery. In both instances, the condition resolved within 2 to 4 weeks. Two dogs developed a seroma at the ventral cervical incision site. One of the seromas required draining, and both resolved without complication. The sutures used to anchor the generator in place loosened in 1 dog, resulting in subcutaneous migration of the generator. This migration was corrected with a second surgical procedure in which the generator was anchored underneath the cervical musculature. No further problems were encountered in this dog.

The current setting tolerated by the dogs ranged from 0.25 to 1.0 mA. Seven dogs had an optimal current of 0.25 mA (the lowest available current setting for the device), and optimal currents in the 3 remaining dogs were 0.50, 0.75, and 1.0 mA. No adverse effects were reported by the owners during the treatment or control periods.

Concurrent antiepileptic drug treatment—Median serum antiepileptic drug concentrations did not differ significantly between treatment and control periods. Changes in seizure frequency that were evident throughout the course of the study were not associated with concomitant changes in antiepileptic drug concentrations in any individual dog.

Owner assessments—Eight of the 10 owners opted to continue using VNS as a form of seizure control in their dogs after completion of the study. One owner decided to keep the device in place but inactive. The device was surgically removed from another dog, because the owner was concerned that the generator may have contributed to periodic lameness of the left forelimb. Surgical removal was uncomplicated. The limb lameness had been detected during physical examination prior to implantation of the device and persisted after the device was removed.

Owners of the 9 dogs in which data on efficacy were collected were questioned regarding their experience participating in the study. Six of 9 owners reported being somewhat or extremely satisfied with their overall experience with the use of VNS in their dogs (median rating, 4; range, 2 to 5). Seven of 9 owners reported being somewhat or extremely satisfied with the incidence of postoperative complications and adverse effects associated with the device (median, 5; range, 2 to 5). Five of 9 owners responded that their dog's overall quality of life had increased somewhat or markedly (median score, 4; range, 2 to 5). Eight of nine owners indicated they would consider using VNS as a method of seizure control if they had another dog with seizures.

Discussion

The dogs evaluated in this study had medically refractory epilepsy, which is defined as recurrent seizure activity despite treatment with antiepileptic medications at putative therapeutic serum concentrations. Additional medical options were limited for these dogs, because all had failed to respond to monotherapy and at the time of initiation of the study were being treated with a combination of 2 antiepileptic drugs at putative therapeutic serum concentrations. Furthermore, all the dogs had a history of cluster seizures and had repeated seizure episodes during a short period. Owners of these dogs were concerned about quality of life issues for their pets as well as for themselves; they worried that the repeated seizure activity and chronic administration of antiepileptic medication were affecting their animal's health and well-being and commented on the substantial financial burden and schedule restrictions that were placed on themselves. Consequently, all were willing to participate in the study in the hopes of achieving better seizure control in their pets.

The use of VNS as a means of seizure control has been evaluated in dogs.[11,21] Preclinical studies were performed in laboratory dogs to obtain preliminary data on the effectiveness of VNS in controlling seizures and establish optimal stimulation parameters for its use.[11] In these studies, seizures were induced in anesthetized dogs by IV administration of either strychnine or pentylenetetraxol, and repetitive stimulation of the cervical portion of the vagus nerve caused termination of seizure activity. Recently, there has been a report[21] on the use of ocular compression to increase vagal tone in dogs with naturally occurring seizures. This indirect method of vagal stimulation resulted in variable short-term success in terminating seizure activity in 7 dogs. However, unlike the results obtained with repetitive electrical stimulation, seizures often recurred after ocular compression was terminated. Our study was undertaken to determine whether electrical VNS has a similar efficacy in naturally occurring seizures of dogs as seen in the experimental model, and to evaluate the safety and tolerability of electrical VNS in nonanesthetized dogs.

Although VNS has been most extensively studied in humans with partial seizures and is only approved for this seizure type, a specific seizure classification was not assessed as an inclusion criterion for this study, because it is sometimes difficult to reliably determine from an animal's history whether a generalized seizure begins as a partial seizure, and recent studies[22,23] have revealed the efficacy of VNS in humans with primary generalized seizures. Therefore, we decided to open the study to all dogs that had seizures for which an underlying cause was not found via diagnostic evaluation. No difference in response to VNS based on seizure classification was detected in this study, but the importance of these findings was limited by the small sample size.

A significant decrease in mean seizure frequency was only detected during the final 4 weeks of stimulation, and was not detected when the full 13-week test periods were evaluated. Because of this discrepancy, it is not possible to unequivocally state that VNS is an effective treatment for seizures in dogs. The final 4 weeks were chosen to represent a period during which the dogs in the study were expected to have seizures, because all dogs had an established seizure frequency of at least 1 seizure/mo. It is possible that the difference between the final 4-week treatment and control periods was attributable to chance and a reflection of the natural fluctuations in seizure frequency. However, the controlled, cross-over design of the study makes this explanation less likely. Alternatively, the difference may reflect an increase in the efficacy of VNS over time. The effectiveness of VNS in controlling seizures improves for up to 24 months after initiation of treatment in human epileptics,[24,25] and it is possible that dogs respond similarly.

Four of 9 dogs had at least a 50% reduction in seizure frequency during the final 4-week period. Two of these dogs had at least a 50% reduction in seizure frequency during the entire 13-week study period. Thus, it appears that dogs vary in their sensitivity to treatment with VNS, with some dogs being quite sensitive to its antiepileptic effect. No common clinical characteristics were apparent among the dogs that appeared to respond better to the treatment. A similar phenomenon has been described in humans; some individuals treated with VNS have a rapid and sustained response to treatment, whereas others respond more gradually and some fail to respond at all.[26] It is not possible to predict the response in any given individual.

The strength of current tolerated by dogs in this study was less than that used in human clinical trials or experimental studies in dogs. To keep the study masked, the current was adjusted such that the dog did not cough. Coughing is a commonly encountered but well-tolerated adverse effect in humans treated with VNS.[18] It is possible that a greater therapeutic effect may have been obtained if an increased stimulus intensity was used. However, no correlation between high current output and device effectiveness has been established in humans.[27]

Serious complications were not detected in any of the dogs. Horner's syndrome, which developed in 2 of the dogs in the study, has not been reported as a complication in humans undergoing surgical implantation of the device.[18] Anatomic differences between dogs and humans most likely account for this discrepancy. In humans, the cervical portion of the vagus nerve is adjacent to, but completely separate from, the sympathetic trunk. In dogs, the 2 nerves are joined as they travel through the neck and are not easily separated. Consequently, the stimulating electrodes were wrapped around the entire vagosympathetic trunk in the dogs in this study, whereas in humans the electrodes are placed around the isolated vagus nerve. Horner's syndrome was believed to have resulted from transient compromise of the blood supply to the sympathetic nerve, which occurred either during isolation of the nerve or during the process of wrapping the electrodes around the nerve trunk. Alternatively, local edema resulting from manipulation of the nerve may have contributed to a transient conduction block. Direct mechanical damage to the nerve seems less likely on the basis of the delay in the onset of signs until 24 hours after surgery and the complete resolution of signs during a 2- to 4-week period. In addition, the degree of experience of the primary surgeon did not appear to play a role in the development of this complication, because it was detected in the second and the last dog on which surgery was performed. Aside from the development of Horner's syndrome, stimulating the entire vagosympathetic trunk did not appear to affect the safety or tolerability of VNS.

Transient bradycardia that was observed in 3 dogs during intraoperative device testing has also been reported as a rare complication in humans.[28] Cardiac effects of VNS can be anticipated because of the vagus nerve's influence on the heart. In humans and dogs, the left vagus nerve has less cardiac input than the right vagus nerve,[29,30] and the left side has been chosen for the site of implantation in efforts to minimize cardiac effects of stimulation. The higher incidence of bradycardia seen in the dogs in this study was expected because of anatomic differences between humans and dogs. In humans, care is taken to wrap the electrodes around the left vagus nerve at a point distal to where most of the cardiac branches leave the nerve. In dogs, the cardiac branches leave the nerve at a more distal point within the thoracic cavity. Consequently, it was not possible to spare the cardiac branches from the effects of direct stimulation. Previous studies on the cardiac effects of VNS revealed that stimulation of the cervical portion of the vagus nerve in anesthetized dogs consistently induced bradycardia or asystole.[27] It was therefore somewhat surprising to find no changes in cardiac rate or rhythm in the dogs when they were evaluated in a nonanesthetized state. It is possible that electrical stimulation of the vagus nerve does not have marked effects on the heart unless there are additional circumstances, such as anesthesia, altering autonomic balance. Alternatively, the lack of cardiac effects in nonanesthetized dogs during device testing may be a function of the stimulus intensity. A stimulus current of 1.0 mA is required for intraoperative testing, whereas the stimulus intensity in awake dogs was dictated by their degree of tolerance, and in only 1 instance was as high as 1.0 mA. Studies[16,18,26,31,32] performed in humans with VNS implants have revealed little if any effect of vagal stimulation on cardiac rhythm or heart period variability in nonanesthetized patients.

Owner satisfaction with the use of VNS appeared to be associated, at least in part, with a decrease in seizure frequency in their dogs. Mean reduction in seizure frequency for the dogs whose owners reported being somewhat or extremely satisfied was 40.4%, compared with mean reduction in seizure frequency of 22.0% for dogs whose owners reported being neutral or somewhat dissatisfied. Interestingly, many owners believed that the device had contributed positively to their dog's quality of life, even if the frequency of their dog's seizures was not reduced. An improvement in

quality of life measures has also been revealed in humans undergoing VNS, and this was independent of changes in seizure frequency.[33-35] However, the fact that owners were no longer unaware of the study results when they were asked to respond to the questionnaire could potentially introduce bias into this assessment. Because all owners were seeking ways to better control their dog's seizures, it is possible that their answers were biased in favor of the device. Nonetheless, 8 of 9 owners reported that they would consider using VNS as a form of seizure control again if they had another epileptic dog.

The means by which VNS exerts its antiepileptic effect is poorly understood. The initial theory that seizure control results from desynchronization of the EEG cannot fully explain the mechanism of action, because subsequent studies in human patients reveal that VNS induces little if any effect on EEG background rhythms.[36,37] The locus ceruleus is believed by many to play a key role in the seizure control associated with VNS, but the mechanism by which this occurs is not known.

The benefits of VNS as a form of seizure control are numerous.[38] First, adverse effects are minimal and not additive with those already frequently encountered with antiepileptic drugs such as sedation and ataxia. Second, because the device is programmed to deliver continual stimulation, there is never an issue with respect to treatment compliance. Third, unlike many antiepileptic medications, the effectiveness of VNS is maintained during prolonged treatment, and individuals do not appear to develop tolerance or become refractory to treatment. Lastly, VNS appears to have no adverse interactions with other methods of seizure control, such as altering the metabolism of antiepileptic drugs. The main disadvantages of VNS are the inability to predict whether an individual is likely to respond to treatment or not and the expense. Presently, the device is available for veterinary applications at a cost of $2,500.

Results of this study suggest that the surgically implanted device has a reasonable margin of safety when used in epileptic dogs, is well tolerated, and is viewed favorably by owners. Furthermore, certain dogs in the study had a reduction in seizure frequency with VNS. The main limitation of this study was the small number of dogs evaluated, which was dictated by the number of devices that were provided for the study. Consequently, the results of this study do not validate the long-term safety or efficacy of VNS in the population of dogs with epilepsy. However, to the authors' knowledge, this was the first controlled clinical trial that evaluated the safety and efficacy of any form of treatment for epileptic dogs. All previous reports have involved retrospective evaluations or open-label prospective studies. Seizure frequency typically fluctuates during the natural course of epilepsy, and owners are more apt to seek additional treatment after seizures become more severe. These 2 factors introduce inherent bias into uncontrolled studies and confound any conclusions regarding treatment recommendations. Our study design, which involved collection of baseline data, placebo controlled cross over study periods, and double masking with respect to treatment order, attempted to minimize these confounding factors and allow for a statistical assessment of efficacy.

An additional limitation that is common to most studies of canine epilepsy is the reliability of data collected by owners. Because few dogs are observed continuously, it is possible that seizures occur and are not observed and documented. The design of our study attempted to minimize this effect on data interpretation, because it was expected that the occurrence of unobserved seizures would be similar between the 2 test periods. In fact, the decision to exclude 1 dog from the evaluation of efficacy data was made because the dog was observed much more closely during 1 test period because of a change in its primary caregiver. Nonetheless, the possibility of unobserved seizures is an additional variable that must be considered in the evaluation of the study results.

It is unlikely that VNS will ever be considered a replacement for antiepileptic medication in veterinary medicine. However, results from this study support its potential use as an alternative form of seizure control when treatment with antiepileptic medications has failed.

[a]Neurocybernetic Prosthesis System, Cyberonics Inc, Houston, Tex.
[b]Model 100 NCP Pulse Generator, Cyberonics Inc, Houston, Tex.
[c]Model 300 NCP Bipolar Lead, 2.0 mm size, Cyberonics Inc, Houston, Tex.
[d]Model 200 NCP ProgrammingWand, Cyberonics Inc, Houston, Tex.
[e]Ancef, SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.
[f]Available from the corresponding author on request.
[g]JMP, version 3.2.6.1, SAS Institute, Cary, NC.

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