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Pilot study of electrical stimulation on median nerve in comatose severe brain injured patients: 3-month outcome

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Primary objective: To determine if electrical stimulation (ES) benefits (waking time, 3-month outcomes) treated coma patients.

Research design: Double blind randomized-controlled study.

Methods and procedures: Ten coma patients; six treatment and four controls, using the 'Respond Select' by EMPI.

Experimental interventions: Treatment group received radial nerve ES applied in 300 ms intermittent pulses at 40 Hz, 15–20 mÅ 8 hours a day up to 14 days of coma; control group received sham stimulation.

Main outcomes and results: ES group emerged from coma mean 2 days earlier than controls, although this result was not statistically significant. At 3 months post-injury, there was no group difference in Glasgow Outcome Scale, although the ES group had improved function over controls as measured by the FIM/FAM (mean of 114 and 64.5, respectively, n.s.).

Conclusions: These data show an interesting trend, although statistical power was limited in this small pilot study, suggesting the need for a larger trial.

Introduction

Electrical stimulation (ES) has been used as a therapeutic method in physical therapy and rehabilitation for decades. The therapeutic potential of electrical currents being used for diverse applications was postulated more than a century ago. This includes treatment of lesions and diseases of the nervous system. ES has been used to treat patients with pain syndromes, and Alzheimer's disease [1, 2]. The interest in ES for severe traumatic brain injury (TBI) and its consequences is not new; it started more

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than a decade ago when electrical stimulation was noted to be beneficial in severely brain injured patients [3].

Significant research related to ES in vegetative states post-stroke, post-trauma and prolonged hypoxia has been performed in the last decade [3–7] using dorsal column stimulation (DCS) [3–5] and median nerve stimulation [6–8]. DCS consists of low electrical currents applied through an epidural or subdural electrode at the C2 level. DCS may hasten arousal, increase cerebral blood flow, improve EEG increasing α-waves while decreasing θ-waves, raise dopamine and noradrenaline levels and lower serotonin in the cerebrospinal fluid (CSF). In a report published in 1992, after a study of 42 cases of post-traumatic and post-stroke vegetative patients treated with DCS, Kanno *et al.* [4] reported that 42.9 % of patients showed clinical improvement. The authors mentioned that the interval from the start of DCS therapy to the first sign of improvement is variable: from 6 months to 5 years [3–5]. The effect of ES via the median nerve was studied in acutely and severely brain injured patients [9]. A low intensity electrical current (20 mÅ) was used to stimulate the peripheral median nerve of subjects with a Glasgow Coma Scale (GCS) who scored between 4–8. The authors reported noticeable improvement of clinical status in stimulated patients in comparison with non-stimulated cases [9].

The median nerve has also been used for the treatment of post-stroke, post-trauma, hypoxic states and imaging, and laboratory measures (EEG, SPECT, catecholamine metabolism) have shown clinical improvement in ES patients versus non-ES patients [6–8].

The concept of ES in severe TBI is based on the hypothesis that electrical currents applied through peripheral routes may reach central areas, activating the neuro-endocrine system to improve functioning after traumatic cerebral damage. It is proposed that the peripheral stimuli go to the ascending reticular activating system (ARAS), which further connects with intralaminar nuclei of the thalamus and then stimulates the cortical layer 1. The locus coeruleus (releasing norepinephrine), and the forebrain basal nucleus of Meynert (releasing acetylcholine), are also involved and stimulate the cortical layer 1, enhancing arousal. However, some other mechanisms may also be possible [7, 10].

Thus, a pilot study was planned to specifically investigate whether patients will have a shorter time out of coma and better functional outcomes at 3 months following severe TBI.

Methods

Subjects

Patients were eligible for the study if they presented with a non-penetrating TBI with an admission Glasgow Coma Scale between 3–8, and enrolled within 72 hours of injury. Patients were required to be between the ages of 18–66. Patients were excluded if they were found clinically to be under alcohol and/or drug intoxication, unless their GCS remained 4–8 in the 24 hours post-admission. Patients with implanted pacemakers or defibrillators were excluded, as were patients with spinal cord injury or pregnancy, to preclude possible negative interactions with ES. Subjects were recruited from a daily survey of the General Surgery and Neurosurgery Intensive Care Units. Since these patients were in coma, written consent from the patient's closest relative was obrained, with patient consent col-

lected as soon as they were cognitively able. This study was conducted with full approval of the University of Virginia Investigational Review Board. Subjects were recruited from October 1998 to August 1999.

Experimental design and random assignment to group

This study is a double-blind, randomized, controlled pilot study of the effect of ES on severe TBI outcome. Patients were randomly assigned to either the treatment or the control groups. A list of random numbers was generated in Microsoft Excel97 using the RANDOM function, and subjects were assigned a number as they were enrolled in this study. All odd-numbered subjects were assigned to the treatment group and all even-numbered subjects were assigned to the control group. Control subjects were given 'sham' stimulation and, thus, and they received no ES, in that they were hooked to a machine that did not have electrodes completing a circuit between the device and the patient. The 'sham' machine had no discernable difference from the functional machine. Patients and families were kept blind to treatment intervention, as was the outcome rater.

Electrical stimulation treatment

The device used to provide electrical impulses was the 'Respond Select' by EMPI. This device has multiple settings that allow various trains of electric pulses. It is connected to two electrodes attached to a cuff that is applied on the volar surface of the right forearm for patients who are right-handed, in order to stimulate the right median nerve (one subject was left-handed and, therefore, ES was applied on the subjects' left median nerve). Stimulation was applied in 300 μs pulses at 40 Hz, and 15–20 mÅ given intermittently (20 seconds on, 40 seconds off). This regimen was found effective in previous studies [10]. The patients in the treatment group received ES 8 hours a day each day they remained in a coma (GCS < 9), for up to 14 days. There were no adverse events relating to ES.

Data collection

Patient history was taken from rescue squad notes, medical records, and family report. The neurobehavioural rater, blinded to treatment condition, collected a daily GCS score before beginning the intervention each day. If the patient was intubated, adjusted GCS (motor and eye scores only) was collected and intubation was recorded in the data. GCS was not collected on days during which patients were sedated (sedation was achieved using Fentanyl/ 25–100 mcg) and/or therapeutically paralysed (paralysis was achieved using Pancuronium/1–5 mg). Sedation and paralysis were given clinically in response to the patient's unstable neurological status, e.g. low GCS and reactivity, signs of decerebration and decortication, high intracranial pressure (ICP), agitation and uncontrolled movements, etc. Treatment groups did not differ in the rate of sedation and/or paralysis.

Outcome assessments

Time out of coma was the first outcome measure taken, defined as the number of days post-injury before the patient reached a GCS of 9 or above. At 3 months post-

injury, patients were assessed with the Glasgow Outcome Scale (GOS), the Functional Independence Measure/Functional Assessment Measure (FIM/FAM), and a neuropsychological assessment if they were able (e.g. no longer in coma and not severely cognitively impaired or deceased). The neuropsychological assessment tested areas of handedness (Oldfield Handedness Inventory), vocabulary/fund of knowledge (Vocabulary subtest of the WAIS-III), verbal fluency (Controlled Oral Word Association test), verbal memory (Rey Auditory Verbal Learning Test), visual memory (Rey Complex Figure), attention (Digit Span subtest of the WAIS-III), psychomotor speed (Digit Symbol subtest of the WAIS-III), along with a pre-morbid IQ estimate (Barona Index).

Results

Data analysis

All data analyses were two-sample *t*-tests assuming equal variance, one-way, with α–0.05 unless otherwise stated. Analyses were performed using SPSS-10. Data are summarized in table 1.

Subjects

Ten subjects were included in this study, with a mean age of 40 (range 19–66). Eight subjects were male and two were female, which is comparable to the gender ratio in other reported studies of severe TBI[11–13]. All subjects were Caucasian, and of the six patients on whom information on education was collected, the mean number of years of education was 14. Seven patients had sustained their injuries in motor vehicle accidents, two were injured in falls, and one was injured when he was struck in the head by a beam.

ES was started a mean of 62 hours post-injury (range 48–72 hours). Six subjects were randomized to ES treatment, and four subjects were randomized to the control group. There were no significant differences between groups in age ($p = 0.84$), or education ($p = 0.07$), although both women were assigned to the treatment group. There was no significant difference between groups on the number of hours elapsed before ES was started ($p = 0.64$). As can be seen in figure 1, there was an interesting difference between groups on initial adjusted GCS (since all patients were intubated, motor and eye scores were the only measures taken) wherein ES patients had a lower score ($\bar{X} = 4.5$) than did control patients ($\bar{X} = 6$). However, this difference was not statistically significant.

Table 1. Mean scores of admission injury severity and outcome measures

Treatment group	*n*	$\bar{X}$ admission GCS	$\bar{X}$ time out of coma	X 3-month GOS	X 3-month FIM/FAM
ES	6	4.5	9.5	3	114.4
Control	4	6	11.5	3	64.5

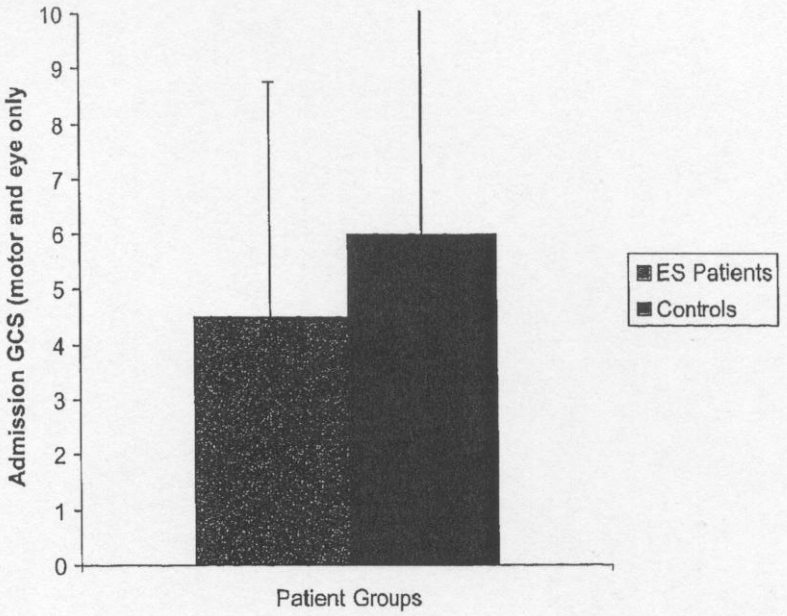

Figure 1. Mean differences in admission Glasgow Coma Score.

Time out of coma

The ES treatment group emerged from coma an average of 2 days earlier than the control group (9.5 days vs. 11.5 days). Although this difference was not statistically significant (p=0.31), the effect was in the direction proposed in the hypothesis. Unfortunately, the statistical power in this study with only 10 patients was calculated to be 0.175, assuming a medium effect size ($d = 0.5$), $\alpha = 0.05$, one-tailed t-test. Thus, it is likely that the study lacked sufficient power to detect a true difference between groups. Figure 2 shows the number of days of time out of coma for the two treatment groups.

Three-month outcome assessment

At the 3-month outcome timepoint, one subject was lost to follow-up (ES group), two subjects were deceased (both in the ES group) and one subject remained obtunded and at GCS of 9 (in the control group).

The Glasgow Outcome Scale (GOS) was, thus, available on nine of the 10 subjects. There were no statistically significant differences between groups, as each group had a mean of 3 (severe disability) with a range from 1 (deceased) to 5 (good recovery).

The FIM/FAM is a more sensitive measure of outcome than the GOS. On the FIM/FAM, the results were in the expected direction, with ES patients having a better functional status ($\overline{X} = 114$) than control patients ($\overline{X}$ mean 64.5). This pattern can be seen in figure 3, although, with the large degree of variability in outcome represented by the error bars (standard deviation), this difference is also not statistically significant.

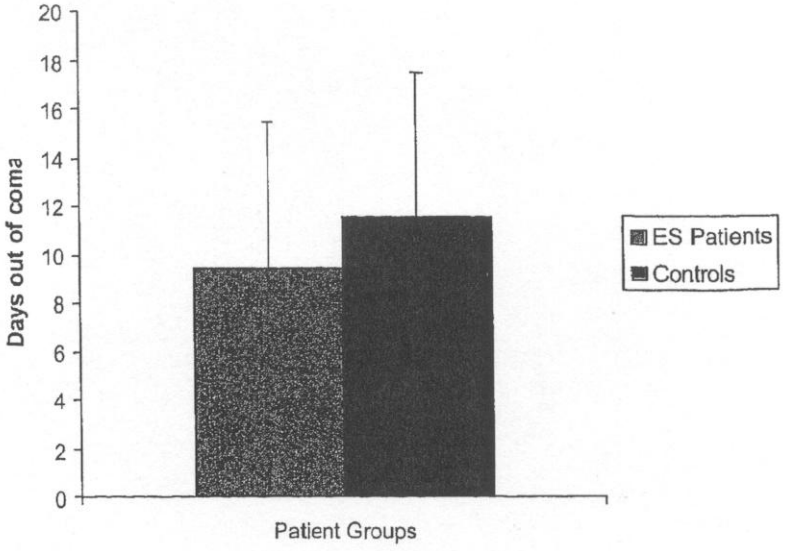

Figure 2. Mean differences in time out of coma.

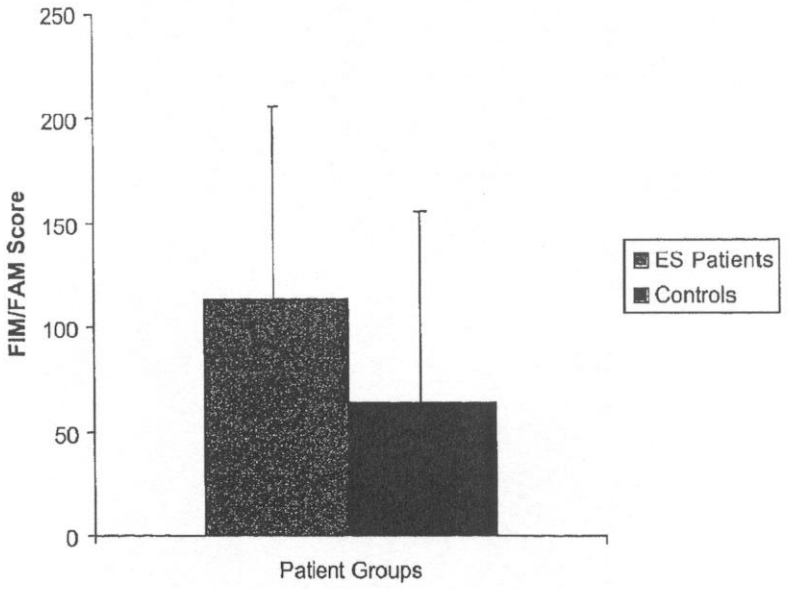

Figure 3. Group differences in functional outcome.

Neuropsychological testing could only be performed on three patients. One patient could only be contacted by telephone, one subject remained obtunded and at GCS of 9, two were severely disabled (GOS = 3) and not able to perform the testing, and two were deceased. Thus, although neurocognitive outcome is important to TBI survivors, neuropsychological testing may not be the most appropriate outcome measures in a study of severe TBI patients who are in a coma at least 48 hours before entering a study.

Discussion

The results of this study suggest that electrical stimulation may be beneficial to longer term outcomes following severe TBI, although conclusions are limited due to small sample size and resulting lack of statistically significant effect. These findings are consistent with previously reported uses of ES with patients in a persistent vegetative state. Kanno *et al.* [4] used DCS for pain and spasticity after cerebrovascular diseases, and extended studies using DCS in patients with long-standing vegetative states after stroke, trauma and prolonged hypoxia. Their results show a clinical improvement for 42.9% of their patients [4, 5], documented with positive changes in EEG, 20% increase in the cerebral blood flow (SPECT), and a more active metabolism of catecholamines [3–5].

The concept of the (right) median nerve stimulation arose as a method to apply ES simply and effectively. This nerve has a large cortical representation and is easily accessible on its peripheral segment. Its direct fibre connections with the cortex as well as its intermediate fibre connections in the brainstem make it a theoretically proper channel for impulse (with a positive effect) transmission and amplification [6–8, 10].

The results of ES on the median nerve in patients with prolonged coma after stroke, trauma, and prolonged hypoxia showed documented (EEG, SPECT, catecholamines metabolism) positive changes in some cases [6–8]. A recent study on ES on the median nerve in STBI shows a clinical improvement in ES versus non-ES cases [10].

The efficacy of ES in post-trauma, -stroke, and -hypoxic brain damage has been suggested and its use should be further examined. In this study, although differences between groups were not significant, results did show a trend towards improved outcome in the ES treated group. Additional research is also required to establish standards and methods of use, explain mechanisms of action, and make improvements. However, sufficient sample sizes in studies of prolonged coma (>48 hours in this study) will be difficult to collect, given that these patients are relatively rare. The prevalence of severe non-penetrating TBI is decreasing [14], probably as a result of improvements in safety, such as the use of air bags. Therefore, a multicentre-trial will be needed to collect data with sufficient subjects to determine if ES results in a truly significant improvement in this population. Until that point, TBI prevention remains the 'treatment of choice' for severe TBI.

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