ORIGINAL RESEARCH

tVNS For Consciousness Recovery in Traumatic Brain Injury Patients

Aishwarya Rai[1], Abhinav Bansal[2], Jasmine Anandabai[3], Shikha Singh[4]

[1]Assistant Professor,[3]Dean and Principal, Jyotirao Phule Subharti College of Physiotherapy, Swami Vivekanand Subharti University, Subhartipuram, Meerut, Uttar Pradesh, India
[2]Associate Professor, Department of Neurosurgery, Subharti Medical College, Meerut, Uttar Pradesh, India
[4]Associate Professor, Department of Physiotherapy, M.M Institute of Physiotherapy and Rehabilitation,MMU, Mullana, Haryana, India

Corresponding Author
Aishwarya Rai
Assistant Professor, Jyotirao Phule Subharti College of Physiotherapy, Swami Vivekanand Subharti University, Subhartipuram, Meerut, Uttar Pradesh, India
Email:raiaishwarya777@gmail.com

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ABSTRACT
Background: TBIs are the leading causes of impairmentand asthenia.It is deemed that approximately1.5-2 million people are injured every year.The rehabilitation of such people can be financially draining and can put further strain on several aspects of such households. The intricate and the diversity of such injuries make it tough topredetermine a standardized treatment protocol for rehabilitation. TENS can be used to alter brain activity by stimulating the vagus nerve. Thus, promoting recovery of consciousness and cognition.**Purpose:** To evaluate the effect oftVNS onthe promotion of cognitive recovery in patients with post-traumatic moderate to severe brain injury and compare traditional neuro-rehabilitative methods with application of tVNS.**Method:** A sample of 58 patients affected with moderate to severe TBI owing to various patho-physiologic sequalae within the age group 16-40 years were selected and divided into two groups-A and B, A was the control group whereas participants of only group B received tVNS in the first ten days of the treatment (acute phase). Outcome measures used for the study were GCS and RLAS-R. **Result:** Patients belonging to group B showed greater cognitive retrieval when compared to patients of group A. tVNS when applied in the acute phase yields better results.**Conclusion:** tVNS is an inexpensive supplementary method and can be inculcated in the early rehabilitation protocol.It is well tolerated and is user friendly and can be easily instilled in the rehabilitation methods.
Keywords: TBI, Cognitive Recovery,tVNS.

INTRODUCTION

A traumatic brain injury (TBI) is a non-degenerative, non-congenital insult to the brain from an external force (mechanical, chemical, thermal, electrical and radiation) possibly leading to temporary or permanent impairment of cognitive, physical, psychosocial functions with an associated diminished or altered state of consciousness.[1]

TBIs are a leading cause of morbidity, mortality, disability and socioeconomic losses in India and other developing countries. It is estimated that nearly 1.5 to 2 million persons are injured and 1 million succumb to death every year in India.[1]

Road traffic injuries are the leading cause (60%) of TBIs followed by falls (20%-25%) and violence (10%). Alcohol involvement is known to be present among 15%-20% of TBIs at the time of injury[1].It is a major cause of preventable demise and impairment. There are different categories for head injuries (HI). Based on pathogenic traits (focal and dispersed); by severity (mild, moderate, severe); and by impact (primary and secondary). Neuromuscular sequelae (such as paralysis, paresis, decreased coordination, poor postural control, abnormal tone, abnormal gait pattern, and abnormal involuntary movements) and cognitive sequelae (such as often occurring altered degrees of awareness) are two possible types of TBI. Between 10-15% of patients with severe TBI are discharged from the hospital in a vegetative state and the prevalence of minimally conscious state is greater than that of vegetative state.[2]), neuro-behavioral (low frustration tolerance, agitation, disinhibition, apathy, emotional lability, mental inflexibility, aggression, impulsivity, and irritability[3]), communication (common language and communication deficits include disorganized and tangential oral or written communication, imprecise language, word retrieval difficulties, and disinhibited and socially inappropriate

language. Additionally, patients may have trouble detecting social signs, talking in distracting situations, and adapting their communication style to fit the needs of the moment.[4] dysautonomia (tachycardia, tachypnoea, hypertension, hidrosis, and hyperthermia due to elevated sympathetic activity after traumatic brain injury). Other symptoms of dysautonomia include decerebrate and decorticate posture, hypertonia, and teeth grinding. The term paroxysmal sympathetic hyperactivity accurately describes this phenomenon.[5]) and secondary complications (Between 12-50% of people with severe TBI develop post-traumatic seizures[6]. Patients with traumatic brain injury (TBI) are susceptible to many secondary impairments and other medical complications because of the increased risk of extended immobility and concomitant injury. Up to 50% of patients with severe brain injury develop gastrointestinal difficulties, 45% develop genitourinary problems, 34% develop respiratory problems, 32% develop cardiovascular problems, and 21% develop dermatological complications[6].)

Notable visceral efferent fibers from the pharynx and larynx of the vagus nerve project to the nucleus ambiguus. The dorsal motor nucleus is the source of its general visceral efferent fibers, which innervate the gut, lungs, and heart. Additionally, the concha of the ear provides sensory afferent connections to the vagus. The vagus visceral afferents go to the thalamus, amygdala, and forebrain through the neural tube supply (NTS), and they continue to various areas of the cortex via the medullary reticular formation. Measured by positron emission tomography (PET), cerebral blood flow (CBF) is altered by transcutaneous vagus nerve stimulation (tVNS). The CBF to the thalamus, hypothalamus, and insula is increased by both high and low degrees of stimulation. In the vagus nerve brain circuitry, there are excitatory and inhibitory neurotransmitters, including NE, serotonin, GABA, and glutamic acid. Chronic tVNS is used for the treatment of patients with resistant depression as it also increases regional CBF in the dorsolateral prefrontal cortex.

Italso alters limbic circuitry to reduce epileptogenesis and enhances mood. tVNS 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 TBI resulting in VS or MCS.[8]

tVNS is a method that has been developed to overcome complications arising from vagus nerve stimulation such as vocal cord disorders and peritracheal hematoma, etc. Anatomical studies of the ear suggest that the tragus, concha, and cymba concha are the places on the human body where there are cutaneous afferent vagus nerve distributions, and it is believed that stimulation of these afferent fibers produces therapeutic effects that are similar to those of regular VNS.

MATERIALS AND METHODS

We conducted an experimental study which included 58 patients that were affected with moderate to severe TBI and were admitted to the neuro-intensive care unit of Chattrapati Shivaji Subharti Hospital (CSSH), Meerut. They were given follow-up sessions post their discharge every 21 days at the out-patient department of Jyotirao Phule Subharti College of Physiotherapy (JRP SCPT)up to six months. The patients were divided into two groups, namely A and B each comprising of 29 subjects. Group A subjects comprised of the control group and were strictly given only various traditional neuro-rehabilitative strategies for their care. Whereas subjects of group B underwent ten sessions of tVNS in their acute stage of rehabilitation along with other management strategies. The study was approved by the University Ethics Committee (Medical), Swami Vivekanand Subharti University, reference no. SMC/UECM/2022/394/200. The UECM is provisionally registered with National Ethics Committee Registry for Biomedical and Health Research (NECRBHR), Department of Health and Research (DHR); registration no. being EC/NEW/INST/2021/1540.

PATIENT ENROLLMENT

Inclusion Criteria

All patho-anatomic and patho-physiologic sequalae (hematoma, contusion, sub-arachnoid hemorrhage, ischemia, diffused axonal injury and vasospasm) were included in the study. Age between 16-40 years old.[9] Both genders, male and female were involved. Initial GCS at the time of admission was< 13. An informed consent from patient or their legal guardian and an independent neurosurgeon.

Exclusion Criteria

Patient was hemodynamically unsteady. Consent not given or withdrawn by the patient party at any given time.A history of any psychotic disorder. Previous surgical interventions on the vagus nerve or if the subject had a history of a vagal lesion or damage. Had a history of any progressive neurological diseases and a history of chronic alcohol consumption or drug abuse.[10]

tVNS Stimulation Regime

A transcutaneous vagus nerve stimulator was used in the study. A set of ear clip electrodes were used for the stimulation procedure. The electrodes were attached to a contact point to the tragus and the cymba conchae of the left ear to ensure maximum stimulation. The tVNS wasset to stimulate for four hours daily, the dosimetry being 25 Hz stimulation frequency, 250 μs pulse with, a 30 sec on/ 30 sec off settings with up to 0.5 mA for the first three days, and subsequently 1 mA for the 7 remaining days[20].

The patients received interdisciplinary rehabilitation during which they had cared for 24-hours by medical personnel. Additionally, they also underwent different neuro-rehabilitative sessions spanning a maximum of 1.5 hours that would constitute various techniques.

This continued until the patient was discharged from the hospital. Following this,each patient was given a follow-up session every 21 days till six months (180 days) in the out-patient department of JRP SCPT.

Tolerability Measures

A convenient monitor was used to measure the blood pressure, respiratory rate, oxygen saturation and pulse rate of each participant throughout the stimulation session. Vitals (heart rate, oxygen saturation, respiratory rate, temperature and blood pressure) were assessed before and after 15 minutes of each stimulation. A healthcare staff (or the investigators themselves) regularly monitored the patients for any signs of discomfort. When observed, if any, including signs of pain or nociception, facial grimace, tachycardia, hidrosis in any body part, or other sympathetic or parasympathetic dynamism was detected, it was noted, and the stimulation was stopped and restarted only after making sure that the patient was stable.

Outcome Measures

The outcome measures used in the study for evaluating the progression of recovery in subjectswereGlasgow Coma Scale (GCS) and Rancho Los Amigos Levels of Cognitive Functioning Scale – Revised (RLAS-R). GCS is a toolused to objectivelyillustratethe extent of impairment of consciousness in allacute medical and trauma patients. The Glasgow Coma Scale is a required component of the NIH Common Data Elements for studies of head injury and the ICD 11 revision and is used in more than 75 countries.[11]

The RLAS-R is a renowned clinical scale used to rate how people with brain injuries recover. As patients awaken and arouse post head injuries, they go through various levels of convalescence on the scale. Each level describes a general pattern of recovery, with a focus on cognition and conduct.

Statistical Analyses

All study data was collected in Microsoft Office Excel 2007. Statistical analysis was performed using EZR Software Version 1.55. Demographic data of the patients including age and gender were summarized. The dependent variables for the statistical analysis were GCS and RLAS-R. Base line data was taken at the beginning of the study (Pretest values) and after the completion of the treatment (Post test values) to analyze the effects of tVNS on cognitive recovery of the patients; an unpaired t-test was used. A level of o.o5 was used to determine the statistical significance.

Table 1: Comparison of Mean and Standard Deviation of Post GCS scores of Group A and B

Group	Mean	N	SD	STD. Error Mean
A	10.2759	29	2.53401	0.47055
B	12.0690	29	2.82756	0.52506

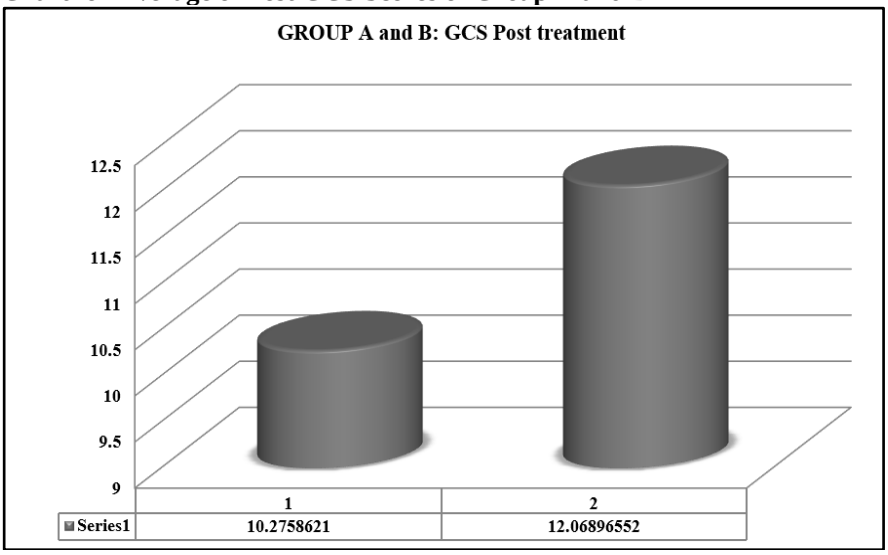
Table 2: Comparison of Mean and Standard Deviation of Post RLAS-R scores of Group A and B

Group	Mean	N	SD	STD. Error Mean
A	7.2069	29	1.93426	0.35918
B	7.7586	29	1.74551	0.32413

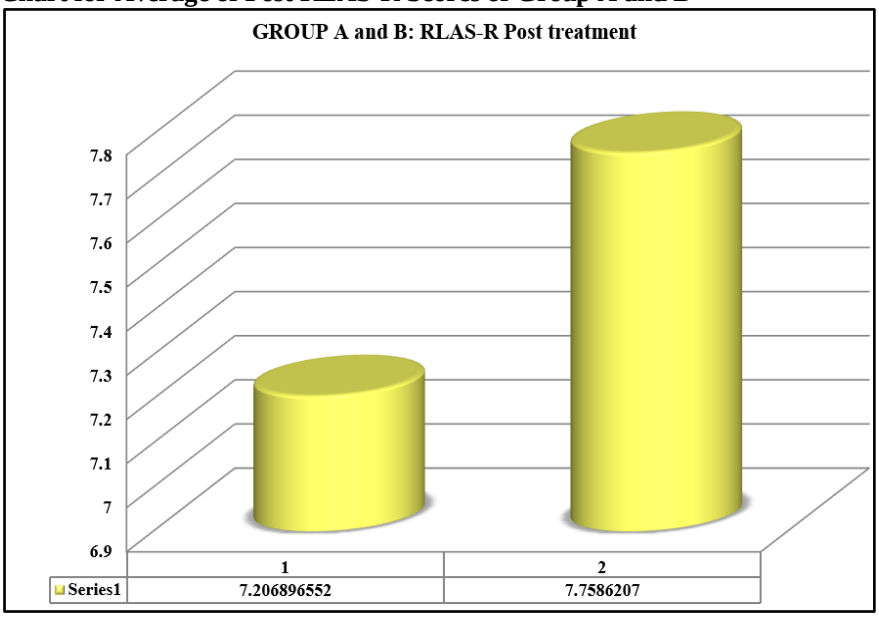
Table: 3: Unpaired t-test for Post Scores of GCS and RLAS-R between Group A and B

	t-test for Equality of Means
Post GCS	0.014
Post RLAS-R	0.259

Graph 1: Bar Chart for Average of Post GCS Scores of Group A and B



Graph 2: Bar Chart for Average of Post RLAS-R Scores of Group A and B



RESULTS

During the study period (December 2020- February 2022) a total of 58 patients were enrolled in the study, and each completed the treatment for the entire duration of 6 months. All 29 patients of group B completed all sessions of tVNS in their acute stage of rehabilitation. An unpaired t-test was applied to find out the significance of values between the post values of GCS and RLAS-R of the groups. Results were analysed using student t-test (unpaired) by using EZR Software Version 1.55. Table-1 shows Comparison of Mean and Standard Deviation of Post GCS scores of Group A and B (A-10.20759 and 2.53401) and (B-12.0690 and 2.82756). Table-2 shows Comparison of Mean and Standard Deviation of Post RLAS-R scores of Group A and B (A- 7.2069 and 1.93426) and (B-7.57586 and 1.74551). Table-3 shows unpaired t-test for Post GCS and RLAS-R between Group A and B (GCS- 0.014) and (RLAS-R- 0.259)

DISCUSSION

The purpose of this study was to provide evidence that tVNS can aid in the process of cognitive recovery in patients that have suffered moderate to severe TBI.

Devin et al. in 2020 suggested that non-invasive applications of VNS target either the auricular branch of the vagus nerve or the cervical branch.The devices used to apply electrical pulses is a transcutaneous electrical stimulation (TENS) device[8]Although TENS is used to activate peripheral nerves to treat pain, it has shown excellent results and has been used to treat disorders of the CNS as well like drug resistant epilepsy, migraine and tinnitus. The vagus nerve can be stimulated using electrical pulses generated by a TENS machine. The most easily accessible branch of the vagus nerve is the auricular branch of the vagus nerve that gives off cutaneous branches to the ear. Although attempts have been made to stimulate the cervical branch of the vagus nerve, the struggle that remains is that it is contained within the carotid sheath and isstrenuous to stimulate and has greater chances of generating various side-effects.

Before starting the procedure, the GCS and RLAS-R scores of the patients undergoing the therapy was recorded (Day 1 of the treatment), and the same was done after the termination of the treatment (Day 180 of treatment). Each patient underwent various neurorehabilitative techniques for a maximum of 1.5 hours daily until their discharge from hospital. Post this, all patients were given follow-up sessions every 21 days up to six months. Periodic follow-ups ensured that the patients followed the home protocol.

The patients involved in the study had little to no side effects to tVNS, none of which had an impact over the study. The most noted side effect associated with tVNS was irritation associated with occasional episodes of erythema over the area where the electrodes were placed. All patients of Group B involved in the study completed all 10 sessions oftVNS stimulation. To minimize potential cardiac risks associated with tVNS, only the left ear was stimulated. Whereas to maximize the effect received by tVNS, both the tragus and the cymba conchae of the ear was stimulated using ear clip electrodes placed in contact with the skin over thementioned areas. Natalia Yakunina et al. in 2017demonstrated that tVNS at the cymba conchae properly activates the vagal pathway and results in its strongest activation, and thus is the optimal location for tVNS therapies applied to the auricle[21]. Bashar W Badranet al in 2018 suggested that stimulation of the tragus activates the cerebral afferents of the vagal pathway and concluded that tVNS is a promising form of VNS[13].

It was observed that patients who received tVNS in the acute rehabilitation phase showed better results

(Group B) compared to patients that did not receive tVNS in the early rehabilitation phase (Group A).

VNS modifies cerebralactivity via numerouscontrivances. Recovery of consciousness is linked to restoration of thalamo-cortical and cortico-cortical connectivity.[14] In a single case report of a patient in UWS after TBI, using PET and EEG outcomes, VNS appeared to reactivate the thalamic-cortical axis for consciousness in a similar manner to deep thalamic stimulation[15]. The vagus nerve afferents terminate in the NTS in the brainstem. From here they activate the neuromodulatory noradrenergic locus coeruleus and raphe nuclei that have noradrenergic and serotonergic cortical projections that influence cortical synaptic function and plasticity[16]. In addition, tVNS modulates cortical excitability in healthy subjects through modulation of GABA-inhibitory circuits[17].

The difference between the post values of GCS and RLAS-R of both the groups were recorded. An unpaired t-test was calculated to record a significant difference in the post GCS and RLAS-R values was also performed.

Jakob Hakon et al. in 2020 demonstrated in their pilot study that tVNS is a feasible and safe VNS strategy for patients following severe TBI and that controlled studies are needed to clarify whether tVNS has a potential to promote recovery of consciousness following severe TBI[20]. Fioravante Capone et al. in 2017 demonstrated that tVNS is safe and tolerable and can produce slight clinical improvements even within a time frame of 10 days.[18]

Apurba Barman et al. in 2016 suggested that the complexity and the heterogeneous nature of brain injuries make it difficult to standardize treatment and rehabilitation and that in a developing country like India, focus should be directed toward rehabilitation interventions that are not only effective and easily applicable but are also low cost.[19] The advantage of applying tVNS is that the family members of the patient can be trained and counseled about the device and its inner workings and can be administered by them at home as well.

LIMITATIONS OF THE STUDY

Although proven to be effective in long term sessions, the biggest limitation of the study was the time and availability of patients for each session. Many patients'parties' lost interest as more time elapsed and seemed disinterested in continuing with the sessions as it was inconvenient for them to travel miles for the follow-ups. Better results could have been achieved if a greater number of sessions had been imparted. However, long hospital stays, and follow-up were an obstacle for such families given their financial constraints.

RECOMMENDATIONS

It is recommended that a greater number of sessions could be given for application of tVNS with less treatment time each day to minimize the side effects. Also, further studies should be done to explore the effects of tVNS in TBI patients owing to such promising results since not much literature is available for application of tVNS in TBI patients.

CONCLUSION

To conclude, it is worth mentioning that tVNS shows a promising application in patients affected with TBI and that tVNS delivered using a TENS device to the tragus and cymba conchae of the ear over left side in the early stages of rehabilitation along with various neurorehabilitative techniques yields better results compared to the traditional methods of rehabilitation. Compared to its invasive counterpart that has several limitations owing to the complications caused by surgical implantation of vagus nerve stimulators, tVNS is a safer option. When applied to the auricular branch of the vagus nerve over the tragus and cymba conchae for 4 hours daily for ten consecutive days in the early stages of rehabilitation of patients affected with moderate to severe traumatic brain injury, results obtained were favourable.tVNS is an economically cheaper supplementary method and can be inculcated in the early rehabilitation protocol. It is inexpensive, well tolerated and user friendly and can be easily instilled in the rehabilitation methods in society especially a developing one such as in India given healthcare is expensive and as it also decreases the burden of the patient on the family members.

TRANSPARENCY, RIGOR AND REPRODUCIBILITY

The study was approved by the University Ethics Committee (Medical), Swami Vivekanand Subharti University, reference no. SMC/UECM/2022/394/200.

A total of 65 patients were enrolled in the study initially, 5 patients dropped out of the study of which 3 withdrew consent after completion of the study and 2 withdrew mid-study. 2 patients expired before the study could be completed owing to completely different reasons. The patients were recruited only after consent from the associated neurosurgeon. All patients were in 24X7 care of the nursing staff until their discharge from the hospital.They received follow-up every 21 days in the OPD till six months.Aishwarya Rai, Jasmine Anandabai and Shikha Singh designed the study. Aishwarya Rai conducted the study with help from Dr. Abhinav Bansal in patient recruitment. Aishwarya Rai prepared the manuscript for publication with important intellectual inputs from all authors. No research funding was applied for the study. The manuscript was revised by all authors, and everyone approved the final document.

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