



## Spinal cord epidural stimulation for voluntary movement after spinal cord injury: current state of the research.

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## Introduction:

The classification system widely accepted and used for spinal cord injury (SCI) is the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI).<sup>1</sup> The ISNCSCI system uses the American Spinal Injury Association Impairment Scale (AIS) classification of A through E, with AIS A being the most severe rating with complete loss of sensorimotor function below the level of injury and AIS E being the least compromised with normal function below the injury level.<sup>1</sup> Generally speaking, it has been conventionally thought that patients with the AIS A and AIS B classifications will not recover the ability to voluntarily walk or functionally move their lower extremities.<sup>2</sup>

However, innovations have emerged, challenging this previously-held assumption. In particular, epidural electrical stimulation has been shown to promote motor patterns in animal models of SCI along with human individuals that have sustained a motor complete SCI.<sup>3</sup> Continuing with this line of research, the first groundbreaking case study reported that a man with clinical and neurophysiological motor complete SCI was able to recover standing ability and volitional movement of his lower extremities with an implanted epidural electrical stimulator turned on.<sup>4</sup> For standing, the authors theorized that spinal stimulation increased the excitability of the spinal circuitry, which re-enabled its capability to generate activation patterns effective for standing in response to weight-bearing related sensory information.<sup>4</sup> The primary theory behind the patient's renewed ability to move his lower extremities while the stimulator was on was an increased excitation of lumbosacral interand motoneurons allowed for those few spared descending supraspinal fibers to properly activate lower extremity muscles.<sup>4</sup>

### <u>Objectives</u>:

- 1. Describe the current state of the research in spinal cord epidural stimulation for voluntary movement after SCI.
- 2. Describe the potential mechanisms underlying this innovation.
- 3. Provide an overview of physical therapy approaches using epidural stimulation.

### **Target Audience**

The primary target audience for this Current State of the Research paper are physical therapists and other therapists working with individuals whom have sustained spinal cord injury.

### Brief Summary

Within the past 10 years, epidural stimulation of the lumbo-sacral spinal cord has shown potential to allow voluntary movement below the spinal cord injury in patients that were once thought to never be able to do so. Questions remain to understand the specific mechanisms of why this works, patient safety and clinical efficacy, and widespread accessibility to these technologies. Nevertheless, the implications for future physical therapy practice cannot be ignored.

# <u>Objective 1: Describe the current state of the research in spinal cord epidural electrical</u> <u>stimulation for voluntary movement after SCI.</u>

In 2011, a case report was published showing that a person with a clinically motor complete SCI could voluntarily move his legs again with surgically-implanted epidural stimulation, a feat that he had not accomplished in over three years.<sup>4</sup> Following this case, the field of spinal cord epidural stimulation for voluntary movement after SCI has drastically expanded. This same research group, located in the United States, demonstrated in three additional individuals with motor-complete SCI (2 – 4 years post injury) that voluntary leg movement and standing was indeed achievable in the presence of epidural stimulation.<sup>5,6</sup> These results were replicated in an independent case study, also located in the United States, within two weeks of implanting the stimulator.<sup>7</sup> This person eventually was able to voluntarily walk using epidural stimulation and a wheeled-walker.<sup>8</sup> Recovery of walking using epidural stimulation has now been demonstrated internationally,<sup>9</sup> in an ongoing trial located in Switzerland.

#### Objective 2: Describe the potential mechanisms underlying this innovation.

Based on epidural stimulation studies using animal models, researchers proposed that this intervention enhances central pattern generation (neuronal networks located in the spinal cord) thereby restoring the ability of these animals to step and walk.<sup>10-13</sup> When high intensity stimulation (above motor threshold) was applied to the lumbar spine of humans with clinically motor complete SCI, a rhythmic pattern of muscle activity was observed in the lower extremities, similar to that of walking.<sup>14</sup> Initially using epidural stimulation for spasticity control in five individuals with motor complete SCI, the stimulation also caused a lower extremity extension muscle response, consistent with the spinal cord neuronal network activation theory.<sup>15</sup>

In 2011, an epidural stimulator was implanted in a man with motor complete but sensory incomplete SCI, with the intent of enhancing these interneuronal networks by providing near-motor threshold stimulation intensity, in order to promote standing and walking in response to sensory information.<sup>4</sup> In a surprising fashion, this patient also regained the ability to voluntarily generate leg movement, leading to two new theories – 1) intact (but clinically undetectable) supraspinal connections still exist and these connections plus spinal cord epidural stimulation allows for sufficient activation of the leg motoneurons; 2) axonal sprouting may have occurred during his seven month training period and this new

wiring in addition to spinal cord epidural stimulation allows for sufficient activation threshold of the leg motoneurons.<sup>4</sup>

Because some individuals rapidly regain this voluntary leg movement after epidural stimulation implantation, the first new theory gained substantial support.<sup>5</sup> However, at least one person regained voluntary leg movement even when the epidural spinal cord stimulator was turned off, suggesting and supporting the second new theory that neuroplasticity of the spinal cord indeed plays a crucial role.<sup>16</sup>

## Objective 3: Provide an overview of physical therapy approaches using epidural stimulation.

There have been various rehabilitation protocols used throughout these studies, and there is currently not a single followed protocol for rehabilitation using cord stimulation. From the studies discussed, rehabilitation protocols consisted mostly of intensive stand training and repetitive stepping with trainers positioned at the knees and pelvis to offer support as needed. A wide variety of parameters have been reported, ranging from multiple times a week for two weeks to multiple months of sessions as well as various durations anywhere from 54 minutes to 7-hour sessions.

When working with patients with SCI, a physical therapist considers intervention planning of a patient with motor complete SCI (AIS A or B) differently than a patient with motor incomplete SCI (AIS C or D). For example, historically, physical therapists may have considered more compensatory intervention strategies when working with individuals with clinically motor complete SCI. Now with the addition of spinal cord epidural stimulation, treatment planning may include more restorative approaches to engage lower extremity muscles and movements such as standing and walking.

## <u>Conclusion</u>

Epidural stimulation shows promise to promote and restore voluntary movement after clinically motor complete SCI, which historically was thought to be impossible. At the moment, this surgical intervention is not yet clinically available to the public, although clinical trials are well underway to explore safety and efficacy (2 sites actively recruiting, ClinicalTrials.gov Identifier: NCT03026816 and NCT02339233). Once questions are addressed regarding safety of the surgical procedure, long term effects, and reimbursement issues, epidural stimulation may be a viable intervention for patients with SCI. Accordingly, the physical therapists' management of these patients would be drastically altered.

## **References**

- 1. Kirshblum SC, Waring W, Biering-Sorensen F, et al. Reference for the 2011 revision of the international standards for neurological classification of spinal cord injury. *J Spinal Cord Med*. 2011;34(6):547-554.
- 2. Scivoletto G, Tamburella F, Laurenza L, Torre M, Molinari M. Who is going to walk? A review of the factors influencing walking recovery after spinal cord injury. *Front Hum Neurosci.* 2014;8:141.
- 3. Gerasimenko Y, Roy RR, Edgerton VR. Epidural stimulation: Comparison of the spinal circuits that generate and control locomotion in rats, cats and humans. *Exp Neurol*. 2008;209(2):417-425.
- 4. Harkema S, Gerasimenko Y, Hodes J, et al. Effect of epidural stimulation of the

lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet (London, England)*. 2011;377(9781):1938-1947.

- 5. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*. 2014;137(5):1394-1409.
- 6. Rejc E, Angeli C, Harkema S. Effects of Lumbosacral Spinal Cord Epidural Stimulation for standing after chronic complete paralysis in humans. *PLoS One*. 2015;10(7):e0133998.
- 7. Grahn PJ, Lavrov IA, Sayenko DG, et al. Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. *Mayo Clin Proc*. 2017;92(4):544-554.
- 8. Gill ML, Grahn PJ, Calvert JS, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nat Med*. 2018;24(11):1677-1682.
- 9. Formento E, Minassian K, Wagner F, et al. Electrical spinal cord stimulation must preserve proprioception to enable locomotion in humans with spinal cord injury. *Nat Neurosci.* 2018;21(12):1728-1741.
- 10. Gerasimenko YP, Avelev VD, Nikitin OA, Lavrov IA. Initiation of locomotor activity in spinal cats by epidural stimulation of the spinal cord. *Neurosci Behav Physiol*. 2003;33(3):247-254.
- 11. Gerasimenko YP, Lavrov IA, Bogacheva IN, Shcherbakova NA, Kucher VI, Musienko PE. Formation of locomotor patterns in decerebrate cats in conditions of epidural stimulation of the spinal cord. *Neurosci Behav Physiol*. 2005;35(3):291-298.
- 12. Ichiyama RM, Gerasimenko YP, Zhong H, Roy RR, Edgerton VR. Hindlimb stepping movements in complete spinal rats induced by epidural spinal cord stimulation. *Neurosci Lett.* 2005;383(3):339-344.
- 13. Lavrov I, Gerasimenko YP, Ichiyama RM, et al. Plasticity of spinal cord reflexes after a complete transection in adult rats: relationship to stepping ability. *J Neurophysiol*. 2006;96(4):1699-1710.
- 14. Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci*. 1998;860:360-376.
- 15. Jilge B, Minassian K, Rattay F, et al. Initiating extension of the lower limbs in subjects with complete spinal cord injury by epidural lumbar cord stimulation. *Exp Brain Res.* 2004;154(3):308-326.
- 16. Rejc E, Angeli CA, Atkinson D, Harkema SJ. Motor recovery after activity-based training with spinal cord epidural stimulation in a chronic motor complete paraplegic. *Sci Rep.* 2017;7(1):13476.