Right Median Nerve Stimulation for Improving Consciousness: A Case Series

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Abstract

Brain injury is a leading cause of mortality, morbidity, and socioeconomic losses in India. Despite the improvements in emergency treatment, persistent coma is still a major clinical problem. Regardless of the etiology of the coma or reduced level of awareness, electrical stimulation may serve as a catalyst to enhance central nervous system functions. The right median nerve is a portal to electrically stimulate and help arouse the central nervous system for persons with reduced levels of consciousness. The mechanisms of central action include increased cerebral blood flow and raised levels of norepinephrine and dopamine. We report findings of seven patients who were given right median nerve stimulation to observe its effect on the consciousness.

Keywords
► right median nerve stimulation
► consciousness
► coma

Survival rates after acute brain injury have improved due to advancements in emergency treatment and car airbags. However, persistent coma continues to be a major clinical problem. Coma is defined as a state of complete unconsciousness from which the patient cannot be aroused. Usually, it evolves within 2 to 4 weeks into either a conscious state or vegetative state. When the first signs of voluntary behavior appear, the patient may be in a minimally conscious state (MCS).1 In this state, the patient is partially conscious, as evidenced by the presence of limited but reproducible signs of awareness. These signs include inconsistent command following, inconsistent but intelligible verbalization, sustained visual fixation, and localization of sound and noxious stimuli. The effects of a variety of medical (dopaminergic drugs, zolpidem, antidepressants), surgical treatment (deep brain stimulation, extradural cortical stimulation, spinal cord stimulation, intrathecal baclofen), and median nerve stimulation have been discussed for patients in vegetative or minimally conscious state.2,3

The right median nerve can be stimulated electrically to help arouse the central nervous system (CNS) for patients with reduced levels of consciousness. The mechanisms of central action include increased cerebral blood flow and raised levels of dopamine.4 In the United States, there is more than 20 years of experience of using nerve stimulation for acute coma after traumatic brain injury (TBI). There is a much longer period of experience by neurosurgeons in Japan with implanted electrodes on the cervical spinal cord for patients in the persistent vegetative state (PVS). However, the use of right median nerve stimulation (RMNS) for patients in the subacute and chronic phases of coma is relatively new. Regardless of the etiology of coma or reduced level of awareness, electrical stimulation may serve as a catalyst to enhance CNS functions.5,6

Cooper et al have explained in detail the mechanism behind the action of RMNS for improving consciousness. The right median nerve has been chosen as a portal to stimulate the brainstem and cerebrum because increased awareness and a better pattern of speech and abilities to calculate have been observed after RMNS. In most patients, whether right- or left-handed, Broca’s motor/speech planning area lies in the left frontotemporal region. Broca’s area has been shown to become more active in position emission tomography (PET) when a patient moves, or even contemplates moving his/her hand, a process mimicked by stimulation of the right median nerve. The cortical representation of the hand is disproportionately large compared with other parts of the

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body. In the brainstem, the ascending reticular activating system (ARAS) maintains the state of wakefulness. Electrical stimulation transcutaneously entering into the median nerve passes up through both the spinothalamic and spinoreticular pathway of the anterolateral system. There are synaptic connections in the spinoreticular pathway and ARAS distributed through the mid pons and lower midbrain. These spinoreticular synapses cause excitation of the locus coeruleus, the center producing norepinephrine in the brainstem, and has direct cortical connections. There is a diffuse input of norepinephrine to cortical layers 1 and 2 from the ARAS. Stimulation of these pathways causes a diffuse arousal process. The ARAS also has direct connections to the basal nucleus of Meynert. This nucleus is well known to be one of the major acetylcholinergic producers within the brain. Stimulation from the ARAS to the basal nucleus of Meynert causes a diffuse acetylcholinergic input to all lobes of the cortex. This causes some amount of arousal, but is also a mechanism for maintenance of long-term potentiated circuitry, most importantly the ability to speak. A separate connection in the anterolateral system is the spinothalamic component that has synaptic inputs directly to the intralaminar nuclei of the thalamus. These nuclei are well known to be causative in the startle response, which may cause a brief hyperawareness. Separate connections within the spinothalamic pathway go directly to the ventral posterolateral (VPL) nucleus of the thalamus. The VPL is responsible for interpreting sensory information from the contralateral hemibody. The stimulation to this nucleus is then processed on through third-order neurons that terminate in the primary somatosensory strip. These stimuli have been shown in blood flow–sensitive sequences of functional magnetic resonance imaging (fMRI) with concomitant median nerve electrical stimulation. Then through multiple connections, impulses are transmitted to Broca’s expressive speech center through arcuate fibers. This stimulation of surviving language pathways after TBI is a mechanism of maintaining the quicker return of speech upon awakening of the comatose patient.7–10

Most of the literature that we have mentioned in discussion available about RMNS had recruited patients with TBI. Here, we present a case series of seven patients with coma or MCS, who were given RMNS post brain damage.

Methods

Our protocol was cleared by the Institutional Ethical Board (New Delhi, India). Informed consent was obtained from the immediate family member of all patients. Stimulation was initiated when the patient’s medical condition stabilized. All patients were admitted at VIMHANS (Vidyasagar Institute of Mental Health, Neuro, & Allied Sciences), New Delhi, India. Patients with severe cardiac arrhythmias, implanted defibrillators, pacemakers, uncontrolled seizures, premorbid neurologic insult, brachial plexus injury, spinal cord injury, and pregnancy were excluded from the study. All patients received regular physiotherapy treatment. They were assessed on the outcome measure JFK Coma Recovery Scale–Revised (JFK-CRS–R). This scale was developed by Giacino et al, and the basic structure is similar to Glasgow Coma Scale (GCS).11 It includes similar visual, motor, and verbal subscales as the GCS. There are, in addition, three other subscales: an auditory function scale, a communication scale, and an arousal scale. It also takes into consideration the consistency of response shown by the patient. Its total score ranges between 0 and 23. It also denotes MCS and emergence from MCS. All patients received RMNS for a period of 3 weeks, for approximately 8 hours per day. The parameters of RMNS were chosen as per the previous studies. Asymmetric biphasic pulses at amplitude of 20 mA (milliamps) with a pulse width of 300 microseconds at 40 Hz (pulse/second) for 20 seconds on and 40 seconds off were used. The stimulator was developed and manufactured by Medicaid System (Chandigarh, India).

Results

Seven patients were enrolled in the pilot project between September 2013 and January 2014. There were three males and four females, ranging in age from 13 to 65 years. The demographic details of all the patients along with their pre and post scores are given in Table 1. RMNS was applied for a period of 3 weeks in all the patients. No follow-up of patients was done after the 3-week period.

Case Summaries

Case 1

A 63-year-old hypertensive, nondiabetic woman was admitted with sudden onset of headache, neck pain, and vomiting. She was diagnosed with a ruptured anterior communicating artery aneurysm. On admission, her GCS was full and there was no focal neurologic deficit. Clipping of the aneurysm was done. Postoperatively patient developed altered sensorium and right-sided hemiplegia. NCCT (noncontrast computed tomography) of the head revealed acute anterior cerebral artery infarct. The patient was kept on elective ventilation postoperatively. She deteriorated neurologically and also developed weakness in her left side 8 days postoperatively. Her GCS had deteriorated to E2M3Vt and MRI (magnetic resonance imaging) of the brain revealed a fresh right middle cerebral artery infarct. Her sensorium kept on fluctuating. The patient developed high-grade fever with breathing difficulty. Once her vital parameters got stabilized, she was started on RMNS (32 days since onset of the ruptured aneurysm). Her pre- and postassessment on JFK-CRS–R was as follows: auditory function scale (localization to sound remained the same), visual function scale (visual fixation remained the same), motor function scale (flexion withdrawal remained the same), oromotor/verbal function scale (oral reflexive movement remained the same), communication scale (remained none), and arousal scale (eye opening without stimulation).
Table 1: Demographic details, pre and post scores of patients

<table>
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<tr>
<th>S. no</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Time since onset (d)</th>
<th>GCS score</th>
<th>JFK-CRS-R score</th>
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<tr>
<td></td>
<td></td>
<td></td>
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<td>Pre</td>
<td>Post</td>
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<td>F</td>
<td>Aneurysm</td>
<td>32</td>
<td>E3M4Vt</td>
<td>E3M4Vt</td>
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<tr>
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<td>48</td>
<td>E2M2Vt</td>
<td>E3M5Vt</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>M</td>
<td>Stroke</td>
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<td>E3M2Vt</td>
<td>E3M2Vt</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
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<td>Stroke</td>
<td>38</td>
<td>E2M4Vt</td>
<td>E3M5Vt</td>
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<tr>
<td>5</td>
<td>26</td>
<td>M</td>
<td>Stroke</td>
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<td>E1M2Vt</td>
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</tr>
<tr>
<td>6</td>
<td>52</td>
<td>F</td>
<td>TBI</td>
<td>30</td>
<td>E2M2Vt</td>
<td>E3M4Vt</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>M</td>
<td>Pineal Tumor</td>
<td>60</td>
<td>E2M5Vt</td>
<td>E3M5Vt</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; GCS, Glasgow Coma Scale; JFK-CRS-R, JFK Coma Recovery Scale-Revised; M, male; TBI, traumatic brain injury.

Case 2
A 30-year-old, normotensive, nondiabetic woman presented with sudden complaints of headache and neck pain. She was diagnosed with bifurcation lobulated aneurysm in the right middle cerebral artery and a right temporal AVM (arteriovenous malformation). On admission the patient was conscious, oriented, and her GCS score was full. There was no focal neurologic deficit. Surgery was performed with clipping of right MCA (middle cerebral artery) aneurysm and embolization of right temporal AVM was done. Postoperatively, the patient developed weakness in the left side of body and her sensorium declined. Her GCS became E2M2Vt. She was started on RMNS almost 48 days after the onset of illness. Her pre and post JFK-CRS-R scores were as follows: auditory function scale (from none to reproducible movement to commands), visual function scale (from none to visual pursuit), motor function scale (from none to localization to noxious stimulus), oromotor/verbal function scale (from none to oral reflexive movement), communication scale (from none to nonfunctional intentional), and arousal scale (from eye opening with stimulation to eye opening without stimulation).

Case 3
A 50-year-old, nonhypertensive, nondiabetic man was admitted with head injury following road traffic accident. NCCT of the head revealed left frontal contusional hematoma with edema, SAH (subarachnoid hemorrhage), and midline shift. The patient experienced weakness in the right side of the body. Left frontotemporalparietal craniotomy with hematoma evacuation and duraplasty was done on the same day. Tracheostomy was done postoperatively. Postoperatively, the patient’s GCS was E3M2Vt and he was started with RMNS almost 20 days after the head injury. His pre- and post-JFK-CRS-R scores were as follows: auditory function scale (auditory startle remained same), visual function scale (visual startle remained same), motor function scale (flexion withdrawal remained the same), oromotor/verbal function scale (oral reflexive movement remained same), communication scale (remained none), and arousal scale (remained the same, eye opening without stimulation).

Case 4
A 65-year-old woman with a known case of hypertension, GERD (gastroesophageal reflux disease), and coronary artery disease was brought to our hospital for neurorehabilitation, post-surgery for left frontotemporal-parietal bleed. The patient arrived at our hospital (VIMHANS) almost 1 month after her surgery. On admission her GCS was E2M4Vt, she was on PEG (percutaneous endoscopic gastrostomy) tube feeding, and had right-sided hemiplegia. She was completely bedbound and dependent on her caregiver for all activities of daily living. She opened her eyes intermittently when given noxious stimulus and was drowsy most of the time. RMNS was started almost 40 days after the onset of stroke. The patient was assessed on JFK-CRS-R. Her pre- and post-response was as follows: auditory function scale (localization to sound remained the same), visual function scale (visual pursuit remained the same), motor function scale (from flexion withdrawal to localization to noxious stimulus), oromotor/verbal function scale (from oral reflexive movement to intelligible verbalization following removal of tracheostomy), communication scale (from none to nonfunctional intentional), and arousal scale (from eye opening with stimulation to eye opening without stimulation).

Case 5
A 26-year-old man, known case of diabetes, hypertension, bronchial asthma, hypothyroidism, and chronic alcoholism, presented with recurrent seizures and loss of consciousness. The patient was diagnosed with left basal ganglia hematoma with brainstem involvement. He was operated for the same. RMNS was started 16 days after the onset of stroke. At that time his GCS was E1M2Vt. He was assessed on JFK-CRS-R. His pre- and post-response was as follows: auditory function scale (remained none), visual function scale (from none to visual startle), motor function scale (abnormal posturing remained), oromotor/verbal function scale (from none to oral reflexive movement), communication scale (remained none), and arousal scale (remained unarousable). On family’s request, RMNS was extended for another 3-week period during which the patient’s response became much
better. His total score became 10 and his response was as follows: auditory function scale (auditory startle developed), visual function scale (visual startle developed), motor function scale (abnormal posturing remained the same), oromotor/verbal function scale (remained none), communication scale (remained none), and arousal scale (developed eye opening with stimulation).

**Case 6**
A 52-year-old hypertensive, diabetic woman was admitted with head injury following road traffic accident. Her initial GCS was E2M2V1 and NCCT of the head revealed depressed fracture of left frontoparietal bone. She had developed weakness in the right-sided body. Left frontotemporal craniotomy with elevation of the depressed bony segment was done. Tracheostomy was done postoperatively. She was started on RMNS almost 30 days after her trauma. Her pre– and post–JFK-CRS-R scores were as follows: auditory function scale (from none to localization to sound), visual function scale (visual startle remained the same), motor function scale (from abnormal posturing to localization to noxious stimulus), oromotor/verbal function scale (oral reflexive movement remained the same), communication scale (from none to nonfunctional intentional), and arousal scale (from eye opening with stimulation to eye opening without stimulation).

**Case 7**
A 13-year-old boy presented with chief complaints of severe headache, vomiting, and drowsiness. MRI of the brain was suggestive of tumor in the pineal region/third ventricle region. VP (ventriculoperitoneal) shunt was inserted within 1 month of the diagnosis. Postoperatively, the patient developed weakness in the right-sided body and a high-grade fever, and he deteriorated neurologically. Once he became afebrile, craniotomy and tumor decompression were done. His postoperative GCS was E2M5V5. Owing to poor GCS after the surgery, the patient was started on RMNS, almost 60 days after the diagnosis. His pre– and post–JFK-CRS-R scores were as follows: auditory function scale (localization to sound remained the same), visual function scale (visual pursuit remained the same), motor function scale (localization to noxious stimulus remained the same), oromotor/verbal function scale (oral reflexive movement remained the same), communication scale (remained none), and arousal scale (eye opening with stimulation remained the same).

**Discussion**
Over the past 20 years, pilot studies of RMNS for acute posttraumatic coma states have been done at East Carolina University and University of Virginia. The neurophysiologic effects of RMNS have been well documented at several neurosurgical centers in Japan using neuroimaging and spinal fluid assays. The experience of using RMNS in the treatment of patients in the PVS or MCS shows that longer periods of electrical stimulation measured in months or years would be needed for these more difficult cases.

Cooper et al presented a series of 25 comatose patients who had been treated with electrical stimulation of the right median nerve. In this double-blind pilot project patients in the treated group scored better on GCS, spent fewer days in the intensive care unit, and showed better GCS scores at 1 month postinjury. They concluded that peripheral electrical stimulation of the right median nerve, through activation of the ARAS, may be sufficient to arouse the moderate to severely comatose patient. Cooper and Kanno presented another series of 12 GCS 4 coma teenagers and young adults treated with early RMNS (teenagers and young adults). They showed good recovery in 4 out of 12 cases and moderate disability in 3 out of 12 cases. Therefore, more than half of these severely brain-injured patients who survived made a satisfactory recovery when the electrical stimulation was begun in the first few weeks postinjury.

In a double-blind randomized controlled study by Peri et al, 10 patients with coma were studied—6 treatments and 4 controls. The treatment group received median nerve electrical stimulation applied in 300 milliseconds intermittent pulses at 40 Hz, intensity 15 to 20 mA, 8 hours a day up to 14 days of coma. The control group received sham stimulation. The treatment group emerged from coma a mean 2 days earlier than controls, although this result was not statistically significant. At 3 months postinjury, there was no group difference in the Glasgow Outcome Scale. However, the treatment group had improved function over controls as measured by the FIM (functional independence measure). They concluded that there is a need for trials with large number of patients.

Liu et al used RMNS to awaken consciousness of six patients (two with brain trauma, one with aneurysm rupture, one with hemorrhagic stroke, and two with hypoxic encephalopathy). All patients underwent SPECT (single-photon emission computed tomography) scan for cerebral perfusion evaluation and neurotransmitter quantification before and after the stimulation. Four patients recovered from consciousness within 35 days. There was no obvious clinical improvement in two patients. Brain perfusion increased in all cases after stimulation. The elevation of neurotransmitter in CSF was found in five out of six cases. They concluded that median nerve stimulation elevates the cerebral blood flow and may influence the patient’s consciousness. Young patients (<= 40 years old) had better results than older patients. A study published by Arumugam et al compared the combined effect of RMNS and multisensory coma stimulation program on the level of consciousness and neurobehavioral function among patients with diffuse axonal injury. They studied nine patients, and concluded that after 2 weeks of stimulation there was a significant improvement in level of consciousness as measured by GCS between the groups. However, there was no significant improvement in neurobehavioral function as measured by Western neurosensory stimulation profile.

**Conclusion**
RMNS is a safe, inexpensive, noninvasive therapy and can facilitate recovery from coma. It is a ray of hope for all those
families of patients who are in coma or vegetative state. The results are promising and we are planning to recruit a larger number of patients for our future study. We plan to study the changes in cerebral blood flow in these patients using PET scan.

References