VAGAL NERVE STIMULATION:

AN INSTITUTIONAL EXPERIENCE

Thesis submitted in partial fulfillment for the requirement of the degree of MCh (Neurosurgery) of SCTIMST

By

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CERTIFICATE

This is to certify that the thesis entitled **"VAGAL NERVE STIMULATION :AN INSTITUTIONAL EXPERIENCE"** is a bonafide work of Dr. Arun PS and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

Prof. Suresh Nair
Professor and Head
Department of Neurosurgery

Date :
Place:

DECLARATION

This thesis titled "VAGAL NERVE STIMULATION : AN INSTITUTIONAL EXPERIENCE" is a consolidated report based on a bonafide study from the period January 2006 to October 2012, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of MCh Neurosurgery examination.

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INTRODUCTION

The goal of curative epilepsy surgery is essentially resection of epileptogenic zone with a functionally acceptable neurological outcome.When this cannot be achieved palliative surgeries become the choice. These procedures reduce the frequency of seizures possibly by limiting the spread of seizure activity. Vagal nerve stimulation (VNS) is one of the palliative surgical procedures frequently performed in the comprehensive epilepsy care unit of our institute.

Vagus nerve stimulation (VNS) is an adjunct treatment option in patients with refractory focal and generalized epilepsy. Although VNS may not be an alternative to resective surgery it is indicated in patients for whom resection is not considered. Since the first human implantation of VNS device in 1988, (reported by Penry)[1] more that 60,000 patients have received VNS therapy worldwide.

OBJECTIVES

To study the role of Vagal nerve stimulation (VNS) in medically refractory epilepsy and to evaluate its effect on seizure palliation, quality of life and care taker satisfaction.

MATERIALS AND METHODS

Retrospective analysis of 20 patients who underwent the procedure of vagal nerve stimulation from (January 2006 - September 2012).

INCLUSION CRITERIA

All the patients who had undergone vagal nerve stimulation (VNS) from our hospital with a minimum followup of 12 months were included.

REVIEW OF LITERATURE

Epilepsy is the second most common chronic neurologic disorder after stroke and affects approximately 0.5%–2%[2] of the population. Nearly 80% of patients can be efficiently treated with one or more antiepileptic drugs(AEDs). Approximately 20% of patients continue to have seizures or experience unacceptable pharmacologic side effects despite optimal antiepileptic treatment . Surgery is a therapeutic alternative for patients with "medically refractory" epilepsy. Drug-resistant epilepsy affects 20% of people. Patients who continue to have disabling seizures or have intolerable side effects due to medications for a period of 2 years or more even after properly supervised trials of medical treatment of 6 months each, twice with monotherapies and once with poly therapy may be considered to have refractory seizures.[3]

Resective epilepsy surgery is possible when the epileptogenic zone can be identified and offers seizure freedom in 60%–90% of patients.A thorough patient selection is the goal of presurgical evaluation. In some patients the epileptogenic zone cannot be defined, may be multifocal , diffuse or may be located in an eloquent brain area. Further addition of a new antiepileptic drug can offer seizure freedom in a maximum 7% of patients. For patients with refractory epilepsy who are unsuitable candidates for curative resective surgery or who have experienced insufficient benefit from such a treatment ,electrical stimulation of the vagus nerve (VNS) is considered a treatment option.

In the past 3 decades there has been a regained interest in neurostimulation both peripheral and intracerebral as a therapeutic option for epilepsy with an extensive number of patients undergoing this modality of treatment.For stimulation, identification of the neural structures to be targeted and the optimal stimulation parameters to achieve efficacy with maintained safety are the main issues to be clarified. Progress in the ongoing research unravelling the complex pathophysiology of the epileptogenic network and the mechanism by which electrical stimulation may interfere, suggests promising practical applicability of different neurostimulation modalities for patients with refractory epilepsy

Early clinical trials suggested modest clinical benefit, showing that VNS decreased the frequency of recurrent partial seizures in adults. Subsequently, a small number of blinded, randomized controlled trials and a larger series of prospective and retrospective studies have evaluated the efficacy of VNS in epilepsy. However, confusion over the utility of VNS in epilepsy continues among practitioners because of the variability in benefit reported across clinical studies, and many questions remain. Importantly, although VNS was only approved in the US for patients 16 years and older with partial epilepsy, its benefit in children and in patients with generalized epilepsy syndromes remain unclear. Furthermore, it is not known whether specific etiologies of epilepsy can predict a better or worse outcome.

HISTORY

The first vagus nerve stimulator was implanted in humans in 1988. However, the historical basis of peripheral stimulation for treating seizures dates back centuries. In the sixteenth and seventeenth centuries following observation from Pelops(in greek mythology , the king of Pisa in Peloponnesus)[4] physicians practised using a ligature around the limb in which a seizure started, to arrest the progress on the hypothesis that the fits originated from the limb itself. In the beginning of the nineteenth century Odier and BrownSequard[5] also supported same hypothesis and opined ligatures are equally efficacious in arresting seizures caused by organic brain disease, such as a brain tumor.

Later on in late 19th century Gowers[6] attributed these findings to a raised resistance in the sensory and motor nerve cells in the brain that correspond with the involved limb. He suggested that this would in turn arrest the spread of the epileptic discharge. He also reported several other ways in which sensory stimulation could prevent seizures from spreading, such as pinching of the skin and inhalation of ammonia. Later, Rajna and Lona[7] demonstrated that afferent sensory stimuli can abort epileptic paroxysms in humans.

Historical overview of VNS therapy[1,2]

1988	First human implant (K. Penry, B.J. Wilder, E. Ramsay)
1994	European Community approval
1996	Five completed controlled studies (n = 454)
1999	United States (FDA) commercial approval for partial epilepsy
2002	>16,000 patients treated worldwide
2008	>46,000 patients treated worldwide
2011	> 60,000 patients treated worldwide

ANATOMICAL BASIS

The vagus is a mixed cranial nerve that consists of 80% afferent fibers originating from the heart, aorta, lungs, and gastrointestinal tract and 20%[8]efferent fibers that provide parasympathetic innervation of these structures and innervation of the voluntary striated muscles of the larynx and the pharynx.

ANATOMY OF VAGUS NERVE AND ITS CONNECTIONS

The vagus nerve carries fibers that include special and general visceral efferents and afferents. The efferents innervate the voluntary striated muscles of the larynx and pharynx, and provide parasympathetic innervation to the heart, lungs, gastrointestinal tract, and other visceral organs of the abdomen **.** Nucleus ambiguus is the centre for the special visceral efferent neurons that innervate the pharyngeal and laryngeal muscles. Recurrent laryngeal branches of the vagus partly innervates the larynx. On the right, the recurrent nerve loops around the subclavian artery and, on the left, around the arch of the aorta. The general visceral efferents is mediated by dorsal motor nucleus. Their actions include bronchial constriction, an increase in pulmonary secretions, a slowing of the heart rate, an increase in gastrointestinal and pancreatic secretions and diverse effects on gastrointestinal sphincters proximal to the splenic flexure.

The afferents originate from receptors in the lungs, aorta, heart, esophagus, gastrointestinal tract, and the aortic chemoreceptors and are visceral in nature **.** It also carries a small myelinated somatic sensory afferent component that carries sensation from the concha of the ear**.** Most of the afferents have a transmission speed greater than 15 m/s **.** Vagal afferents originate primarily from neurons in the nodose ganglion and send their projections mostly to the nucleus of the solitary tract, as well as to the medial reticular formation of the medulla, the dorsal motor nucleus of the vagus, the area postrema and the nucleus cunneatus**.** There are multiple transmitter

systems involved in processing vagal afferent input **.** Glutamate transmission which is decreased after lesioning of the nodose ganglion has been shown to decrease cholecystokinin (CCK) and neurotensin as well and also binding in the nucleus of the solitary tract. Neuropeptide angiotensin **,** has been demonstrated in the dorsal medulla and appear to be important in visceral reflexes **.**There are multiple projections between the nucleus of the solitary tract and the hypo thalamus, amygdalar nuclei, dorsal raphe, nucleus ambiguus, dorsal motor nucleus of the vagus, parabrachial nucleus, and the thalamus, which in turn projects to the insular cortex**.**

The diffuse projections of vagal afferents[9] directly or via the nucleus of the solitary tract are summarized in Fig.1 **.** These pathways are supposed to mediate reflexes that are important for visceral function such as coughing, vomiting,swallowing, and baroreceptive reflexes. The projections to the hypothalamus are important in feeding behaviour and satiety as well as blood pressure and volume homeostasis. The pathway to the thalamus continues to the insular cortex and appears to be the substrate for any consciousness of visceral sensation. The wide distribution of vagal afferents either directly or via projections from the nucleus of the solitary tract and the ascending reticular system explains the profound effects of vagal stimulation .

8—10 somata of the efferent fibres are located in the dorsal motor nucleus and nucleus ambiguus. Nucleus of the solitary tract is supplied by afferents arising from nodose ganglion. The nucleus of the solitary tract has widespread projections to numerous areas in the forebrain as well as the

brainstem, including important areas for epileptogenesis such as the amygdala and the thalamus. There are direct neural projections into the raphe nucleus, which is the major source of serotonergic neurons and indirect projections to the locus coeruleus and A5 nuclei that contain noradrenegic neurons. Finally, there are numerous diffuse cortical connections. The diffuse pathways of the vagus nerve mediate important visceral reflexes such as coughing, vomiting, swallowing, control of blood pressure, and heart rate. Heart rate is mostly influenced by the right vagus nerve, which has dense projections primarily to the atria of the heart.

The current rationale for vagus nerve stimulation as treatment for epileptic seizures is that stimulation of its diffuse connections to the brain can have a widespread influence on numerous central nervous system (CNS) structures. There is substantial evidence that the nucleus of the solitary tract as well as the locus coeruleus are involved when the vagus nerve is stimulated. Evoked potentials during stimulation of the vagus nerve were registered in the cerebral cortex, hippocampus, thalamus, and cerebellum.

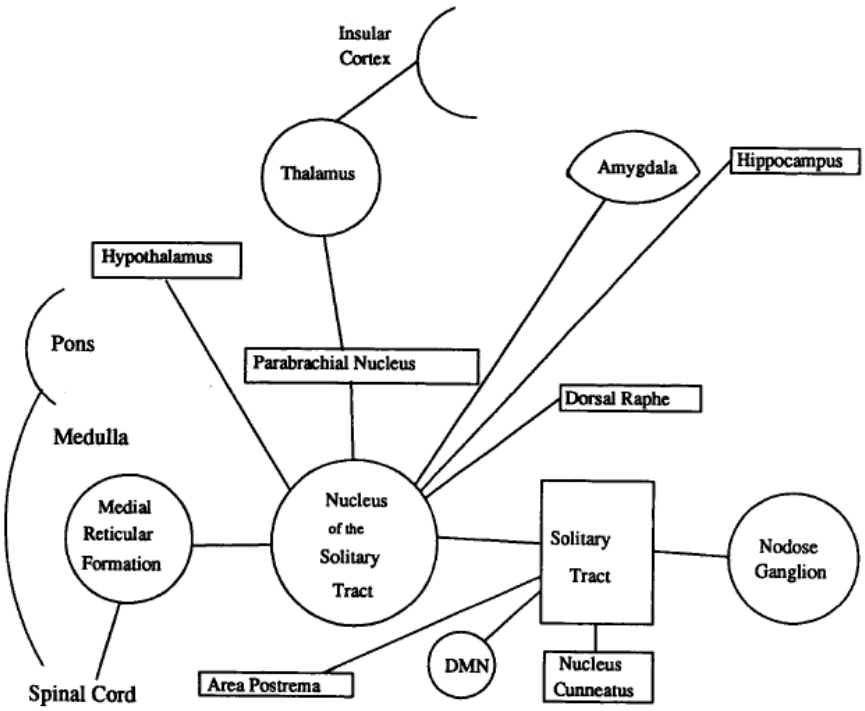

Fig 1: Schematic of vagal visceral afferent projections. The nodose ganglion contains the somata of vagal afferents. The axons enter the solitary tract and terminate in the nucleus of the solitary tract, the area postrema, the nucleus cunneatus, and the dorsal motor nucleus of the vagus (DMN). The nucleus of the solitary tract has a wide projection either directly or via the parabrachial nucleus. The lines represent most ascending pathways. Some descending pathways are also present but not illustrated (e.g., insular cortex projections to the nucleus of the solitary tract).[9]

REFLEXES MEDIATED BY VAGAL AFFERENTS

The study of vagal afferents in cardiovascular reflexes has demonstrated the importance of these fibers in the regulation of heart rate and blood pressure. The best studied reflex is the baroreflex. An increase in pressure sensed by pressure receptors in the large vessels, particularly the aorta, and heart travels via the vagus. Stimulation of these afferents results in

cardiac slowing due to a decrease in sympathetic tone and an increase in vagal efferent output. Some of the cardiac afferents are unmyelinated and respond to increased volume . Activation of these fibers affects blood pressure regulation by decreasing renin production and inhibiting vasopressin release. In dogs, the tonic inhibitory effect of vagal afferents on sympathetic outflow is mediated primarily by the right vagus. The vagal efferent innervation to the heart is also asymmetric, with the right vagus innervating the sinoatrial node and the left vagus innervating the atrioventricular node. Studies in the dog show that the right vagus produces a greater slowing in heart rate when compared to stimulation of the left vagus.

The integration of vagal cardiovascular afferents is in the nucleus of the solitary tract and the paramedian reticular nucleus . There are ascending pathways to the hypothalamus that influence the release of vasopressin . There is also a projection to the central amygdala nuclei . The vagal pulmonary afferents are primarily stretch receptors that mediate the Herring-Breuer and J-receptor-mediated reflexes . These reflexes lead to an increased respiratory drive with deflation and a drive for exhalation with increased stretch associated with inflation. Some pulmonary afferents appear to mediate the increase in heart rate and the decrease in peripheral vascular resistance with lung inflation. The J receptors are activated when there is a rise in pulmonary capillary pressure. J-receptor afferents are unmyelinated and stimulation of the J receptors causes apnea, bradycardia, hypotension, and a decrease in the monosynaptic reflexes of the hind limb of the cat . The cough reflex can also be activated by vagal afferents sensitive to irritants.

The vast majority of gastrointestinal vagal afferents are unmyelinated, provide information about visceral distention, and help regulate the control of secretion of digestive juices, emptying of the stomach, and satiety. The satiety effect of systemically administered CCK is partly mediated by the vagal GI afferents; section of the abdominal vagus diminishes the satiety effect of systemically administered CCK . Vagal afferents also produce a tonic inhibition of insulin secretion.

STIMULATION STUDIES

The effects of stimulating the vagus nerve depend on the frequency and intensity of the stimulus. For instance, by stimulating the nerve so that only the largest myelinated fibers are activated there is a reflex increase in heart rate secondary to activation of afferents carrying pulmonary stretch-receptor information (Paintal, 1973)[8,10]. At higher stimulus intensities, there may be little change in heart rate because of activation of baroreceptor afferents, which produces reflex bradycardia. When most of the fibers are activated there will be bradycardia. As the diffuse projections of the nucleus of the solitary tract would suggest, stimulation of vagal affferents can have profound effects on CNS function.

Stimulation of the cervical vagus in experimental animals can produce evoked potentials in the cerebral cortex , the hippocampus , the thalamus and the cerebellum . In humans, esophageal stimulation produces a cerebral response with a latency of around 100 m/s. The conduction velocity of the peripheral component of this response suggests a value in the range of 5-8.5

m/s**.**Stimulation of vagal afferents can depress the monosynaptic reflex of flexor and extensor hind limb muscles . Vagotomy reduces the inhibitory effects of CCK on rat exploratory behaviour .

Spinothalamic neuron activity in the thoracic cord is reduced by vagal afferent activation, suggesting a role of cardiac afferents in processing cardiac pain information . Noci-oceptive reflexes in animals (i.e., tail-flick reflex) are inhibited by stimulation of vagal afferents or the nucleus of the solitary tract . This antinocioceptive effect is blocked by naloxone . These findings of vagal afferent-induced depression of motor and nocioceptive reflexes illustrate an effect on the descending reticular system controlling spinal cord function. In an analogous manner, vagal afferents appear to be able to modulate cortical activity via ascending reticular systems.

EEG EFFECTS OF VAGAL AFFERENT STIMULATION

The effects of vagal stimulation that are most relevant to its antiepileptic properties are the modulation of electroencephalographic (EEG) activity and sleep states. Depending on the stimulus parameters used, vagal stimulation in animals can produce EEG synchronization, desynchronization, rapid eye movement (REM) sleep, or slow wave sleep (SWS)[11]**.** High frequency (24-50 Hz) vagal stimulation can produce orbital-frontal cortex EEG fast activity, and this finding was initially ascribed to hypotension produced by stimulation (Bailey and Bremer, 1938 [12]). Subsequent experiments on “encephala isole” cats in which vagal stimulation does not produce hypotension, showed that stimulation of the vagus(50 Hz at 0.1- to 2-V

intensities) produces EEG synchronization. Zanchetti[13] et al showed that EEG desynchronization and blocks sleep spindle occurrence during SWS . Stimulation of the nucleus of the solitary tract at low frequencies (1-16 Hz) produces EEG synchronization, whereas high-frequency (>30 Hz) stimulation results in EEG desynchronization .

Chase and colleagues (1966,1968)[14] performed definitive experiments to demonstrate EEG changes that were associated with activation of specific nerve fiber types of the vagus. In cats, stimulation of the vagus at frequencies above 70 Hz and at intensities greater than 3 V produce EEG desynchronization. At frequencies above 70 Hz and at intensities less than 3 V, where stimulus parameters would only effectively activate myelinatedfibers, vagal stimulation produces EEG synchronization.At 20-50 Hz and 10V stimulation, the EEG becomes desynchronized. Chase and Nakamura[8,14] showed that the stimulus intensities and frequencies that produce desynchronization were shown to stimulate fibers that conduct at 1-15 m/s .

Sleep cycling may be affected by vagal stimulation . In the "encephaleisole" cat, vagal stimulation can produce both SWS and REM sleep. Stimulation (30-50 Hz, 1-2 V) of the medulla in the region of the nucleus of the solitary tract produces SWS (Puizillout and Foutz, 1976[8,15]). Direct current stimulation (15-40 s) of the vagus first produces EEG desynchronization, then SWS (Penaloza Rojas, 1964[16]). Sleep spindle activity can be blocked by vagal stimulation (Zanchetti et al., 1952[13]). These studies provide convincing evidence that stimulation of the vagus nerve can have

profound effects on the EEG and sleep states of experimental animals. These effects are presumably mediated by vagal afferent activation of the nucleus of the solitary tract and brainstem reticular formation centers.

Stimulation that activates slower conducting fibers appears to be most effective in producing EEG desynchronization. Because seizures are a product of abnormal synchronization, one may hypothesize that stimuli that produced desynchronization of the EEG may have antiepileptic properties.

ANIMAL EXPERIMENTS

The first animal experiments mainly investigated VNS-induced electroencephalograph (EEG) effects[8,14]. Depending on the stimulus parameters used, vagus nerve stimulation can induce EEG synchronization, EEG desynchronization, rapid eye movement sleep or slow wave sleep in animals. This was explained by the fact that different types of nerve fibers in the vagus nerve are activated when different stimulus parameters (frequency and intensity) are used. Synchronization of the EEG was observed when weak stimuli activating myelinated A and B fibers were used. Desynchronization resulted when stimuli with higher output and frequency activated unmyelinated C-fibers. Because epilepsy is characterized by a paroxysmal abnormal synchronicity of EEG, it was believed that vagus nerve stimulation could suppress seizures by desynchronizing the EEG. The effect of vagus nerve stimulation on clinical behaviour and electroencephalographic epileptic activity in different animal models was studied. VNS blocks interictal spike activity induced by strychnine applied to the cortex of a cat. Zabara

et al[17,18] found that generalized seizures in dogs induced by pentylenetetrazol and strychnine were inhibited by vagus nerve stimulation and made an estimation about optimum stimulation parameters.

Woodbury and Woodbury[19]established the anticonvulsant efficacy of VNS in rats after induction of seizures with pentylenetetrazol, mercaptoproprionate and maximal electroshock, which are validated animal models for simulating human epilepsy. According to their research the anticonvulsant effect is directly related to the fraction of unmyelinated C-fibers that are stimulated. Chronic VNS also reduced the frequency of recurrent spontaneous seizures in monkeys with alumina gel foci. Results of these animal studies led to the development of an implantable device for human use and the first human trials for VNS as treatment of epilepsy.

The Argument for Vagus nerve Stimulation

According to Kwan and Brodie[20] ,fourty-seven percent of epilepsy patients will obtain seizure freedom with the first antiepileptic medication in monotherapy. Fourteen percent will obtain seizure freedom with the second drug in monotherapy and then there will be diminishing returns. Usually these patients will be receiving polytherapy.

Vagus nerve stimulation (VNS) received approval for medical use by the European authorities in 1994 therapy and received U.S.Food and Drug Administration (FDA) approval in July 1997[21]- VNS is ‘‘indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and

adolescents over 12 years of age with partial onset seizures which are refractory to antiepileptic medications."

VNS may stop or shorten seizures and clusters of seizures. VNS may improve the postictal period. Patient may feel a sense of empowerment.

Today, about fifteen years later, VNS was even called the emerging third pillar of epilepsy treatment, besides antiepileptic drugs (AEDs) and epilepsy surgery. More than 60,000[21] stimulators had been implanted for the treatment of epilepsy by November 2011 (Cyberonics Inc) and an increasing number of patients are now getting reimplanted after battery-end-of-service of the pulse generator

VNS—Possible mechanism of action

The VNS is a pacemaker-like device that sends mild, intermittent electrical pulses through a lead to the left vagus (usually) nerve. Action potentials are activated via a negative electrode that initiates action potentials, which travel afferently (via sensory fibers) to subcortical nuclei and cortex, and efferently via motor fibers; the latter action potentials, if successfully propagated, could cause side effects.

Mechanisms of action have been explored in a number of animal models. VNS has been shown to attenuate pentylenetetrazole(PTZ)–and maximal electroshock (MES)–induced seizures (Woodbury & Woodbury, 1990[19]), and adds to acute abortive effects on seizures (McLachlan, 1993[22]). VNS is associated with regional induction of fos activity in the rat brain

(Naritoku et al., 1995[23]). The vagus nerve projects to the nucleus tractus solitarius and parabrachial nucleus, and VNS stimulation thereby can access the limbic, autonomic, and reticular structures of the forebrain (Henry, 2002[23]). The vagus nerve also projects to noradrenergic and serotonergic systems of the brain and spinal cord; it activates the amygdala, insula, hypothalamus,periaqueductal graymatter, and the thalamus (Vonck et al., 2001[4])

The use of VNS in epilepsy arises from the serendipitous experimental finding that extracranial vagal stimulation desynchronizes the EEG in animals. As hypersynchrony is a feature of epileptic discharges and arousal with EEG desynchronization blocks interictal epileptiform activity in animal models and in man, it was reasonable to test VNS for antiepileptic action in experimental epilepsy. Several studies have shown that VNS prevents, terminates or attenuates seizures in various animal models , including both generalized (PTZ, strychnine, maximal electroshock) and partial (penicillin and alumina-gel foci, amygdala kindling) seizures.

Zabara[17,18] showed that VNS suppressed within 0.5–5 seconds, seizures induced by continuous strychnine infusion in a dog. Seizures returned 10 minutes after the termination of VNS. Thus the effects are rapid, but outlast stimulation by some minutes, being half maximal 5 minutes after termination. Sustained stimulation over a period of 60 minutes had a cumulative effect. Such observations, together with considerations of battery life and the need to avoid damage to the vagal nerve by prolonged

stimulation, have led to the general use in humans of a schedule of 30 second stimulation at 5 minute intervals.

Despite extensive experimental studies and some human data , the mode of action of VNS is unknown. With the stimulus parameters used in clinical practice, vagal C-fibres are unlikely to be stimulated, and destruction of C-fibres by capsaicin does not reduce the efficacy of VNS in animals. The main central afferent connection of the vagus is the nucleus of the tractus solitarius (NTS), which projects to the locus coeruleus (LC) and adjacent parabrachial nucleus, dorsal raphe, nucleus ambiguus, cerebellum, hypothalamus, thalamus, insula, medullary reticular formation and other brainstem structures, several of which are known to modulate seizures in various models. Both chronic lesioning and acute inactivation of the LC reduce the anticonvulsant effects of VNS. The locus coeruleus has been found to have extensive diencephalic, brainstem and cortical projections and the role of these has not been explored by lesioning studies.

Another possibly relevant pathway is the projection of the NTS through the parabrachial nuclei to the substantia innominata and zona incerta. Stimulation of the areas facilitates, while inhibition may suppress generalized seizures. An alternative anatomical interpretation is proposed by Rafael and Moromizato[24], who suggest that stimulation at mid-cervical level activates only nocioceptive and proprioceptive afferents, which terminate in subnuclei of the spinal trigeminal nucleus (but not the NTS). These have projections to the cerebellum, medial accessory olivary nucleus, brainstem reticular nuclei, LC,

raphe and superior central nuclei. Changes in various neurotransmitters have been demonstrated , including an elevation of CSF GABA in man but whether these are secondary or have a primary role in the mechanism of action of VNS is unknown.

Photon emission tomography (PET) studies in man have shown changes in blood flow in numerous cortical and subcortical structures but with inconsistent results between subjects. Similarly, fos-staining has indicated activation by VNS at several apparently unrelated sites. In experimental animals VNS can produce desynchronizationor synchronization of the EEG, depending on the stimulus parameters used; but significant EEG changes in man have not been demonstrated–Despite the growing number of patients treated with VNS and the successful exploration of novel and promising indications within and even outside the neurological field, the precise mechanism of action of VNS in influencing the brain in a therapeutically efficacious manner, remains to be elucidated.

Treatment for epilepsy as well as other pathological conditions is mainly based on evidence-based information rather than on rational deductions from basic research in the pathophysiology or the mode of action of neurostimulation because many of these issues currently remain unclarified. This is also the case for many other medical treatments especially for neurological conditions that arise from a complex physiological substrate like the human nervous system. In the past 10 years interesting findings have arisen from different types of research. However, these findings have so far

not been useful for practical application in the sense that predictive factors for clinical response or practical guidelines for optimising stimulation parameters have been identified. Functional imaging techniques such as PET, SPECT and more recently fMRI allow to non-invasively measure neuronal activity as reflected by changing rCBF.

Based on the established clinical efficacy of VNS as a treatment for epileptic seizures, a condition of cortical origin, it is supposed that electrical stimulation of the vagus nerve can acutely and/or chronically change neuronal activity within the brain. Identification of the localization(s) and nature of these supposed changes may be investigated with the mentioned techniques. As VNS in a clinical setting consists of an implanted programmable biomedical system that can be turned off and on, activation studies are suitable to evaluate intracerebral functioning in relation to electrical stimulation at a certain distance. Moreover, the correlation of VNS-induced rCBF changes with VNS-induced reduction in seizure frequency is a powerful experimental design that can be performed in humans to study the mechanism of action and potentially identify predictive factors for positive clinical outcome.

In the past, different modalities of functional imaging have been used in VNS research, some of them in small patient groups at a time when VNS was still an emerging novel treatment. There are limited numbers of studies in animals. Interesting results firstly arose from a study by Henry et al[23] who examined the acute effects of VNS using PET. Correlation of acute VNS-induced rCBF alterations and chronic therapeutic responses showed that

bilaterally increased thalamic rCBF correlated with a decreased seizure frequency in responders after 3 months of treatment. Several other studies, using PET, SPECT and recently fMRI examined rCBF alterations after chronic VNS treatment leading to further identification of potential key structures involved in the mechanism of action. However no uniform functional pathway addressed by VNS to exert its effect from the cervical part of the vagus nerve to the brain cortex was outlined.

ANTICONVULSANT ACTION OF VNS IN EXPERIMENTAL STUDIES

YEAR	INVESTIGATORS	MODEL	ANIMAL	RESULTS
1938	Bailey and Bremer [12]	NA	Cat	Induced frontal fast activity
1952	Zanchettiet al.[13]	Strychnine	Cat	Blocked interictal spiking
1961	Magnes et al.[24]	NA	Cat	Desynchronized EEG
1966	Chase et al. [14]	NA	Cat	Synchronized or desynchronized EEG in thalamus and Cortex
1968	Stoica and Tudor [25]	Strychnine	cat	Increased or decreased cortical spiking
1971	O'Brien et al. NA [26]	NA	monkey	Elicited cortical evoked potentials
1977	Puizillout and Foutz[15]	NA	Cat	Induced REM sleep
1985	Zabara[17,18]	Strychnine	Dog	Aborted seizures
1990	Lockardet al.[27]	Alumina	monkey	Reduced seizure frequency
1991	Woodbury & Woodbury[19]	Maximal electroshock	Rat	Reduced seizure severity
1992	McLachlan[22]	Penicillin/PTZ	Rat	Reduced interictal spikes and seizure duration
1999	Fernandez-Guardiola et al.[28]	Amygdala kindling	Cat	cat Delayed kindling, stage IV never reached

SUMMARY OF MODE OF ACTION OF VNS

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Functional anatomy:-

Multiple projection pathways identified, through nucleus of the tractus solitarius to:
locus coeruleus, parabrachial nucleus, dorsal raphe, nucleus ambiguus, cerebellum, hypothalamus, thalamus, insula, medullary reticular formation, substantia innominata, zona incerta.
Lesioning/inactivation of locus coeruleus reduces the anticonvulsant effect.

PET:-

Blood flow increased in rostral medulla, right post-central gyrus, hypothalami, thalami, insulae, cerebellum.
Blood flow decreased in hippocampi, amygdalae, posterior cinguli.

Electrophysiology:-

EEG desynchronized or synchronized in cat.
Little effect on in man.
Evoked potential latencies increased in man, or no effect.

Neurochemistry:-[29,30,31]

Serotoninergic: csf 5-hydroxyindole acetic acid increase.
Serotoninergic: Activation of loculus coeruleus.
Dopaminergic: csf homovanillic acid elevated.
GABAergic: csf GABA elevated; Vth nerve nucleus response to Gasserian stimulation reduced;
vagal nerve lesioning by ibotenic acid reduces threshold to picrotoxin & bicuculline but not strychnine .
VNS induces fos production in superior colliculus, amygdala, cortex, post-lateral thalamus and hypothalamus

Trials in VNS:

The efficacy of VNS in treating epilepsy has been demonstrated in numerous clinical trials. With the successful implantation of the device, clinical studies were performed to achieve FDA approval. Two pilot studies (E01 and E02[32]) demonstrated the safety and efficacy of VNS in humans. Minimal adverse effects were encountered and those were limited to hoarseness and

tingling in the neck. Shortly thereafter, a randomized active control study (E03) was performed in 1992[33], again demonstrating the efficacy of VNS in reducing seizure events. In 1994, the European Community approved the use of the NeuroCybernetic Prosthesis for VNS in the treatment of refractory epilepsy. The two major studies were titled E03 and E05[34], were multicenter, double-blind, and randomized trials. In both studies high frequency stimulation (30 Hz) and low frequency stimulation (1 Hz) were compared. Patients receiving low frequency stimulation constituted the control group. Both these studies were short-term, each lasting 3 months. Respectively, 114 and 199 patients were randomized and implanted. In both studies, mean seizure reduction was significantly higher in the high frequency stimulation group than in the low frequency stimulation group (24.5% and 6.1% in E03 and 28% and 15% in E05)[35]. Similarly, the number of responders (patients with 50% seizure reduction) was significantly higher in the high stimulation group in both studies. Although these types of studies are fundamentally necessary for the establishment of indication of the treatment, they have numerous limitations. The effect of VNS as a long-term treatment of epilepsy was definitively demonstrated by evaluating the results of all patients from 5 open prospective long-term clinical trials. The aggregate responder rate of these studies (n = 440) was 43% at 3 years.

In July 1997, the US FDA approved the use of this device as an adjunct to active therapy for refractory epilepsy in adult and adolescents older than 12 years of age[36,37].

In a retrospective 12-year follow-up study, Uthman et al.[38] found a mean seizure reduction of 26% after 1 year, 30% after 5 years, and 52% after 12 years with VNS treatment. Forty-eight patients were followed up in this study group. The added benefit of prolonged stimulation includes drug reduction in this patient population with the potential gain of decreased polypharmacy and its adverse effects. Overall, in terms of efficacy, VNS will offer a decrease in seizure frequency close to 50% in a third of the patients.

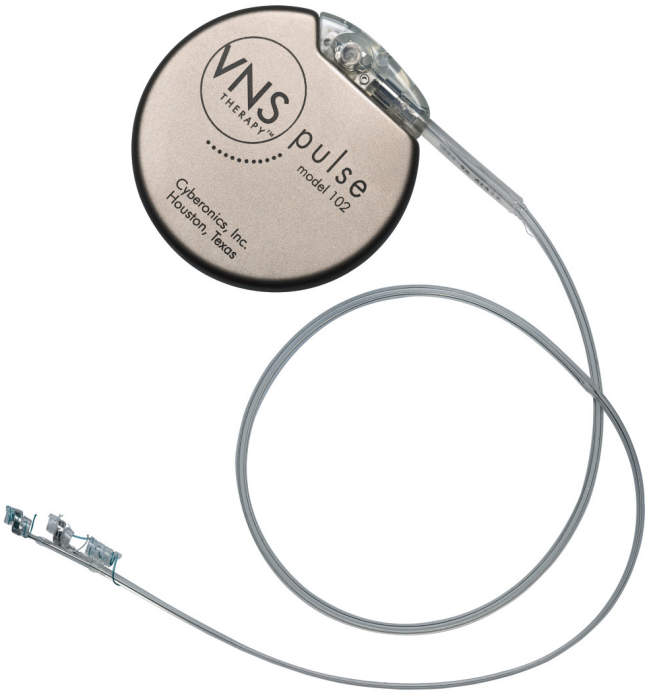
In addition to its demonstrated efficacy in focal epilepsies, other studies have shown that VNS has positive effects on various types of generalized seizures and epilepsies, including idiopathic generalized epilepsy and Lennox–Gastaut syndrome [39]. Among others, Murphy has published a study confirming the effect of VNS in the long-term treatment of children with refractory focal and generalized seizures. From the practical point of view, we need data from open-label studies performed under natural clinical conditions. Several multicenter and open-label studies have already been published. All of them demonstrated positive long-term effects of VNS in patients with various types of epilepsy. Some of these studies included patients pooled from centres in different countries.

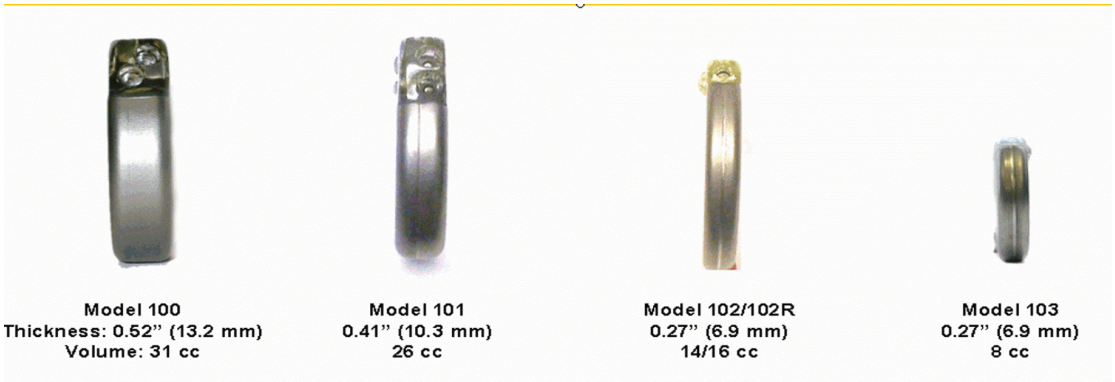
Technological Development

Given the success of VNS in animal models, Dr.Jacob Zabara[15,16], a neurophysiologist from Temple University who had been the driving force behind the VNS basic science studies, collaborated with Terry Reese, an electric engineer with pacemaker technology experience, to further developed

this technology. At that time, Reese was the vice president of Intermedics, a medical device company.

Results of VNS testing in monkeys were equivocal and Intermedics decided not to pursue this technology. After company restructuring, Reese was no longer with Intermedics, and he and Zabara incorporated Cyberonics in December of 1987. In 1988, William Bell, a neurosurgeon working with J. Kiffen Penry, a neurologist, implanted the first VNS device in a 25-year-old man at Wake Forest Bowman Gray Medical School in North Carolina[23,40]. This device was a programmable stimulating device called the NeuroCybernetic Prosthesis.





Model 100
Thickness: 0.52" (13.2 mm)
Volume: 31 cc

Model 101
0.41" (10.3 mm)
26 cc

Model 102/102R
0.27" (6.9 mm)
14/16 cc

Model 103
0.27" (6.9 mm)
8 cc

Stimulation Technique

PRACTICAL AND SURGICAL DETAILS

Human experience is confined to a single device, the Neurocybernetic Prosthesis (NCPr) developed and marketed by Cyberonics (Webster, TX, USA)[41]. The system comprises: a pulse generator, a lead incorporating a bipolar electrode, tether and connectors, a tunnelling tool, a programming wand with control software and a magnet.

The electrode array comprises 2 silicone helices each with three turns, with a platinum ribbon electrode within the middle turn. Threads are attached to position the coils around the nerve. A third helical coil is located further caudally to tether the lead to the nerve. The generator is a disc of 55 mm diameter and 13.2 mm thick, weighing 55 mg. Both before and after implantation it can be interrogated and programmed by radio-frequency signals from the wand which is connected to the serial port of a laptop computer.

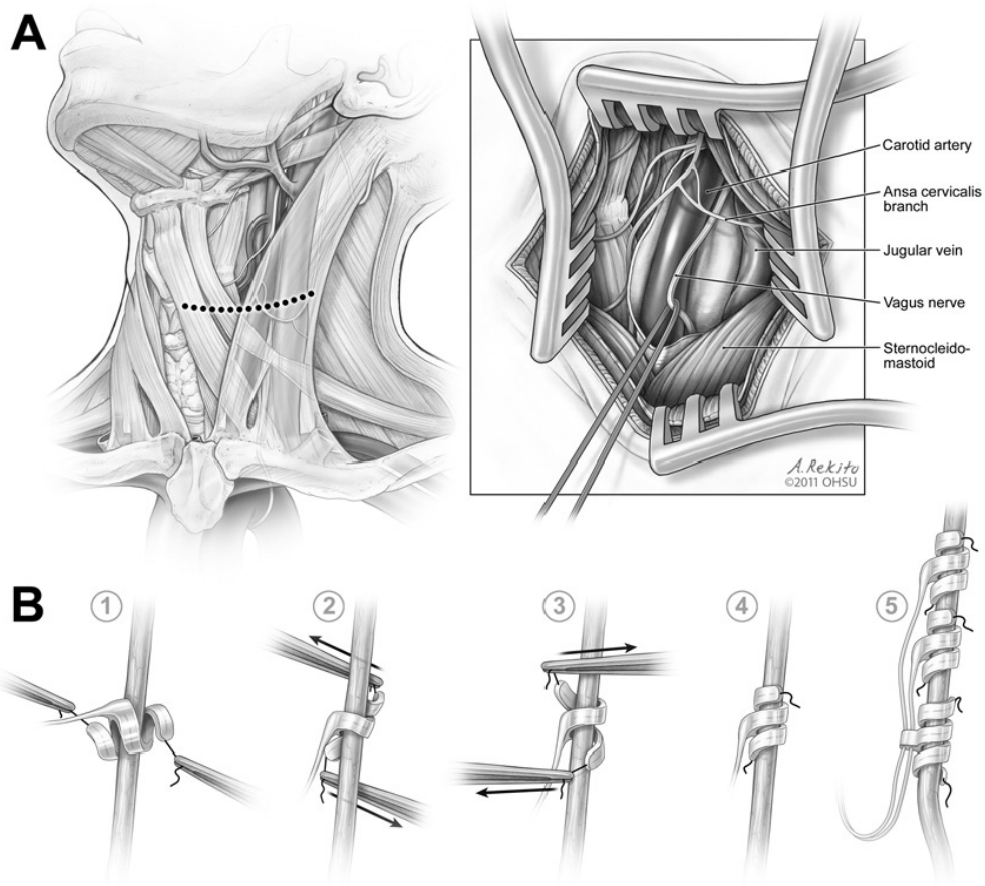
Output current, pulse width and frequency, the duration of each stimulus train and intervals between trains can be selected. The software also tests the integrity of the generator and lead during implantation. The settings can subsequently be recovered by interrogating the generator. A hand-held magnet can be used to turn on stimulation when briefly placed over the generator and settings for magnet-activated stimulation can also be programmed. If the magnet is left in place over the generator, the device is

inactivated; this facility can be used to suspend stimulation at times when side-effects would be inconvenient.

Implantation is performed under general anaesthesia and the surgical procedure takes approximately 1 hour in experienced hands. The electrodes are placed through an incision over the anterior border of the left sternomastoid midway between the mastoid process and the clavicle. The nerve is identified in the carotid sheath, is mobilized and lifted with vessel loops. The coils are applied to the vagus and gentle traction applied to the threads to wrap them around the nerve. A horizontal incision is then made, centred on a point below the mid-point of the left clavicle and a subcutaneous pouch is prepared to receive the generator. The tunnelling tool is used to pass the connectors of the lead from the cervical to the thoracic incision. The lead is plugged into the generator. This is then interrogated by means of the wand and a lead integrity test is run. Procedures for starting stimulation vary.

It is recommended that stimulation be withheld for 2 weeks[42] as current may track along pathways formed by postoperative oedema. Subsequent ramping up of current is determined by clinical response, tolerability and timing outpatient visits to suit the convenience of the patient. An increase in current as small as 0.25 mA is generally experienced as disagreeable. The patient complains of discomfort or pain in the neck, jaw, face or teeth, and may suffer a paroxysm of coughing. The voice may be strikingly altered. These symptoms rapidly subside, so that after two or three cycles of stimulation the patient reports them as being unpleasant but tolerable and

within a few hours significant discomfort has generally disappeared. Current escalation continues until a good therapeutic response is obtained, or adverse symptoms become persistent or until the maximum available setting of 3.5 mA is reached.



Illustrations depicting the surgical procedure for implantation of a VNS system. **A:** The head is positioned in slight extension with a 15° rotation to the right *(* A left-sided transverse incision is created in a skin fold at approximately the C5–6 level, below the carotid artery bifurcation. After dividing the platysma, the sternocleidomastoid muscle and jugular vein are retracted laterally to reveal the vagus nerve (illustrated here elevated by a vessel loop). The vagus nerve travels within the carotid sheath, while branches of the ansa cervicalis cross the exposure deep to the platysma but superficial to the sheath. **B:** Steps for implantation of the vagus nerve anchor and electrode coils. The coil is oriented perpendicular to the nerve and gently stretched using the attached tensioning sutures (1). The midpoint of the stretched coil is slid around the nerve (2). Each end of the coil, aided by its material "memory," is coiled around the vagus nerve (3 and 4). Proper configuration of 3 coils

Typically, the current output is adjusted to tolerance, using a 30-Hz signal frequency with a 500-msec pulse width for 30 seconds of "on" and 5 minutes of "off" time[42]. These "default" settings were used in the initial double-blind studies in patients who were randomly assigned to receive high levels of stimulation. A handheld magnet is given to the patient or his/her caregiver. Stimulation can be modulated or terminated via this magnet. Several generator models have been developed with each successive model having smaller dimensions to improve cosmetic outcome .

Indications for Use

The initial FDA approval for VNS use in the US in 1997[40] was as an "adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications." Since then, thousands of devices have been implanted in patients in the US. As is true for antiepileptic drugs, VNS was initially approved for the narrow indication of drug-resistant partial epilepsy. There is increasing evidence that VNS is effective in the symptomatic generalized epilepsies[43], in refractory idiopathic ("primary") generalized epilepsies, in Lennox-Gastaut epilepsy[44], and other seizure disorders in the paediatric population.

Another promising role for VNS is in the management of treatment-resistant depression[45]. The idea of using VNS as a treatment for clinical depression was based on several different observations: the improved mood and cognition of patients with epilepsy after VNS therapy, as well as the fact

that several anticonvulsant medications are used as mood stabilizers and antidepressants in bipolar mood disorder. In addition, brain regions that are critical in mood regulation (orbital cortex, limbic system) are targets of VNS. In a recent literature review, Daban et al.[45] found that open-label studies demonstrated the safety and efficacy of VNS in treatment-resistant depression. However, the only double-blinded study was associated with inconclusive results. Furthermore, appropriate patient selection and optimal VNS dose have not been well established. Despite these limitations, interest in VNS for use in treatment-resistant depression is likely to continue as more clinical data are collected and evaluated.

Stimulation parameters available with The NCP system[45]

Parameter	**Units**	**Range**	**Typical values**
Output current	Milliamperes (mA)	0-3.5 mA	1.25 mA
Signal frequency	Hertz (Hz)	1-3- Hz	30 Hz
Pulse width	Microseconds (us)	130-1000 us	500us
Signal-ON -time	Seconds (S)	7s(Rapid cycle-60 s	30s
Signal –OFF-time	Seconds-minutes (s,min)	14s (rapid cycle-180min	5 min
Lead impedance	Kilo-Ohms(Kohms)	1-7 Kohms	3-4 kohms

OUTSTANDING ISSUES

Mode of action:An understanding of the mode of action has not been found essential to either the acceptance or effective use of novel antiepileptic drugs (AEDs). Nevertheless, establishing the mechanisms underlying the anticonvulsant action of VNS would enhance its credibility and might facilitate

the identification of optimal treatment protocols and of suitable or unsuitable co-medication, and selection of the most appropriate patients[46,47,48].

Stimulation parameters. The standard protocol of 30 second stimulation at 5 minute intervals was selected on the basis of the duration of effect in animal models, but has not been shown to be optimal in man. At least three other schedules are in use: 'rapid cycling'[49,50]: 7 second stimulation at 0.3 minute intervals, 1 minute continuous stimulation at 5 minute intervals, and 30 seconds at 1.8 minute intervals. No formal studies have compared these protocols nor determined whether there are different indications for their use[51,52].

Interactions with drugs.Studies of mode of action offer some evidence that the effects of VNS are mediated by specific neurotransmitters[53]. If this is so, there may also be synergy or antagonism between VNS and particular drugs, which need to be considered when VNS is used in patients taking AEDs, or other agents.

Identification of candidates. Although the controlled trials included only patients with partial seizures, it appears from uncontrolled reports and post-marketing experience that VNS exhibits the same, modest efficacy in a wide range of epilepsies and seizure types, both partial and generalized. In pharmacotherapy of epilepsy, a wide spectrum of action is generally regarded as an advantage, but until a wide spectrum of action is reliably established, or narrower indications are more clearly defined, there will be justified concern that vagal nerve stimulation is not being used optimally. At present it appears

that VNS should be considered in any patient with undoubted epilepsy, demonstrably resistant to appropriate medication administered to and who is not a candidate for potentially curative resective surgery[54,55]. The definition of medical intractability may be disputed, and similar considerations will apply as in conventional surgery. It is a matter of concern that VNS may be viewed, both by physicians and patients, as a safe, inexpensive alternative to respective surgery. As the latter offers to some categories of patients a 70–85% chance of complete seizure control, it is important that VNS should only be undertaken after full consideration of other surgical options, and in the context of a comprehensive epilepsy program. Vagal nerve stimulation offers palliative treatment approximately equivalent in efficacy to callosotomy, and a randomized trial of VNS and callosotomy would be valuable.

Benefits other than seizure control. There is some anecdotal evidence that VNS improves cognition, particularly in patients with learning disability and may improve mood and quality of life. As noted above, quality of life measures were included in some uncontrolled paediatric trials and benefits were claimed. Clark et al[56]. report enhancement of retention memory in a robust controlled study in man. Unfortunately, this effect was seen only at levels of current too low to influence seizure frequency in most subjects. Further randomized studies of cognitive, affective and behavioural changes during VNS at therapeutic levels are urgently required.

Vagal nerve stimlation as an alternative to pharmacotherapy.

Although side-effects of VNS are inescapable, they are well tolerated and cause less distress and impairment of quality of life than do the cognitive side-effects of most AEDs. If further experience of VNS in intractable epilepsies is favourable, the question must arise as to whether this treatment may not also be suitable for some patients whose seizures are controllable with AEDs, but only at a cost of unacceptable side-effects. Comparative cost/benefit studies against AEDs in less refractory populations must be the next step[57,].

Cost-benefit. The efficacy of vagus nerve stimulation appears to be comparable to, or greater than, that of any one of the newer antiepileptic drugs; however, trial use of a drug can rapidly be abandoned if unsuccessful, whereas undertaking treatment by VNS involves a minimum commitment to the cost of the device and its implantation. Nevertheless, across a sample of 15 patients including responders and non-responders, the cost of VNS was recovered by savings in direct medical costs within 2 years[58].

Regulatory status. Vagal nerve stimulation is recognized as effective by the US Food and Drug Administration, Medicare and the central advisory board of Blue Cross-Blue Shield. The device has E.U. CE approval. A report of the American Academy of Neurology's Therapeutics and Technology Assessment Subcommittee, Fisher and Handforth[61] concludes the evidence of efficacy to be of Class I[59,60], except for use in idiopathic generalized epilepsies and children, where is it of Class III.

In the acute stimulation condition, the correlation with positive clinical outcome involves rCBF changes in limbic structures which is in line with of reasoning about VNS interfering with the epileptic network as described by Bertram and colleagues. They observed a monosynaptic excitatory input from the thalamus to the limbic structures of the medial temporal lobe. Together with known connections to cortical and sub cortical structures, the thalamus may exhibit a powerful modulating role in the synchronization of this neuronal circuit. Vagus nerve stimulation may influence this neuronal circuitry via inhibition of the thalamus. The finding of specific changes in rCBF following an initial single stimulation train may be useful to identify responders before patients are implanted with a permanent device. This would imply the application of SPECT in patients in whom the vagus nerve is transcutaneously stimulated, e.g. with the use of transcutaneous electrical nerve stimulation (TENS) [62]devices.

The findings from studies investigating VNS-induced rCBF at different relevant time periods during VNS treatment put together with other functional imaging studies using different designs point to a central role of the thalamus and medial temporal lobe structures in the mechanism of action of VNS. Further studies specifically investigating the influence of different stimulation parameters on rCBF in these structures in humans and animals may eventually provide practical guidelines and lead to improved clinical outcome. Deep brain stimulation is an emerging treatment for epilepsy and the structures identified in VNS research have already proven to be valuable targets for direct stimulation. Performing functional imaging study designs in

patients treated with VNS and DBS may be an interesting avenue to further clarify the mechanism of action of anti-epileptic treatments as well as the pathophysiology of epilepsy

CLINICAL TRIALS

Acute Effects and Side Effects

Five (EO1–EO5)[32,33] acute-phase clinical studies involving the NCP System have been conducted in a total population of 454 patients. The purpose of the studies was to determine whether adjunctive use of electrical stimulation of the left vagus nerve could reduce seizure frequency in patients with refractory epilepsy. The EO1 and EO2 studies were two pilot studies that enrolled 15 patients with refractory partial epilepsy, 14 of whom received stimulation. In one patient the NCP device was explanted because of a surgical complication resulting in unilateral vocal cord paralysis that resolved 9 months later. The degree of response ranged from no improvement to complete cessation of seizures, with a mean reduction of 46.6%. In none of the patients did the seizure disorder appear to be exacerbated by VNS. Of 14 patients, 5 reported a reduction in seizure frequency of at least 50%. None of the patients reported transient or permanent serious side effects. The most common side effects were noted only during actual stimulation of the nerve and consisted of hoarseness and local neck/throat paresthesia. These effects became milder after a few months of stimulation. No negative cardic or gastrointestinal effects were observed on electrocardiogram monitoring and measurements of gastric acid output.

The EO3 (114 patients) and EO5 (196 patients) studies were both randomized, blinded, active control trials in which patients with refractory partial epilepsy were randomly assigned into two treatment groups. Patients assigned to treatment with “high” stimulation parameters (30 Hz, 30 seconds on, 5 minutes off, 500 us pulse width) were believed to receive therapeutic treatment. Treatment with “low” stimulation parameters (1 Hz, 30 seconds on, 90–180 minutes off, 130 us pulse width) was considered to be nontherapeutic. The primary efficacy endpoint was the percentage reduction in seizure rate measured over a period of 12 weeks. Adverse events were assessed at each patient visit. In the high stimulation groups there was a mean reduction in seizure frequency of 24% in the E03 study and 28% in the EO5 study. This is a statistically significant decrease in seizure frequency when compared with baseline seizure frequency ($p < 0.05$; $p < 0.0001$) and seizure frequency reduction in the low stimulation groups (6% in the EO3 study and 15% in the EO5 study), p - 0.02 ; p < 0.02.

The most common treatment-related adverse events were attributable to vagal innervation of the larynx during current “on” periods and consisted of voice alteration, coughing, throat paresthesia and discomfort, and dyspnea. Treatment was well tolerated, with 97% of patients continuing in the long-term follow-up phase of the study. Surgery-related complications included left vocal cord paralysis in two patients, lower facial muscle paresis in two patients, and fluid accumulation over the generator that required aspiration in one patient. All these complications resolved. Infection around the device occurred in three patients.

VNS had no effect on concurrent AED serum levels or on body chemistry. Rigorous blinded collection of autonomic measures revealed no effect on weight, serum gastrin, or cardiac and pulmonary function tests. Electrical stimulation of the left vagus nerve has no demonstrable effects on visceral functions when administered at levels that do not exceed comfort. The EO4 study was an open study in which 116 patients with all types of epilepsy and patients under 12years of age were stimulated. In this study 29% of the implanted patients had a seizure reduction of more than 50%.

Long-term Efficacy and Safety

Long-term data (>3 months) were collected on all available EO1 through EO4 study patients. These long-term follow-up data are uncontrolled because they come from an open-label protocol in which both the AED medications and NCP device settings were allowed to be changed. Patients initially randomized to low stimulation parameters were changed to high stimulation parameters. George et al[53] reported 18 months efficacy analysis in 50 patients exiting the EO3 study and Salinsky et al[53] reported efficacy data in 100 of 114 patients from the EO3 study who were treated for 1 year. Results indicated that VNS remains effective over time, and a trend toward improved seizure control with longer use of VNS was observed. Response during the first 3 months of treatment is predictive of long-term response.

Chronic side effects were identical to those observed during the randomized trials and consisted mainly of mild hoarseness during stimulus delivery. Several other reports on long-term treatment with VNS confirm these

findings. In our own study, up to 10% of patients became seizure-free for a period of 12 months or longer. A trend toward improved seizure control with longer use of VNS was observed. Response during the first 3 months of treatment seemed predictive of long-term response. Ben-Menachem et al[64]. published data on 64 patients with follow-up of up to 5 years. The study included patients with partial seizures, Lennox-Gastaut syndrome[65], and primary generalized seizures. A large reduction in seizure frequency and severity over long periods of time was experienced by 44% of patients. VNS seems equally efficacious for Lennox- Gastaut syndrome and primary generalized seizures but results from larger patient groups are necessary. Two patients became pregnant and have given birth to healthy babies.

Experience in Children

Experience with VNS in children is less extensive than it is in adults, but results seem promising. Two studies in children reported seizure frequency reductions of 60% in 80% and 50% in 38%[66]. One study in 60 children[69] with mean age of 15 years reported a reduction in seizure frequency similar to that in adults. Median reduction of seizure frequency was 44%. A gradual increase in efficacy up to 18 months postoperatively was observed. The predominant seizure type in this study was complex partial (57%), followed by generalized tonic-clonic seizures (27%). No particular seizure or epilepsy type appeared usually sensitive or resistant to VNS[67]. Adverse events during stimulation included fever, coughing, colds and voice alteration[68]. No patients dropped out, and side effects subsided over time.

CURRENT MANAGEMENT PARAMETERS

In many epilepsy centers VNS is a routinely performed treatment for patients who are unsuitable candidates epilepsy surgery[69] or who have had insufficient benefit from such treatment. The patients` are initially included in a presurgical evaluation protocol including video-EEG monitoring, optimum magnetic resonance imaging, positron emission tomography, and neuropsychologic examination. Results of these examinations are discussed in the epilepsy surgery meeting by a multidisciplinary team. Patients who are considered unsuitable candidates for resective surgery can be includedin phase-III drug trials with new AEDs or they can be offered implantation with a vagus nerve stimulator[70].

Absolute contraindications for implantation of a vagus nerve stimulator are limited to previous left or bilateral cervical vagotomy. A stimulator will not be implanted when there is evidence of progressive intracerebral disease. Other conditions that need special attention are cardiac arrhythmias, respiratory diseases such as asthma, and pre-existing hoarseness, gastric ulcers, vasovagal syncope, and coexisting neurologic diseases other than epilepsy. Patients who were evaluated for epilepsy surgery several years ago when treatment with a vagus nerve stimulator was not yet routinely available are reconsidered at the epilepsy surgery meeting and are re-evaluated with magnetic resonance imaging or other investigations when necessary.

Patients are extensively informed about the efficacy, side effects, implantation procedure, and ramping up procedure. After informed consent is

obtained they are admitted to a neurosurgical unit for 48 hours[72]. The surgical procedure is performed under general anesthesia and lasts about 1 hour. Patients leave the hospital with the stimulator unprogrammed. During a clinic visit 2 to 4 weeks after the operation, the vagus nerve stimulator is programmed to continuous intermittent stimulation, starting with an initial 0.25–0.50 mA output current, depending on individual patient tolerance. Every 2 to 4 weeks the stimulation output current is gradually ramped up by 0.25–0.50[73] until clinical efficacy or patient tolerance is reached. When patients are used to the electrical stimulation they are provided with the magnet. At every clinic visit seizure frequency and side effects are assessed. AEDs remain unchanged during ramping up. Tapering of AEDs may be considered when seizure freedom is achieved. After ramping up patients are seen every 3 to 4 months.

Outcome parameters specific for VNS

Scoring systems used to measure outcomes after epilepsy surgery include those developed by Engel and the ILAE[74]. Studies of VNS outcome have analyzed seizure frequency reduction based on the Engel system or modifications of it, reductions in the use of antiepileptic medications, and improvements in quality of life, which are typically associated with seizure reduction.

Although there are few published data, subjective components of the Engel system may contribute to low interrater agreement and subsequent difficulty in comparing reported outcomes. Similarly, the interrater agreement

of classifications documenting seizure frequency reduction,such as the ILAE system, after implantation for VNS is unknown. With the introduction of new techniques in andapproaches to the management of refractory epilepsy, it is clearly necessary for any scoring system to remain applicable. McHugh et al.[75] have proposed a tailored scoring system to address VNS specific issues, including a non linear change in seizure frequency, changes in ictal and postictal severity, and magnet use.

McHugh classification[75]

Class I	80-100% reduction in seizure frequency A-improved ictal or postictal severity B-no improvement in ictal or postictal severity
CLASS II	50-79% reduction in seizure frequency A-improved ictal or postictal severity B-no improvement in ictal or postictal severity
CLASS III	0-50% reduction in seizure frequency A-improved ictal or postictal severity B-no improvement in ictal or postictal severity
CLASS IV	Magnet benefit only
CLASS V	No improvement

For clinicians to adequately inform their patients,VNS outcome classifications must demonstrate a high degree of inter rater reliability. The Engel and ILAE seizure frequency reduction classification systems are used widely and show a very good degree of interrater reliability when evaluating

outcomes of resective epilepsy surgery. Seizure frequency is a significant outcome measure when assessing outcomes following surgery for medically intractable seizures. However, with adjunctive treatments such as VNS, assessment must ultimately reflect quality of life. Seizure reduction has been associated with an improved quality of life. Although seizure freedom is very rarely achieved with VNS, the Engel system is widely used to classify outcome. There is also inconsistency in classifying seizure frequency outcome following VNS implantation, and this can prevent the evaluation of efficacy.

In a recent meta analysis of 3321 patients, W P Rodgers et al[74] identified outcomes based on the Engel system for approximately 80% of the patients. Following VNS implantation, many such reported outcomes classify seizure frequency changes by using modifications of the Engel system, more akin to seizure frequency assessment in the ILAE system. Concerns regarding applicability of the Engel system in the treatment effects of VNS have led to the proposal of new classification scheme to address certain VNS-specific issues.

COMPLICATIONS

The precise mechanism by which VNS modulates seizure activity and its locus of action remains the subject of much conjecture. Vagus nerve stimulation induces a significant prolongation of somatosensory evoked potentials[77], but does not alter visual, auditory, or cognitive evoked potentials. Much interest has been centered on its effects at the level of the brainstem,

both as a site of epileptogenesis and as a regulator of seizure propagation. Vagal stimulation evokes responses in regions as widespread as the cerebral cortex, hippocampus, brainstem, thalamus, and cerebellum; its antiepileptic actions may relate to effects on these areas via the brainstem reticular activating system. Overall, VNS appears directly or indirectly to activate a wide array of neuroanatomical structures.

Transient side effects of VNS[77] occur frequently and include hoarseness or voice changes (20–66%), cough (7-45%), dyspnoea (6–25%), headache (14–24%), nausea (7–15%), and a tingling sensation in the throat or neck spasms (11%). These complications are usually dose-dependent and occur during stimulus delivery. Occasionally, VNS results in significant adverse neurological effects including vocal cord paralysis and facial muscle paresis. These effects occur in approximately 1% of all patients. Electrode breakage and device infection are relatively common surgical complications, with published rates being similar to those of other chronically implanted devices such as baclofen pumps and deep brain stimulators. One of the challenges that occurs in treating children with stimulator implantation is the tendency of some children to manipulate manually the device or the associated incision. Many children with medically intractable multifocal epilepsy have suffered severe brain insults and have significant developmental delay. Often such children are incapable of vocalizing concerns or complaints and will instead tend to pull at the device or incision. This can prove to be troublesome for families and health care providers alike.

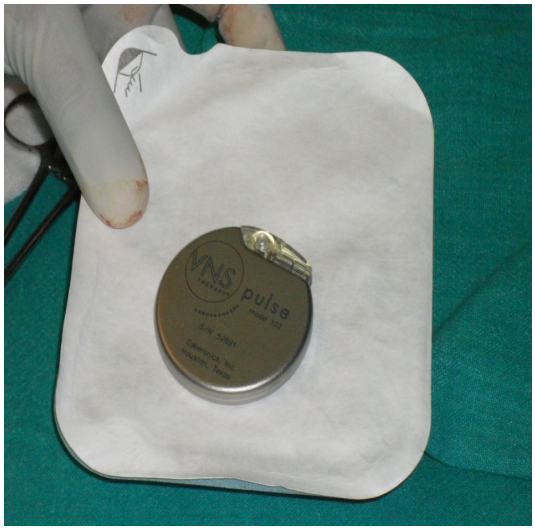
SURGICAL TECHNIQUE followed in our institute

Anaesthesia:General anaesthesia

Lead

Tunneler

The system comprises: a pulse generator, a lead incorporating a bipolar electrode, tether and connectors, a tunnelling tool, a programming wand with control software and a magnet.

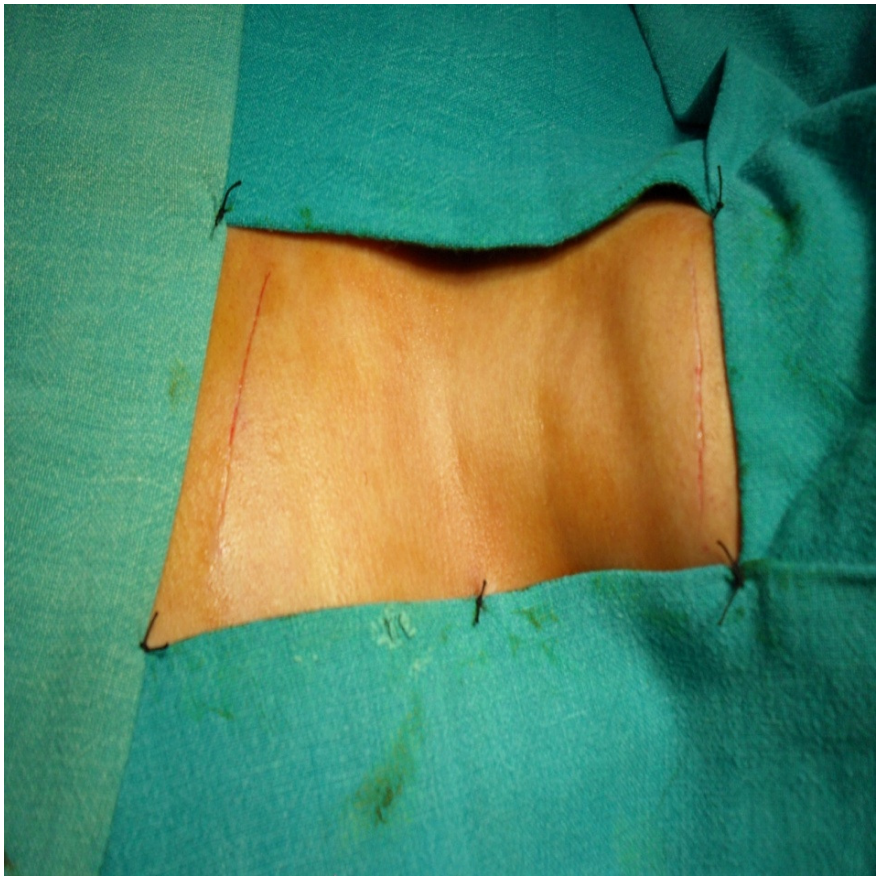


Pulse generator

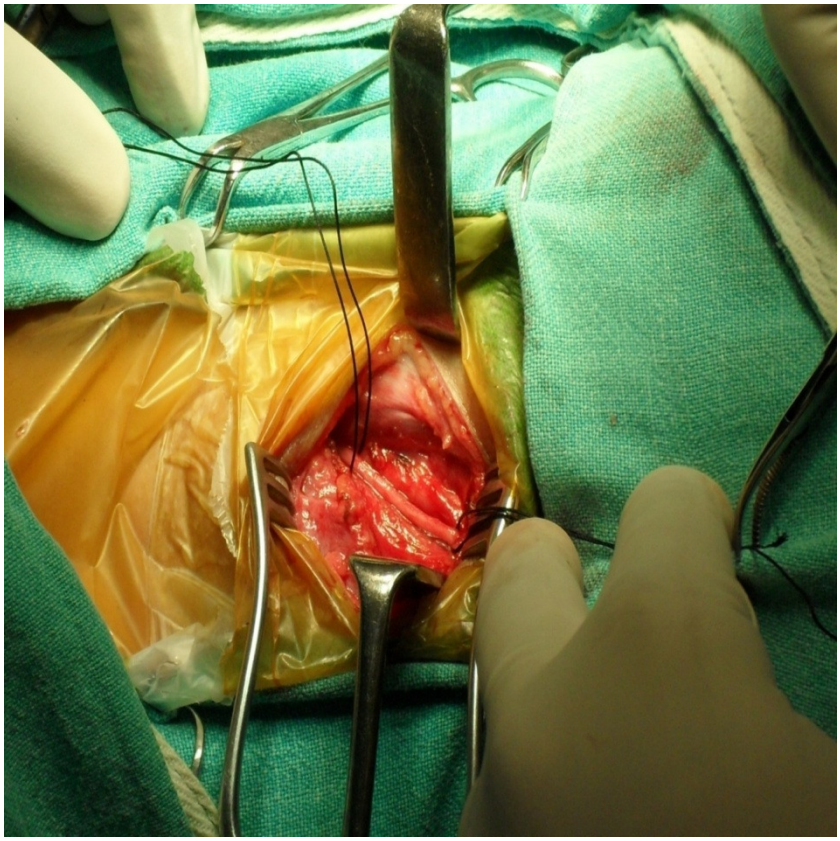
Magnet

Position: Supine with neck extended and head supported on a head ring and slightly turned to the right.

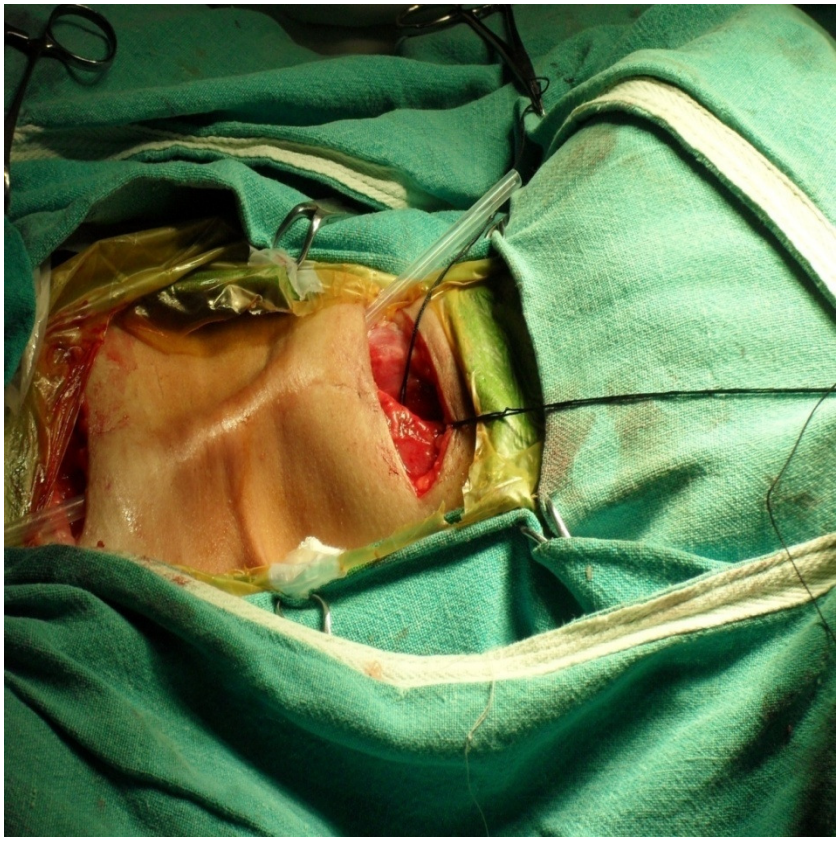
Incisions:Two skin incisions 1;over the anterior axillaryfold and another horizontal skin crease incision at the level of cricoid cartilage.



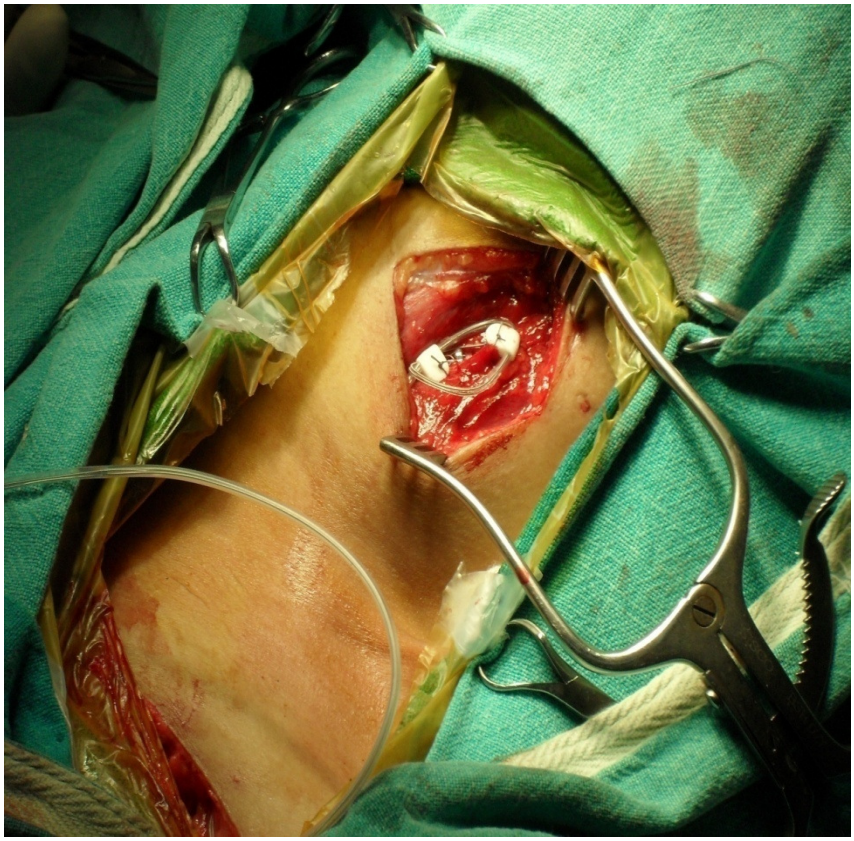
Procedure: Skin preparation done, exposing the area. The entire proceure is done under an operating microscope. The neck incision is deepened through a plane medial to the sternocleidomastoid. The carotid sheath is identified and opened. The vagus nerve is exposed between the jugular vein and the carotid artery.At this level the nerve tends to lie towards the posterior aspect of the carotid sheath. The nerve is exposed to a length of 3cms distal to recurrent laryngeal nerve.



The incision over the anterior axillary fold is deepened in a superior direction till the pectoralis fascia and a pouch with 3 finger breadth is made so that the pulse generator can be placed within it without tension on the skin.A tuneller is then passed from neck to the chest incision superficial to the sternocleidomastoid.The central steel pointer of the tunneller is removed and the plastic sheath left in situ.



The electrode is then passed through the plastic sheath from caudal to cranial direction. The 3 electrodes are then wrapped around the left vagus nerve. This is aided by pulling the small thread at the end and taking it around the vagus.A loop of electrode is made inferior to the inferior electrode and another loop is made superiorly above the superior most electrode and these are held in position by three stay sutures taken through the “tie downs” using a 3-0 non absorbable suture.

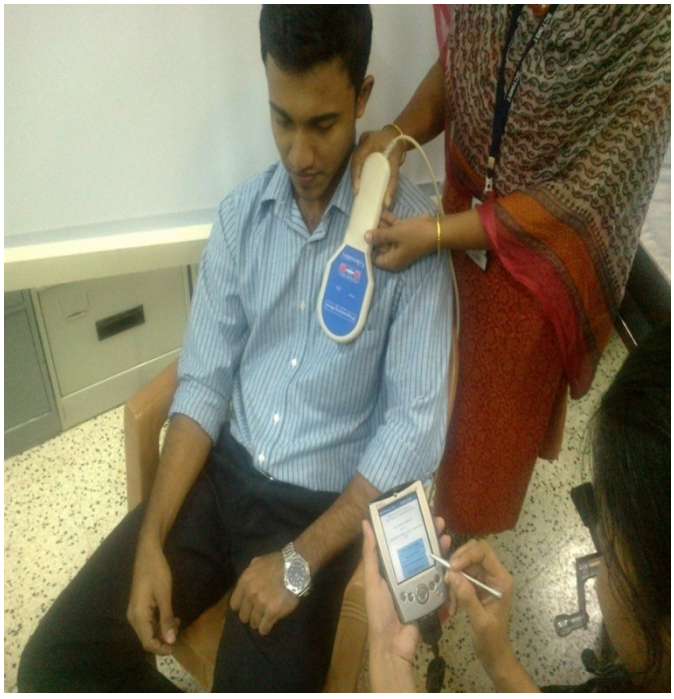


The lead on the other end of the electrode is passed to the pulse generator completely and using a screw-driver the nail is tightened (seen through the plastic cover over it).A stay suture is passed through the space provided for it on the pulse generator and the pulse generator is checked for impedance. While checking the impedance generator is kept few millimetres away from the wand.The position of the pulse generator in the pouch is such that the wires and the electrode are not in relation to the skin to avoid irritation and necrosis of the skin. Both wounds are closed in 2 layers.

POST IMPLANTATION PROGRAMMING

We prefer the wound to heal and sutures removed ie after a week before programming.It can be program wand guided or computer aided.Impedance tested with a standardised lead test 1-2 k ohms.

Current of 0.25 mA is started with and later with a increments of 0.25 mA to reach a current strength of 2-3 mA.Frequency was set at 20-30 Hz and the pulse width was 500 us On time is 30 seconds and off time is minutes.



RESULTS

Current study evaluated the role of VNS as palliative procedure for refractory epilepsy in 20 patients registered in our comprehensive epilepsy programme.

DEMOGRAPHIC PROFILE

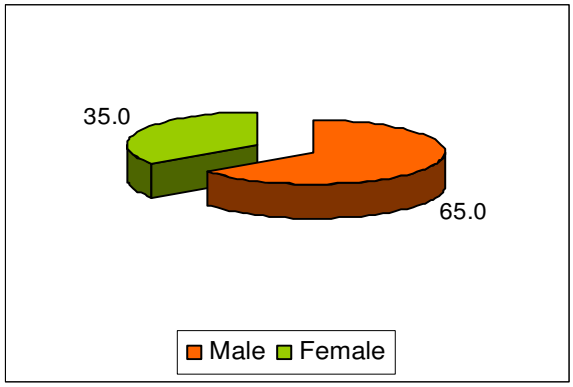
Table I**: DEMOGRAPHIC AND CLINICAL PROFILE**

Number (n)		20
Sex	Male	13 (65%)
	Female	7 (35%)
Age at VNS implantation		22.3 ± 4.8
Age at epilepsy onset		6.2 ± 4.3
Epilepsy duration		16.0 ± 5.0
Previous epilepsy surgery		2 (10%)
Neurological examination		
Normal		19
Focal deficit		1
Cognitive assessment		
Normal		3
Mild deficit		8
Severe deficit		9
IQ		
Mean+SD		51.0 ± 8.4
Median		50.0

Table II **Distribution according to gender**

Gender	n	Percent
Male	13	65.0
Female	7	35.0

Figure II: **Distribution according to gender**



Majority of our patients were males (65 %) and may be an incidental observation. Majority of the patients have cognitive decline with mean IQ of 51.0± 8.4.On examination there was some evidence of lobar dysfunction in majority of the patients.

Table III **: ANTECEDENTS**

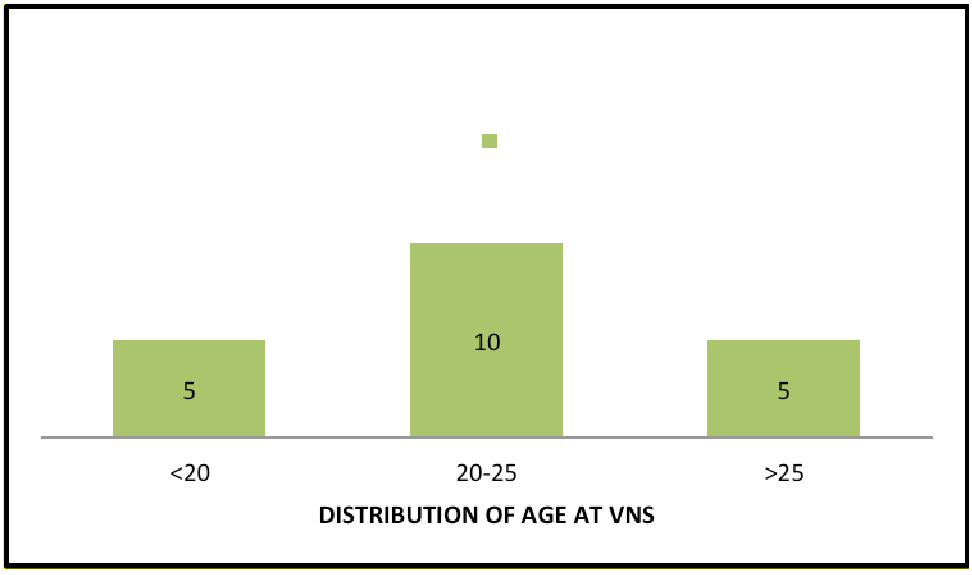
Antecedents	**n**	**Percent**
Perinatal hypoxia	3	15%
Meningoencephalitis	3	15%
Trauma	1	5%
Neonatal hypoglycaemia	2	10%

Antecedents were present in nearly 45 % of the patients. It included perinatal asphyxia , meningoencephalitis , trauma and neonatal hypoglycaemia**.** We saw that most of the antecedents were perinatal.2 patients had childhood meningoencephalitis.One patient had traumatic brain injury with bifrontal contusion and seizure developed as a sequelae to that.

Table IV **: Distribution according to age at VNS**

Age at VNS	N	Percent
< 20	5	25.0
21 – 25	10	50.0
26 – 30	5	25.0
Mean + SD	22.3 ± 4.8	
Median	24.0	

Figure III :



The median age of our patients were 22.3 ± 4.8 and median age was 24.0.They were classified into three groups. First group comprised of patients younger than 20 years of age. Second group consisted of patients 20-25 years of age and third subgroup consisted of age >25 years of age. Youngest patient was 13 years of age and oldest was 29 years of age. The device was not implanted in patients younger than 12 years of age.

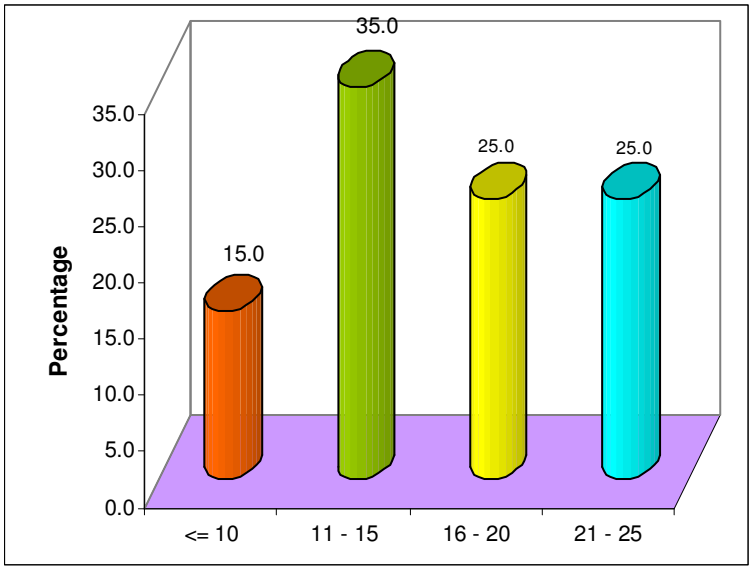
Table V : **Distribution according to age at onset of seizures**

Age at onset	Count	Percent
< 1	5	25.0
2 – 5	4	20.0
6 – 10	6	30.0
> 10	5	25.0
Mean + SD	6.2 ± 4.3	
Median	7.0	

Table VI : **Distribution according to duration of seizures**

Duration of seizures	Count	Percent
<= 10	3	15.0
11 – 15	7	35.0
16 – 20	5	25.0
21 – 25	5	25.0
Mean + SD	16.0 ± 5.0	
Median	15.5	

Fig IV : **Distribution according to duration of seizures**



The majority of the patients had seizure onset at younger age group with a mean age of seizure onset at 6.2 ±4.3 years. Around 25 % of the patients had their onset of seizures during infancy. Our patients presented with long history of refractory seizures with mean duration of 16.0 ± 5.0 years. That itself shows the seizure burden of the patient.

Seizure profile (Table VII)

Focal	Simple partial	1(3.55%)
	Complex partial	18(90.0)
	Secondary generalization	11 (55.0%)
Generalised	GTCS	2(10.0%)
	Atypical absence	2(10.0%)
	Tonic	2(10.0%)
	Atonic	3(15.0%)
One seizure type		6(30%)
Seizure with Falls		19(95%)
Seizure clusters		18(90%)

Majority of the patients had polymorphic seizures, with complex partial seizures predominating. Almost all patients had seizure clusters and falls which constitutes the most debilitating. Generalised tonic-clonic seizures and atonic seizures were there in a subset of patients.

Table VIII **: Distribution according to antiepileptic medications**

Antiepileptic medications tried	Count	Percent
4 – 6	8	40.0
7 – 10	12	60.0
Mean + SD	6.8 ± 1.4	
Median	7.0	

Most of the patients had been tried on multiple AEDs before being evaluated for VNS with mean AED of 6.8±1.4 .Almost all groups of antiepileptic drugs had been tried.Some patients developed adverse effects of AEDs also.

Table IX **: Distribution according to Antiepileptic medications at the time of surgery**

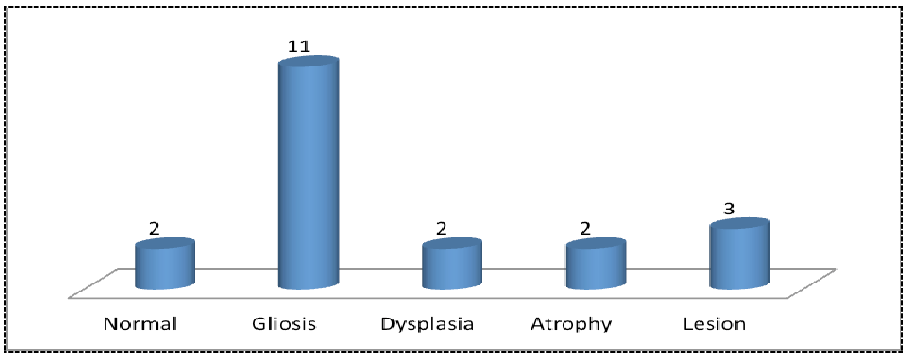
Antiepileptic medications now	**Count**	**Percent**
2	3	15.0
3	13	65.0
4	4	20.0

Most of our patients had used at least 3 AED at the time of surgery.

ICTAL CORRELATE IMAGING DATA (Table X)

MRI	Count	Percent
Normal	2	10.0
Gliosis	11	55.0
Dysplasia	2	10.0
Atrophy	2	10.0
Lesion	3	15.0

FIGURE V:



The primary role of MRI in workup of medically refractory epilepsy is to find out any resectable correlates or if any resectable correlates are found is it overlapping eloquent areas.Majority nearly 90 % of our patients had some abnormality.The most frequent pathology was gliosis (55%).The MRI was normal in about 2 % of patients.In 3 of the patients the epileptogenic zone was overlapping the eloquent area.

ICTAL CORRELATE –ELECTRICAL DATA (Table XI)

Generalised IEDS:		7(35%)
Focal IED:	Temporal: Frontal : Hemispheric: PHR :	3(15%) 6(30%) 1(5%) 2(10%)
Multifocal IED:		8(40%)
EEG Ictal pattern:	Localised: Lateralised: Uncertain: Bilateral independent: Diffuse :	7(35%) 5(25%) 4(20%) 2(10%) 4(20%)

EEG formed the baseline workup of all patients. Both the ictal and interictal EEG were monitored. Bilateral and independent ictal origin constituted one indication for VNS and present in 10 % of cases and in another 20% of patients it was diffuse.Electroradiological discordance has to be noted.

Surgical indications

Only patients who had no resectable correlates were included.

Table XII: **Distribution according to indication for surgery**

Indication for surgery	**Count**	**Percent**
Multiple MRI lesions unsuitable for resection	6	30.0
Bilateral or multifocal independent ictal origin	9	45.0
Multiple seizure types without definite resectable correlate	5	25.0
Electro radiological discordance	3	15.0
Epileptogenic zone overlapping eloquent area	3	15.0
Surgical failure	2	10.0

VNS was offered to those patients who didn't have any resectable correlates.Indications were as shown in the table. There were two cases of previous surgical failures. One patient had undergone right anterior temporal lobectomy in 1995 and amygdalohippocampectomy in 1995 and the other patient had undergone right frontal lesionectomy in 2001. Three patients had their epileptogenic zone overlapping eloquent cortex. One had a left pareito-occipital porencephalic cyst and 2 others had lesion in the motor cortex.

Figure VI:

Table XIII**: Distribution according to follow up duration on years**

Follow up duration on years	Count	Percent
<= 2	3	15.0
3 – 5	11	55.0
6 – 7	6	30.0
Mean + SD	4.4 ± 1.8	
Median	4.0	

The median followup period was 4.4 ± 1.8 years. During followup period the patient's seizure frequency was evaluated and any implant related complications were looked for.Their implant settings were also reviewed.

Operative and stimulation parameters

STIMULATION PARAMETERS (Table XIV)

PARAMETER	UNIT	VALUES
Output current	Milliamperes(mA)	2-3.5 mA
Signal frequency	Hertz(Hz)	30 Hz
Pulse width	Microseconds(us)	500 us
Signal on-time	Seconds(s)	30 s
Signal off-time	Seconds(s)	300 s
Lead impedance	Kilo-ohms(Kohms)	1-2 Kohms

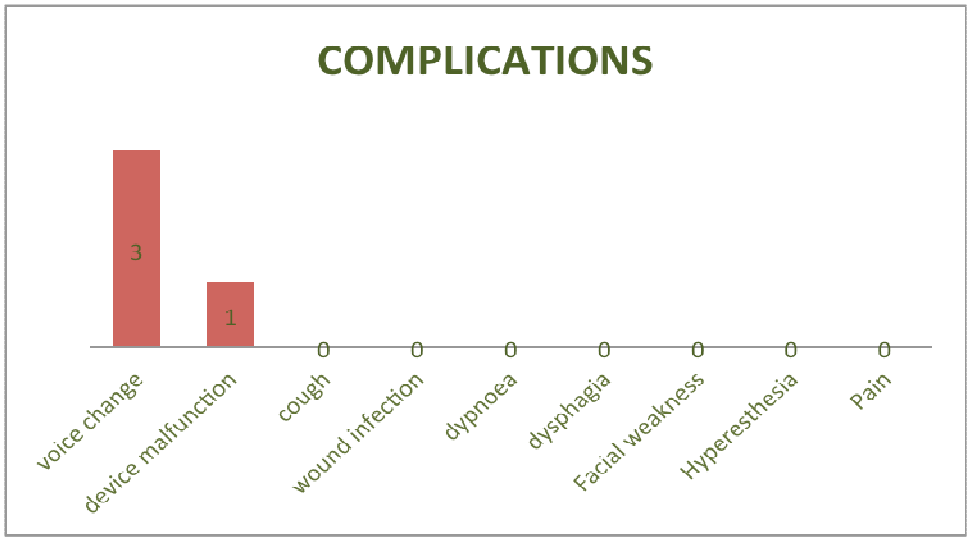
IMPEDANCE VALUES		
	Mean ± SD	Median
3 months	1.67± 0.7	1.75
1 year	1.56± 0.8	1.50
Last followup	1.75±0.7	1.75

The range of the output current was from 1 - 3.5 mA and the mean was 2.75 ±0.78 mA. The most frequent duty setting was 30s ON/3 min OFF (duty cycle 16%).In our patients the lead impedance was between 1.5 and 2.5 kohms.One patient had high impedance following implantation and local wound site infection was first thought of .She was administered a course of antibiotics.Ultimately the wound was reexplored and connections rechecked but no abnormalities were noted and reassembled.After that the device started functioning with normal impedance values.

Table (XV) **Distribution according to complication**

Complications	Count	Percent
Nil	16	80.0
Voice Change	2	10.0
Device malfunction	1	5.0
Cough	0	0
Dyspnoea	0	0
Dysphagia	0	0
Facial weakness	0	0
Hyperaesthesia	0	0
Pain	0	0
Wound complications	0	0

FIGURE VII



Only 15% of the patients had complications. It included voice change and persistent dysarthria in one of the patient. As the symptoms became intolerable and as there was no useful seizure outcome the device was explanted after 1 year of follow up. One more patient had persistent voice change after surgery but tolerable. One of the patients in our group had high impedance following implantation and was diagnosed as device malfunction due to unknown cause.

Table (XVI) : **Seizure outcome**

Seizure outcome	3months	1year	Last visit
>50%- Class I	3 (15%)	5(25%)	5(25%)
<50%- Class II	5 (25%)	8(40%)	7(35%)
No improvement/ Worsening- ClassIII	12(60%)	7(35%)	8(40%)

Figure VIII

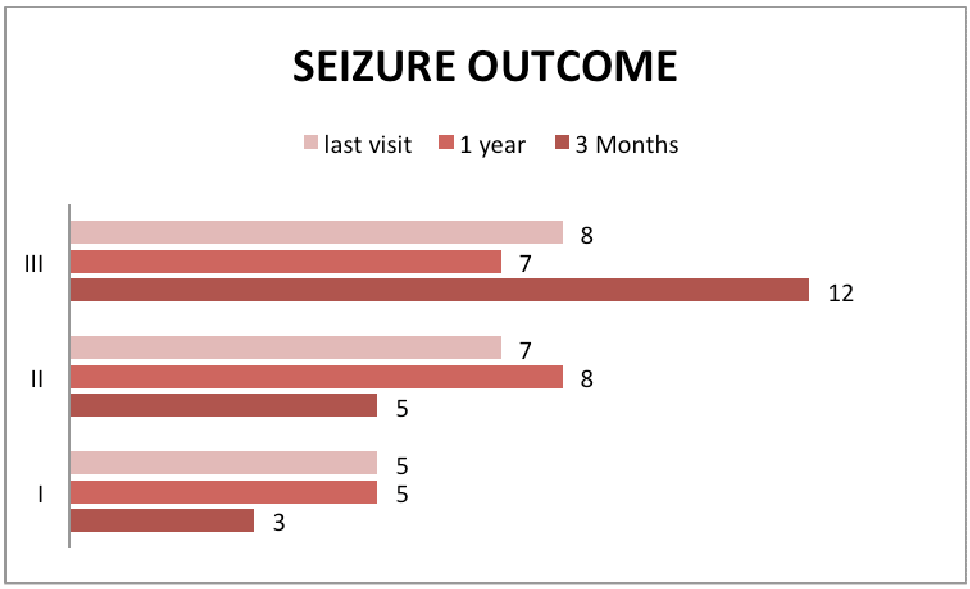


Table (XVII): **McHugh Outcome**

Mc Hugh outcome	**3 months(n**	**I year**	**Lastfollowup**
IA	0	0	0
IB	0	0	0
IIA	2	3	4
IIB	1	2	1
IIIA	3	5	4
IIIB	2	3	3
IV	3	2	2
V	9	5	6

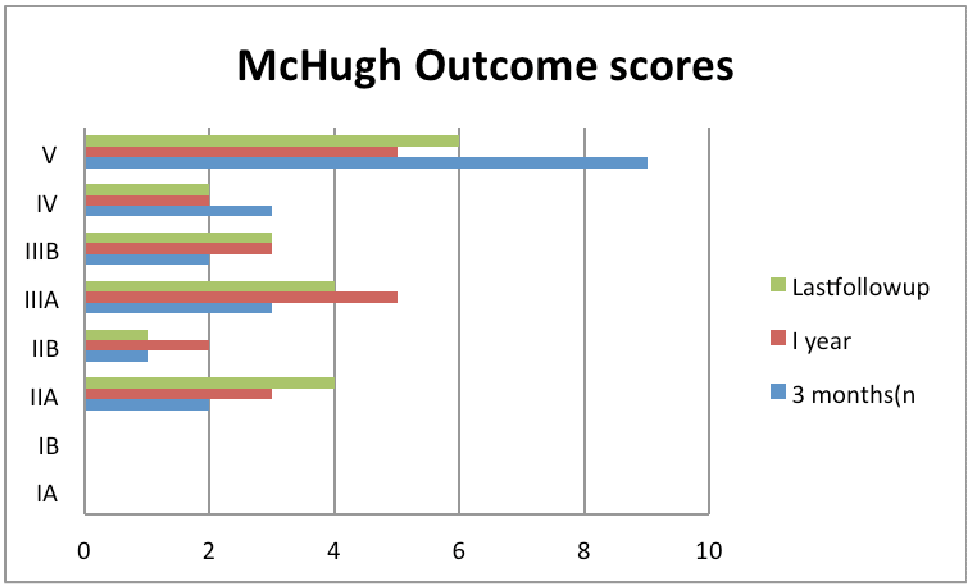
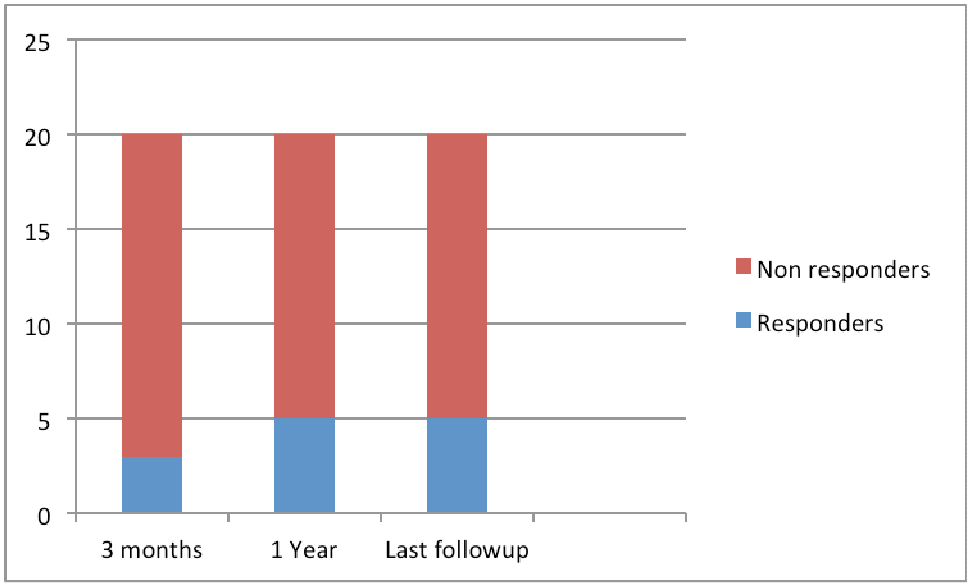


Figure IX:



Responders:McHugh I and II and >50 % reduction
Nonresponders:McHugh III,IV and V and < 50 % reduction seizures

In our study responders were 15 % at 3 months and at 1 year and last followup it was around 25%.In about 20 % of patients there was some reduction in seizure severity in the form of decreased clusters and status.We used the McHugh classification for assessment of outcomes. It was assessed

in 3 points of time .One at 3 months, 1year and last follow up post implantation.We can observe that the effect of VNS is at an interval on follow up(p value0.01).Most of the patients who gained seizure control initially continued to do so in follow up.

Table (XVIII) : **Comparison between and preoperative and post implantation seizure frequency**

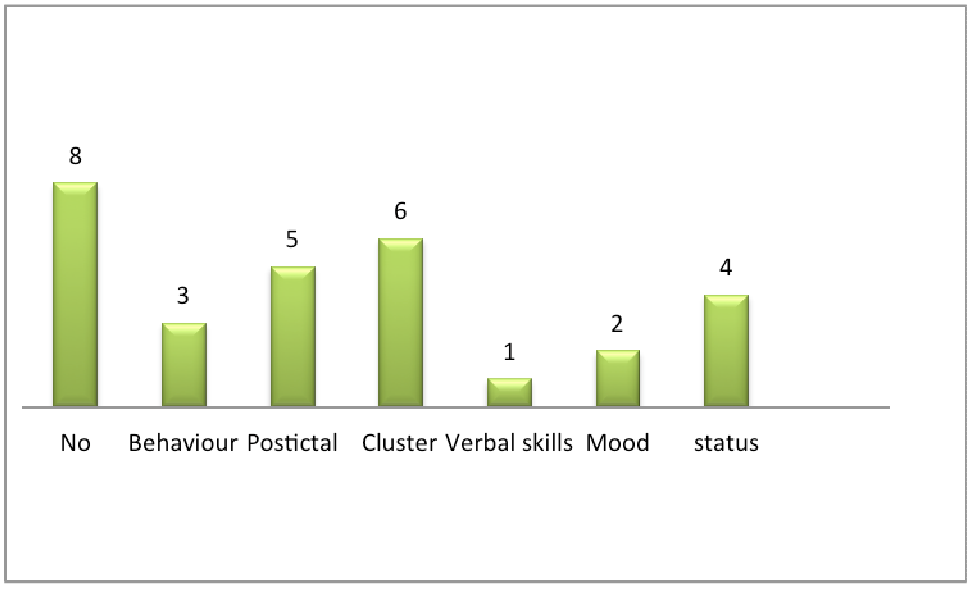
	Preoperative	1 year FU	Last followup
All seizures			
Range	10-150	3-120	4-120
Median	71± 52.7	52.7±44.3	51.2±46.4
p Value		0.05	0.05
CPS			
Range	15-140	10-120	12-125
Median	69.5 ±54.3	57.3±42.3	55.3±40.3
p value		0.05	0.05
Atonic			
Seizures	0-150	00-120	0-120
Range	65.2±52.2	39.1±38.8	34.0±36.7
Median		0.01	0.01
p value			
GTCS	0-60	0-20	0-15
Range	8.6±14.6	2.2±0.9	2.1±1.0
Median		0.01	0.01
p value			

Even though sample size is less,it was found that atonic seizures and GTCS responded slightly better in comparison to complex partial seizures with statistical significance.

Table (XIX): **Distribution according to quality of life improvement**

Quality of life improvement	Count
No improvement	8
Behaviour	3
Postictal state	5
Seizure cluster	6
Verbal skills	1
Mood	2
Status	4

Fig X:



Quality of life post procedure has been assessed in our patients. We have evaluated the behavior, mood, postictal state, clusters, verbal skills and episodes of status. Majority of the patients has no significant improvement in quality of life. Around 25 % of the patients have noteworthy improvement in seizure clusters and postictal state.

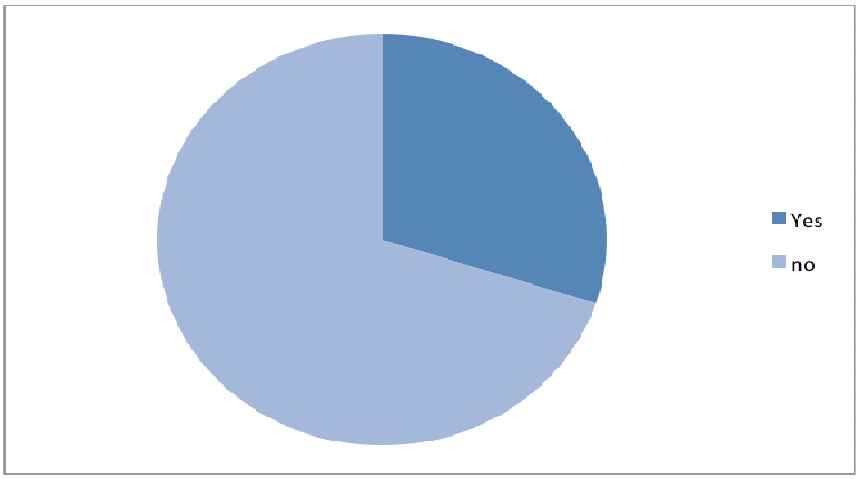
Table(XX) : **Distribution according to patient functional status**

Patient functional status	Count	Percent
Independent	8	40.0
Dependent	12	60.0

Table (XX1):**Distribution according to care taker satisfaction**

Care taker satisfaction	Count	Percent
Yes	6	30.0
Not satisfied	14	70.0

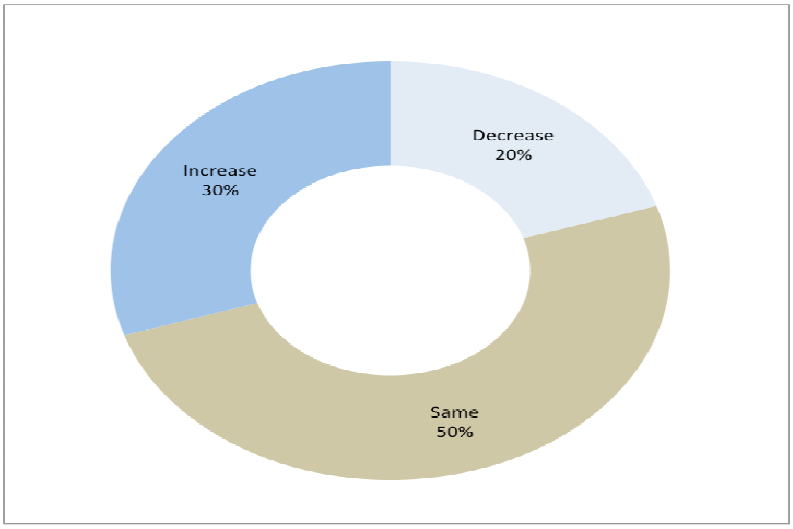
Figure XI:



Care takers were not satisfied in 55% of the patients. Most of them commented on questionnaire and interviews that the procedure too costly and not worthy of the expenditure.

Impact on AED usage

Figure XII



The study also evaluated the impact of the procedure on antiepileptic medications. While the antiepileptic medications remained the same in 50 % of the patients ,in 20% it was reduced and that included the obviously responder group.

DISCUSSION

The US FDA in July 1997 has approved the use of VNS as an adjunctive therapy in the treatment of epilepsy for adults and adolescents over 12 years of age. We attempted to study this procedure with respect to seizure palliation,impact on quality of life and care taker satisfaction, by a retrospective analysis of the records of 20 of our patients with atleast 1 year followup.

Mean age of VNS implantation was 22.3 ±4.8 years(Tab IV & FigIII). The youngest patient in our group was 13 years and oldest was 29 years . Eventhough FDA has approved its use only in children more than 12 years, there are studies about its safety and efficacy in children younger than 12 years of age also. R E Elliott et al[79] in 2011 has evaluated the role of VNS in 141 consecutive patients with refractory epilepsy and found similar response rates in the pediatric age group.Our experience with the pediatric group is limited, as 75% of our patients are older than 20 years .5 patients in the age group 13-20 behaved the same as that of the other groups. The male preponderance of the procedure seen in our series appears to be incidental.

In our series 85% of the patients had poor cognitive status with a mean IQ of 51.0± 8.4(Table I) .On gross neurological examination 2 patients had focal neurological deficits. Antecedents were present in nearly 45 % of patients(Table III) in the form of perinatal asphyxia in 2 patients , meningoencephalitis in 3

patients ,neonatal hypoglycemia in 2 and 1 patient has history of trauma with bifrontal contusion at the age of 7 years.

Majority of our patients had childhood onset of epilepsy with mean age of onset as 6.2±4.3 (Table V)and with mean seizure duration of 16.0±5.0(Table VI) .Almost all patients had complex partial seizures(Table VII) with frequent clusters,falls and status.These parameters indicate the high burden of seizures in these patients.

Before considering VNS, all our patients were thoroughly investigated for any possibility for resective epilepsy surgery.MRI abnormalities were present in majority of the patients(TableX,FigV) .They also had diffuse and bilateral independent electrical abnormalities .The patients were given the option of VNS when no ideal resectable coordinates (Table XII) were found, or after failed epilepsy surgery. In our mean follow-up of 4.4±1.8(Table XIII) years we evaluated the seizure outcome using the VNS specific McHugh classification. McHugh et al 2007[75] has come with a new classification system which is a tailored scoring system which will address VNS specific issues like non linear change in seizure frequency,changes in ictal and postictal severity and magnet use. W P Rodgers et al[74] found that the inter rater reliability of the McHugh scale was superior than Engel and ILAE classification for VNS outcome studies .

Comparison with current literature				
SERIES	**YEAR**	**NO**	**MONTHS OF FU**	**>50% REDUCTION**
BenMenachem et al[58,82]	1994	67	3.5	38.7
Vonck et al[84,85]	1996	15	12	67
Sirvan et al[86]	2000	45	3	66.7
Chavil et al[78]	2003	29	24	61
Murphy et al[81]	2003	96	3	45
De Herdt et al[60]	2007	138	12	59
Ghaemi et al[83]	2010	144	24	61.8
Elliott et al[68,87]	2011	141	3	64.8
Current study	2013	20	28	25

On comparison with similar studies in the literature,our seizure outcome is slightly less at all times of followup. One of the reasons for the difference may be the fact that we had a subset of patients who belongs to the so called 'difficult to treat' epilepsy population, while most of the studies when reviewed consisted of a population of the patients who belong to the so called 'favorable treatment' group. It included atonic seizures,GTCS and syndromic epilepsies;Lennox Gastaut syndrome or West's syndrome[62] or VNS was offered as rescue procedure while waiting for resective surgery. In our series the procedure has been used as a palliative procedure for a subset of patients with difficult to treat epilepsy when no other options were left.

In our study responders were 15 % at 3 months(Table XVII and Fig IX) and at 1 year and at last follow-up it was around 25%.In about 20 % of patients there was some reduction in seizure severity in the form of decreased clusters and

status.Current literature suggests that 1/3rd [2]of the patients experience a seizure reduction of at least 50%,1/3 experience a more moderate reduction of seizure frequency and in the remaining 1/3 there is little or no reduction. According to Uthaman[43] et al the patients can be divided into 3 categories: 1)those with a rapid onset of effects (weeks), 2) those with gradual onset of effects (months or years) and 3) those with no effect at all. Our study also showed similar results.15 % responded rapidly and 25 % after a gap of 1 year on follow-up. Nakken et al [35]2003 in his study found that the improved control was not only maintained but also increased over time. 75 % of our patients has no useful response in our studies.

In our patients we observed that generalized tonic clonic seizures and atonic seizures has slightly more response rate when compared with other seizure types(Tab XVIII)

Salinsky et al [87]and R George et al[88] also from their clinical study found the observation that the effects of VNS are noteworthy for atonic and GTCS. Maromi Nei et al[65] studied the role of vagus nerve stimulation in generalized seizures only and found >80% reduction in seizure severity in 33% of patients. When used in Lennox-gastaut syndrome Helmers et al[89] and Frost et al[89] found a reduction of seizures of >80% in 35 % of patients. All these raise a question as to whether VNS can be used for broader indications.D E Connor Jr[2] et al evaluated the role of VNS and found that VNS can be offered as an option in patients who are in the waiting list as candidates for resective epilepsy surgery.

The study also evaluated the impact of the procedure on antiepileptic medications(FigXI).While the antiepileptic medication remained the same in 50 % of the patients , in 20% of patients it was reduced and that included 'obviously responder' group.In the non responder group the antieplileptic medication had to be altered and most of them developed adverse effects compelling to change over to other AEDs. K O Nakken [35] et al in his study found that 40 % of the antiepileptic drugs were reduced compared to the baseline period. However only minor subset among these patients were responders. They concluded that alterations had only marginal influence on seizure frequency. The observed reduction in seizure frequency may be a true effect of chronic intermittent VNS, a synergestic effect between the VNS and the AEDs, possibly a reflection of the natural history of the disease or may be a placebo effect.

Quality of life post procedure(TabXIX & Fig X) has been assessed in our patients. We have evaluated the behavior, mood, postictal state, clusters, verbal skills and episodes of status. Even though majority remained unchanged, a few had mild improvement in cognition. For them the improvement in the seizure clusters as well as seizure status and postictal state itself lead to improved QOL. Murphy et al[81] found improved quality of life in patients including change in mood and behavior in 33% of the patients.

Around 60% of our patients were partially or totally dependent for their ADL(Tab XX). Care givers were not satisfied in 55% of the patients(TabXXI). Most of them commented on questionnaire and interviews that the procedure was

too costly and not worthy of the expenditure. Most of the patients were attending special schools or doing nothing.

Only 15% of the patients had complications(Table XV and Fig VII).It included voice change and persistent dysarthria in 2 of the patients. As the symptoms became intolerable and as there was no useful seizure outcome,one of the device was explanted after 1 year of follow up. One more patient had persistent voice change after surgery but tolerable. One patient in our group was noted to have a relatively higher impedance (3 Kohm) following implantation and initially a local infection was suspected and a course of antibiotics was administered.As the impedance remained persistently high she was reexplored and all connections rechecked but no abnormality was found.

No mortality was noted during the follow-up period. Most of the patients had mild and transient voice change, cough and tingling sensation in the throat during ON period of the device. Ben Menachem et al [57](33%), Handforth et al (44%) and Degiorgio et al [90](55%) reported complication rates but majority were minor and transient complications. Mortality was noticed as 1-1.5% of patients across different series and majority has been attributed to SUDEP. Studies concluded that no increased mortality risk could be attributed to VNS.

Replacement of the pulse generator was done in 5/20 patients after 4 years of follow up due to end of service of the pulse generator. No complications were associated with the procedure.

Stimulation parameters of our VNS study group has been as per standard schedule (Table XIV). The range of the output current was from 1 - 3.5 mA and the mean was 2.75 ±0.78 mA. The most frequent duty setting was 30s ON/3 min OFF (duty cycle 16%).Compared to most studies comparing the stimulation parameters of the system our group has mean low impedance values.During follow up 2(10%) patients reported that self-managed activation of the generator with the magnet at the time of seizure onset lead to suppression or shortening of the seizure. Murphy et al[91] found that about 50% of their patients benefitted from on-demand activation of the generator. Rapid cycling has been used as required. The seizure outcome has not been assessed independently.

Compared with AEDs , VNS has no compliance problems, and no risk of idiosyncratic or CNS adverse effects and no need for regular blood monitoring.The magnet may give some patients a feeling that they are able to control their seizure disorder as the patient can turn off the stimulation at any time. The cost benefit analysis has not been done for our study.

With an implant cost of around Rs 4.5-5.5 lakh plus replacement of the stimulator after the end of service it is appreciated that it is a significant and continued economical burden to the family. On interviews and questionaires the care givers expressed worries about the cost of the implant. In Western literature,Boon et al [85]compared epilepsy related direct cost and compared with preimplantation data and came out with a positive result favoring cost

effectiveness of VNS.However in the indian scenario economic burden will remain an important issue unless there is government support.

Limitations of our study are that it is an uncontrolled retrospective study with a limited sample size. Cost benefit analysis was also not done. Quality of life assessment is also limited as in the case of any retrospective analysis.

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CONCLUSIONS

The procedure VNS has a modest seizure outcome with acceptable complication rate as a palliative procedure in a subgroup of patients with medically refractory epilepsy with no resectable correlates.

It has got some impact on the quality of life of patients in the form of decreased seizure clusters,status and postictal state.

The effect of VNS is seen after an interval on follow-up.

Eventhough atonic seizures and GTCS form only a small subgroup,the procedure seems to be more effective in them.

It may be worthwhile as a palliative option in a subset of patients with intractable seizures.

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PROFROMA

Name: VNS No

Hospital No: Gender

Age:

ILAE Diagnostic classification:

Seizure descriptions:

- Age at onset:
- Semiology:
- Frequency:
- Duration of epilepsy
- Seizure related disabilities:

Seizure type:

Falls/injuries;

Clustering:

Status epilepticus:

AED's tried so far:

Current AED's:

Routine EEG:

VideoEEG

- Interictal:
- Ictal:

Invasive monitoring(if available)

- Interictal:
- Ictal:

Functional mapping(if available):

Neuroimaging:

MRI:

Any other

Neuropsychological dysfunction:

IQ:

Lobar dysfunction:

WADA test;

Speech localization

Contralateral memory support

Visual fields:

Why not a candidate for focal resective surgery?

1-multiple MRI lesions 2-Bilateral or multifocal independent ictal origin

3-Multiple seizure types 4 –Electroradiological discordance 5-patient refused surgery

6-epileptogenic overlapping eloquent area- 7-psychiatric or behavioural problems

8-Surgical failure 9-others (Financial)

FOLLOWUP:

Date of VNS:

Date of visit:

VNS Parameters:

Current strength:

Frequency:

Pulse width:

On time (s):

Off time (s):

Side effects:

Voice change:

Cough:

Dyspnoea:

Dysphagia:

Facial weakness:

Hyperaesthesia of skin:

Pain:

Local wound infection:

Wound site edema

Battery failure:

Others (specify)

Percentage seizure reductions-

Spasms:

Myoclonus:

Absences

Tonic

Atonic:

Head drops;

SPS:

CPS:

GTCS:

QOL:

Behaviour:

Alertness;

Postictal state:

Seizure clusters:

Verbal skills:

Mood:

ADL: Independent/dependent

Care giver opinion:

ABBREVATIONS FOR MASTERCHART

AG ONSET	Age at onset
Comorbi	Comorbidities
SZ Dura	Duration of seizures
No	Number of seizure types
	1- One type
	2- 2 types
	3- >2 types
SZ Freq	Seizure frequency per month
Falls	Associated falls
Clusters	Associated clusters
Status	Associated status epilepticus
AED Trie	AEDs tried
AED Cu	AED on usage at the time of surgery
MRI	1-Normal 2-Gliosis 3-dysplasia 4 atrophy 5 lesions
VEEG IE	Video EEG interictal
VEEG IC	Video EEG ictal
IQ	Intelligance Quotient
Lobar dy	Lobar dysfunction
CAN	Indications for surgery
	1-multiple MRI lesions 2-Bilateral or independent ictal
	Origin 3Multiple seizure types 4 electroradiological
	Discordance 5 patient refused surgery 6epileptogenic zone
	Overlapping eloquent area 6 psychiatric or behavioural
	Disturbances 8 surgical failure

VNS:	Date of surgery
Complis:	Complications;
	1 No 2 voice change 3 Cough 4 Dyspnea 5 Dysphagia
	Weakness 6 hyperesthesia of skin 7 pain 8 fluid accumulation
	9 infection 10 device malfunction 11 device damage 12 others
FLWUP	Follow up duration in years
DATE	last followup date
SZ FREQ	Post operative seizure frequency
AED	Number of antiepileptic drugs after surgery
QOL	Quality of life 1 No improvement 2 Behaviour
	3Post ictal state 4 seizure clusters 5 verbal skills
	6 mood
PATIENT	Patient functional status after surgery (ADL) independent or
	Dependent
CARE GIV	Care giver satisfied Y satisfied Mo-Moderately satisfied N Not Satisfied
STATUS	ss special school Nil: not doing anything o-otherwise
% Redu	Percentage of reduction of seizures
Outcome	I> 50% reduction II < 50 % III No Change or worsened
McHugh	Mchugh VNS outcome score
Out 3 mo	Out come at 3 months
Out 1 yr	Out come at 1 year
Out LF	out come last followup
Current	current strength

Freq	Frequency
Width	pulse width
Imp	Impedance

NAME	H NO	AGE	GENDER	AG ONSET	age vns	COMORBI	SZ DURA	NO	SZ FREQ	FALLS	CLUSTER	STATUS	AEDS TRIE	AED CUR	MRI	VEEG IE	VEEG IC	IQ	LOBAR DY	CAN	VNS	COMPLIS	FLWUP	DATE	SZ FREQ	AED	QOL
HARI	250521	29	MALE	0.5	23	NIL	22.5	1	8-9/MO	y	y	y	7	3	2	y	y	37	y	2	7/13/2006	1	7	10/6/2012	4-6/mo	2	1
ragees	9701434	26	MALE	9	26	NIL	17	2	15-16/mo	y	y	n	4	2	2	y	y	72	n	8	6/24/2006	1	7	9/15/2011	15-20/mo	2	2 3
rajila	9108522	32	female	9	29	NIL	20	1	7-8/mo	y	y	n	5	2	3	y	y	38	y	8	7/20/2006	1	7	6/1/2009	7-8/m0	3	1
hassan	226754	26	MALE	0.5	24	NIL	23.5	2	12-15/mo	y	y	n	8	3	1	y	y	58	n	4 &7	1/11/2007	1 &2	6	4/17/2009	14-16/mo	4	1
kiran	248223	27	MALE	11	24	y	15	1	12-16/mo	y	y	y	8	3	2	y	y	44	y	1	3/21/2007	1	6	7/24/2008	20-24/mo	3	1
bhushan	221469	22	MALE	0.9	22	NIL	21	2	30-40/mo	y	y	y	10	3	3	y	y	50	y	6 &9	5/10/2007	1	6	8/6/2012	6-8/mo	2	2,4 5
ravi	24302	14	MALE	4.5	14	y	9.5	1	50-60/mo	y	y	n	5	3	2	y	y	40	y		4/9/2008	2	5	7/1/2010	30-45/mo	3	2 5
pintu	281628	22	female	12	24	NIL	10	1	60-70/mo	y	y	y	5	3	2	y	y	45	y	8	6/30/2008	1	4	5/15/2009	20-25/mo	2	5 ,6
niroop	237797	15	MALE	0.9	15	y	14	2	4-6/mo	y	y	n	6	4	2	y	y	60	y	2 & 3	7/4/2008	1	4	12/28/2012	2-4 /mo	2	y
vivek	269005	24	MALE	11	24	NIL	13	2	30-40/mo	y	y	n	7	3	2	y	y	40	y	1 & 2	9/26/2008	1	5	1/4/2013	20-30/mo	2	1
majeed	234787	27	MALE	8	24	NIL	14	1	50-60/mo	y	y	y	6	3	5	y	y	59	y	6	14/9/2009	1	5	11/16/2012	25-30/mo	3	1
atreyee	273548	25	female	9	22	NIL	12	1	6-7/mo	y	y	y	9	3	4	y	y	44	y	4 & 9	4/30/2009	1	4	11/3/2012	4-5/mo	3	2,3 and 6
paresh	250220	18	MALE	2	18	NIL	16	2	40-50/mo	y	y	y	6	3	2	y	y	54	y	1 & 2	5/21/2009	2	4	12/10/2012	20-25/mo	3	4 & 5
shilpa	280899	31	female	12	27	NIL	17	2	20-30/mo	y	y	n	7	3	4	y	y	62	y	2	7/3/2009	1	4	1/13/2010	15-20/mo	3	1
harsh	273817	17	MALE	11	17	NIL	6	2	20-25/mo	y	y	n	8	2	5	y	y	52	y	2	1/7/2010	1	3	11/28/2012	8-12/mo	3	2 7
parijat	289111	12	MALE	0.1	12	y	12	2	30-40/mo	y	y	y	7	3	2	y	y	42	y	1 & 6	6/24/2010	1	3	6/15/2013	20-25/mo	3	y
vishnu	309793	27	female	5	27	y	22		4-6/mo	y	y	n	6	3	5	y	y	52	y	1,3 &4	9/17/2010	8	3	3/10/2011	1-2/mo	3	3
neeharika	288360	28	female	4	28	y	24	3	30-35/mo	y	y	y	7	4	2	y	y	44	y	2	1/19/2011	1	2	2/14/2012	40-45/mo	4	7
sonia	343436	24	female	6	24	NIL	18	2	18-20/mo	y	y	y	7	4	1	y	y	56	y	3	9/7/2012	1	0.6	10/13/2012	18-20/mo	4	1
irshad	291464	21	MALE	8	21	NIL	13	1	50-60/mo	y	y	n	7		2	y	y	50	y	1 2	2/8/2012	1	1.5	29-2-2013	50-60/mo	3	2

NO	SZ FREQ	PATIENT	CARE GIV	status	% redu	out 3 mo	out	Mc hugh	pre sz	pre sx	current	freq	width	imped		off		
1	8-9/MO	dep	mod	NIL	25%	III	II	III A	8	n	2.5	30	500	1.5	30	3		
2	15-16/mo	dep	no	NIL	0%	III	III	IV	8	y	2.5	30	500	2		3		
1	7-8/mo	dep	no	NIL	0	III	III	V	8	y	2.75	30	500	2.25	30	3		
2	12-15/mo	dep	no	NIL	0	III	III	V	8,9	n	3	30	500	1.75	30	3		
1	12-16/mo	dep	no	ss	0	III	III	V	8	n	2	30	500	1.5	30	3		
2	30-40/mo	i n	y	NIL	50	II	I	II A	8,9	y	2.75	30	500	2	30	5		
1	50-60/mo	dep	mod	NIL	20	III	II	III A	8	n	2.25	30	500	1.25	30	5		
1	60-70/mo	dep	y	NIL	60	II	I	II B	8	n	2.5	30	500	1.75	30	5		
2	4-6/mo	dep	no	SS	25	III	II	III A	8,9	n	2.5	30	500	1.5	30	3		
2	30-40/mo	dep	no	o	20	III	II	IIIB	6 & 8	n	2.5	30	500	2.25	30	3		
1	50-60/mo	dep	y	o	50	III	I	II A	8	n	3	30	500	1.75	30	5		
1	6-7/mo	dep	no	ss	20	III	II	III A	8	n	3	30	500	1.5	30	3		
2	40-50/mo	dep	y	SS	50	I	I	II B	2 4 9	n	2.75	30	500	1.25	30	3	60	500
2	20-30/mo	dep	mod	NIL	20	III	II	III B	2,8	n	3	30	500	1.75	30	5	30	500
2	20-25/mo	dep	y	SS	50	III	I	II A	2,8	n	2.25	30	500	1.75	30	5		
2	30-40/mo	dep	y	SS	30	III	II	III A	6& 8	n	2.75	30	500	2	30	3		
	4-6/mo	dep	no	NIL	10	III	II	III B	1,4.3 ,8	n	2	30	500	2	30	5		
3	30-35/mo	dep	no	O	0	III	III	V	2,3 &8	n	2	30	500	1.5	30	5		
2	18-20/mo	dep	no	NIL	0	III	III	V	4 8	n	2	30	500	2.5	30	5		
1	50-60/mo	dep	no	O	0	III	III	IV	8	n	23	30	500	2	30	3		