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Vagus Nerve Stimulation to Augment Recovery from Severe Traumatic Brain Injury Impeding Consciousness: A Prospective Pilot Clinical Trial

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Abstract

Objectives—Traumatic brain injury has a high morbidity and mortality in both civilian and military populations. Blast and other mechanisms of traumatic brain injury damage the brain by causing neurons to disconnect and atrophy. Such traumatic axonal injury can lead to persistently vegetative and minimally conscious states, for which limited treatment options exist, including physical, occupational, speech and cognitive therapies.

More than 60,000 patients have received vagus nerve stimulation for epilepsy and depression. In addition to decreased seizure frequency and severity, patients report enhanced mood, reduced daytime sleepiness independent of seizure control, increased slow wave sleep, and improved cognition, memory, and quality of life.

Early stimulation of the vagus nerve accelerates the rate and extent of behavioral and cognitive recovery after fluid percussion brain injury in rats.

Methods—We recently obtained FDA approval for a pilot prospective randomized crossover trial to demonstrate objective improvement in clinical outcome by placement of a vagus nerve stimulator in patients who are recovering from severe traumatic brain injury. Our hypothesis is that stimulation of the vagus nerve results in increased cerebral blood flow and metabolism in the forebrain, thalamus and reticular formation, which promotes arousal and improved consciousness, thereby improving outcome after traumatic brain injury resulting in minimally conscious or persistent vegetative states.

Discussion—If this study demonstrates that vagus nerve stimulation can safely and positively impact outcome, then a larger randomized prospective crossover trial will be proposed.

Keywords

Epilepsy; minimally conscious state; traumatic brain injury; vagus nerve stimulation; vegetative status; clinical trial

Introduction

Traumatic brain injury (TBI) affects over 1 million American people, resulting in heterogeneous neurological outcomes that in severe cases entail high morbidity and mortality.¹ Recent progress in intensive care potentially decreases mortality for severe TBI cases, but survivors may be left with impaired consciousness resulting in vegetative or minimally conscious states (VS or MCS). VS demonstrate the complete absence of behavioral evidence for self or environmental awareness, with spontaneous eye opening along with evidence of sleep-wake cycles on EEG.^{2, 3} By contrast, MCS is defined as a condition of severely altered consciousness in which minimal, clearly discernible, but inconsistent behavioral evidence of self or environmental awareness on a reproducible or sustained basis is demonstrated.² Recovery of consciousness after 12 months is unlikely in adults and children with traumatic brain injuries, and even less likely to occur if there is an anoxic component to the injury.⁴

The main neuropathological abnormality in VS patients is thought to be subcortical damage, resulting from damage to the white matter of the cerebral hemispheres and/or the thalamus leaving disconnected intact cortex unable to function.⁵ It has been suggested that functional neuroimaging methods are more sensitive than anatomic methods in distinguishing patients in VS from those in MCS, because the former can evaluate corticothalamic function,⁶ preserved residual cognitive function, and some degree of conscious awareness in minimally conscious patients unable to follow commands or communicate reliably.^{7, 8} Patients with MCS demonstrate more continuous improvement and have significantly more favorable outcomes by 1 year post injury than those diagnosed with VS.⁹ Thus, length of time that MCS patients are in MCS may not predict their outcome.¹⁰ In addition, there are no time intervals for possible permanency of the VS.¹¹ At present there is no efficacious therapy for VS or MCS patients.

Vagus Nerve Stimulation

The vagus nerve has special visceral efferent fibers that project to the nucleus ambiguus from the pharyngeal and laryngeal muscles. Its general visceral efferent fibers arising from the dorsal motor nucleus innervate the heart, lungs, and viscera. The vagus also has sensory afferent projections, notably from the concha of the ear. The vagus' visceral afferents travel via the tractus solitarius to the thalamus, amygdala and forebrain, and via the medullary reticular formation to other cortical areas.¹²⁻¹⁴ In these vagus nerve related brain circuitries, there are excitatory and inhibitory neurotransmitters, including NE, serotonin (5-HT), γ -aminobutyric acid (GABA), and glutamate.^{14, 15} The vagus nerve contains myelinated A- and B- and unmyelinated C-fibers, conveying sensory information from viscera.¹⁵

The vagus' diffuse projections mediate a number of visceral reflexes including the baroreceptive response, coughing, vomiting and swallowing. Projections to the hypothalamus affect appetite, blood pressure and volume homeostasis.

In 1938, Percival Bailey stimulated the severed proximal end of the vagus nerve in cats resulting in cortical EEG (electroencephalogram) changes.¹⁶ Fifty years later neurophysiologist Jacob Zabara developed his vagal nerve stimulator that reduced strychnine-induced seizures in dogs¹⁷. His work was duplicated in other species including monkeys¹⁸ and rats.^{19, 20} Pilot studies with the human VNS for epilepsy began in November 1988.²¹ Seven of the first nine patients implanted saw a reduction in seizure frequency and two patients were seizure-free at one year.^{21, 22}

The Food and Drug Administration approved the VNS for the treatment of epilepsy in 1997. Clinical trials with VNS for epilepsy have been performed as crossover trials with the stimulator on or off and as randomized prospective trials with low versus high levels of stimulation.²³ The FDA approved VNS for treatment resistant depression in 2005.²⁴ Currently over 60,000 patients have been implanted with VNS.^{25, 26}

VNS directly and indirectly modulates subcortical and cortical brain function via chronic intermittent repeated electrical stimulation of the vagus nerve. Although only cleared by the FDA for medically refractory epilepsy and depression, it is under investigation for a wide variety of disorders, including Alzheimer's disease, migraine, multiple sclerosis, and eating disorders.²⁷ Recent studies in Alzheimer's patients demonstrate that many either improve or do not decline after device implantation.²⁸ Transcutaneous VNS may attenuate postoperative cognitive dysfunction in elderly patients,²⁹ and VNS may improve cognitive impairment and quality of life in cerebral palsy patients via seizure suppression and interictal discharge reduction.³⁰

Kumaria and others have proposed VNS as a treatment for TBI.³¹ VNS has improved behavioral and cognitive recovery after fluid percussion brain injury in rats.^{32, 33}

Seizures on EEG are represented by abnormal synchronization of neuronal activity. Desynchronization, then, should diminish seizure activity. VNS was first hypothesized to work via desynchronization of the EEG¹³ and this has recently been supported by electrophysiologic data³⁴. Michael Chase and colleagues demonstrated in cats that the frequency dependent effect of VNS on EEG was due to activation of particular fibers at varying frequencies.¹³ VNS-induced seizure suppression is attributed to activation of vagal A- and B- fibers,³⁵ although C-fibers were originally thought to be responsible for its effects.¹⁹ VNS at frequencies above 70 Hertz and intensities greater than 3 Volts were shown to be desynchronizing. If the intensity was dropped to less than 3 Volts, only myelinated fibers were stimulated, and the EEG would be synchronized. Lower frequencies (20 to 50 Hertz) and higher voltages were also shown to be desynchronizing. Desynchronization was shown to be the result of stimulation of vagus fibers that conduct at 1 to 15 m/s.³⁶ It has also been suggested that VNS can modulate cortical synchrony and excitability via the action of acetylcholine on muscarinic receptors, indicating sensory processing and neural plasticity in anesthetized rat auditory cortex.²⁵

Early studies suggested that, unlike in animals, VNS did not affect human EEG regardless of level of alertness.³⁷ On longer follow-up, however, at a mean of 16.8 months after implantation, EEG changes were seen after VNS, with desynchronization dominating over synchronization and diminished inter-ictal spiking.³⁸ Long term VNS treatment has reduced interictal epileptiform discharges (IEDs) in adult patients with epilepsy.^{39, 40} In children, a decrease in the number of IEDs has also been seen as early as three months after stimulator implantation.⁴¹ Despite understanding some of the properties of stimulation that are most likely to result in EEG desynchronization, we still do not have a clear understanding of the exact mechanism of VNS.

Altered neurotransmitter levels and cerebral blood flow

Vagus projections via the tractus solitarius and medullary reticular formation may be responsible for the anti-epileptic impact and other effects of VNS. In rat studies, the hippocampus and striatum have altered metabolism after VNS.⁴² VNS also results in an increase in the endogenous stem cell proliferation in the adult rat dentate gyrus of hippocampus that could be mediated in part by changes in hippocampal noradrenergic activity.⁴³ NE loss in brain increases neuronal damage following focally induced limbic status epilepticus, and the protective effect of brain NE has already been demonstrated in epilepsy and other neurological disorders, including learning and memory.⁴⁴ Also in rats, neuronal activity in the locus ceruleus is directly modified by VNS,⁴⁵ which increases extracellular norepinephrine concentrations in the rat cortex, hippocampus, and amygdala,^{46, 47} that may enhance recognition memory in human subjects.⁴⁸ It has been suggested that VNS initially enhances the firing activity and pattern of norepinephrine neurons of the locus ceruleus, and subsequently those of 5-HT neurons of the dorsal raphe nuclei via tractus solitarius, contributing to the efficacy of VNS for depression.⁴⁹

VNS led to an increase in the levels of the inhibitory transmitter GABA in partial epilepsy patients.⁵⁰ VNS may also modulate the cortical excitability of brain areas associated with epileptogenesis via GABA_A receptor plasticity.⁵¹

In addition, acute VNS induced specific expression of nuclear fos gene that is an immediate early gene and a marker for neuronal activation in several forebrain structures, including the amygdala, cingulate cortex, hypothalamus, the brainstem, locus ceruleus, noradrenergic nuclei, and thalamus.⁵² Chronic VNS significantly increased staining of FosB (a marker of chronic neuronal activation) bilaterally in tractus solitarius, locus ceruleus, parabrachial nucleus, dorsal raphe nuclei, and in many cortical and limbic areas of brain including those involved in mood and cognition^{53, 54}. The VNS effects were more widespread than those caused by the antidepressants.⁵⁴ Locus ceruleus neurons impact Fos protein expression, suggesting a plastic mechanism for diminishing epileptogenesis.⁵⁵ These structures activated by the vagus may play an important role in the control of epilepsy, recognition memory, and control of arousal^{47, 56, 57}.

Projections to the frontal cortex and cingulate gyrus are highlighted on positron emission studies of patients receiving the vagus nerve stimulator for depression.⁵⁸ Decreased

excitatory and increased inhibitory neurotransmission are observed after both acute and chronic VNS.^{46, 50}

VNS also leads to changes in cerebral blood flow as measured by positron emission testing (PET). Both high and low levels of stimulation increased cerebral blood flow in humans to the bilateral thalami, hypothalami and insular cortices.⁵⁹⁻⁶¹ Chronic stimulation induces similar cerebral blood flow changes in humans.⁶² Chronic VNS for treatment of patients with resistant depression also increases regional cerebral blood flow in the dorsolateral prefrontal cortex.⁶³ It is thought to alter limbic circuitry to reduce epileptogenesis and enhance mood.⁶⁰ It is likely that VNS results in increased cerebral blood flow and metabolism in the forebrain, thalamus and reticular formation,⁶⁰ which promotes arousal and improved consciousness,⁶⁴ thereby improving outcome after TBI resulting in VS or MCS.

VNS for epilepsy

Of the 0.3% of the general population that are active epileptics, two-thirds are controlled by medical therapy, and one-third are refractory even after 18 months of aggressive therapy with two standard anti-epileptic agents.⁶⁵ If such patients do not have a focally resectable lesion resulting in their epilepsy, or continue to seize after resection of such a lesion⁶⁶, they are possibly candidates for alternative surgical therapy, such as stimulation.

VNS for epilepsy demonstrates increasing benefit after a greater period of time. Five-year follow-up of 26 patients revealed that while seizure frequency decreased from baseline by 28% at one year, it further dropped to 72% less than baseline at five years,⁶⁷ indicating a persistent and cumulative effect of VNS on seizures.²³ A 12-year experience also supports that VNS is safe and effective long term treatment for epilepsy.⁶⁸ A recent meta-analysis of VNS outcomes including 74 clinical studies with 3321 patients with intractable epilepsy revealed VNS is effective in reducing seizure frequency by 50% in approximately 50% of patients, with a delayed benefit more than 1 year after surgery²⁶. One study of children demonstrated potential reduction in seizure severity and improvement in well-being without a reduction in seizure frequency⁶⁹.

VNS seizure patients report enhanced mood,^{70, 71} reduced daytime sleepiness and increase alertness⁷² independent of seizure control, increased slow wave sleep,⁷³ improved cognition,⁷⁴ memory,⁷⁵ and quality of life.^{71, 76} Children with VNS are noted to have enhanced verbal communication, school performance,⁷⁷ quality of life, and cost savings.⁷⁸ Grill, et al. described 2 nonverbal children (8 and 9 years) who began to speak within months of VNS implantation for the treatment of refractory epilepsy.⁷⁹ A slight improvement in alertness and communicative skills was also observed in young patients with Dravet syndrome by VNS.⁸⁰

The most common device-related complications were infection or lead breakage.⁸¹ The sudden unexplained death in epilepsy rate in VNS patients drops from 5.5 per 1000 over the first two years, a rate comparable to that of other epilepsy cohorts, to 1.7 per 1000 thereafter.⁸² Hoarseness, other vocal changes, coughing during stimulation, and exacerbation of sleep apnea^{83, 84} are the most frequent complaints of patients undergoing

VNS.⁸⁵ These symptoms are thought to be due to proximity of the stimulator to the recurrent laryngeal nerve.⁸⁶

VNS is FDA cleared for MRI scanning; a transmit and receive head coil is used with a 1.5 Tesla scanner, and more recent data suggests 3.0 Tesla scanners are also safe⁸⁷. MRIs have been performed with the stimulator turned on to evaluate the impact of the stimulation.⁸⁸⁻⁹⁴ In one study, the patient had a seizure on the table and diffusion weighted imaging demonstrated transient ischemia at the focus, which returned to normal at seizure completion.⁹⁵

Traumatic Brain Injury (TBI) and Impaired Consciousness

Diffuse axonal injury (DAI), the most frequent cause of persistently VS and MCS⁹⁶ after brain injury, occurs as a result of rapid acceleration-deceleration injury of the axons, sometimes in conjunction with delayed axonal disconnections. It can be defined as the occurrence of diffuse damage to axons in the cerebral hemispheres, corpus callosum, and brain stem with three different grades.⁹⁷ Impaired consciousness is postulated to be due to damage to forebrain arousal inputs from thalamic and midbrain structures.⁹⁸⁻¹⁰⁰ In rats, neuronal disconnection appears to occur due to breakdown of the subaxolemmal cytoskeletal network.^{101, 102} Diffuse injury causes axonal degeneration near the neuron cell body leading to neuronal atrophy rather than apoptosis.^{103, 104} Such atrophy has been quantified by structural imaging in human TBI;¹⁰⁵ the brain appears to melt away while cranial fluid-filled spaces enlarge on serial scans in the severely injured patient.¹⁰⁰

The majority of patients who will recover from a post-traumatic vegetative state improve within the first six months, and recover to severe disability or become minimally conscious.⁴ Current treatment after the acute phase of TBI consists of cognitive, physical, occupational and speech therapy in conjunction with neuropsychological care and optimal management of concurrent medical problems. A randomized trial of cognitive versus home therapy in military TBI patients revealed no benefit for the former.¹⁰⁶ There is a tremendous need for development of therapies with a direct ability to improve function in the post-TBI.

Diagnostic and prognostic value of functional neuroimaging in patients with VS or MCS

The rate of misdiagnosis between VS and MCS is as high as 40%,^{107, 108} due to insufficiently sensitive standardized neurobehavioral assessment scales. It is expected that fMRI might supplement conventional neurological examination in the classification and prognosis of those patients. The differentiation between VS and MCS could better predict the patient prognosis and even influence clinical management because of the critical neuropathological differences between these two groups of patients,³ indicating that MCS and VS are actually distinct physiological entities with different brain integrative capacities.

VS patients potentially demonstrate a residual neural encoding of basic sound attributes without further high order processing of functional integration, whereas MCS patients have a more elaborate level of processing, and more cortico-cortical function connectivity as

compared with VS patients.^{109, 110} Self-related auditory stimuli can induce more extended neural activity and cerebral processing in the anterior cingulate cortex in patients with MCS.¹¹¹ Those data indicate key structures in the cortical language network remain functional in MCS, despite the absence of consistent command following enabling reliable communication.

The patients' own name by a familiar voice (personally meaningful information) can also activate the cerebral cortex in both VS and MCS patients.¹¹² Some VS and MCS patients demonstrated speech comprehension which correlated with their subsequent behavioral recovery 6 months later,¹¹³ A percentage of VS or MCS patients can willfully two-way communicate and modulate their brain function via mental imagery, inconsistent with a clinical behavioral response,¹¹⁴ indicating their higher intact cognitive function. These findings indicate the potential role of functional neuroimaging in the diagnostic and prognostic evaluation of these patients.

More preserved functional default network connectivity was demonstrated in MCS patients than VS patients, proportionate to the extent of their impaired consciousness.¹¹⁵ Some MCS patients may have a severe deficit of resting cerebral activity sufficient to preserve cerebral networks necessary for recognition and interaction, but not to drive these networks spontaneously,¹¹⁶ which provides the anatomic and physiological foundation for electric stimulation.

VS patients demonstrated more widespread regional thalamic abnormalities than MCS patients, and these differences potentially explain their clinical profile¹¹⁷ as a result of the critical role of the thalamus in regulation of arousal and human consciousness.⁶⁴ Functional restoration of thalamocortical disconnection (prefrontal and anterior cingulate cortices) in the VS patient paralleled recovery of consciousness.¹¹⁸ Via partially preserved conscious processing that is not detected by behavioral assessment, some VS or MCS patients have the capacity to learn trace conditioning, which is a good predictor of recovery.¹¹⁹ fMRI revealed a VS patient preserved some degree of conscious awareness,⁸ and axonal regrowth has been observed in late recovery from MCS.¹²⁰ In addition, the depth and breadth of preserved cognitive function in VS or MCS patients can be detected by a hierarchy of cognitive tasks.⁷ Those findings suggest that a correlation between structural lesions and functional damage may predict individual patient prognosis.¹²¹

Augmenting arousal with deep brain stimulation (DBS)

Direct stimulation of brain centers that project to mesial forebrain cortex has been used in an attempt to arouse patients with impaired consciousness. DBS is a neurosurgical procedure in which small holes are drilled in the skull so that electrodes can be passed through the cortex and underlying white matter into thalamic nuclei or basal ganglia, and then connected to an impulse generator in the chest wall. The majority of patients receiving DBS have had Parkinson's disease, essential tremor, depression or epilepsy. Attempts to treat VS with DBS have had mixed results. A 1993 French study of 25 patients with bilateral DBS into the centromedian and parafascicular nuclei reported that half were unchanged from baseline, and the remainder had increasing levels of awareness but remained vegetatively disabled.¹²²

Ten year follow-up of 12 post-traumatic VS and MCS patients who received either centromedian and parafascicular nuclei or mesencephalic reticular formation stimulation in a Japanese study demonstrated that the few MCS patients who improved were able to return to functional lives.¹²³ More recently, Schiff et al targeted the anterior intralaminar thalamic nuclei with DBS in a MCS patient six years after brain injury and demonstrated improved arousal, motor, and communication abilities.¹²⁴

Augmenting arousal with VNS

DBS entails drilling holes in the skull and passing electrodes through about eight centimeters of brain into deep nuclei, and thus carries the risk of causing cerebral hemorrhage, among other complications. A less invasive alternative for promotion of arousal in the brain is stimulation of the vagus nerve in the neck, which activates numerous areas including the locus ceruleus, resulting in increased cerebral norepinephrine.⁴⁶ Afferent and efferent pathways coursing through the thalamus, are associated with conscious sensibilities and activities.⁶⁴ The medullary reticular formation is associated with the reticular activating system, which is important in arousal.

VNS also decreases seizure activity and IEDs in the brain.^{125, 126} Such epileptiform activity is frequently present, though not always diagnosed, in the injured brain.¹²⁷ Enhanced mood and cognition, particularly at low levels of stimulation (0.5 mA),⁴⁸ are also observed.

Early stimulation of the vagus nerve accelerates the rate and extent of behavioral and cognitive recovery after fluid percussion brain injury in rats, and provides indirect evidence that the brain's norepinephrine system may have a positive effect on the recovery of function following TBI.^{32, 33} Interestingly, VNS appears to mediate some of these positive effects by attenuation of cerebral edema ipsilateral to the side of the injury.¹²⁸ A second mechanism by which stimulation appears to exert positive effects is through a reduction in injury to GABAergic inhibitory neurons within the cerebral cortex and possibly the hippocampal formation following rat TBI, which facilitates the recovery of behavioral function.¹²⁹ GABA_A receptor-mediated neuronal inhibition can be also enhanced by VNS,⁵¹ which may contribute to the clinical efficacy of VNS.

TBI triggers a cerebral inflammatory response.¹³⁰ VNS potentially attenuates the systemic inflammatory response via inhibition of tumor necrosis factor (TNF) synthesis, preventing the shock development during endotoxemia.¹³¹ In contrast, vagotomy significantly increased TNF synthesis and promoted rats to develop lethal shock.¹³¹ The nicotinic acetylcholine receptor $\alpha 7$ subunit on immune cells surrounding the vicinity of cholinergic axon terminals is required for VNS modulated acetylcholine inhibition of inflammatory response.¹³² These receptors transmit the cholinergic signal into inhibition of TNF release and inflammation. Acetylcholine-producing memory T cells in the spleen are required for inhibition of cytokine production via macrophages by VNS, and consequently these T cells can relay neural signals in a vagus nerve circuit that controls innate immune responses.¹³³ Thus, vagal function has been considered as the cholinergic anti-inflammatory pathway.¹³⁴

VNS prevents an increase in TNF in mice following TBI via upregulation of the gastric peptide hormone ghrelin.¹³⁵ Intriguingly, ghrelin receptor expression was detected in tissues

from the rat dorsal motor nucleus of the vagus and ghrelin promotes neural proliferation in those nuclei.¹³⁶ Acute VNS can also significantly reduce intestinal TNF levels and prevent intestinal permeability in mice following TBI.¹³⁷ Intestinal inflammation also reduced neuron proliferation from the dorsal motor nucleus of the vagus in rats which can also be attenuated by ghrelin.¹³⁸

Accumulating evidence strongly supports the idea that inflammation and the immune response play a critical role in the pathophysiology of epilepsy.¹³⁹⁻¹⁴³ For example, pro-inflammatory mediators like cytokines prominently in glia and to a lesser extent in neurons might play an important role in the development of epileptogenesis. The functional interactions between cytokines and classic neurotransmitters such as glutamate and GABA favor the establishment of chronic neuronal hyperexcitability and injury, and network reorganization, thus promoting seizures and synaptic plasticity.^{139, 144, 145} Cytokine induction in patients with refractory epilepsy was altered by long-term VNS, indicating an immunomodulatory effect of VNS.¹⁴⁶ VNS can modulate the immune system via rebalancing of pro-inflammatory and anti-inflammatory cytokines in patients with refractory epilepsy.¹⁴⁷

Brain injury and inflammation also results in disruption of the blood brain barrier (BBB).^{139, 141} BBB impairment is intimately associated with epilepsy, followed by neuronal loss and impaired functions.¹⁴⁸⁻¹⁵² The extravasated albumin via increased BBB permeability into the brain's extracellular space binds to astrocytic transforming growth factor (TGF) β receptors and induces astrocytic transformation and dysfunction, a cascade of events initiated by increased BBB permeability that leads to neuronal excitotoxicity and loss, and eventually epilepsy.¹⁵² This compromised BBB can be induced by TBI, and can last several days to weeks or even years after the acute event.¹⁵³ Unresolved BBB damage following TBI results in cerebral edema, inflammation, epilepsy, cognitive disabilities, neurodegenerative pathologies such as Alzheimers disease, or death.¹⁵³ VNS can attenuate BBB disruption after TBI in mice¹⁵⁴ and modulate the inflammatory response in epilepsy patients.¹⁴⁷ Transcutaneous VNS has also been proposed to attenuate postoperative cognitive dysfunction in elderly patients by decreasing inflammatory response.²⁹

A Pilot Prospective Randomized Crossover Clinical Trial

The purpose of this pilot study is to demonstrate objective improvement in clinical outcome by placement of a vagus nerve stimulator in patients with impaired consciousness who are recovering from severe traumatic brain injury. Our hypothesis is that stimulation of the vagus nerve results in increased cerebral blood flow and metabolism in the forebrain, thalamus and reticular formation⁶⁰, which promotes arousal and improved consciousness⁶⁴, thereby improving outcome after traumatic brain injury resulting in minimally conscious or persistent vegetative states. Our primary outcome measure is clinical improvement on two validated brain injury outcome assessment scales. A secondary outcome measure is demonstration of increased activity in the forebrain and thalamic regions as assessed by functional magnetic resonance imaging. If this study demonstrates that vagus nerve stimulation can safely and positively impact outcome, then a larger randomized prospective crossover trial will be proposed.

Twelve subjects will participate in a prospective randomized crossover pilot study for eighteen (18) months after device implantation. Subjects will cross over between no stimulation (device off) and stimulation (device on) every three months for six periods yielding a total trial time of 18 months. The trial will be unilaterally blinded in that subjects and researchers assessing outcome measures will not know if the devices are on or off. Subjects will be randomized at study initiation to on or off for the first three months and then switched to the opposite setting every three months for the duration of the study (18 months). There will NOT be a control group of patients without impaired consciousness or brain injury.

Inclusion criteria include age between 18 and 60, and having sustained a moderate to severe traumatic brain injury (Disability Rating Scale¹⁵⁵ score of 18 to 29, Table 1) more than 4 months from starting the study, with or without concurrent seizure activity. While patients who have had craniotomies may be enrolled in the study, those with hydrocephalus or active intracranial pressure elevation will be excluded as treatment of their ongoing neurosurgical disease will confound evaluation of their outcome. Exclusion criteria include prior vagotomy, retained metal contraindicating an MRI, concurrent active severe medical problems that render surgery to place the device unsafe, a history of sleep apnea, myocardial infarction or arrest, cardiac conduction abnormalities, and conditions which could prevent the patient from surviving the duration of the study. Pregnancy or intent to become pregnant during the course of the study will also result in exclusion from the study. Patients with pre-existing central nervous system disease or associated comorbidities that may not allow for 18 month follow-up will also be excluded. Stable orthopedic or other traumatic body injuries are not a contraindication.

A rehabilitation medicine physician will evaluate each patient prior to implantation of the vagus nerve stimulator. In addition to standardized assessments in speech, physical and occupational therapy, patients will be assessed with the FIMTM instrument and Functional Assessment Measure (FIM+FAM). (Table 2) and the JFK Coma Recovery Scale (Table 3)¹⁵⁶. Brain MRI will be performed to assess the extent of traumatic injury at enrollment. Resting and activation functional magnetic resonance imaging will provide an assessment of pre-operative cerebral activity and EEG will be used to assess baseline pre-operative neuronal electrophysiologic activity and eliminate the possibility that subclinical seizures contribute to the patient's poor neurologic status.

Patients enrolled in the study will receive concurrent standard of care treatment through the Veterans Administration Hospital System prior to enrollment, for the duration of treatment, and following withdrawal from the study. Such care will include optimal pharmacologic management, including cognitive effectors such as bromocriptine or methylphenidate, which must be initiated prior to enrollment rather than during the study period. Anticonvulsants will be administered if indicated and may be altered as medically necessary during the study period. Physical, occupational, speech, and cognitive therapy will be continued during the study.

Surgical implantation of the vagus nerve stimulator will be performed under general anesthesia using standard techniques¹⁵⁷. The device components will be provided by

Cyberonics and consist of a titanium-housed 5.2 by 5.2 by 0.7 centimeter pulse generator with a lithium carbon monofluoride battery, and a 43 centimeter lead wire with two platinum/iridium helical electrodes and a tethering anchor. The battery life is estimated at six years, but is affected by stimulation parameters.

Vagus nerve stimulators are implanted on the left side since studies in dogs have demonstrated that stimulation of the right vagus slowed heart rate more than stimulation of the left¹⁵⁸. A three to four centimeter horizontal incision is made in a left mid-neck crease extending from the medial aspect of the sternocleidomastoid muscle to the midline. A separate subclavicular incision is made for the generator. We bluntly generate a subcutaneous pocket the size of the generator and then perform tunneling for the stimulator lead from the cervical to the infraclavicular incision, taking care to pass over the clavicle. The lead is pulled through with the tunneling device and attached to the generator with a hex screwdriver. The generator is then tucked into the infraclavicular pocket to avoid movement during the duration of the procedure, but leaving sufficient slack on the lead to allow easy manipulation and placement.

Attention is then returned to the cervical incision where the vagus nerve is found nestled in between the common carotid artery and internal jugular vein just medial to the sternocleidomastoid muscle. The two vagus nerve stimulator helical electrodes, and a third anchor tether coil are then applied in a cranial to caudal fashion using vascular forceps. After wound closure, but prior to removal of drapes and reversal of anesthesia, lead impedance is checked with a 14 second one milliamper, 20 Hertz pulse to ensure that the helical electrodes are in good contact with the nerve and the lead is inserted into the generator correctly. Bradycardia on testing would suggest that the leads were placed too cranial along the course of the nerve and are impinging on cardiac branchpoints¹⁵⁹.

Patients will be able to resume rehabilitation one day after device implantation. Since the optimal stimulation parameters to arouse patients from impaired consciousness are unknown, just before beginning the randomized trial, we will perform a supervised stimulation parameter titration trial. The device will be turned on and set to deliver 30 second pulses every five minutes at the lowest current of 0.5 milliamperes. The frequency will be set at 10 Hz and the current will be increased at 0.5 mA intervals to 2.5 mA. If no impact is seen the frequency will be increased at 10 Hz intervals and the trial repeated with increasing current until maximal settings of 30 Hz and 2.5 mA are reached. The patient will be closely observed for one hour after each parameter change both for changes in level of awareness and for distress. If there are any signs of discomfort including grimacing, tachycardia, diaphoresis, fidgeting or more classical sympathetic or parasympathetic overdrive symptoms the stimulation parameters will be titrated back down.

Assuming the titration trial does not reveal settings that have an immediate impact on consciousness, we will initiate stimulation at 0.5 milliamperes, 0.5 millisecond pulse-width, 30 Hertz for 30 seconds, then off for 5 minutes, as has been optimized from cognition studies of epilepsy patients^{48, 160}. Randomization to stimulation or no stimulation will begin two weeks after the implantation surgery. Patients who are clinically unchanged after three months of stimulation will have the current increased by 0.5 milliamperes for every three

months of stimulation that they fail to improve, to a maximum level of 2.5 milliamperes over 24 months (figure). If patients appear uncomfortable, first frequency, then on-off times and finally current will be titrated down to minimize discomfort.

Patients implanted with VNS for this study will be continuously monitored for alterations in clinical status. This monitoring will consist of daily checking vital signs (heart rate, blood pressure, temperature and peripheral oxygen saturation) as well as mental status. If patients have alterations in any of the above, they will be evaluated by medical personnel and if necessary, referred to the principal investigator to ensure that no adverse event has occurred that would necessitate altering stimulation.

Although not a formal measure of outcome assessment, EEG will be utilized if necessary to ensure that patients are not having subclinical seizure activity, as frequently occurs in brain injured patients. Patients noted to have interictal spikes will be administered antiepileptics as clinically indicated, and have the stimulation parameters of their vagus nerve stimulator titrated for optimal seizure control if necessary.

As a safety measure in case the patient has a medical emergency, patients are discharged from the hospital with a magnet which prevents any stimulation from occurring when held over the generator.

Patients and their caretakers will also be advised to stay away from functioning microwave ovens as these can be associated with heating of the device. They will further be advised not to touch or attempt to manipulate the device under the skin.

Outcomes will be assessed by a rehabilitation medicine physician blinded to device status at three month intervals with the FIM™ instrument and Functional Assessment Measure (FIM +FAM, Table 2) which has been found reliable and validated by numerous studies in severely brain injured patients¹⁶¹⁻¹⁶⁴. The JFK Coma Recovery Scale (Table 3) which has been independently validated as an outcome measure in brain injured patients with impaired consciousness^{156, 165} will also be used to evaluate outcome. Patients will be followed for a minimum of 18 months after enrollment unless they or their legal surrogates choose to leave the study.

Functional MRI with resting and activational parameters will be performed pre-operatively and at three month intervals. We will utilize a transmit and receive head coil with the patient placed head first into the scanner. We will utilize an average head SAR of 1 to 2.24 W/kg for a 70 kg patient and dB/dt < 10T/s as described previously⁸⁷. The temperature probe overlying the electrode will be placed directly over the skin incision used for electrode placement at the medial aspect of the sternocleidomastoid. The actual distance to the electrode is therefore approximately a few centimeters, but dependent on the thickness of patient's skin, subcutaneous fat, and neck musculature. The probes placed in the patient's ipsilateral axilla and on the scalp will vary in distance depending on the patient's body habitus. Based on our previous surgical experience demonstrating that any damage to or manipulation of the vagus nerve intraoperatively immediately tends to affect heart rate, we would expect to see changes in heart rate if diathermy of the nerve occurs, and thus we will continuously monitor heart rate.

All patients will have 3 temperature probes (overlying the device, ipsilateral axilla and cranial) and heart rate monitors in place with continuous monitoring throughout the duration of the MRI scan to ensure that diathermy does not occur. An increase in temperature of one degree centigrade on any part of the patient's body, or a change in heart rate of greater than 20 beats per minute will result in cancellation of the MRI study.

The major caveats limiting data interpretation are that every injured brain will have unique pathology, and most will exhibit varying rates of spontaneous recovery¹⁶⁶. Determining how much recovery is occurring spontaneously, and how much is due to stimulation is particularly difficult in the first six months after injury when it is more likely for patients to have dramatic improvements. The FIM+FAM scale has previously been able to show significant levels of improvement after an intervention with 18 treated TBI patients versus untreated controls¹⁶⁷. If we see a trend towards benefit with stimulation, but without statistical significance, then we would propose a follow-up trial with a greater number of patients and longer experimental period (e.g. patients would receive stimulation or not, for six month periods rather than three months before crossing over.) We will work with a statistician to calculate the number of patients we need to enroll in order to achieve a significant result.

Failure to demonstrate any effect of vagus nerve stimulation could be due to several factors including genuine lack of efficacy, incorrect stimulation parameters or insensitive outcome measures. Regarding the latter possibility, the FIM+FAM scale has been found to be among the most sensitive and reliable outcome measures after TBI¹⁶², but other scales such as the Coop/Wonka charts, Neurobehavioral Rating Scale, Frenchay Activity Index, and the Sickness Impact Profile^{168, 169} have also been validated for use in TBI populations¹⁶⁴. Neuropsychiatric rehabilitation personnel, caregivers and others who are observing the patient will be asked what changes they have noticed in the patient when stimulation is initiated, and scales tailored to look for these particular modalities will be added to the assessment protocols enacted every three months.

If a patient progresses through the 18-month trial without improvement at stimulation parameters up to 2.0 mA, surrogate consent, Institutional Review Board (IRB) approval, and additional funding will be sought to continue titration up to 3.5 mA and 130 Hertz, which are the maximal stimulator settings¹⁶⁰. If funding is not obtainable at that time, subjects or their surrogates will still be given the option to continue stimulation and titration with only IRB approval. Subjects or their surrogates will also have the option to have the device turned off or explanted.

Patients who recover from their minimally conscious state during the course of the study, and are competent to make their own decisions, will be given the option to continue with the study as planned, or withdraw from the study according to their personal wishes. If they elect to withdraw from the study, they may continue with stimulation, have the device turned off, or explanted.

Conclusions

Compelling evidence exists to suggest that vagus nerve stimulation may improve outcomes after severe brain injury. The clinical trial for which we have obtained FDA IDE clearance will be the first step in determining the efficacy of VNS for improvement of consciousness after severe brain injury.

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Patients will all receive pre-op fMRI, clinical assessment and device placement and then be randomized to:

figure.

The study design is that after device implantation patients will be randomized to either of two groups. They will then cycle through three month periods where the device is alternately turned on and off at gradually increasing stimulation parameters. Assessments will be performed at periodic intervals as indicated.

Table 1**Disability Rating Scale (abridged)**

Modalities Tested:
Eye opening
0-spontaneous 1-to speech 2-to pain 3-none
Communication ability
0-oriented 1-confused 2-inappropriate 3-incomprehensible 4-none
Motor response
0-obeying 1-localizing 2-withdrawing 3-flexing 4-extending 5-none
Feeding (cognitive ability only)
0-complete 1-partial 2-minimal 3-none
Toileting (cognitive ability only)
0-complete 1-partial 2-minimal 3-none
Grooming (cognitive ability only)
0-complete 1-partial 2-minimal 3-none
Level of Functioning
0-completely independent 1-independent in special environment
2- mildly dependent 3-markedly dependent 4-moderately dependent
5-totally dependent
Employability
0-not restricted 1-selected jobs 2-sheltered workshop 3-not employable

Table 2	
FIM™ instrument and Functional Assessment Measure (FIM+FAM)	
Modalities Tested:	
Self Care Items:	Feeding, grooming, bathing, dressing upper body, dressing lower body, swallowing
Sphincter Control:	Bladder management, bowel management
Mobility Items:	Bed/chair/wheelchair, toilet, tub or shower, car transfer
Locomotion:	Walking vs wheelchair, stairs, community access
Communication Items:	Comprehension, expression, reading, writing, speech intelligibility
Psychosocial Adjustment:	Social interaction, emotional status, adjustment to limitations, employability
Cognitive function:	Problem solving, memory, orientation, attention, safety judgement
	Points given for each modality range from 7 for complete independence to 0 for total assistance

Table 3**JFK Coma Recovery Scale (abridged)**

Modalities Tested:

Auditory Function: 0 to 4 points – none to consistent movement to command

Visual Function: 0 to 5 points – none to object recognition

Motor Function: 0 to 6 points – none to functional object use

Oromotor/Verbal Function: 0 to 3 points – none to intelligent verbalization

Communication: 0 to 2 points – none to functional and accurate

Arousal: - to 3 points – unarousable to at attention

Table 4

Stimulation parameters

	Initial	Range through study
On time	30 sec	
Off time	5 minutes	
Output current	0.5 mamp	0.5 to 2.5 mamp
Frequency	10 Hz	10 to 30 Hz
Pulse Width	500 usec	
Magnet current	0.5 mamp	
Magnet duration	60 sec	
Magnet pulse width	500 usec	