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# Feasibility, safety and efficacy of transauricular vagus nerve stimulation in a cohort of patients with disorders of consciousness

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Vagus nerve stimulation
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*Dear Editor*

Disorders of consciousness (DOC) are one of many neurological diseases for which there is still no curative treatment. The majority of therapeutic options performed in these patients have focused on accelerating clinical recovery through pharmacological interventions, environmental stimulation or, more recently, using neuromodulatory brain stimulation techniques, among others [1]. Vagus nerve stimulation (VNS), has recently been used in neurorehabilitation based on its effects on cortical plasticity [2]. Two recent case reports using VNS have shown promising results for increasing the level of consciousness in two patients in Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS) after severe traumatic brain injury [3,4]. However the role of VNS in DOC has not been systematically studied.

We prospectively enrolled chronic adult patients with DOC who were more than six months post injury, and were receiving rehabilitation in our facility between May 2018 and January 2019. We included only patients with no changes in at least five Coma Recovery Scale-Revised (CRS-R) scores performed weekly in the four weeks before inclusion. The experimental intervention consisted of forty, 30-minute transauricular (left tragus) VNS (Parasym® CE) sessions administered twice a day (five days per week). Stimulation parameters (sinusoidal waveform; pulse width: 250 us; frequency: 20 Hz; amplitude: 1.5 mA) were chosen according to previous studies [4].

All patients included in the study were assessed with the CRS-R at baseline (T0), week 1 (T1), week 2 (T2), week 3 (T3), and week 4 (T4: end of treatment) with a further follow-up 4 weeks after the termination of stimulation. Each subject's heart rate (HR) and blood pressure (BP) were monitored during all treatment sessions. Additionally, during the first VNS session, subjects were monitored by a multimodal monitor that included continuous ECG.

Our primary outcome measure was the number of subjects presenting any improvement in at least one item in the CRS-R evaluation at one time point. We also recorded the type and number of behavioral responses. Safety was primarily assessed by analysis of treatment-emergent adverse events (TEAEs). The main feasibility endpoint was the number of participants who completed the therapy protocol.

The final sample included 14 patients aged 40.2 (SD: 16.1) years (12.1 ± 6.4 months postonset) with acquired brain injury. Six patients were in VS/UWS and eight patients were in Minimally Conscious State (MCS) (Table 1).

Although the clinical diagnosis remained unchanged during the study, we found a significant improvement in total CRS-R scores at the end of the 1-month follow-up ($p = 0.04$). None of the VS patients at admission showed any change in the CRS-R total scores, while five of the eight MCS patients at admission showed an improvement during the duration of the study ($p = 0.02$). The CRS-R improved in only one MCS patient at the end of the treatment (T4). This patient and four more subjects showed improvement at one month follow-up (T4+4). Four responders showed an improvement in only one CRS-R subscale (motor subscale: $n = 3$; visual subscale: $n = 1$), while one responder showed improvements in more than one CRS-R subscale.

Eight mild AEs were reported from a total of 560 sessions performed. All AEs were considered common medical conditions without obvious relations to VNS. No relevant ECG alterations were observed. HR and BP were not modified by VNS ($p > 0.05$ in all comparisons). Two patients missed one of the VNS sessions programmed for nonclinical reasons. The missed session was replaced in these two cases at the end of the stimulation period.

To our knowledge this is the first reported case series addressing feasibility, safety and efficacy issues in a sample of patients with DOC, including VS/UWS and MCS patients of different etiologies and chronicity. Our results suggested that the use of transauricular VNS is feasible and preliminarily safe in DOC patients and that it may improve behavioral responses when applied to MCS patients. Neurophysiological and neuroimaging data have suggested that clinically defined MCS patients show partially preserved brain connectivity and maintain limited but effective cortical plastic properties, which may allow them to present better behavioral responses and better clinical responses to therapeutic interventions than VS/UWS subjects [5]. This aspect could explain the differences in improvements experienced by our MCS patients when compared to those in VS/UWS.

Four of our five responders showed appreciable clinical improvement in the motor subscale of the CRS-R. Different studies have shown that VNS is able to effectively modulate motor responses and facilitate motor learning through GABAergic neuromodulation mechanisms [6]. The GABAergic neurotransmission system has also been implicated in the clinical improvement

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**Table 1**
Results.

| ID | Age (Years) | Gender | Etiology | Disease Duration (Months) | CRS-R (Diagnosis) T0: Baseline | CRS-R (Diagnosis) T4: End of treatment | CRS-R (Diagnosis) T4+4weeks: Follow-up |
|---|---|---|---|---|---|---|---|
| 001 | 65 | Female | Hemorrhage | 27 | 6 (VS/UWS) | 6 (VS/UWS) | 6 (VS/UWS) |
| 002 | 45 | Male | Hemorrhage | 7 | 6 (VS/UWS) | 6 (VS/UWS) | 6 (VS/UWS) |
| 003 | 20 | Male | Traumatic | 10 | 8 (VS/UWS) | 8(VS/UWS) | 8 (VS/UWS) |
| 004 | 70 | Female | Anoxia | 12 | 8 (VS/UWS) | 8(VS/UWS) | 8 (VS/UWS) |
| 005 | 28 | Male | Anoxia | 21 | 8 (VS/UWS) | 8(VS/UWS) | 8 (VS/UWS) |
| 006 | 39 | Male | Anoxia | 6 | 8 (VS/UWS) | 8(VS/UWS) | 8 (VS/UWS) |
| 007 ® | 30 | Female | Hemorrhage | 8 | 8 (MCS-) | 8 (MCS-) | 9 (MCS-) |
| 008 ® | 35 | Male | Traumatic | 9 | 9 (MCS-) | 9 (MCS-) | 10 (MCS-) |
| 009 | 38 | Male | Traumatic | 10 | 10 (MCS-) | 10 (MCS-) | 10 (MCS-) |
| 010 ® | 21 | Male | Traumatic | 15 | 10 (MCS-) | 10 (MCS-) | 12 (MCS-) |
| 011 ® | 21 | Female | Traumatic | 12 | 11 (MCS-) | 11 (MCS-) | 12 (MCS-) |
| 012 | 45 | Male | Traumatic | 7 | 12 (MCS-) | 12 (MCS-) | 12 (MCS-) |
| 013 | 46 | Female | Traumatic | 20 | 14 (MCS-) | 14 (MCS-) | 14 (MCS-) |
| 014 ® | 60 | Female | Anoxia | 6 | 14 (MCS+) | 15 (MCS+) | 17 (MCS+) |

CRS-R, Coma Recovery Scale-Revised; MCS, Minimally Conscious State; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome. Responders are marked with an R.

experienced by these patients after the administration of zolpidem and intrathecal baclofen [1].

The benefits of VNS require time to emerge. Basic principles of experience-dependent neural plasticity suggest that intensive repetition over time is necessary for a therapeutic procedure to induce and sustain clinically significant changes [7].Similarly, clinical improvements after repetitive tDCS have been described in DOC patients even years after the brain injury [8], suggesting that although some neurophysiological changes can be detected after few sessions, persistent clinical changes may require a continuous application of the technique to be detected.

The evaluation of cardiovascular parameters and the low frequency of AE detected in our study confirms that tVNS, considering the stimulation parameters used here, is also a safe and well-tolerated procedure in patients with DOC.

Our results should be interpreted with caution considering the lack of a control group and the small sample size. However, the percentage of responders was unusual high considering the chronicity required for inclusion [9]. Additionally, all subjects included showed no noticeable behavioral changes according to CRS-R scores in the month before inclusion. Finally, the pattern of responders described here is consistent with what is already known in the literature regarding brain stimulation in patients with DOC [5,8,10].

In conclusion, this exploratory study provides preliminary data suggesting that transauricular VNS could be a safe and effective tool to facilitate consciousness recovery in severely brain-injured patients. These promising findings deserve confirmation in a well-controlled clinical trial, especially considering that this technique seems to be safe, affordable, technically easy to handle and well-tolerated in this population.

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## Submission declaration and verification

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## Declaration of competing interest

None.

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