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Transcutaneous Vagus Nerve Stimulation in Patients With Severe Traumatic Brain Injury: A Feasibility Trial

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Objectives: Preclinical studies have shown that surgically implanted vagus nerve stimulation (VNS) promotes recovery of consciousness and cognitive function following experimental traumatic brain injury (TBI). The aim of this study is to report the feasibility and safety of a noninvasive transcutaneous vagus nerve stimulation (tVNS) in patients with persistent impairment of consciousness following severe TBI.

Materials and Methods: The feasibility of tVNS was evaluated in five patients presenting with diffuse axonal injury and reduced dominant EEG activity one month following severe TBI. tVNS was applied to the left cymba conchae of the external ear using a skin electrode four hours daily for eight weeks. Possible effects of tVNS on physiological parameters and general side effects were recorded. In addition, we report the rate of recovery using coma recovery scale revised (CRS-R).

Results: The tVNS regime of four hours daily for eight weeks was feasible and well tolerated with little side effects and no clinically relevant effects on physiological parameters. Three patients showed improvements (>3 points) in the CRS-R following eight weeks tVNS.

Conclusion: We demonstrated that tVNS is a feasible and safe VNS strategy for patients following severe TBI. Controlled studies are needed to clarify whether tVNS has a potential to promote recovery of consciousness following severe TBI.

Keywords: vagus nerve stimulation, Transcutaneous vagus nerve stimulation, traumatic brain injury, feasibility study

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INTRODUCTION

Severe traumatic brain injury (TBI) is the leading cause of long-term disability in young adults and poses a major socioeconomic challenge (1). Severe TBI is associated with various focal hemorrhagic brain lesions as well as diffuse axonal injury (DAI) and subsequently widespread disruption of neuronal connectivity (2,3). Impairment of consciousness is a key feature in patients suffering from severe TBI, and has been associated with impaired neuronal connectivity in and between regions that regulate arousal and awareness, including disruption of thalamo-cortical and cortico-cortical networks (4). Different states of consciousness have been defined based on assessment of pure reflexive behavior, as in the vegetative state/unresponsive wakefulness syndrome (VS/UWS), or on occurrence of purposeful behaviors distinct from reflexes as in the minimally conscious state (MCS) (5,6). The degree of recovery depends on the severity and type of injuries and generally the presence of DAI lesions is an indicator of very severe injury and a prognostic marker for poor outcome (3).

The sparse evidence-based treatments available for patient in persistent VS/UWS and MCS renders novel therapeutic options urgently needed (4). In the clinical setting, vagus nerve stimulation (VNS) represents an established adjunctive therapy for patients with drug resistant epilepsy and is approved for treatment resistant major depression (7,8) but data from animal studies also suggest that VNS may have beneficial effects on recovery of consciousness and cognitive function following experimental TBI (9,10). In addition, a recent case report of a patient lying in a VS/UWS for 15 years after TBI describes how one month of VNS resulted in an increase of general arousal, sustained attention, body motility and

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visual pursuit, indicating a transition from VS/UWS to MCS (11). The higher level of consciousness following VNS has been associated with increased activity within thalamo-cortical networks relevant for recovery of consciousness as determined by PET and fMRI (11). To our knowledge this finding has not yet been replicated probably because studies of the effect of VNS in humans with TBI are complicated for practical and ethical reasons as traditional VNS is expensive and invasive with irreversible implants. Thus, external stimulation paradigms are of great interest.

Transcutaneous vagus nerve stimulation (tVNS) is a novel noninvasive method of VNS targeting the superficial auricular branch of the vagus nerve that supplies the skin of the cymba conchae on the outer ear (12,13). tVNS does not involve the inherent risks of surgical electrode implantation and has the advantages that therapy can easily be stopped or removed in case the patient does not respond intentionally to VNS. Despite having the potential of providing a robust vagal afferent input to the brain (14), tVNS is associated with an inherent risk of incompliance and needs active involvement by the patients or caregivers several times per day.

The application of tVNS in patients with impaired consciousness has to our knowledge not been investigated previously. Therefore, in this study we aimed to examine whether it is safe and feasible to carry out tVNS in patients in VS/UWS and MCS after TBI. Furthermore, we describe the recovery of consciousness during the eight weeks of tVNS.

MATERIALS AND METHODS

We conducted a prospective single-armed open-label feasibility study, including five patients suffering from very severe TBI that were admitted to a highly specialized neurorehabilitation department at the University Hospital of Copenhagen. The patients received interdisciplinary rehabilitation during daytime, were consulted by the medical staff on daily basis and received 24-hour nursing support. The study was approved by the local scientific ethics committee of the capital region of Denmark (H-18003882) and by the Danish data protection authority (VD-2018-92/I-Suite number: 6329).

Patient Enrollment

Inclusion criteria were: age > 17 years, patients diagnosed with persistent VS/UWS or MCS > 28 days after severe TBI, MRI verification of DAI, EEG verification of low frequency dominant activity and a written informed consent from patient's proxy and an independent medical doctor.

Exclusion criteria included retained metal contraindicating MRI, when tVNS in advance was deemed not feasible due to, for example, lesions in the left ear, severe agitation or concurrent active severe medical problems, pregnancy and language barrier (non-Danish speaking patient due to uncertainty in assessment of level of consciousness by the Coma Recovery Scale-Revised [CRS-R]) (15). A rehabilitation neurologist evaluated each patient prior to inclusion. Patients enrolled in the study, received concurrent highly specialized neurorehabilitation and necessary medical treatments (for infection, pain, epileptic seizures etc.) during the period of tVNS stimulation.

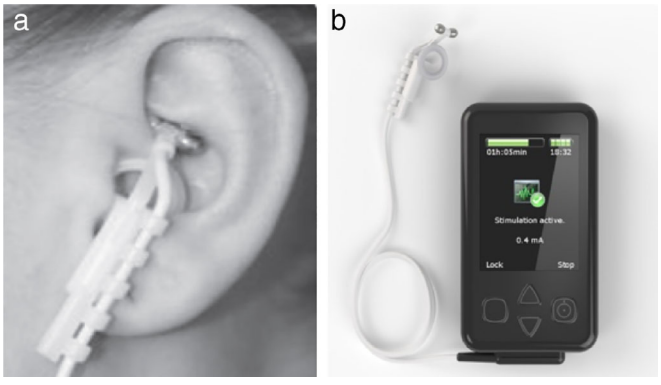

Figure 1. Transcutaneous vagus nerve stimulation (t-VNS) Nemos device (Cerbomed, Germany) with extern stimulator connected with an electrode to be placed in the auricular tract at the cymba conchae. [Color figure can be viewed at wileyonlinelibrary.com]

tVNS Stimulation Regime

We used the transcutaneous Vagus Nerve stimulator Nemos® (Cerbomed, Germany; CE-marked 2011). The device comprises a small portable stimulation unit, a connector cable, and a cutaneous electrode that is placed in the auricular tract with a contact point to the surface of the cymba conchae (Fig. 1). tVNS was set to stimulate four hours daily according to a fixed pulse program (25 Hz stimulation frequency, 250 µs pulse with, 30 sec on/ 30 sec off; standard settings, Cerbomed, Germany) with up to 0.5 mA for the first three days, and subsequently 1 mA for the remaining eight-week period. The algorithm was based on experiences of effective and tolerated stimulation escalation and intensities from clinical studies in patients with drug resistant epilepsy (16).

Tolerability Measures

We used a portable patient monitor (IntelliVue MP5, Philips) for measuring blood pressure and pulse rate. Blood pressure and pulse rate and pain assessment scores were assessed before and 15 min after each stimulation onset and observation for signs of skin irritation was carried out following stimulation. During stimulation A project nurse or the nurse in the patient's rehabilitation team regularly monitored signs of discomfort. If any signs of discomfort including signs on pain/nociception, grimacing, tachycardia, diaphoresis or any other sympathetic or parasympathetic overdrive symptoms were detected, this was noted, and the stimulation was titrated back down or stopped.

Behavioral Measure

An authorized Danish version of the CRS-R was used for clinical evaluation of consciousness levels during the eight weeks of tVNS (15). The CRS-R is a preeminent assessment scale for evaluating and differentiating between patients in the vegetative/unresponsive wakefulness syndrome (VS/UWS), the MCS and patients emerged from minimal conscious state (EMCS) (17–19). The scale consists of six subscales that investigate auditory, visual, motor, oromotor/verbal, communication, and arousal functions. The operational definitions of VS/UWS, MCS, and EMCS is presented in Supporting Information Table 1. The total score ranges from 0 to 23, and a low score is associated with basal reflexes and rudimentary behavior, whereas a higher score is indicative of more intentional conduct (20). Each patient was examined on enrollment and once a week thereafter. The test was carried out at the same time each week by the same neuropsychologist.

Statistical Analyses

Study data were collected in the REDCap (Research Electronic Data Capture). Statistical analyses were performed using PRISM 8 (Graphpad). Data are presented as mean ± SD. $p < 0.05$ was defined significant. Effect of tVNS on physiological parameters (delta between prestimulus and 15 min after onset of stimulus) was calculated for each stimulation, and mean delta values were calculated for each individual. Statistical comparisons were performed at the group level, using a one sample *t*-test against a theoretical mean of zero.

RESULTS

During the study period (July to December 2018), there were a total of eight relevant candidates of whom two were excluded due to language barrier and one patient was unable to cooperate to the MRI scan. Among the five patients included in the study, three patients were rated in VS/UWS and two in the MCS state at the time of inclusion. The age-span ranged from 21 to 80 years with a median age of 67 years. The time from acquired TBI until onset of tVNS intervention ranged from 31 to 95 days with a median of 41 days (Table 1).

All five patients completed the eight-week experimental period. A complete four-hour stimulation was achieved in a median of 43 days out of the total 56 experimental days (range 28-52). Patients had a median of four days with zero stimulation (range 2-9; Fig. 2a). The main reason for lack of stimulation was changing staff not familiar with device and technical challenges such as an uncharged battery, recurrent skin/electrode contact problems due to hyperhidrosis. In a single case (patient 2), the device frequently lost contact with the skin, which was likely due to an unusual anatomy of the auricle, combined with the fact that the patient was motorically restless making it difficult to get a proper contact between the ear and the electrode. In two patients tVNS had to be paused for two to three days due to complications to TBI (onset of hydrocephalus and status epilepticus).

There was no effect of tVNS on physiological parameters when assessed before and 15 min after stimulation onset (ΔPulse: −0.52 ± 2.15 bpm, n = 5, $p = 0.62$; ΔMAP: 0.08 ± 2.01 mmHg, n = 5, $p = 0.93$; ΔSystolic BP: 0.14 ± 2.12 mmHg, n = 5, p = 0.89; Δdiastolic BP: 0.00 ± 2.02 mmHg, n = 5, $p = 0.99$) (Table 1).

One patient experienced intermittent itching of the ear during stimulation, though not to a degree that influenced the amount stimulation. The stimulation intensity was not reduced for any of the participants. Three patients exhibited improvement (>3 points) in the CRS-R and score during the experimental period. In more detail, two patients progressed into EMCS going from MCS and UWS before tVNS and one patient went from UWS into MCS during the eight weeks of tVNS (Fig. 2a; Table 1).

DISCUSSION

The purpose of the present study was to evaluate the feasibility and safety of tVNS in patients recovering from severe TBI. We found that tVNS four hours daily for eight weeks is a feasible and safe stimulation regime for patients in persistent VS/UWS or MCS admitted to a highly specialized neurorehabilitation department. The patients had little or no side effects to tVNS, none of which influenced total amount of stimulation received. Three out of five patients showed improvements CRS-R scores after the eight-week experimental period.

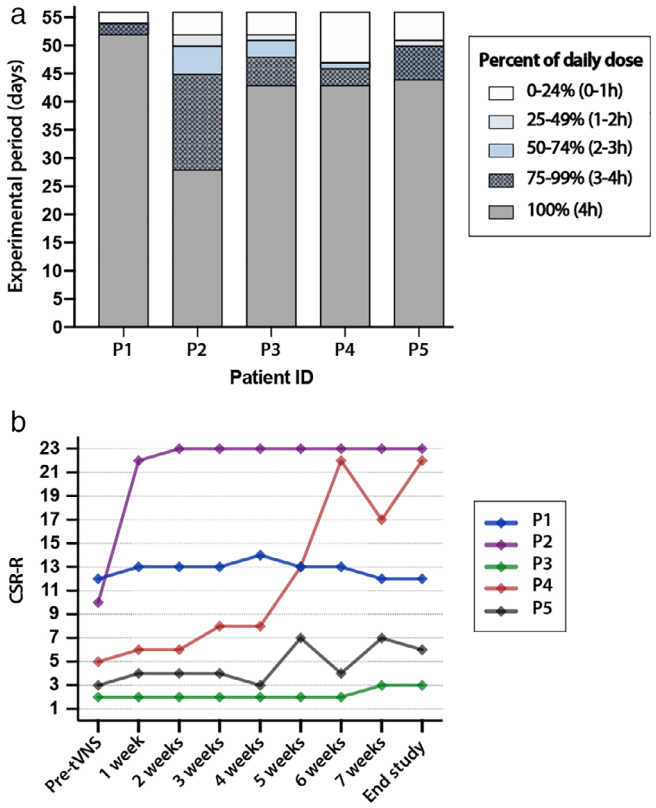

Figure 2. (a) Stimulation data, indicating daily dose achieved for individual subjects during the 56 days experimental period. (b) Individual Coma Recovery Scale-Revised (CRS-R) scores. [Color figure can be viewed at wileyonlinelibrary.com]

Transcutaneous stimulation of the cymba choncha has been verified to activate similar afferent brainstem- and cerebral networks as implanted VNS (14,21–23). However, tVNS specifically stimulates afferent vagus nerve fibers, and therefore theoretically minimizes the potential cardiac risks related to efferent fiber activation of the implanted VNS. In a recent review of tVNS for other neurological and psychiatric conditions, it is reported that tVNS is generally well tolerated, with the most common side effect being skin irritation at the stimulation site (24). In addition, Kreuzer et al. specifically showed that 10 weeks of tVNS did not cause arrhythmic effects assessed by electrocardiography (25). These findings align well with the results of the present study where the primary side effect was local itching around the stimulation site.

Post traumatic epilepsy (PTE) is a common sequela of severe TBI that usually develops in the post-acute phase. In the present study one patient had the first seizure four weeks before study onset, and another patient developed PTE during the eight-week study period. Several processes have been suggested to be involved in the epileptogenesis following the trauma, including maladaptive plasticity and modulation of cortical intrinsic neuronal excitability (26,27). It has been suggested that VNS may have a protective effect against PTE. As PTE is often medically difficult to control and rarely suitable for epilepsy surgery due to the

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Table 1. Summary of Patient Information and Behavior Assessments.

Patient ID	#1	#2	#3	#4	#5
Age/gender	67 years/Male	67 years/Male	24 years/Female	21 years/Male	80 years/Male
Primary brain injuries	Contusions, SDH, tSAH	Contusions, tSAH, ICH	Contusions, tSAH	Contusions, SDH	Contusions, SDH, t-SAH
Days in PTA before t-VNS	95	31	34	83	41
Behavior					
CRS-R before tVNS/end of study	12/12	10/23	2/3	5/22	3/6
State of consciousness before tVNS	MCS	MCS	UWS	UWS	UWS
State of consciousness end of study	MCS	EMCS	UWS	EMCS	MCS
Physiological parameters					
ΔPulse (bpm)	−0.4 ± 7.6	3.1 ± 11	−2.3 ± 9.0	−1.9 ± 6.3	−1.1 ± 5.5
ΔMAP (mmHg)	0.1 ± 5.7	−3.3 ± 8.8	2.0 ± 8.2	0.8 ± 5.4	0.8 ± 7.1
ΔSystolic BP (mmHg)	0.7 ± 9.9	−3.2 ± 11.8	2.7 ± 9.0	0.2 ± 5.9	0.3 ± 11
ΔDiastolic BP (mmHg)	−0.3 ± 6.0	−3.4 ± 10.1	1.6 ± 9.2	1.1 ± 6.5	1.0 ± 6.7
CNS active medicine					
Medicine before study onset	Chlorprotixene, melatonin	Melatonin, mianserin, morphine	Morphine, garbapentin	Levetiracetam, mianserin, melatonin,	Fentanyl
Medicine during experiment	Chlorprotixene, melatonin	Melatonin, mianserin, morphine	Morphine, garbapentin, baklofen	Levetiracetam, lamotrigine, mianserin, melatonin, morphine	Fentanyl, lamotrigine, phenytoin

Physiological parameters are listed as mean difference in pulse and blood pressure between pre-tVNS and 15 min after tVNS onset.
BP, blood pressure; CRS-R, Coma Recovery Scale-Revised; MAP, Mean arterial pressure; SDH, subdural hematoma; tSAH, traumatic subarachnoid hemorrhage; tVNS, transcutaneous vagus nerve stimulation.

widespread/diffuse character of the cortical injury, tVNS may therefore be a specific beneficial treatment option for PTE (28).

VNS may modulate brain function via various mechanisms. Recovery of consciousness is linked to restoration of thalamocortical and cortico-cortical connectivity (6). 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 as deep thalamic stimulation (29). The vagus nerve afferents terminate in the nucleus tractus solitarius 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 (30,31). In addition, tVNS modulates cortical excitability in healthy subjects through modulation of GABA-inhibitory circuits (32). Finally, animal studies have shown that VNS increases the expression of the brain-derived neurotrophic factor (BDNF) which is a key regulator of neuronal plasticity (33,34). Thus, evidence suggests that tVNS may potentially promote brain plasticity and connectivity between thalamic and cortical areas relevant for recovery of consciousness. However, mechanistic studies of VNS in patients with TBI are warranted.

There are some limitations to the current study. First, this is a relative short, single-arm, uncontrolled pilot study conducted in a highly specialized rehabilitation department where the patients have scheduled several daily sessions of interdisciplinary rehabilitation, which might have influenced the feasibility.

We tested a single four-hour stimulation regime, which has been used previously for other conditions, but other strategies may be more feasible, that is, several shorter daily sessions. Also, higher stimulation intensities and duration were not tested.

Three out of five patients presented with improved consciousness levels according to the CRS-R following tVNS. Some degree of recovery during rehabilitation following severe TBI is expected, and whether the increase of CRS-R presented in this study is higher than expected is speculative due to the relatively low sample size and lack of a control group. The study aimed to examine the feasibility and safety of tVNS in patients with severe TBI. Further studies, including a controlled randomized clinical trial, are needed to elucidate the clinical significance of tVNS following TBI.

In addition, we only assessed consciousness during the eight weeks of stimulation, and future studies should address whether the potential effects of tVNS on consciousness are permanent, or if termination of the stimulation causes regression to lower levels of consciousness. Also, other measures such as the Rancho Los Amigos Level of Cognitive Function Scale could supply additional information on patients' cognitive ability in future studies (35).

CONCLUSIONS

This study has demonstrated that tVNS delivered to the left cymba chonca is feasible and safe in patients with severe TBI. tVNS may be a promising supplementary candidate therapy for recovery after severe TBI being well tolerated, noninvasive, and inexpensive. Randomized controlled trials are needed to determine whether tVNS improves the recovery of consciousness after severe TBI.

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Authorship Statements

Anne Sabers, Christian P. Hansen, Ingrid Poulsen, Melika Moghiseh, and Christoffer M.L. Øland designed the study. Christoffer M.L. Øland, Jakob Hakon, Ingrid Poulsen, and Melika Moghiseh conducted the study, including patient recruitment, data collection, and data analysis. Jakob Hakon prepared the manuscript draft with important intellectual input from Anne Sabers, Christian P. Hansen, Ingrid Poulsen, Melika Moghiseh, and Christoffer M.L. Øland. The manuscript was critically revised by all authors, and all authors approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENTS

In this work, the authors have performed an open-label trial to determine if transcutaneous VNS is safe and feasible to use in patients that have had severe traumatic brain injuries and are in a reduced state of consciousness. The authors demonstrate no serious adverse events related to tVNS, and this works sets the stage for future randomized and blinded clinical trials that must take place to determine whether tVNS is efficacious in promoting recovery.

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A short, concise paper. Well written and easy to read. Scientifically sound.

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