*Original article*

# Dorsal column stimulation improves awareness in persistent vegetative state patients

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***SUMMARY: Aims.*** *The issue of how to treat patients in a vegetative state remains grossly unresolved. Nevertheless, dorsal column stimulation has shown promise and warrants further investigation. We therefore conducted a prospective controlled study on the effects of dorsal column stimulation in 214 patients in a persistent vegetative state following global anoxia, stroke or head injury for 20 consecutive years (1986-2005).*

***Materials and Methods.*** *After of the diagnosis of persistent vegetative state was confirmed, a dorsal column stimulator was implanted at the C2-C4 level, and patients underwent a daily 12-hour daytime stimulation protocol featuring continuous 15 min on/15 min off cycles. Signs of awareness of self and surrounding were scored on an ad-hoc scale, and patient responses were classed as excellent, positive or no change.*

***Results.*** *In 109 of 201 patients (54%) responses were positive or excellent, and post-traumatic persistent vegetative state patients aged below 35 with baseline regional cerebral brain flow over 20 ml/100g/minute responded particularly well.*

***Conclusions.*** *Further evidence-oriented studies are required to determine those likely to benefit from this type of treatment.*

***KEY WORDS:*** *Consciousness, Dorsal column stimulation, Minimally conscious state, Persistent vegetative state.*

## INTRODUCTION

There are countless victims of severe brain damage, massive stroke, anoxic/hypoxic events and other significant afflictions of the brain who remain in a so-called “persistent vegetative state” for extended period, or indeed their remaining life span. Described by Jennett and Plum in 1971 as a lack of awareness of one’s self and the surrounding environment, despite preservation of autonomic, brainstem and sleep/wake cycle functions, it is nevertheless difficult to assert whether or not a vegetative state may be permanent. Analysis of outcomes in VS patients has shown that if no recovery is seen within 3 months of non-traumatic or 12 months of traumatic brain injury, the vegetative state is likely to remain permanent or persistent[13], but this is by no means a given. Hence criteria-based diagnosis of PVS[17,18] needs to be accompanied by prolonged observation of the patient by an expert, as there is a danger of misinterpreting evidence of awareness[5]. In particular, VS can be easily confused with minimally conscious state[4], in which there is, however, minimal evidence of awareness, which can be a precursor to recovery.

The aetiology behind PVS will affect its background pathology, but there are generally variable but significant changes in the cortex, and, most consistently, the sub-cortical white matter and thalami[1]. Based on

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**LIST OF ACRONYMS AND ABBREVIATIONS:** CM-pf = CentroMedian-parafascicular nucleus; CNS = Central Nervous System; CT = Computed Tomography; DCS = Dorsal Column Stimulation; EEG = ElectroEncephaloGraphy; MRI = Magnetic Resonance Imaging; rCBF = regional Cerebral Brain Flow; PVS = Persistent Vegetatative State; SPECT Single Photon Emission Computed Tomography.

the location of this CNS damage, PVS patients can be arbitrarily classified as either global or multifocal. To a great extent these sub-groups reflect the underlying causes of the initial injury, as global ischemia and anoxia tend to result in more diffuse "global" damage, whereas head injury, stroke and similar conditions generate multiple, but more circumscribed, "focal" lesions. Both types of PVS patients can, however, retain clinical brainstem reflexes, and functional imaging studies have recently confirmed activity in some cortical areas of these patients[19].

The lack of a significant breakthrough in PVS treatment thus far is primarily due to poor understanding of the basic mechanisms of consciousness, and how damage to these mechanisms are able to cause such a profound deficit. However, based on the supposition that an absence of an adequate supply of sensory input to certain brain systems critical for awareness may be involved, researchers have proposed various methods of attempting to bridge this sensory stimulation gap[2,3,21]. Stimulation systems attempted have varied in terms of the type of sensory input provided and the point of application, which may be either external and internal methods of applying the stimulation have been used. The results obtained have been equally variable, and treatment of PVS via systematic sensory input is a long way from being evidence-based[12]. Moreover, the conceptual basis of applying sensory stimulation, one of the most common methods, is still rather vague.

The general aim of this treatment, however, is to activate non-specific brainstem systems or enhance selective attention via the application of selective stimulatory input. Promising results have been achieved by the application of more or less specific types of stimulation at different points in the sensory pathways, i.e., by external stimuli or by implanted electrodes. Deep brain stimulation of the CM-pf thalamic nuclei and mesencephalic reticular formation, for example, has been shown by several Authors[2,21] to bring about improvement in awareness. Dorsal column stimulation[7,20], median nerve stimulation[3] and external sensory stimulation by various means (from simple stimuli to music) have also yielded encouraging results.

The search for a less invasive means of conveying a massive sensory stimulation to the non-specific systems (i.e., without implanting electrodes into the brainstem), combined with our clinical observation that PVS patients treated with dorsal column stimulation for spasticity also improve cognitively[7], led to the current clinical research into this technique, ongoing since 1986[6,8,9,10].

| Cause | < 35 Years | > 35 Years | Total (% on 201 patients) |
|---|---|---|---|
| Trauma | 83 | 23 | 106 (52.7%) |
| Cerebrovascular disease | 12 | 33 | 45 (2.4%) |
| Anoxia | 30 | 20 | 50 (24.9%) |

**Table 1.** Total number of cases by age distribution and cause

## ☐ MATERIAL AND METHODS

❒ **Patients.** A total of 214 patients in PVS were treated using DCS during the period 1986 to 2005. Their underlying brain injury was due to head trauma, stroke or global anoxia (Table 1). All patients met the accepted criteria for PVS, and had remained in that state for at least 3 months in non-trauma and 1 year in trauma cases. Legal guardians and other close relatives, were informed as to the method of treatment, the associated risks, and the current understanding of its effects in PVS patients. Informed written consent was subsequently obtained, and the study was approved by the legal and ethical committees of our institution. The regulations adopted by these bodies conform to the internationally adopted ethical standards for clinical treatment and research (Declaration of Helsinki).

The patients were clinically evaluated by at least two teams of neurosurgeons, and the family was interviewed to determine their knowledge of any signs of awareness.

The patients' condition was scored according to the scale adopted at our institution (Table 2), and family members were instructed to observe their relatives under treatment, paying particular attention to any responses to familiar external stimuli. In some cases

| Evaluation of results | |
|---|---|
| The patients best signs should be as below: | |
| *Excellent response* | When the patient has:<br>- a purposeful movement like;<br>- a behavioral expression;<br>- swallowing when food or water is placed in the month;<br>- and/or spoken meaningful words. |
| *Positive response* | When the patient has:<br>- emotional response (the reaction towards various stimuli is rich emotional expression);<br>- 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);<br>- some pattern of opening and closing eyes when a specific stimulus is detected. |

**Table 2.** Evaluation of results.

patients were monitored via video in order to detect any responses.

All patients were assessed by EEG, cranial CT, brain MRI, and SPECT r-CBF before treatment was initiated.

❒ **Stimulator implantation.** Surgery was performed under general anaesthesia, with the patients prone with the neck fully flexed. Initially the Resume, then the X-trel, and finally (after the year 2000, when it became available in Japan) the Medtronic Itrel 3 System (Medtronic Inc., USA) were implanted through a 5-cm median incision in the posterior neck, reaching down to the level of the 7th cervical vertebral process (Figure 1).

The muscles were dissected away from the midline, and laminotomy of the 5th cervical vertebra was performed. Under fluoroscopic control, electrodes were then inserted through the epidural space along the mid-line at the 5th cervical level, towards the cranial side, and then embedded at the levels of the 2nd, 3rd and 4th cervical vertebrae using a C-arm. The battery and receiver were subcutaneously implanted in the lateral abdominal region, and the leads connecting these with the stimulator were passed under the skin (Figure 2 and 3).

The surgery was well tolerated in patients who had not displayed any signs of pre-operative PVS complications, and the internal position of the stimulator both favoured daily care and reduced the risk of infection.

❒ **Stimulation protocol.** After a 3-7 day post-surgical recovery period, the stimulation protocol

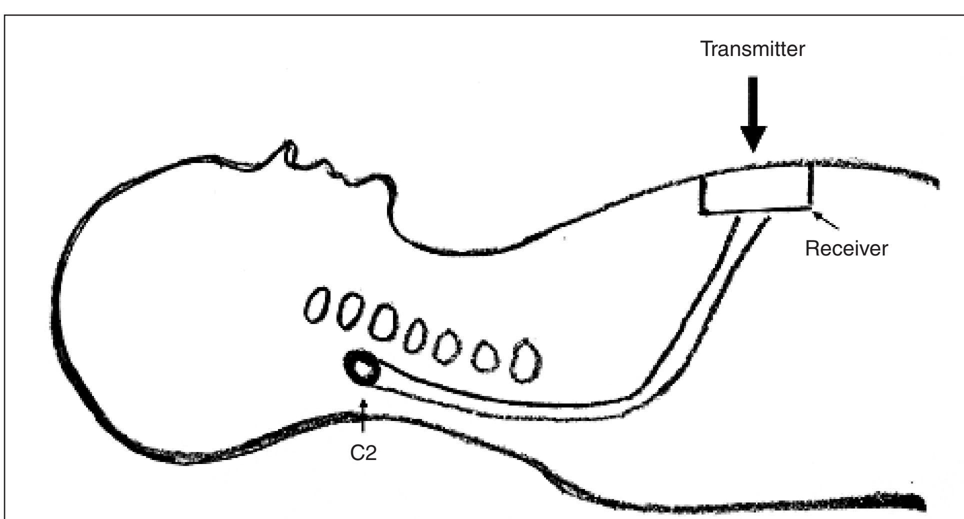


**Figure 1.** Stimulator set-up.

Figure 2. Stimulator in situ.

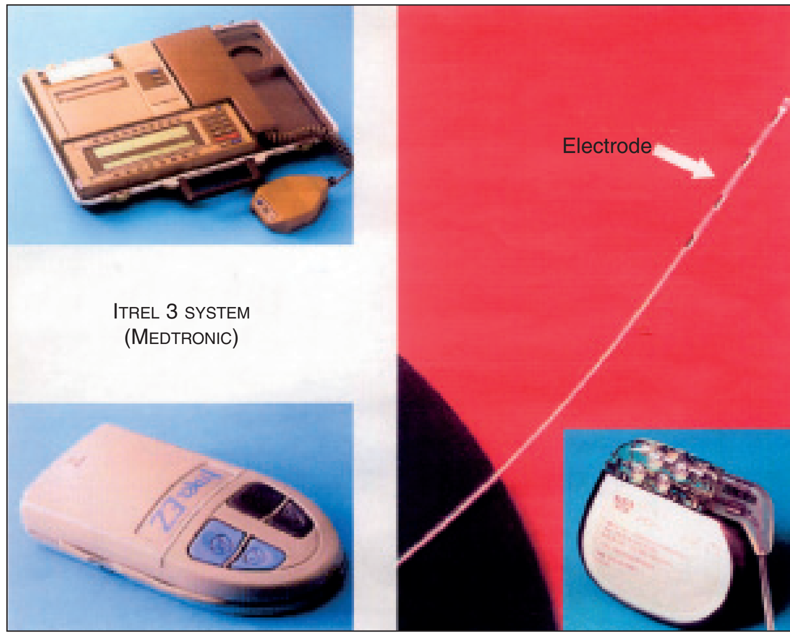


Figure 3. The Itrel 3 stimulation system.

was begun. This involved 12 hours of daytime stimulation.

Taking the caudal and cranial sides as the positive and negative poles, respectively, the posterior columns were stimulated at amplitude 2.0-3.0 V, pulse width 120 microseconds, and rate 70 Hz, in 15 minutes on/15 minutes off cycles.

These stimulation parameters were chosen as sub-threshold, as a motor response was generally provoked at or above 4V.

❐ **POST-OPERATIVE EVALUATION.** The operating neurosurgeons were responsible for patient follow-up, but staff and relatives were also asked to independently observe the patients and report any change in their conditions. Changes were accepted if reported by all observers.

The pre-operative criteria were also used to evaluate the patients after surgery. Clinical teams and relatives made exhaustive daily reports. Results were grouped as per the criteria in Table 2 at 3-and-a-half months after the stimulation was commenced, even though some changes were observed as early as 4 weeks following implantation. Patients were scored as having excellent, positive or unchanged responses, and then grouped accordingly.

| Response to DCS | Trauma | Cerebro-vascular disease | Anoxia | Total |
|---|---|---|---|---|
| Excellent and positive | 68 | 22 | 19 | 109 (54.2%) |
| Unchanged | 38 | 23 | 31 | 92 (45.8%) |
| *Total* | *106* | *45* | *40* | *201 (100%)* |

**Table 3.** Responses according aetiology.

## ☐ RESULTS

Of the total of 214 patients, 13 were lost to follow-up, and implanted stimulation devices had to be removed from two patients due to adverse tissue reactions.

The Table 3 shows the distribution of the responses according aetiology.

Preliminary analysis showed an overall clear tendency of those aged under 35 at the start of the stimulation programme to achieve a more positive outcome (Table 4).

This age difference was also seen in when patients were grouped according to underlying aetiology (Table 5).

Table 5 also shows that a large percentage of under-

35s with PVS of traumatic origin achieved positive to excellent results.

Indeed, 60 out of the 68 trauma patients (88.2%) showing improvement were aged below 35, as compared to patients with other aetiologies, in whom the age factor did not appear to have such a large influence.

r-CBF SPECT studies were performed in 58 patients, and revealed a clear relationship between r-CBF levels and stimulation. An increase in r-CBF levels was observed more often in patients whose pre-operative rCBF levels were higher than 20 ml/100g/min on average (Table 6).

| Response to DCS | < 35 Years | > 35 Years |
|---|---|---|
| Excellent | 30 (24.0%) | 8 (10.5%) |
| Positive | 49 (39.2%) | 22 (29.0%) |
| Unchanged | 46 (36.8%) | 46 (60.5%) |
| *Total* | *125 (100%)* | *76 (100%)* |

**Table 4.** Outcome according to age.

| Response to DCS | < 35 Years | > 35 Years |
|---|---|---|
| Trauma | 60 (75.9%) | 8 (26.7%) |
| Cerebrovascular disease | 6 (7.6%) | 16 (53.3%) |
| Anoxia | 13 (16.5%) | 6 (20.0%) |
| *Total* | *79 (100%)* | *30 (100%)* |

**Table 5.** Excellent and positive outcome according to age by aetiology group.

## ☐ DISCUSSION

External stimulation techniques have largely been replaced by internal implants in PVS patients. The aim is to supply focused stimuli powerful enough to elicit a response, by placing electrodes in direct contact with sensory pathways.

Direct cortical and brainstem stimulation have been tested[2,21], but to minimize invasiveness we elected to use epidural spinal electrodes. This had the dual advantage of providing significantly more powerful sensory stimulation input than the external somatosensory techniques investigated[3] without compromising safety. Indeed, this technique has been thoroughly investigated and standardized for other conditions such as spasticity and pain.

Although the same standardized technique was directly transferred to our study, PVS treatment study design is inevitably hampered by several major obstacles, which we have not yet manage to overcome. Indeed, Lombardi et al. in 2002[12] found that only 3 controlled clinical trials - one only randomized - had thus far been performed, and there was therefore insufficient evidence of any effectiveness of sensory stimulation in PVS patients.

This uncertainty is also compounded by sociopolitical and ethical issues affecting the treatment of PVS, and close collaboration between physicians and relatives is required, effectively precluding the possibility of blinding and randomization.

Furthermore, our patient sample may have suffered from existing bias resulting from the admission & referral criteria, treatment practice, and other factors out of our hands. Nevertheless, with the cooperation of relatives and the relevant authorities, we were granted a unique opportunity to observe a group of patients undergoing a rare type of treatment, and show that it does appear to possess some effectiveness in certain individuals.

Although the current role of pre-operative assessment is merely as a reference for post-operative findings, as shown by our results they may also serve as criteria for selecting patients likely to respond.

We can supplement this information with that obtained from detailed structural and functional imaging of the brain, which may also yield clues as to the nature of consciousness and the deficits characteristic of PVS. Nonetheless, at this stage very little is known regarding the possible mechanisms by which DCS may act on the presumed, and plentiful, factors involved in consciousness.

Mirroring our results, particularly in younger patients, there have been reports that cervical DCS increases rCBF in animals and humans[14], and thereby promotes neuroplasticity.

The way in which DCS affects CBF may be mediated by central (brainstem) pathways[15], and it may also exert an activating effect on residual functionally

| rCBF results | Excellent outcome |
|---|---|
| > 20 ml/min/100 gm | 42% |
| < 20 ml/min/100 gm | 5% |

**Table 6.** Overview of rCBF results

active areas of the cortex and thalami by stimulating the non-specific sensory pathways.

The better response to DCS seen in our patients with PVS of traumatic and, to some extent, CVD origin, in whom multifocal damage is more common, lends weight to this hypothesis. It is also in line with the benefits seen in similar studies on different types of stimulation involving the activation of periaqueductal, non-specific thalamic and reticular structures[11]. This could be brought about by the activation of higher-level neurotransmitters and the alpha-1 sympathetic system, concomitantly increasing CBF levels[15,16]. That being said, without more detailed structural and functional investigations, we cannot yet indicate the most probable mechanisms with any certainty, and our results, albeit promising, remain empirical in nature.

## □ CONCLUSIONS

According to our results, DCS does display some beneficial effect on the reactivity of certain PVS patients to stimuli, indicating that a degree of cognition is present in treated patients.

Although we are currently unable to speculate on the process behind this improved reactivity, or indeed whether this was merely a stage in the natural recovery of awareness to external stimuli, we did see some functional improvement, particularly in post-traumatic patients under 35 years of age with average pre-treatment rCBF values greater than 20 ml/100g/min. Added to the fact that the stimulation approach investigated facilitated patient care and their re-integration into their home environment, these promising results appear to justify further studies along similar lines.

## □ REFERENCES

1. Adams JH, Graham DI, Jennett B. The neuropathology of the vegetative state after an acute brain insult. Brain 2000; 123 ( Pt 7) 1327-1338.
2. Cohadon F, Richer E. [Deep cerebral stimulation in patients with post-traumatic vegetative state. 25 cases]. Neurochirurgie 1993; 39 (5): 281-292.
3. Cooper JB, Jane JA, Alves WM, Cooper EB. Right median nerve electrical stimulation to hasten awakening from coma. Brain Inj 1999; 13 (4): 261-267.
4. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI et al. The minimally conscious state: definition and diagnostic criteria. Neurology 2002; 58 (3): 349-353.
5. Jennett B. Thirty years of the vegetative state: clinical, ethical and legal problems. Prog Brain Res 2005; 150: 537-543.
6. Kanno T, Kamei Y, Yokoyama T. Treating the vegetative state with dorsal column stimulation. Proc Soc Treat Coma 1992; 1: 67-75.
7. Kanno T, Kamei Y, Yokoyama T, Jain VK. Neurostimulation for patients in vegetative status. Pacing Clin Electrophysiol 1987; 10 (1 Pt 2): 207-208.
8. Kanno T, Kamel Y, Yokoyama T, Shoda M, Tanji H, Nomura M. Effects of dorsal column spinal cord stimulation (DCS) on reversibility of neuronal function--experience of treatment for vegetative states. Pacing Clin Electrophysiol 1989; 12 (4 Pt 2): 733-738.
9. Kanno T, Kamei Y, Yokoyama T, Shoda M, Tanji H, Nomura M. [Effects of neurostimulation on the reversibility of neuronal function: experience of treatment for vegetative status.] No Shinkei Geka 1988; 16 (2):157-163.
10. Kanno T, Okuma I. Electrical neurostimulation for vegetative state. Proc Soc Treat Coma 2003;12: 3-5.
11. Glickstein SB, Ilch CP, Golanov EV. Electrical stimulation of the dorsal periaqueductal gray decreases volume of the brain infarction independently of accompanying hypertension and cerebrovasodilation. Brain Res 2003; 994 (2): 135-145.
12. Lombardi F, Taricco M, De Tanti A, Telaro E, Liberati A. Sensory stimulation of brain-injured individuals in coma or vegetative state: results of a Cochrane systematic review. Clin Rehabil 2002; 16 (5): 464-472.
13. Medical aspects of the persistent vegetative state (part 2). The Multi-Society Task Force on PVS. N Engl J Med 1994; 330 (22): 1572-1579.
14. Meglio M, Cioni B, Visocchi M, Nobili F, Rodriguez G, Rosadini G et al. Spinal cord stimulation and cerebral haemodynamics. Acta Neurochir 1991; 111 (1-2): 43-48. 19
15. Patel S, Huang DL, Sagher O. Evidence for a central pathway in the cerebrovascular effects of spinal cord stimulation. Neurosurgery 2004; 55 (1): 201-206.
16. Patel S, Huang DL, Sagher O. Sympathetic mechanisms in cerebral blood flow alterations induced by spinal cord stimulation. J Neurosurg 2003; 99 (4): 754-761.
17. Royal College of Physicians. Prolonged disorders of consciousness: national clinical guidelines. A report of a working party. London: Royal College of Physicians, 2013.
18. Royal College of Physicians. The vegetative state: guidance on diagnosis and management. Clin Med 2003; 3 (3): 249-254.
19. Schiff ND, Ribary U, Moreno DR, Beattie B, Kronberg E,

Blasberg R, Giacino J, McCagg C, Fins JJ, Llinás R, Plum F. Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. Brain 2002; 125 (Pt 6): 1210-1234.

20. Visocchi M, Cioni B, Pentimalli L, Meglio M. Increase of cerebral blood flow and improvement of brain motor control following spinal cord stimulation in ischemic spastic hemiparesis. Stereotact Funct Neurosurg 1994; 62 (1-4): 103-107.

21. Yamamoto T, Katayama Y. Deep brain stimulation therapy for the vegetative state. Neuropsychol Rehabil 2005; 15 (3-4): 406-413.