Vagal Nerve Stimulation With Low Level Lasers Of Two Different Frequencies, Assessed By QEEG
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Citation

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Abstract
In this paper we develop a pilot study to study the use of LLLT for VNS in normal subjects, and to assess its effects by QEEG. Twenty normal subjects from 22 to 46 years, paired in age and gender were studied recording QEEG in three experimental condition: Basal record (10 minutes), Laser stimulus (10 minutes), and Post-Laser stimulus records (10 minutes), with VIOLET (10 subjects), and RED/VIOLET (10 subjects) lasers. VIOLET laser provoked a decrement of Absolute Alpha Power values during the vagal stimulation experimental condition in all 10 cases. In 3 cases occurred a partial recovery of Absolute Alpha Power values, throughout the post-vagal stimulation phase. RED/VIOLET laser provoked an increment of the Absolute Alpha Power values during the vagal stimulation experimental condition in 9 cases. In the case in whom occurred a decrement of the Absolute Alpha Power values during the vagal stimulation, it called the attention that an increment in the Absolute Gamma Power values were found. We can conclude that the results using LLLT with the VIOLET laser might be effective in the treatment of epilepsy, because a reduction of brain activity can induce a decrement of paroxysmal activity. The results using the RED/VIOLET LLLT for VNS might be useful in conditions in which it is necessary to induce an increment of brain activity in many conditions, like in depression, neurorehabilitation, in coma, in disorders of consciousness, in dementia, and in some patients complaining autism. Of course, this is a pilot study. It is necessary to explore in future studies the whole EEG spectrum and other variables like Relative Powers in the different EEG bands. Moreover, it is necessary to run protocols on different diseases.

INTRODUCTION
The use low-level laser therapy (LLLT), has been increasingly used in diverse areas of medical practice, such as prevention of tissue death, pain relief, reduction of inflammation, and regenerative medicine, stroke, etc.(1-6)

LLLT has been reported in mice experimental models to stimulate, preserve and regenerate cells and tissues. The mechanism of action involves photon absorption in the mitochondria (cytochrome c oxidase), and ion channels in cells leading to activation of signaling pathways, up-regulation of transcription factors, and increased expression of protective genes (possibly mediated by light absorption by opsins). Mice have shown an improvement improved memory and learning using LLLT. Secondary effects of photon absorption include increases in ATP, a brief burst of reactive oxygen species, an increase in nitric oxide, and modulation of calcium levels. Tertiary effects include activation of a wide range of transcription factors leading to improved cell survival, increased proliferation and migration, and new protein synthesis.(7-10)

Several clinical trials have affirmed that LLLT is a non-invasive technique and that it has important relevance in neurological diseases, such as stroke, traumatic brain injury, degenerative brain disease, spinal cord injury, and peripheral nerve regeneration. Nonetheless, there are still controversies on the efficacy of LLLT to treat neurologic diseases, because several papers reported negative results on this area. Numerous technical factors have been proposed to discuss these non-satisfactory results, such as a large number wavelength, fluence, irradiance, treatment timing and repetition, pulsing, polarization, etc. Moreover, most of these clinical trials have been developed using clinical scales, and not objective ancillary test to assess brain function. Furthermore, studies on the effect of LLLT on the brain function in normal subjects are scarce.(10, 11)

On the other hand, the electrical stimulation of the vagus nerve has been investigated as a feasible method for
controlling intractable epilepsy. Pilot studies and randomized controlled trials have subsequently shown that chronic vagal nerve stimulation can improve the control of intractable seizures. Experiments in acute and chronic animal models of epilepsy provide mechanistic insight into the acute abortive, acute prophylactic, and chronic progressive prophylactic, anti-seizure effects of vagus nerve stimulation (VNS) observed in human epilepsies, and demonstrate antiepileptogenic effects of VNS in the kindling model. Anatomic-physiologic studies, experimental epilepsy studies, and human imaging, EEG, and CSF studies suggest that multiple mechanisms underlie the antiseizure effects of VNS and that alterations of vagal parasympathetic efferent activities do not underlie these antiseizure effects. (3, 12-17)

Several vagal nerve electric stimulators have been developed over the years, but the most recent treatments have used subcutaneous chronic implanted devices in different places to stimulate the vagus nerve. (18-20), but studies using LLLT for VNS are scarce. (10)

The superior portions of the vagus nerves are attached by multiple rootlets to the medulla. The vagus nerves exit the skull through the jugular foramina. In the neck, each vagus nerve lies within the carotid sheath, between the carotid artery and the jugular vein. In the upper chest, the vagus nerve runs on the right and left sides of the trachea. Most vagal efferent projections are of parasympathetic type to the heart, lungs, stomach and intestines, liver, pancreas, and kidneys. These efferent connections originate from preganglionic neurons located in the dorsal motor nucleus of the vagus and in the nucleus ambiguous, in the medulla. The vagal parasympathetic efferent synapse on neurons located in parasympathetic ganglia. These ganglia are located in or near the target organs. The two vagus nerves are asymmetric with regards to cardiac innervation. The left vagus nerve carries most of the parasympathetic fibers that less densely innervate the ventricles, and the right vagus nerve carries most of the parasympathetic fibers that more densely innervate the cardiac atria. Therefore, vagal anatomy favors left (over right) vagus stimulation to avoid cardiac effects. Stimulation of the different fibers of the vagus individually and together can dramatically evoke different responses in electroencephalogram (EEG) recordings-weak stimulation of the vagus recruits the A and B fibers and causes a synchronization of the EEG, whereas higher stimulation, which also recruits C-fibers, causes a EEG desynchronization reported that high-level stimulation of the vagus (maximally recruiting C-fibers), prevented chemically or electrically-induced seizures and reduced the length of seizures in progress. (21-26)

fMRI studies demonstrated the action of vagal nerve activation. The majority of afferent vagal fibers enter the brain through the jugular foramen and synapse onto the nucleus tractus solitarius, the first central relay of vagal afferents, which then project directly and indirectly to various structures in the brain (e.g., locus coeruleus, dorsal raphe nucleus, periaqueductal lgray) implicated in the mechanism of action of VNS in epilepsy. The vagus nerve afferents have some disynaptic projections to the thalamus and hypothalamus (via the NTS and the spinal trigeminal nucleus). Most of the widespread vagal projections to cerebral structures traverse three or more synapses. (27-31)

In this paper we develop a pilot study to study the use of LLLT for VNS in normal subjects, and to assess its effects by QEEG.

MATERIAL AND METHODS

Twenty normal subjects from 22 to 46 years, paired in age and gender were studied recording QEEG in three experimental condition: Basal record (10 minutes), Laser stimulus (10 minutes), and Post-Laser stimulus records (10 minutes), with VIOLET (10 subjects), and RED/VIOLET (10 subjects) lasers. (10, 11)

LLLT was applied by a neurologist (MCA) in the neck, left side. Subjects were continuously monitored by bed side monitors (Electrocardiogram, blood pressure, and body temperature) to early diagnose any complication. Participants received LLLT administration with the Erchonia® EAL Laser (VIOLET OR RED/VIOLET lasers).

QEEG was recorded and processed using the MEDICID 06 machine, NEURONIC, S.A. (Cuba). EEG Spectrum was calculated for all leads, according to the 10-20 System for locating EEG electrodes. The narrow band model for was used for the EEG quantitative analysis. QEEG brain mappings were compared for the peak of Alpha activity in the three experimental conditions (Figure 1). The technique for QEEG recording and processing can be found elsewhere. (32)
Figure 1
Using the narrow band EEG Narrow band quantitative analysis, brain mappings were compared for the peak of Alpha activity in the three experimental conditions.

Informed consent was obtained for all participants. The Ethical Committee of the Institute of Neurology and Neurosurgery approved according to the “World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects”.

RESULTS
QEEG RESULTS USING LLLT WITH VIOLET LASER
As it will be shown in Figures 2 to 11, LLLT using VIOLET laser provoked a decrement of Absolute Alpha Power values during the vagal stimulation experimental condition in all 10 cases. In 3 cases occurred a partial recovery of Absolute Alpha Power values, throughout the post-vagal stimulation phase.

Figure 2
QEEG results from Case 01, using VIOLET LLLT.
Figure 7
QEEG results from Case 06, using VIOLET LLLT.

Figure 8
EEG results from Case 07, using VIOLET LLLT.

Figure 9
QEEG results from Case 08, using VIOLET LLLT.

Figure 10
QEEG results from Case 09, using VIOLET LLLT.

Figure 11
QEEG results from Case 10, using VIOLET LLLT.

QEEG RESULTS USING LLLT WITH RED/VIOLET LASER

From Figure 12 to 21, it is shown how the LLLT using RED/VIOLET laser provoked an increment of the Absolute Alpha Power values during the vagal stimulation experimental condition in 9 cases. In the case in whom occurred a decrement of the Absolute Alpha Power values during the vagal stimulation, it called the attention that an increment in the Absolute Gamma Power values were found (Figure 21).

Figure 12
QEEG results from Case 01, using RED/VIOLET LLLT.

Figure 13
QEEG results from Case 02, using RED/VIOLET LLLT.

DISCUSSION

Our results showed that LLLT using VIOLET laser
provoked a decrement of Absolute Alpha Power values during the vagal stimulation experimental condition in all 10 cases, meanwhile in 3 cases occurred a partial recovery of these values throughout the post-vagal stimulation phase.

When vagal stimulation was performed using RED/VIOLET laser an increment of the Absolute Alpha Power values occurred during the vagal stimulation experimental condition in 9 cases. In the case in whom occurred a decrement of the Absolute Alpha Power values during the vagal stimulation, an increment in the Absolute Gamma Power values were found.

VNS is increasingly used for the treatment of refractory epilepsy,(12, 13, 15) using implanted subcutaneous electrical devices, but studies using LLLT for vagal nerve stimulation are really scarce.(10)

There are several hypotheses to explain the VNS anti-seizure effects. Several authors have proposed that VNS might antagonize seizures by desynchronizing electrocerebral activities. Early neurophysiologic studies found that VNS can induce EEG desynchronization in cats. Moreover, it has been postulated that desynchronizing these hypersynchronous activities would confer antiseizure effects on VNS.(3, 33-35)

Anesthetized cats demonstrated EEG desynchronization during VNS in the earliest experiment. Later studies showed that VNS also can induce increased EEG synchronization and can decrease interictal epileptiform EEG discharges in animals, depending on the frequency of stimulation.(15, 24, 36)

Salinsky and Burchiel studied quantitative scalp EEG measures in six partial epilepsy patients after more than 6 months of chronic VNS. Acquisition of EEG occurred during maximal arousal. Series of EEG acquisition consisted of three epochs lasting 60 seconds each, recorded sequentially just before a train of VNS, during VNS, and just after VNS. Visual interpretation of the EEGs during the baseline, activation, and post-activation conditions did not show any changes across these conditions in any individual. Quantitative frequency analysis of activities at each of the standard 10–20 system electrodes did not show significant differences in total power across these conditions in any individual. Even with averaging of quantified data across the entire group, no significant differences by condition were shown for total power, median frequency, or power in any of the standard frequency bands. Therefore, these authors did not report significant quantitative effects of VNS on the human EEG.(37)

On the contrary, VNS stimulation with VIOLET laser produced a decrement in the value of Absolute Power Alpha values, which is in concordance with the EEG desynchronization reported in other human and animal studies. (3, 33-35)

Other studies in depressed patients, who did not have seizures, the use of VNS-synchronized BOLD-fMRI studies of VNS activity has shown VNS-induced activity in the orbitofrontal and parieto-occipital cortex bilaterally, the left temporal cortex, the hypothalamus, and the left amygdala, along with an overall diffuse increase in brain activity.(38, 39)

This finding might be related to our findings that RED/VIOLET LLLT produced an increment of the Absolute Alpha Power during the vagal stimulation experimental condition.

Elger et al. demonstrated an antidepressant effect of VNS in patients included in a randomized control trial assessing VNS for refractory seizures.(40) These mood improvements were sustained at 6 months of follow-up and were shown to be independent of anti-seizure effects. Furthermore, surrogate markers of mood alteration such as improved psychosocial function, attention, temperament and the ability to cooperate have been reported in association with VNS.(40-42)

We can conclude that the results using LLLT with the VIOLET laser might be effective in the treatment of epilepsy, because a reduction of brain activity can induce a decrement of paroxysmal activity.

The results using the RED/VIOLET LLLT for VNS might be useful in conditions in which it is necessary to induce an increment of brain activity in many conditions, like in depression, neurorehabilitation, in coma, in disorders of consciousness, in dementia, and in some patients complaining autism.

Of course, this is a pilot study. It is necessary to explore in future studies the whole EEG spectrum and other variables like Relative Powers in the different EEG bands. Moreover, it is necessary to run protocols on different diseases. LLLT has been demonstrated to be a non-invasive technique and therefore,(10, 11) this paper opens new ideas for the
application of LLLT for vagal stimulation in future studies.

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