Dorsal Column Stimulation in Persistent Vegetative State (PVS)

Tetsuo Kanno, Morita Isao, Sachiko Yamaguchi, Tetsuya Yokoyama, Yoshifumi Kamei, S.M. Anil, Kostadin L. Karagiozov

Department of Neurosurgery, Fujita Health University 1-98, Dengakugakubo, Kutsukake-cho Toyoake, Aichi, 470-1192, JAPAN

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Abstract

Objectives: The problem of the possibility for treatment of patients in vegetative state remains grossly unresolved, and Dorsal Column Stimulation (DCS) seemed promising in some studies, requiring further attention. Material and Method: A prospective controlled study for 20 consecutive years (1986-2005) was performed on the effect of DCS in 214 patients in persistent vegetative state, resulting from global anoxia, stroke and head injury. After confirming the condition of PVS, a dorsal column stimulator at the C2-C4 level was implanted, stimulating according to a protocol 15min on / 15 min off during day-time only.

The results were evaluated with a scale, detecting signs of awareness of self and surrounding. Results: Excellent and positive results were obtained in 109 of 201 patients(54%), but better in those aged below 35, in PVS of traumatic origin and with rCBF over 20 ml/100g/min. Conclusions; These findings indicate that further evidence based oriented studies are needed to detect those who are going to benefit from this treatment method.

Dorsal Column Stimulation in Persistent Vegetative State (PVS)

Severe brain injury victims, in their huge proportions, and adding to them the patients suffering from massive stroke, anoxic/hypoxic and other massive axonal affections, constitute a numerous population in our society, of which significant part is hopelessly disabled. One of the resulting conditions of such severe brain damage is the "persistent vegetative state", described by Jennett and Plum in 1971 as lack of awareness for self and surrounding environment, despite preservation of autonomic, brainstem and sleep/wake cycle functions. The decision to declare vegetative state as permanent is not easily determined, but an analysis of the outcome in such patients has given clear indications that 3 months after in non-traumatic, and 12 months after in traumatic ethiology, the vegetative state can be considered permanent or persistent(1). The diagnosis of PVS requires the presence of certain criteria (2,3) and expert observation of the patient over sufficient period of time is needed to avoid any misinterpretation of the evidence of awareness(4). One important condition to differentiate from is the minimally conscious state(5), where minimal, but definite evidence of awareness exists and it can lead to recovery in PVS. The background pathology in PVS differs with the cause, and changes affect to variable, but usually significant extent the cortex, sub-cortical white matter and thalami, most consistently the last two locations (6). In all this existing pathological variability
we can arbitrarily create two sub-groups, in which the predominant CNS damage is either global or multifocal.

These two types to great extent reflect the underlying causes of damage (global ischemia and anoxia tend to produce more diffuse “global” type, contrary to head injury. Stroke and similar affections, that produce multiple, but more circumscribed, “Multifocal” affections. Some brain-stem reflexes can be intact clinically in PVS patients. Recent functional imaging has confirmed that some cortical areas, as islands, are active in there patients (7).

The approach to the treatment of PVS, in any of its variations, most often focusing on systematic sensory input, has not yet gained necessary level of evidence to recommend evidence based treatment(8). The conceptual basis of applying sensory stimulation, one of the frequently used methods, is still poorly understood and aims to activate as a background the non-specific brain-stem systems or apply selective type of input and enhance selective attention.

The scientific community working on the problem has been attracted by the observation of promising results when applying more or less specific modalities of stimulation at different points of the sensory systems. The stimuli have been applied externally or by internalized electrodes. Deep brain stimulation has been used by Cohadon F, Richer E in 1993(9), and more recently, by Yamamoto, T and Katayama, Y,(10) finding improvement in such paritnes after stimulation of CM-pf thalamic nuclei or mesencephalic reticular formation. Dorsal column stimulation(11,12), median nerve stimulation by Cooper, J, Jane JJ, et al. in 1999(13) and external sensory stimulation of different modalities (from simple stimuli to music) were applied with promising results too.

Finding the most appropriate way of conveying a massive sensory stimulation input to the non-specific systems without having to internalize electrodes in the brain stem, as well as the clinical observation of the senior author that PVS patients treated with DCS for spasticity also improve cognitively (14), lead to the current approach of clinical research on the problem since 1986 by the team of the senior author(15,16,17,18).

Material and Methods

Population data

For the period 1986-2005, 214 patients in PVS have been treated with DCS. The brain affection was the result of head injury, stroke and global anoxia (Table 1). All patients met the accepted criteria for PVS and were at least 3 months in non-traumatic and 1 year in traumatic cases after the causing primary brain damage (as adopted in [1]). For the admission criteria, although on random basis from the area from which patients are attended by the department, it was not possible to clear them from possible existing biases emerging from other sources of referral, type of practice, and other uncontrollable by the researchers factors. The method of treatment was explained to the legally representing and often to other close relatives in view of the perspectives and expected outcome of the PVS, the risks associated with the method of treatment and the current status of understanding of its effects on the patient.
With the realistic expectations explained, they were providing an informed consent, compatible and on the basis of the legal and ethical committee regulations adopted at our institution, where the trial was approved. These regulations conform to the internationally adopted ethical standards for the performance of clinical treatment and research (The Declaration of Helsinki).

The clinical evaluation was done by at least two teams of neurosurgeons and the family was interviewed for the presence of any awareness in the appropriate way. The patients condition was scored according to the adopted at our institution scale (Table 2). Family members were also instructed to observe their relatives under treatment by following their behavior to external stimuli that are familiar to them. Some patients were video monitored to detect certain responses. The patients had an EEG study, CT and MRI of the brain, and SPECT r-CBF studies.

**Implantation of the stimulator**

Patients were operated under general anesthesia, in prone position with the neck fully flexed. The "Medtronic Itrel 3 System "(Medtronic INC. USA) was used in the latest group of patients, once it became available in Japan (after the year 2000). Before that the Resume, followed by the X-trel systems, were used. A5-cm median incision was made on the posterior neck reaching down to the 7th cervical spinous process level (Fig1).

After dissection of the muscles away from the midline, laminotomy of the 5th cervical vertebra was performed. Electrodes were inserted under fluoroscopic control with a C-arm through the epidural space along the mid-line at the 5th cervical level toward the cranial side and indwelled at the 2nd, 3rd and 4th cervical levels. The leads were passed under the skin, and connected to the battery and receiver subcutaneously implanted in the lateral abdominal region [Fig.2,3].

The general condition of all patients, if no complications of the PVS have emerged pre-operatively, was permitting the surgery to be tolerated well. The internalization of the stimulator was very convenient for better daily care and the reduction of the risk of infection.

**Stimulation Protocol**

After recovering over the immediate post-operative period, the stimulation was usually initiated 3-7 days after surgery. A daily stimulation for about 12 hours during day time was performed, Referring to the cranial and caudal sides as the negative and positive poles, respectively, the posterior columns were stimulated at an amplitude of 2.0-3.0 V. a rate of 70Hz and pulse width of 120 microsecs using a cyclic mode of 15 minutes on and 15 minutes off. The stimulation parameters were chosen as sub-threshold, as we usually obtained motor response at or above 4V.

**Postoperative evaluation**
The patients were followed-up by their treating neurosurgeons, nursing staff and relatives independently, and a change in the condition was accepted if reported by all observing parties.

The evaluation postoperatively was done according to the same criteria as pre-operatively. The thorough observation by the clinical teams and relatives was recorded daily. We adopted a system of result grouping according to the criteria in Table 2, at 3 and a half months after the beginning of stimulation, even if some of the changes were observed as early as 4 weeks after implantation. In this way three groups of treated patients were obtained according to results: excellent, positive and unchanged.

**Results**

Out of the 214 patients, 13 were lost to follow-up. In 2 patients the implanted stimulation devises had to be removed because of tissue reactions. The distribution of the results according to etiologies is given on table 3/.

At a preliminary analysis there was a clear tendency for better results in the patients age groups below 35 years at the time of beginning the stimulation (table 4).

The excellent and positive results in different etiology groups also differed in relation to the age (Table 5).

From table 4 is evident that the excellent + positive results in age over 35 are only 39.5% (10.5 + 28.9%), compared to age below 35 where this percentage is 63.2 (24+39.2%). On table 5 is also seen a predominance of excellent + positive results in PVS in age group below 35 with traumatic etiology -60 out of 68 pts with trauma that improved (88.2%) were below 35, compared to patients with other etiologies where the young age factor did not play such important role.

The r-CBF SPECT studied were performed in 58 patients. There was a relation between r-CBF levels and the effect of stimulation. An increase was seen more often in patients, where the rCBF pre-operatively was at values more than 20 ml/100g/min in average (Fig.4)

**Discussion**

One of the main reasons for the absence of significant breakthrough in the treatment of PVS is related to the lack of understanding of those basic mechanisms of consciousness, whose damage is responsible for the resulting deficit. Presuming the absence of proper supply of sensory input to certain critical for awareness systems in the brain, the investigators have provided different methods for sensory stimulation (9, 10, 13). This stimulation varies in sensory modality and the point of the sensory systems where it inputted. External and internal methods of applying the stimulation have been used.

With the aim of supplying enough powerful and focused stimuli to specific parts of the sensory systems, external stimulation has been replaced with internal, via electrodes in direct contact with sensory pathways. The methods applied the stimulation via cortical or brainstem stimulation(9,10) To avoid the bigger
invasiveness of intracerebral electrodes, our study used spinal epidural electrodes. On the other hand, it provided significantly more powerful input of sensory stimulation than the external somatosensory applied by other authors (13). Its safety has been broadly investigated as this technique has been standardized before for other types of indications (spasticity, pain) and its application was directly transferred for the purpose of treating PVS.

The design of a study on the treatment of PVS faces several major obstacles, not resolved by our study either. In an analysis by Lombardi, F. et al. in 2002 (8), have been found 3 controlled clinical studies, one only randomized, insufficient to conclude for effectiveness of sensory stimulation in PVS. The uncertainty of effectiveness and the ethical issues related to the irreversibility of the PVS, often specific to the cultural and social background, made this study to be conducted in a way. Requiring close collaboration between physicians and relatives, without the possibility of blinding and properly randomizing it. In spite of these limitations, the possibility of continuing performing the study, permitted by relatives and authorities, allowed an unique observation of a group of patients under a rarely performed method of treatment, as it was indicating effectiveness. The current role of the preoperative investigations is only of a reference for the postoperative findings. They however can be used as criteria in the proper selection of patients where the results can be optimal.

The detailed structural and functional imaging of the brain can yield also further clues for the understanding of consciousness and the mechanisms of its affection in PVS. The possible mechanisms interfering with the ability to interact with the surrounding are multiple and very little is known on the relation of DCS and the effects it produces on the systems presumably involved in the condition. The classical inference of the relation of the reticular formation has been through the whole course of studying this problem. There have been reports that cervical DCS increases rCBF-in animals and humans (19), and by that may improve the background for neuroplasticity. The better results in patients who are younger favor this possibility. The mechanisms of affecting the CBF are probably mediated by central (brainstem) pathways (20) and the contribution of the activating effect of residual, functionally active cortical areas, unaffected by the etiology cortical and thalamic areas by stimulating the non-specific sensory pathways is another possible mechanism. That is indicated by the better response to the DCS treatment of patients with traumatic and to some extent, CVD etiology, where such incompleteness and multifocal type of affection is expected. That is also in conformity with the beneficial effect of similar, but different in type of stimulation other studies, where periaqueductal, non-specific thalamic and reticular structures are activated (21).

Some higher level of neurotransmitters and alpha-1 sympathetic activation may play a role in this process, also increasing the CBF(20,22). Unfortunately until now we cannot indicate with certainty on the most probable mechanisms, and more intrinsic and detailed structural and functional investigational methods will be awaited to be applied. That leaves our results even promising, empirical in nature.
Conclusions

The DCS has beneficial effect of the reactivity of some PVS patients to stimuli, indicating elements of cognition, with the real process behind remaining questionable if this improved reactivity is the background of the natural recovery of awareness to external stimuli.

However, per se, it leads to functional improvement, facilitating patients care and making them more easily to re-integrate to their home environment.

There are apparently better expectations for patients younger that 35, of traumatic etiology and average rCBF more than 20ml/100g/min. As the current study indicates promising effects, it appears justifiable further conduction of studies in the same direction with design expecting better levels of evidence.

Tables

Table 1: Total number of cases-age distribution and cause (201 cases)

<table>
<thead>
<tr>
<th>Cause</th>
<th>&lt; 35 Yrs</th>
<th>&gt; 35 Yrs</th>
<th>Total (100%-201 pat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAUMA</td>
<td>83</td>
<td>23</td>
<td>106 (52.7%)</td>
</tr>
<tr>
<td>CVD</td>
<td>12</td>
<td>33</td>
<td>45 (2.4%)</td>
</tr>
<tr>
<td>ANOXIA</td>
<td>30</td>
<td>20</td>
<td>50 (24.9%)</td>
</tr>
</tbody>
</table>

Table 2: 
Evaluation of Results: The patients best signs should be as below:

**EXCELLENT RESPONSE**
When the patient has a purposeful movement like –
- A behavioral expression
- Swallowing when food or water is placed in the month
- and / or spoken meaningful words

**POSITIVE RESPONSE**

1. Emotional Response
The reaction towards various stimuli is rich emotional expression

2. Visual Response
The patient has an eye ball movement and a gaze consistently toward the visual stimulus and / or seeking response toward the visual stimulus moving slowly in the visual field

3. Some pattern of opening and closing eyes when a specific stimulus is detected
Table 3: Distribution of single or multiple clipping with each aneurysm type

<table>
<thead>
<tr>
<th></th>
<th>Trauma</th>
<th>CVD</th>
<th>Anoxia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent and Positive</td>
<td>68</td>
<td>22</td>
<td>19</td>
<td>109 (54.2%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>38</td>
<td>23</td>
<td>31</td>
<td>92 (45.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>45</td>
<td>40</td>
<td>201 (100%)</td>
</tr>
</tbody>
</table>

Table 4: Outcome according to the age

<table>
<thead>
<tr>
<th></th>
<th>&lt; 35Yrs</th>
<th>&gt; 35 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>30 (24%)</td>
<td>8 (10.5%)</td>
</tr>
<tr>
<td>Positive</td>
<td>49 (39.2%)</td>
<td>22 (28.9%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>125 (100%)</td>
<td>76 (100%)</td>
</tr>
</tbody>
</table>

Table 5: Excellent and positive outcome according to age

<table>
<thead>
<tr>
<th></th>
<th>&lt; 35Yrs</th>
<th>&gt; 35 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>60 (75.9%)</td>
<td>08 (26.7%)</td>
</tr>
<tr>
<td>CVD</td>
<td>06</td>
<td>16</td>
</tr>
<tr>
<td>Anoxia</td>
<td>13</td>
<td>06</td>
</tr>
<tr>
<td>Total</td>
<td>79 (100%)</td>
<td>30 (100%)</td>
</tr>
</tbody>
</table>

References

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