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The use of epidural spinal cord stimulation in patients with chronic disorders of consciousness – neuroimaging and clinical results

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Abstract. – OBJECTIVE: Chronic disorders of consciousness are considered as a serious unresolved problem complicated by significant medical, social, and economic burden. Therefore, improving the conditions and facilitating the rehabilitation management of these patients is of particular interest. In recent years, interesting results of the use of spinal cord stimulation in patients with chronic disorders of consciousness appeared in the world literature, which makes the use of this technique promising in this category of patients.

PATIENTS AND METHODS: We analyzed the results of high cervical spinal cord stimulation, both, in tonic and "Burst" modes, in 21 patients with chronic disorders of consciousness and severe spasticity managed in the last two years in FRCC ICMR. In 9 of them pre- and post-stimulation fMRI before and right after the stimulation was also performed for brain functional connectivity assessment.

RESULTS: Improvement of the consciousness level was observed in 38.1% (n = 8) and a decrease in spasticity was obtained in 52.4% (n=11) of the patients. The difference in CRS-R score before and after spinal cord stimulation was statistically significant (p=0.028). The fMRI results revealed an increase in functional connectivity of the right anterior insula with several areas that are part of the Dorsal Attention, Visual and Default Mode networks after spinal cord stimulation.

CONCLUSIONS: Epidural spinal stimulation at the upper cervical spine level demonstrated its effectiveness in patients with chronic diseases of consciousness of various etiology. Evaluation of the effect of specific stimulation modes requires further controlled study in larger group of patients.

Key Words:
Chronic disorder of consciousness, Spinal cord stimulation, Burst technique, fMRI.

Introduction

The improvement of neuroresuscitative and neurorianimatory techniques in the last years has led to an exponential increase of the phenomenon of persistent vegetative state and minimal consciousness state (PVS-MCS) among severe brain damage survivors. Individuals who suffered from a significant damage of the central nervous system, if properly cared for, can still maintain functioning areas of the brain which however do not consent them to establish a valuable contact with the environment, so they are totally dependent. There should be no doubts about the ethical obligation to assist them in the best possible way, however this represents a tremendous cost for the society and mostly for the close relatives in terms of emotional stress, life reorganization and economic loss. Moreover, their total dependence from caregivers significantly impacts on their survival, so techniques and advanced protocols for maximizing their residual brain functions and helping them to improve significantly their clinical condition can lead to better quality of their clinical status and ultimately to longer survival and easier and at the same time more efficacious management routine. In the last years several indications appeared in the relevant literature[1-3] about the potential positive impact of dorsal col-

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Table I. Types of chronic impairment of consciousness in the study group.

CDC types in the study group	Number of patients, n	Percentage of patients (%)
PVS	7	33.3%
MCS "-"	8	38.1%
MCS "+"	5	23.8%
Emergence from MCS	1	4.8%
Total	21	100%

umn spinal neurostimulation for improving the clinical condition of patients with highly compromised consciousness. These indications are based as a matter of fact on single case reports or at the most on a very limited number of studied patients. Whilst numerically relevant patients' investigations are scarce[3].

We started managing systematically patients with highly compromise conscious state in the last 2 years using spinal neuromodulation coupled with intense rehabilitation. In the present study we report our short-term results of the clinical management of 21 patients with chronic disorders of consciousness due to severe brain damage. Also, the results of fMRI connectivity analysis, conducted in 9 patients from this group, are here reported.

Patients and Methods

We retrospectively analyzed results of test spinal cord stimulation (SCS) in 21 patients with chronic disorders of consciousness due to severe brain damage of various etiologies who underwent treatment and rehabilitation at the FSCC RR in the years 2020 and 2021. The main indication for test SCS was severe spasticity. Chronic disorders of consciousness were a concomitant condition in this group of patients and all interventions in the group had an ethical approval of local ethical committee. In total, test SCS was performed in 11 men (52.4%) and 10 women (47.6%). The average age of patients was 36.4 ± 11.6 years.

Chronic disorders of consciousness were represented by persistent vegetative state (PVS) and various types of minimally conscious state (MCS). The most common type of CDC in the study group was MCS "+" (8 patients, 38.1%). These data are showing in Table I.

All patients were assessed by Revised Coma Recovery Scale (CRS-R) before and after the procedure. The median score of the CRS-R before the neuromodulation was 7 points [5 points; 11 points].

The most common etiological factor for CDC was traumatic brain injury (10 patients, 47.6%). Other etiological factors for CDC were anoxic brain injury and various types of strokes. The etiology of brain damage in patients in the study group is shown in the Table II.

The research was approved by the local ethical committee. The relatives of the patients were informed about potential risks and benefits of the procedure before the electrode implantation.

In this group we implanted eight-contact electrodes (Octrode®) on the cervical epidural spine under intraoperative X-Ray control. The procedure was performed according to the technique described in the accompanying documentation by the medical device manufacturer (Abbott Medical). Immediately following implantation, the electrode was connected to an external pulse generator *via* testing cable for further mode selection.

During the test period of neuromodulation, we used tonic mode, "Burst" mode or both, depending on the individual response to stimulation. The duration of the neuromodulation test was

Table II. Types of etiology for CDC in the study group.

CDC etiology	Number of patients, n	Percentage of patients (%)
Anoxic brain injury	7	33.4%
Traumatic brain injury	10	47.6%
Ischemic stroke	1	4.7%
Hemorrhagic stroke	3	14.3%
Total	21	100%

determined according to the individual patient's response to stimulation and the risk of infectious complications.

Full neurological examination was performed daily by a neurologist not aware of the stimulation technique used in the individual patient. The result of the stimulation was considered as the best result achieved during the entire course of SCS. Clinical assessment was performed according to the CRS-R scale.

Functional MRI Scanning Parameters

Resting-state functional and anatomical images were acquired the day before the installation of the stimulation system and right after its removal using a 1.5 T Siemens Essenza® (Siemens, Ltd., Munich, Germany) MRI scanner with an eight-channel head coil. Each resting state functional run consisted of 300 T2*-weighted echoplanar images (EPIs). The imaging parameters were as follows: 3.9 × 3.9 mm in-plane voxel size, covering the whole brain volume 4.0 mm slices, interslice gap 0.8 mm, repetition time (TR) = 3670 ms, echo time (TE) = 70 ms, 64 × 64 matrix. In addition to the functional images, we collected a high-resolution T1-weighted anatomical scan for each participant (192 slices, resolution 1 × 1 × 1 mm, TR = 10 s, TE = 4.76 ms, 256 × 256 acquisition matrix). Patients were not sedated during the scanning procedures.

Functional Connectivity Analysis

The data were processed using the CONN functional connectivity toolbox (http://www.nitrc.org/projects/conn), version 19c and SPM12 (http://www.fil.ion.ucl.ac.uk/spm). The first 2 dummy volumes were excluded from analysis. The preprocessing procedure consisted of realignment of functional images (motion correction), slice timing correction, co-registration, segmentation of structural data, normalization into standard stereotactic Montreal Neurological Institute (MNI) space, outlier detection/scrubbing using the artifact detection tool (ART) (http://www.nitrc.org/projects/artifact_detect), and spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum. Denoising was performed by removing the following confounders by linear regression: the blood-oxygen-level dependent (BOLD) signal from the white matter and CSF masks (5 principal components of each signal); scrubbing (the number of regressors corresponded to the number of identified invalid scans); motion regression (12 regressors: 6 motion parameters16 first-order temporal derivatives). The resulting signals were band-pass filtered at 0.008-0.12 Hz.

Statistical Analysis

Data collection and statistical processing were carried out using the STATISTICA 10 (StatSoft) program. The results of the study were considered statistically significant at p-value < 0.05.

Using the CONN Networks atlas (functional connectivity toolbox), which generates 32 ROI's, we conducted a ROI-to-ROI analysis to create a 32 × 32 functional connectivity maps. A bivariate correlation was used to determine total linear temporal associations between each of the resulting 992 ROI-to-ROI functional connections. Second-level analyses of group differences in functional connectivity between 1st and 2nd fMRI-session (contrast post-SCS minus pre-SCS) was conducted through the CONN toolbox and FDR-corrected, $p < 0.05$, one-way. As a nonsense covariate statistical model included the number of days of stimulation.

Results

Electrodes were placed at cervical spine level (C2 -C5, C3 -C6) in all patients (n = 21). The median duration of SCS period in the study group was 4 days [3 days; 5 days]. Tonic mode was used most frequently (12 patients, 57.1%). The other neuromodulation modes here utilized were "Burst" (5 patients, 23.8%) and a combination of "Burst" and tonic modes (4 patients, 19.1%). Data are summarized in Table III.

Table III. Distribution of neuromodulation modes in the study group.

Neuromodulation mode		Number of patients, n	Percentage of patients (%)
Tonic		12	57.1%
"Burst"		5	23.8%
Mixed	Tonic followed by "Burst"	3	14.3%
	"Burst", followed by Tonic	1	4.8%
Total		21	100%

Positive changes in the level of consciousness during neuromodulation such as appearance of gaze fixation, enhanced nonverbal contact, emergence of various emotional reactions, appearance of attempts to follow simple instructions or follow simple instructions with full compliance were observed in 8 patients (38.1%). Decrease in spasticity was obtained in 11 patients (52.4%).

The median score of the CRS-R after neuromodulation increased to 8 points [6 points; 12 points]. The difference in CRS-R score before and after SCS was statistically significant (p=0,028).

Functional MRI was performed in 9 patients. Five patients were stimulated in tonic mode, one patient underwent "Burst" mode stimulation, and one patient was stimulated in mixed mode (tonic, then "Burst"). We observed increased functional connectivity after SCS-therapy in comparison to the before SCS-therapy condition between the following resting networks: Visual, Dorsal attention, Salience and Default mode network. Table IV shows the differences in functional connectivity between post-SCS and pre-SCS session at the network and subnetwork level, as well as t-values and adjusted p-values.

The right anterior insula (within the salience network) was the main node of increase in functional connectivity after SCS-therapy. There was an increase in functional connectivity of this area with visual areas (Salience - Visual network connection) as well as with the posterior cingulate cortex (Salience – Default Mode network connection) and left anterior eye field (Salience – Dorsal Attention network connection). There was also an increase in functional connectivity between the cuneus and right frontal eye field (Visual – Dorsal Attention network connection) as compared to the examination before SCS-therapy.

4 patients (19%) in total received a permanently installed neurostimulator due to the favorable effect of the stimulation technique.

Discussion

The main finding of the present investigation was an increase in functional connectivity of the right anterior insula with several areas that are part of the Dorsal Attention, Visual and Default Mode networks. The insula region, according to numerous literature reports[4-7], is involved in a wide range of functions such as visceral sensitivity, interception, pain, motor, and a wide range of cognitive functions. Also, several studies[8-11] confirm the association of this area with wakefulness levels. Moreover, a study of Zhang et al[12] showed that increased functional connectivity between the insula, inferior parietal lobe and temporal pole is associated with recovery of consciousness in patients with DOC. Thus, our preliminary results showing an increase in the functional connectivity of the insula region may indicate a possible positive effect of SCS-therapy in patients with chronically impaired consciousness.

There are albeit scarce indications in the literature on the possible positive effect of high cervical spinal epidural stimulation on the reticular system, thus justifying the use of this technique in PVS/MCS patients. We demonstrated in our study that functional connectivity can be improved mostly at the level of anterior insula, thus giving some possible basic explanations on the potential usefulness of the technique used in the present patients.

The "Burst" mode of SCS is widely applied in patients with chronic neuropathic pain syndrome, however its use in patients with chronic disorders of consciousness has not been described yet in the literature[13,14]. There were five patients stimulated in "Burst" mode alone and four patients stimulated in mixed modes in our group. It is known that cyclic Burst stimulation, in connection with tonic mode, allows to save the charge of the generator, which extends its service life before changing[13,14]. The usage of Burst stimulation in CDC patients requires further controlled research

Table IV. Differential functional connectivity between post-SCS and pre-SCS fMRI session.

Functional connection (ROI–ROI), contrast after SCS minus before SCS	Network-level connections	t-value	p-value, corr
Anterior Insula r - Frontal eye field l	Salience -Dorsal attention	5.71	0.001863
Cuneus - Frontal eye field r	Visual - Dorsal attention	5.69	0.001863
Anterior Insula r - Occipital cortex	Salience - Visual	5.47	0.001863
Anterior Insula r - Cuneus	Salience - Visual	4.98	0.002403
Anterior Insula r - Middle occipital gyrus l	Salience - Visual	3.68	0.008696
Anterior Insula r - Posterior cingulate cortex	Salience - Default mode	3.60	0.008696

in a larger group of patients, in order to assess its potential useful effect on the recovery of consciousness. Furthermore, it would be important in our opinion to evaluate the specific contribution of spasticity and chronic pain relief in PVS/MCS patients and, as a consequence, a possible positive effect of Burst SCS on the recovery of consciousness.

In nine patients we performed a detailed fMRI evaluation of the residual functions in apparently no-functioning brains, and we demonstrated objectively that revivable functions can be present and visually demonstrated with the technique here described, a fact which to our opinion gives further strength to the present study.

Actually, the resting state fMRI protocol here used gives the possibility of objectively evaluating the effectiveness of the various management protocols, electro stimulation based, TCS and/or pharmacological ones, in these very difficult-to-treat patients.

Conclusions

Epidural spinal stimulation at the upper cervical spine level demonstrated its effectiveness in patients with chronic diseases of consciousness of various etiology. Evaluation of the effect of specific stimulation modes requires further controlled study in larger group of patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

All interventions in the group obtained the ethical approval from the Ethics Committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology.

Informed Consent

All patients or their legal representatives provided written informed consent.

Authors' Contribution

A.N. Vorobyev: conceptualization, investigation, methodology, writing- original draft, data curation. M.D. Varyukhina: methodology, writing- original draft, formal analysis, data curation. L.A. Mayorova: conceptualization, investigation, methodology, writing- original draft, formal analysis, data curation. K.M. Puzin: data curation, resources. M.L. Radutnaya: data curation, resources. A.A. Yakovlev: conceptualization, supervision, writing-review and editing. A. Spallone: supervision, methodology, writing-review and editing.

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