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Review Article

Spinal cord stimulation for spinal cord injury patients with paralysis: To regain walking and dignity

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Abstract

Spinal cord injury (SCI) usually leads to disconnection between traversing neuronal pathway. The impairment of neural circuitry and its ascending and descending pathway usually leave severe SCI patients with both motor disability and loss of sensory function. In addition to poor quality of life, SCI patients not only have disabling respiratory function, urinary retention, impaired sexual function, autonomic dysregulation but also medical refractory neuropathic pain in the long term. Some translational studies demonstrated that spinal networks possess a dynamic state of synaptic connection and excitability that can be facilitated by epidural spinal cord stimulation. In addition, preliminary human studies also confirmed that spinal cord stimulation enables stepping or standing in individuals with paraplegia as well. In this review, we examined the plausible interventional mechanisms underlying the effects of epidural spinal cord stimulation in animal studies. Following the success of translational research, chronic paralyzed subjects due to SCI, defined as motor complete status, regained their voluntary control and function of overground walking and even stepping for some. These progresses lead us into a new hope to help SCI patients to walk and regain their independent life again.

Keywords: *Paralysis, Spinal cord injury, Spinal cord stimulation*

Introduction

In the United States, it has been estimated to be 1,275,000 paralyzed patients due to severe spinal cord injury (SCI) and around 25,000 persons from severe SCI in Taiwan [1-3]. This inevitably leads to huge quality of life impact and economic burden to the patient, family, and society [4]. So far, there is no available treatment options for SCI patients with paralysis to improve their lost motor or sensory function at chronic stage. In addition, these patients usually have several coexistent disabilities including impaired respiratory function, urinary retention, impaired sexual function, autonomic dysregulation, and medical refractory neuropathic pain [5-8]. There is increasing experimental animal models of SCI to reveal the progress of neurological recovery through the advance of reparative interventions. Based on this, phase 1 clinical trials are initiated after some treatments have been shown possibility of translatable to patients with mild-to-moderate SCI. However, it is still lacking about the evidence for the efficacy of any specialized treatment designed to reanimate or reconnect the injured spinal cord in human [9,10]. For these clinically complete SCI patients (zero muscle power and loss of sensory function), defined as the American Spinal Injury Association Impairment Scale A, even intense rehabilitative program does not lead to voluntary control of movement. Improvement of ambulatory function is usually found with activity-based rehabilitation in patients who retain volitional movements of the legs after SCI [11]. However, Sherwood *et al*. found that about 84% of clinically complete SCI patients had surface EMGs and motor unit activity in response to several infralesional maneuvers. These patients were defined as "motor discomplete" [12-14]. Given the advance of neuromodulation for neural circuit and neural plasticity, there are growing translational and preliminary clinical evidences to show the benefit of using spinal cord stimulation for motor discomplete SCI patients with paralysis and uncontrolled neuropathic pain of lower limbs, what previously thought impossible to improve spontaneously at chronic stage. In this review, we first showed that translational evidences to decipher the mechanistic of how the neuromodulation with epidural spinal stimulation might work to repair the disconnected spinal cord and followed by

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recent promising clinical reports relating the effectiveness of spinal cord stimulation for severe SCI with paralyzed lower limbs.

Therapeutic mechanism underlying lumbosacral epidural spinal cord stimulation for paralysis

Therapeutic potential of spinal cord stimulation for paralyzed or transected spinal cord has been demonstrated in several animal studies [15]. Spinal rats (deprived of brain control), cats, and primates were able to show stepping pattern only under epidural spinal cord stimulation and this causal relationship was established based on the dependence of sensory feedback associated with weight bearing [16-19]. Activation of spinal synaptic circuit can be confirmed through examination of the evoked responses recorded through EMG. In addition, combination with medical treatment 5-Ht agonist (quipazine) enhanced the improvement of spinal cord stimulation on numbers of plantar steps and quality of stepping. This suggests that complementary benefit on impaired spinal neural circuits could be achieved through both epidural spinal cord stimulation and medical treatment [20]. In order to answer the question about the role of sensory input from the ipsilateral or contralateral lesion sides and how sensory input from the non-deafferented side compensate for the loss of afferent input over deafferented side, Lavrov *et al*. elucidated the recovery of coordinated activity of hindlimbs in rats with complete spinal cord transection and unilateral deafferentation [21]. The afferent information arising from the non-deafferented side, however, eventually could only mediate limited restoration of hindlimb movements on the deafferented side. Another study using spinal cord stimulation in swine models of SCI found that proximity of the stimulating electrode to the dorsal roots entry zone across individual vertebral segments was a crucial factor to evoke higher motor responses and further illustrated the association between anatomy of spinal cord and the effects of spinal cord stimulation [22]. These researches suggest that epidural spinal neuromodulation leading to improvement of stepping is primarily mediated through ipsilateral spinal ascending inputs that transmit and connect to the regional locomotor networks. Furthermore, multisource sensory inputs including proprioception and cutaneous sensory inputs help rat models of SCI synergistically reintegrate with epidural spinal cord stimulation to promote postural balance [23].

Recovery of locomotion of lower limbs in the spinal cats through lumbosacral spinal stimulation or four limbs with cervical spinal stimulation suggested that neuromodulation over spinal cord could elicit activation of intrinsically organized spinal circuits [24,25]. A computational modeling study also revealed that epidural spinal stimulation engaged spinal circuits inter-neuronal processing through the recruitment of myelinated afferent fibers, instead of direct influence on motor neurons or interneurons [26]. Taken together, these researches support that epidural spinal cord stimulation-induced stepping or overground walking first requires synergistic effect from both multisource sensory input and transsynaptically propagation to engage motor neurons and generate voluntary motor movement over legs [21]. These findings are consistent with what we saw in rats models or human with severe SCI [27,28]. The mechanistic of functional recovery after SCI has also been investigated through both physiological and anatomical methods. Even transection and disconnection of long descending supraspinal tracts in rodents has been totally irreversible, Courtine *et al*. showed that propriospinal relay connections that bypass one or more injury sites are able to mediate spontaneous functional recovery and supraspinal control of stepping [17]. This implicates that strategy toward enhancing and remodeling the relay neuronal connections might generate alternative therapeutic efficacy to cross SCI lesions and repair it [Figure 1] [16].

Lumbosacral epidural spinal cord stimulation for volitional motor control of lower limbs

Herman *et al*. first demonstrated that, in addition to locomotor rehabilitation, spinal cord stimulation over dorsal epidural and lumbosacral segments regain ability of overground walking on a locomotor-assisted treadmill [29]. Although the subject had suffered incomplete motor SCI at C5/6 for 3.5 years before included in study, resume of ambulation was not achievable after intense rehabilitation programs. The combination therapy using epidural spinal cord stimulation with partial weight-bearing therapy further facilitated walking speed with 2 times more and significant reduction of effort for overground walking [30].

Harkema *et al*. reported their breakthrough attempt of using similar surgical technique by surgically implanted epidural

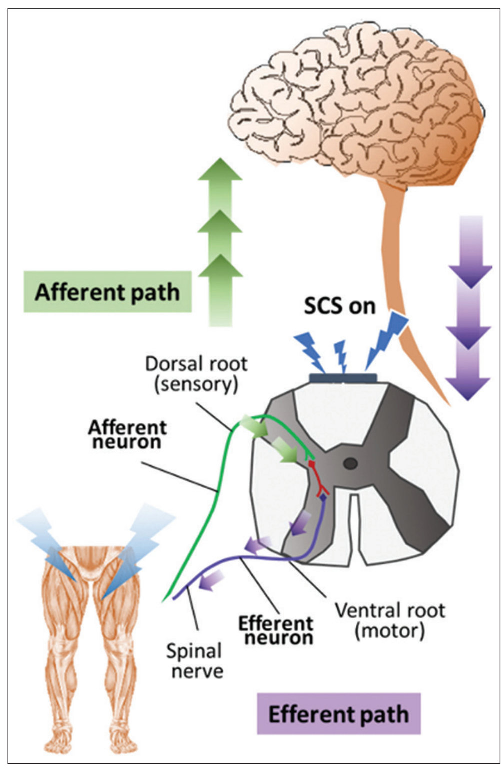

Figure 1: Epidural spinal cord stimulation repairs regional impaired neural circuitry and enhances synaptic connection of damaged spinal cord from both afferent and efferent inputs

spinal stimulation electrode over lumbosacral segment (around T11, T12, and L1) for a 23-year-old male remained paralysis 3.4 years after traffic accident [28]. What is different from previous works is the enrolled subject with motor complete and sensory incomplete paraplegia. Seven months after implantation, the patient recovered supraspinal control of some leg movements, but only during epidural stimulation. Prestimulation around 9 months physical rehabilitation failed to reach assisted standing or overground walking [31]. On the contrary, comparable 10-month design physical programs as well as activity-coordinated specified stimulation improve subject's voluntarily control stepping and standing. This report implicated that task-specific spinal cord stimulation could reactivate previously possible dormant spinal circuitry and enhance neural plasticity [32]. In addition to this report, a follow-up study enrolled 3 more patients (2 with complete motor and sensory paralysis). Similar to their finding from the first subject, neuromodulation through epidural spinal cord stimulator over lumbosacral area enables the recovery of intentional movement of lower limbs from all 4 subjects with complete paralyzed motor function [33]. Furthermore, these subjects were able to process auditory and visual cues and demonstrate fine motor output in the lower limbs in response to these signals. This research established spinal cord stimulation as a fundamentally new intervention to enable motor activity in individuals diagnosed with chronic and motor complete SCI.

At another follow-up investigation, these subjects showed epidural spinal stimulation inducing EMG activity over lower limb muscles, only during standing instead of sitting position [34]. This implied that to reproduce effective EMG activity in order to execute and achieve full weight-bearing standing relies on weight-bearing related sensory input and integration. Furthermore, more coordinated EMG patterns for standing were only evoked when cathodes over caudal array region where contacts were close the lumbo-sacral junction of

Table 1: Clinical studies of spinal cord stimulation for spinal cord injury patients, including patients' characteristics, stimulation design, specific task-related physical rehabilitations, and outcome

	Level of spinal cord injury	ASIA grading	Implant of spinal cord stimulator	Level	Specialized rehabilitation and stimulation program	Level of functional recovery
Harkema *et al.*	C7/T1 subluxation withmotor complete SCI (1)	B	Restore Advanced, Medtronic, Medtronic Specify 5-6-5	T11/T12/L1	7 months local motor training	Full weight-bearing standing with assistance provided only for balance for 4.25 min
Angeli *et al.*	C7 (2), T5 (2) withmotor complete SCI	A (2), B (2)	Restore Advanced, Medtronic, Medtronic Specify 5-6-5	T12/L1	6 months local motor training	Process of conceptual, auditory and visual input to regain relatively fine voluntary control of paralysed muscles
Angeli *et al.*	C5 (1), T1 (1), T4 (2) with motor complete SCI	A (2), B (2)	Restore Advanced, Medtronic, Medtronic Specify 5-6-5	T12/L1	Using EMG to identify. the extensor and flexor muscle groups that were activated by stimulating each epidural anode and cathode combination at 2 Hz Spatial maps of motor activation during low frequency (2 Hz) bipolar electrode stimulation Several combinations of programs (anode and cathode combinations at a specific voltage) for different motion configurations at the same frequency were given sequentially	2 over ground walking, 2 standing
Wagner *et al.*	C4 (1), C7 (2) incomplete SCI	C (2), D (1)	Restore Advanced, Medtronic, Medtronic Specify 5-6-5	T11/T12/L1	Simulated map of motor neuron activation following EES targeting the L1 and S2 posterior roots Configuration of spatiotemporal EES for walking Using an implanted pulse generator with real-time triggering capabilities for activating spatiotemporal EES for walking	Regain voluntary control of previously paralyzed muscles without stimulation
Grahn *et al.*	T6 complete SCI (1)	A	Restore Sensor Sure Scan MRI, Medtronic Specify 5-6-5	T11/T12/L1	2 weeks of multi-modal rehabilitation	Intentionally control task-specific muscle activity
Gill *et al.*	T6 complete SCI (1)	A	Restore Sensor Sure Scan MRI, Medtronic Specify 5-6-5	T11/T12/L1	Two-program interleaved EES (left and right) 43 weeks of multimodal rehabilitation including standing and step	Independent stepping and walking using front-wheeled walker

SCI: Spinal cord injury, C: Cervical, T: Thoracic, L: Lumbar, ASIA grading: American Spinal Injury Association grading, EES: Epidural electrical stimulation spinal cord with stimulating parameters configured at frequencies within 25–60 Hz. Taken together, these clinical studies suggest that individualized stimulation configurations and design of specific task-related physical rehabilitations are both important and are shown in Table 1. Furthermore, even in the lack of connections due to injured spinal cord, spinal synaptic plasticity and connection within spinal circuitry can generate effective motor function. The improvement of synaptic plasticity and reanimation of disconnected spinal cord after neuromodulation may explain why some severe SCI patients only acquire independent standing and trunk stability, while others achieve stepping and walking over the ground under continuously epidural spinal stimulation [35].

Grahn *et al*. aimed to replicate the findings at the Mayo Clinic [36]. They enrolled a motor complete SCI patient at level of T6 and found that, within 2 weeks, spinal cord stimulation of subject enabled volitional control of task-specific muscle activity, voluntary control of rhythmic muscle activity to produce step-like movements during lying on the side, independent standing, and intentional control of step-like movements and rhythmic muscular contraction when assisted with partial weight bearing support [36]. During a longer follow-up with 1-year additional multimodel rehabilitation, the same subject improved further to regain stepping on the treadmill with minimal support or independently [37]. In accordance with previous research, their findings confirmed that epidural spinal cord stimulation along with intense and tailored physical rehabilitation programs could resume the volitional control of lower limbs muscular contraction [21,27]. Different from these studies using continuous epidural spinal stimulation, Wagner *et al*. chose a closed-loop and adaptive design of epidural spinal stimulation for SCI patients with permanent motor deficit or motor complete [38]. Specifically, the spatiotemporal paradigm first identified electrode configurations that target the posterior roots that project to spinal cord regions, containing motor neurons involved in mobilizing the hip, knee, and ankle joints. 3D kinematics and ground reaction forces were recorded simultaneously to provide real-time feedback for the delivered trains of spatially selective stimulation. In accordance with the sequential movement related to the stepping or rhythmic activities of legs, previously configured stimulation parameters were set to match these individually intended movements to trigger and finish overground walking after a few months of training and rehabilitation for patients. This study showed that spatiotemporal epidural spinal stimulation not only more effectively enabled completely or partially paralyzed individuals to walk overground but also allowed them to adjust leg movements to stand and walk over a range of speeds for durations as long as 1 hour.

Conclusion

There are growing evidences to show the benefit of using epidural spinal cord stimulation to excite regional impaired neural circuitry from SCI and facilitate voluntary control of lower limbs, which were motor complete without neuromodulation. Although we need more clinical evidences to statistically show the effects of resuming walking capability, lumbosacral epidural spinal cord stimulation as well as intense multimodal physical rehabilitation have opened a window for those severe SCI patients. In the future, patient-tailored brain–spinal interface and closed-loop control of injured spinal cord might provide a new way to restore the communication of brain and spinal cord and functionality of paralyzed patients.

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Conflicts of interest

There are no conflicts of interest.

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