REHABILITATION OF PATIENTS IN LATE PERIOD AFTER SPINAL CORD INJURY: A META-ANALYSIS OF LITERATURE DATA

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Objective. To analyze the literature on rehabilitation of patients in late period after spinal cord injury from the standpoint of evidence-based medicine.

Material and Methods. The study design is a meta-analysis of publications with levels 1a, b, c, and 2a evidence and a level A recommendations. An electronic search was conducted in the PubMed, Web of Science, Scopus, Cochrane Library, CrossRef, AO Spine, Eurospine, ResearchGate, eLIBRARY, and MEDLINE databases, and in references of key articles. Inclusion criteria were systematic reviews, randomized controlled studies, multicenter cohort studies with a level 1a, b, c, and 2a evidence and level A recommendations for adult patients with long-term sequelae of spinal cord injury (more than 4 months after injury). Exclusion criteria were topic articles, clinical cases, observations, cohort uncontrolled studies, experimental articles, reports, articles with levels 2b, c, 3a, b, 4, and 5 evidence and level B, C, and D recommendations, pediatric patients, early period after spinal cord injury (less than 4 months), and non-traumatic lesions of the spinal cord.

Results. The search returned 108 articles with publication date within 1997–2019. The inclusion criteria was met by 65 publications: 33 systematic reviews, 12 randomized controlled studies, 19 multicenter studies; and one open prospective study was included in the review due to the particular treatment method used. The greatest evidence base for the rehabilitation of patients in the long-term period after spinal cord injury is presented for physical methods of rehabilitation. The most effective are locomotor training to develop skills of movement. Auxiliary verticalization and robotic devices are needed to restore and improve proprioceptive innervation. In case of violation of the spinal tracts, the restoration of motor functions occurs due to the activation of supraspinal interneuronal connections. Epidural electrical stimulation of the lumbar thickening of the spinal cord activates a generator of voluntary movement of the limbs and, in combination with training of proprioceptive sensitivity, leads to a regression of movement disorders. The constant use of electrostimulation blocks proprioceptive sensitivity and inhibits the recovery of spinal conductivity. Parameters of clinical application are not defined for areas of regenerative medicine.

Conclusion. The main problem in rehabilitation of patients in late period after spinal cord injury is the lack of a unified concept, developed strategies of rehabilitation technologies, and criteria for assessment of the initial status and treatment efficiency.

Key Words: late period after spinal cord injury, rehabilitation in late period after spinal cord injury, treatment in late period after spinal cord injury.

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Despite the great number of publications, the main trends in rehabilitation of patients in the late period after spinal cord injury have not been defined from the standpoint of evidence-based medicine. Many of them are either at the experimental stage or have not been defined for the clinical study or describe individual clinical cases.

The aim of the study is to analyze the literature on rehabilitation of patients in the late period after spinal cord injury from the standpoint of evidence-based medicine.

The study design is meta-analysis of publications with levels 1a, b, c, 2a evidence and level A recommendations.

Material and Methods

An electronic search was conducted in the PubMed, Web of Science, Scopus, Cochrane Library, CrossRef, AO Spine, Eurospine, ResearchGate, eLIBRARY, and MEDLINE databases, as well as in the references of the key articles.

Inclusion criteria were as follows: systematic reviews, randomized controlled studies, multicenter cohort studies with a level 1a, b, c, and 2a evidence and level A recommendations for adult patients with long-term sequelae of spinal cord injury (more than 4 months after injury).

Keywords for the search were: chronic spinal cord injury, rehabilitation of patients with chronic spinal cord injury, treatment of patients with chronic spinal cord injury.

Exclusion criteria were topic articles, clinical cases, observations, uncontrolled cohort studies, experimental articles, reports, articles with levels 2b, c, 3a, b, 4, and 5 evidence and level B, C, and D recommendations, pediatric patients, early period after spinal cord injury (less than 4 months), and non-traumatic lesions of the spinal cord.

The period of search was April 2016 – March 2019.

Results and Discussion

The search returned 108 articles with publication date within 1997–2019. Among those, the inclusion criteria were met by 65 publications: 33 systematic reviews, 12 randomized controlled studies, and 19 multicenter studies. In addition, one open prospective study (long-term 48-month follow-up period) was included in the review due to the particular treatment method used. The topics of the publications are presented in Table.

Regarding the consequences of the spinal cord injury, it is one of the most disabling types of trauma for the patient and expensive in terms of treatment and rehabilitation among other types of injuries. More than 2 million people in the world live with the consequences of spinal cord injury, including physical, social, psychological and emotional disorders that affect the victim's family, friends, employers, the society, and the healthcare system as a whole [2].

Studies of the effects of spinal cord injury highlight various aspects. Nowrouzi et al. [2] analyzed papers on the problems of long-term spinal cord injury. The most published and cited topics are pathology/medical history, treatment and epidemiology.

A bibliometric review study by Liu et al. [3] revealed 5,607 articles on rehabilitation of patients with spinal cord injury in 1997–2016 with an annual increase in their number. The most active country is the USA. Publications of the last 20 years can be divided into three stages: until 2005 is the initial period, publications on the current situation; 2005–2011 is the period of rapid development, it includes papers on solutions to the posed problems; after 2011 is the period of slow development, the decline in publication activity due to the development crisis, the search for effective technical means, such as artificial intelligence, the brain-computer interface, stem cell therapy, breakthrough in reformation of the existing technologies [3].

Rehabilitation of patients with spinal cord injury is based on pathomorphological changes in both the nervous system, i.e. the spinal cord substance, and the organism as a whole and is divided into phases starting from the moment of injury: acute, subacute, and chronic stages. The acute and subacute phases are combined into one neurorecovery stage (12–18 months after injury), the stage after neurorecovery is called the chronic phase [4]. In the domestic literature, the corresponding (in terms of time characteristics) division is the classification of the periods of the traumatic disease of spinal cord (TDSC) by O.A. Amelina [5]: acute (from several days to 3–4 months), intermediate (1–2 years), and late (indefinite in duration).

Rehabilitation in the acute and subacute stages is aimed at stimulating and enhancing neurorecovery processes, maximal restoration of lost functions, prevention of secondary complications and creation of optimal conditions for the long-term maintenance of the patient's health [6].

The late period of the spinal cord injury is characterized by persistent neurological disorders and altered functional status of the patients.

Currently, there are no generally accepted approaches to the condition assessment, care, and rehabilitation methods for patients with traumatic spinal cord disease in both acute and late periods of the disease [7–10].

Results of a systematic review by Burns et al. [4] show that the evidence base on many key issues of rehabilitation after spinal cord injury is limited. There is not enough information on the time of rehabilitation, its nature, volume (intensity, frequency, duration), the role and impact of the physical and psychological characteristics of the patient, the type of injury, profitability and efficience of alternative methods. The methods of recovery from spinal cord injury are not systematized, and the term "rehabilitation" includes surgical, physical and mechanical methods without evaluating the results and effectiveness and, in most cases, it presents a "black box" or a "Russian nesting doll" [11].

In recent years, attempts were made to systematize and classify the main rehabilitation technologies: Van Langeveld et al. [10] analyzed the methods of 10 rehabilitation centers in Holland and Germany [10]; there is the SCIRehab project in the USA [8], Rapidi et al. [12] assessed the work of European rehabilitation centers. The main conclusions in organizing care for patients with the consequences of spinal cord injury are the following: assistance provided by doctors experienced in the rehabilitation of such patients, conducting programs that include multidisciplinary teams, patient-oriented approach taking into account the patient's functional status, his needs, the period after injury, and life-time monitoring with periodic hospitalizations.

There is no doubt that the nature and content of rehabilitation methods should vary depending on many factors: the period of the disease, injury level, neurological status, and social aspects. In addition, the time, type, intensity and duration of treatment are determined not only based on the medical report but also depending on the health care policy and financing [4].

The problem for assessing both the initial state of patients and the rehabilitation results is the lack of uniform scale and questionnaires. The most common are the ASIA scale for assessing neurological status, SCIM and FIM scale for assessing functional status, and a 10- or 15-meter walk test for gait assessment.

The later rehabilitation begins from the moment of injury, the worse its results and the quality of the patients' life [13–17]. The effectiveness of rehabilitation is also affected by the patient's age, education level [13], body weight [18, 19], marital status, and repeated hospitalizations (dynamic observation by a team of specialists) [8, 10, 12].

Reviews by Hyun et al. [20] and Huang et al. [21] demonstrate the key objectively confirmed areas of neurorehabilitation therapy for patients with complete spinal cord injury. Patients in the late period after spinal cord injury are no longer told that there is nothing that can be done. The mechanisms of neurorehabilitation therapy include neuromodulation, neuroprotection, remyelination or neurorestoration, neuroplasticity, axonal regeneration, modulation of anti-inflammatory responses, neurogenesis, angiogenesis, and neuronal replacement. Partial functional recovery and an

Table

Distribution of articles on research topics and study design

Publication topic	Study design	Number of publications
Bibliographic reviews	systematic reviews	2
Problems of classification, areas of rehabilitation, outcomes	– systematic reviews;	5
	– multicenter studies	15
Physical rehabilitation methods	– systematic reviews;	8
	– multicenter studies;	1
	– randomized controlled studies	7
Epidural electrical stimulation	– systematic reviews;	13
	– multicenter studies;	2
	– randomized controlled studies	5
Neuronal regeneration, cell technologies	– systematic reviews;	5
	– multicenter studies;	1
	– prospective study	1

improvement in the quality of life was noted after stem and embryonic cell transplantation, intrathecal administration of neurotrophic factors at the conus medullaris and intramuscular injection of cell suspension. Electrical stimulation of denervated muscles is effective for maintaining the muscle mass, blood perfusion, and the cosmetic effect. Limb neuroprosthetic interfaces help patients to adapt to certain types of daily activities. Robotic simulators are based on sensory afferent activity and feedback. Neurotization techniques offer such options as transplantation of a peripheral nerve into the spinal cord above and below the injury level, transplantation of the anterior spinal nerve roots to improve the innervation of the bladder [20]. Neurorehabilitation includes complexes of locomotor training in combination with robotic devices. A promising approach is a combination of several techniques taking into account the functional state of the patient in the late period after spinal cord injury. However, the possibilities of these processes in relation to the spinal cord injury, as well as their effectiveness, are limited [21]. According to the authors, no clinical trials for patients in the late period after spinal cord injury showed functional improvements. The most effective delivery method and the amount of the required substance have not been determined for stem cell implantation. Experimental developments (pluripotent stem cells, neurotrophic factors, anti-inhibitors, biopolymers) and their combination with physical methods have also not been determined for clinical use [20, 21].

The possibilities and prospects of regenerative medicine in the chronic phase of the traumatic spinal cord injury were presented by Dalamagkas et al. [22]. Late period of the injury is characterized by termination of inflammatory processes, neuroplasticity and spontaneous regeneration. Promising regenerative technologies that can be introduced into clinical practice include neurospheres (populations of human nerve stem cells capable of renewal and differentiation into the main types of CNS cells after several generations); a line made of biomaterial and neuronal stem cells to create a drawbridge at the level of damage; transplantation of Schwann cells and cord blood mononuclear cells; bacterial enzyme acting on scar tissue; gene therapy using a modified chondroitinase gene; nanostructured matrices based on graphene oxide, fibrin, and hydrogel; chitosan- and laminin-based biomaterial. Currently, these technologies are at the experimental stage with single clinical cases; indications and methods of their application have not yet been defined [22].

In order to assess the effectiveness and safety of acidic fibroblast growth factor aFGF, an open prospective clinical study was conducted with a long-term result of 48 months. According to the authors of [23], aFGF is a safe and affordable treatment method although with slight functional improvement.

Among the physical methods of rehabilitation, locomotor training, treadmill walking and exercises on robotic and visually oriented devices are the most often analyzed.

Systematic reviews devoted to the analysis of the effectiveness of training on robotic devices in comparison with other musculoskeletal training strategies (treadmill, body support, electrical muscle stimulation, training in orthoses, gait training) did not find statistically significant differences in assessing the level of independence of movement, distance and speed [24–29]. A randomized controlled trial by Galea et al. [30] revealed a better result when teaching the patients with chronic traumatic disease of the spinal cord to walk using conventional locomotor training than robotic devices.

Comparative analysis of the effectiveness of exercises on robotic devices for patients with incomplete spinal cord injury demonstrated their higher effectiveness in improving movement than that for conventional training but only in the acute period of the disease [17, 31].

Dobkin et al. [32] and Lucareli et al. [33] have not obtained evidence of the higher efficiency of the treadmill exercises than gait training alone.

Visually oriented exercises and treadmill training equally improve endurance and gait [34, 35]. The effectiveness of feedback training aimed at activating dysfunctional neural networks of the spinal cord is shown in a review by McDonald et al. [36].

A randomized controlled study by Boswell-Ruys et al. [37] demonstrated efficiency of conventional "sitting without support" type of training compared to the untreated control group.

An actively used method for treating patients in the late period of spinal cord injury is epidural electrical stimulation (EES).

Motor neurons are the only channel through which motor commands reach the muscles. Conductivity of motor neurons is controlled by the brain stem through a system of interneurons and supraspinal connections. Both the conductivity of motor neurons and the neuromodulatory effect of the brain stem are impaired in spinal cord injury [38]. If the spinal cord is damaged, a critical number of motor neurons survive, but they cannot carry action potentials and are electrically unresponsive. They can become electrically active due to neuromodulatory factors acting through the system of supraspinal connections. Thus, the neural networks of the brain and the spinal cord can be the main factor the functional activity of which determines the restoration of active voluntary movements of the limbs. Modulation of the supraspinal connection system results in a gradual restoration of spinal excitability and the appearance of muscle contractions [39, 40]. Another mechanism of EES action is considered to be the stimulation of interneuronal connections through the activation of proprioceptive innervation [41].

In 1911, a generator of voluntary limb movements was described as accumulation of interneurons localized in the lumbar enlargement of the spinal cord. The generator is activated by mediators of the supraspinal neural network and initiates sequential activation of the thigh and lower leg muscles, then flexion of the foot, knee and thigh [40]. The rehabilitation effects of spinal cord stimulation have been widely shown in animal studies, which demonstrated the ability to move independently when applying EES during a treadmill walk despite the complete loss of function without EES [42–45]. The performed experiments indicate that the motor pattern in EES requires a combination with the sensory information. Restoration of the walking ability must be combined with a vertical load on the limbs; this factor plays a critical role in the rehabilitation of people with spinal cord injury using EES [46–49].

The use of an electric field in the dorsal epidural space activates the neuronal structures both inside and outside the spinal canal. The spinal canal and its content present a heterogeneous conductor with several neuronal structures, which cause various reactions upon electrical stimulation. The cerebrospinal fluid has the highest conductivity followed by the white matter of the spinal cord. In addition, the orientation of the fibers (longitudinal or transverse), the descending angle from the spinal cord, and the internal distribution of intraspinal fibers and the gray matter have an impact on conductivity. The most important factor determining the current distribution during EES is the width of the cerebrospinal fluid space between the electrode and neuronal structures. Other important factors are the size and orientation of the nerve fibers: larger fibers are the first to be stimulated, since they cross the electric field in the transverse direction and have a lower threshold than the fibers extending in the longitudinal direction. Therefore, when the electrode is placed close to the spinal cord, the transverse segmental part of the afferent system is the one that is mainly stimulated. The location of an electrode should be at the level of cerebrospinal fluid accumulation for stimulation of the anterior motor neurons and intraspinal neurons and at the level of all dural sac structures for the distribution of excitation [50].

Lumbosacral EES allows one to improve the motor and sensory functions, pelvic organ function in patients with long-term consequences of spinal cord injury. In most cases, implantation of devices for chronic stimulation is used after test stimulation. Chronic EES requires constant placement of the implantable electrode on the dural sac, laminectomy, implantation of a pulse generator device with its subsequent connection and adjustment [44]. The operation of such devices is not always convenient for patients [47]. In addition, the authors mention the risks of surgical infection, postoperative instability, and spinal deformity. The electronic stimulator under development, which is made of soft materials and capable of simultaneously conducting electrical and neurochemical stimulation of the spinal cord, has not yet passed clinical trials. The configuration of the electrodes, as well as the parameters necessary to stimulate motor activity, depend on the anatomy of the spinal cord, the severity of the injury and the electrode placement. The strategy of selecting individual EES parameters for each patient is laborious [44]. Transcutaneous stimulation of the lumbar spinal cord and temporary EES may serve as an alternative [42, 43, 45]. These techniques are more functional for patients when combined with locomotor training courses. The use of periodic (course) temporary targeted stimulation of the spinal cord for selective activation of the sensorimotor network in order to improve motor characteristics seems to be promising in people with spinal cord injury [48, 51].

EES efficiency depends on the electrode location, disease duration, and residual functions. However, in general, it has a positive effect on the gait speed, endurance, and tolerance of physical activity [52, 53].

Jones et al. [17] conducted a randomized controlled study of patients with incomplete spinal cord injury in the late period after injury in order to evaluate the effectiveness of early or delayed motor training in combination with EES and showed its greater efficiency compared to intrathecal administration of neurotransmitters.

A multicenter study by Wenger et al. [54], which involved 16 clinics, determined the EES protocols for the lumbar segments of the spinal cord reproducing the natural activation of the motor neuron during movement. The combination of selective spinal implants and software modulates the movements of the extensor and flexor in real time, which allows training the patient's gait.

The effectiveness of EES for improving the function of the upper limbs in patients with tetraparesis in incomplete spinal cord injury has been confirmed [55]. Normal functioning of the hand is the most important problem for people with spinal cord injuries at the cervical level.

Studies in healthy people and patients with spinal cord injury and cerebral palsy indicate that even transcutaneous electrical stimulation at the lumbar enlargement leads to increased excitability of the lumbar spinal neural structures, activation of afferent systems, including dorsal roots with their mono- and polysynaptic projections to motor nuclei, an increase in the speed of impulses along nerve conductors and the structures of the neuromuscular system [43, 56].

Another aspect of the use of EES in the late period of a traumatic spinal cord injury is neuropathic pain syndrome [57]. Moreno-Duarte et al. [58], when analyzing nine randomized controlled trials, noted a reduction in pain in six of them without any significant negative effect of stimulation.

The disadvantage of EES is that it is capable of effectively generating a reliable musculoskeletal reaction after spinal cord injury in rodents but not humans [41, 42, 45, 51, 56]. The main pathophysiological aspect of this is the lack of proprioceptive innervation in rats. Clinical and experimental studies show that it is the combination of EES with locomotor training that plays a crucial role in the activation of spinal neural networks and formation of a significant voluntary motor response of the muscles [56]. Moreover, the effect of using chronic EES is observed only during its implementation and only in combination with training [41, 45, 49, 56].

Computer simulations, preclinical and clinical experiments demonstrated that continuous EES blocks proprioceptive innervation by activating the inhibitory networks involved in movement and reduces or abrogates the conscious perception of the leg position. The destruction of proprioceptive information during a continuous EES impairs the ability of the spinal cord to coordinate the formation of a motor pattern after injury. It is the mechanism of proprioceptive communication that plays a crucial role in the reorganization of residual descending paths and the restoration of motor activity in traumatic spinal cord disease. Periodic stimulation, on the contrary, does not allow blocking of proprioceptive information thus providing reliable control over the motor activity of neurons. This demonstrates the importance of defining stimulation protocols that take into account the preservation of proprioceptive information [41, 44, 51, 54].

Conclusion

The main problem in rehabilitation of patients in the late period after spinal cord injury is the lack of a unified concept, developed strategies of rehabilitation technologies and criteria for assessment of the initial status and treatment efficiency. This is due to the fact that there are no protocols for the application of known treatment methods, many approaches are still at the stage of experimental studies and clinical observations. In addition, specialists in various fields participate in rehabilitation of such patients.

The largest evidence base in rehabilitation of patients in the late period after spinal cord injury is presented for physical rehabilitation methods. The most effective ones are locomotor training for developing movement skills. Auxiliary verticalisation and robotic devices are required for restoration and improvement of proprioceptive innervation.

In case of degeneration of the spinal tracts, the restoration of motor functions occurs due to the activation of supraspinal interneuronal connections. EES of the lumbar enlagement of the spinal cord activates a generator of voluntary movement of the limbs and, in combination with training of proprioceptive sensitivity, leads to a regression of movement disorders. The constant use of EES blocks proprioceptive sensitivity and inhibits the recovery of spinal conductivity.

Clinical application parameters have not been yet defined for the areas of regenerative medicine.

There is a shift in paradigm in rehabilitation of patients with traumatic spinal cord injury. Historically, the therapy has been focused on teaching the compensatory strategies, then, with an understanding of neuroplasticity, comes the neuromuscular technologies for restoration of the lost functions, and robotic devices, artificial intelligence, and additive technologies are being actively introduced. The combination of approaches at the stages of treatment with taking into account the neurological and functional status presents the best choice of a rehabilitation program for patients with consequences of the spinal cord injury.

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References

1. **Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009).** [Electronic resource]. URL: http://www.cebm.net oxford-centre-evidence-based-medicine-levels-evidence-march-2009.
2. **Nowrouzi B, Assan-Lebbe A, Sharma B, Casole J, Nowrouzi-Kia B.** Spinal cord injury: a review of the most-cited publications. Eur Spine J. 2017;26:28–39. DOI: 10.1007/s00586-016-4669-z.
3. **Liu X, Liu N, Zhou M, Lu Y, Li F.** Bibliometric analysis of global research on the rehabilitation of spinal cord injury in the past two decades. Ther Clin Risk Manag. 2018;15:1–14. DOI: 10.2147/TCRM.S163881.
4. **Burns AS, Marino RJ, Kalsi-Ryan S, Middleton JW, Tetreault LA, Dettori JR, Mihalovich KE, Fehlings MG.** Type and timing of rehabilitation following acute and subacute spinal cord injury: a systematic review. Global Spine J. 2017;7(3 Suppl):175S–194S. DOI: 10.1177/2192568217703084.
5. **Amelina OA.** Spinal cord injury. Clinical neurology with the basics of medical and social expertise, ed. by A.Yu. Makarov. St. Petersburg, 1998:232–248. In Russian.
6. **Mazwi NL, Adeletti K, Hirschberg RE.** Traumatic spinal cord injury: recovery, rehabilitation, and prognosis. Curr Trauma Rep. 2015;1:182–192. DOI: 10.1007/s40719-015-0023-x.
7. **Maharaj MM, Hogan JA, Phan K, Mobbs RJ.** The role of specialist units to provide focused care and complication avoidance following traumatic spinal cord injury: a systematic review. Eur Spine J. 2016;25:1813–1820. DOI: 10.1007/s00586-016-4545-x.
8. **Whiteneck G, Gassaway J, Dijkers M, Backus D, Charlifue S, Chen D, Hammond F, Hsieh CH, Smout RJ.** The SCIRehab project: treatment time spent in SCI rehabilitation. Inpatient treatment time across disciplines in spinal cord injury rehabilitation. J Spinal Cord Med. 2011;34:133–148. DOI: 10.1179/107902611X12971826988011.
9. **Kirshblum SC, Waring W, Biering-Sorensen F, Burns SP, Johansen M, Schmidt-Read M, Donovan W, Graves DE, Jha A, Jones L, Mulcahey MJ, Krassioukov A.** Reference for the 2011 revision of the international Standards for Neurological Classification of Spinal Cord Injury. J Spinal Cord Med. 2001;34:547–554. DOI: 10.1179/107902611X13186000420242.
10. **Van Langeveld SAHB, Post MWM, van Asbeck FWA, Postma K, Ten Dam D, Pons K.** Development of a classification of physical, occupational, and sports therapy interventions to document mobility and self-care in spinal cord injury rehabilitation. J Neurol Phys Ther. 2008;32:2–7. DOI: 10.1097/NPT.0b013e3181663533.
11. **Whyte J, Hart T.** It's more than a black box; it's a Russian doll: defining rehabilitation treatments. Am J Phys Med Rehabil. 2003;82:639–652. DOI: 10.1097/01.PHM.0000078200.61840.2D.
12. **Rapidi CA, Tederko P, Moslavac S, Popa D, Branco CA, Kiekens C, Varela Donoso N, Christodoulou N.** Evidence based position paper on Physical and Rehabilitation Medicine (PRM) professional practice for persons with spinal cord injury. The European PRM position (UEMS PRM Section). Eur J Physi Rehabil Med. 2018;54:797–807. DOI: 10.23736/S1973-9087.18.05374-1.
13. **Teeter L, Gassaway J, Taylor S, LaBarbera J, McDowell S, Backus D, Zanca JM, Natale A, Cabrera J, Smout RJ, Kreider SE.** Whiteneck G. Relationship of physical therapy inpatient rehabilitation interventions and patient characteristics to outcomes following spinal cord injury: the SCIRehab project. J Spinal Cord Med. 2012;35:503–526. DOI: 10.1179/2045772312y.0000000058.
14. **Abdul-Sattar AB.** Predictors of functional outcome in patients with traumatic spinal cord injury after inpatient rehabilitation: in Saudi Arabia. Neuro Rehabilitation. 2014;35:341–347. DOI: 10.3233/NRE-141111.
15. **Scivoletto G, Morganti B, Molinari M.** Early versus delayed inpatient spinal cord injury rehabilitation: an Italian study. Arch Phys Med Rehabil. 2005;86:512–516. DOI: 10.1016/j.apmr.2004.05.021.
16. **Sumida M, Fujimoto M, Tokuhiro A, Tominaga T, Magara A, Uchida R.** Early rehabilitation effect for traumatic spinal cord injury. Arch Phys Med Rehabil. 2001;82:391–395. DOI: 10.1053/apmr.2001.19780.
17. **Jones ML, Evans N, Tefertiller C, Backus D, Sweatman M, Tansey K, Morrison S.** Activity-based therapy for recovery of walking in chronic spinal cord injury: Results from a secondary analysis to determine responsiveness to therapy. Arch Phys Med Rehabil. 2014;95:2247–2252. DOI: 10.1016/j.apmr.2014.07.401.
18. **Horn SD, Smout RJ, DeJong G, Dijkers MP, Hsieh CH., Lammertse D, Whiteneck GG.** Association of various comorbidity measures with spinal cord injury rehabilitation outcomes. Arch Phys Med Rehabil. 2013;94(4 Suppl):S75–S86. DOI: 10.1016/j.apmr.2012.10.036.
19. **Tian W, Hsieh CH, DeJong G, Backus D, Groah S, Ballard PH.** Role of body weight in therapy participation and rehabilitation outcomes among individuals with traumatic spinal cord injury. Arch Phys Med Rehabil. 2013;94(4 suppl):S125–S136. DOI: 10.1016/j.apmr.2012.10.039.
20. **Hyun JK, Kim HW.** Clinical and experimental advances in regeneration of spinal cord injury. J Tissue Eng. 2010;2010:650857. DOI: 10.4061/2010/650857.
21. **Huang H, Sun T, Chen L, Moviglia G, Chernykh E, von Wild K, Deda H, Kang KS, Kumar A, Jeon SR, Zhang S, Brunelli G, Bohbot A, Soler MD, Li J, Cristante AF, Xi H, Onose G, Kern H, Carraro U, Saberi H, Sharma HS, Sharma A, He X, Muresanu D, Feng S, Otom A, Wang D, Iwatsu K, Lu J, Al-Zoubi A.** Consensus of clinical neurorestorative progress in patients with complete chronic spinal cord injury. Cell Transplant. 2014;23 Suppl 1:S5–S17. DOI: 10.3727/096368914X684952.
22. **Dalamagkas K, Tsintou M, Seifalian A, Seifalian AM.** Translational regenerative therapies for chronic spinal cord injury. Int J Mol Sci. 2018;19.pii:E1776. DOI: 10.3390/ijms19061776.
23. **Ko CC, Tu TH, Wu JC, Huang WC, Tsai YA, Huang SF, Huang HC, Cheng H.** Functional improvement in chronic human spinal cord injury: Four years after acidic fibroblast growth factor. Scientific Reports. 2018;8:12691. DOI: 10.1038/s41598-018-31083-4.
24. **Fisahn C, Aach M, Jansen O, Moisi M, Mayadev A, Pagarigan KT, Dettori JR, Schildhauer TA.** The effectiveness and safety of exoskeletons as assistive and rehabilitation devices in the treatment of neurologic gait disorders in patients with spinal cord injury: a systematic review. Global Spine J. 2016;6:822–841. DOI: 10.1055/s-0036-1593805.
25. **Mehrholz J, Harvey LA, Thomas S, Elsner B.** Is body-weight-supported treadmill training or robotic-assisted gait training superior to overground gait training and other forms of physiotherapy in people with spinal cord injury? A systematic review. Spinal Cord. 2017;55:722–729. DOI: 10.1038/sc.2017.31.
26. **Hayes S, James Wilcox CR, Forbes White HS, Vanicek N.** The effects of robot assisted gait training on temporal-spatial characteristics of people with spinal cord injuries: A systematic review. J Spinal Cord Med. 2018;41:1–15. DOI: 10.1080/10790268.2018.1426236.
27. **Swinnen E, Duerinck S, Baeyens J-P, Meeusen R, Kerckhofs E.** Effectiveness of robot-assisted gait training in persons with spinal cord injury: a systematic review. J Rehabil Med. 2010;42:520–526. DOI: 10.2340/16501977-0538.
28. **Cheung EYY, Ng TKW, Yu KKK, Kwan RLC, Cheing GLY.** Robot-assisted training for people with spinal cord injury: a meta-analysis. Arch Phys Med Rehabil. 2017;98:2320–2331.e12. DOI: 10.1016/j.apmr.2017.05.015.
29. **Fisahn C, Aach M, Jansen O, Moisi M, Mayadev A, Pagarigan KT, Dettori JR, Schildhauer TA.** The effectiveness and safety of exoskeletons as assistive and rehabilitation devices in the treatment of neurologic gait disorders in patients

with spinal cord injury: a systematic review. Global Spine J 2016;6:822–841. DOI: 10.1055/s-0036-1593805.

30. **Galea MP, Dunlop SA, Davis GM, Nunn A, Geraghty T, Hsueh YS, Churilov L.** Intensive exercise program after spinal cord injury ("Full-On"): study protocol for a randomized controlled trial. Trials. 2013;14:291. DOI: 10.1186/1745-6215-14-291.
31. **Nam KY, Kim HJ, Kwon BS, Park JW, Lee HJ, Yoo A.** Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review. J Neuroeng Rehabil. 2017;14:24. DOI: 10.1186/s12984-017-0232-3.
32. **Dobkin B, Barbeau H, Deforge D, Ditunno J, Elashoff R, Apple D, Basso M, Behrman A, Harkema S, Saulino M, Scott M.** The evolution of walking-related outcomes over the first 12 weeks of rehabilitation for incomplete traumatic spinal cord injury: the multicenter randomized Spinal Cord Injury Locomotor Trial. Neurorehabil Neural Repair. 2007;21:25–35. DOI: 10.1177/1545968306295556.
33. **Lucareli PR, Lima MO, Lima FP, de Almeida JG, Brech GC, D'Andrea Greve JM.** Gait analysis following treadmill training with body weight support versus conventional physical therapy: a prospective randomized controlled single blind study. Spinal Cord. 2011;49:1001–1007. DOI: 10.1038/sc.2011.37.
34. **Yang JF, Musselman KE, Livingstone D, Brunton K, Hendricks G, Hill D, Gorassini M.** Repetitive mass practice or focused precise practice for retraining walking after incomplete spinal cord injury? A pilot randomized clinical trial. Neurorehabil Neural Repair. 2014;28:314–324. DOI: 10.1177/1545968313508473.
35. **Field-Fote EC, Roach KE.** Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Phys Ther. 2011;91:48–60. DOI: 10.2522/ptj.20090359.
36. **McDonald JV, Becker D, Sadowsky CL, Jane JA, Conturo TE, Schultz LM.** Late recovery following spinal cord injury. Case report and review of the literature. J Neurosurg. 2002;97(2 Suppl):252–265. DOI: 10.3171/spi.2002.97.2.0252.
37. **Boswell-Ruys CL, Harvey LA, Barker JJ, Ben M, Middleton JW, Lord SR.** Training unsupported sitting in people with chronic spinal cord injuries: a randomized controlled trial. Spinal Cord. 2010;48:138–143. DOI: 10.1038/sc.2009.88.
38. **Frigon A, Rossignol S.** Functional plasticity following spinal cord lesions. Prog Brain Res. 2006;157:231–260. DOI: 10.1016/s0079-6123(06)57016-5.
39. **Bennett DJ, Li Y, Harvey PJ, Gorassini M.** Evidence for plateau potentials in tail motoneurons of a wake chronic spinal rats with spasticity. J Neurophysiol. 2001;86:1972–1982. DOI: 10.1152/jn.2001.86.4.1972.
40. **Johnson MD, Heckman CJ.** Gain control mechanisms in spinal motoneurons. Front Neural Circuits. 2014;8:81. DOI: 10.3389/fncir.2014.00081.
41. **Formento E, Minassian K, Wagner F, Mignardot JB, Le Goff-Mignardot CG, Rowald A, Bloch J, Micera S, Capogrosso M, Courtine G.** Electrical spinal cord stimulation must preserve proprioception to enable locomotion in humans with spinal cord injury. Nat Neurosci. 2018;21:1728–1741. DOI: 10.1038/s41593-018-0262-6.
42. **Gerasimenko Y, Gorodnichev R, Puhov A, Moshonkina T, Savochin A, Selionov V, Roy RR, Lu DC, Edgerton VR.** Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans. J Neurophysiol. 2015;113:834–842. DOI: 10.1152/jn.00609.2014.
43. **Gerasimenko Y, Gorodnichev R, Moshonkina T, Sayenko D, Gad P, Edgerton VR.** Transcutaneous electrical spinal-cord stimulation in humans. Ann Phys Rehabil Med. 2015;58:225–231. DOI: 10.1016/j.rehab.2015.05.003.
44. **Calvert JS, Grahn PJ, Zhao KD, Lee KH.** Emergence of epidural electrical stimulation to facilitate sensorimotor network functionality after spinal cord injury. Neuromodulation. 2019;22:244–252. DOI: 10.1111/ner.12938.
45. **Musienko P, Heutschi J, Friedli L, van den Brand R, Courtine G.** Multi-system neurorehabilitative strategies to restore motor functions following severe spinal cord injury. Exp Neurol. 2012;235:100–109. DOI: 10.1016/j.expneurol.2011.08.025.
46. **Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y, Ferreira C, Willhite A, Rejc E, Grossman RG, Edgerton VR.** Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet. 2011;377:1938–1947. DOI: 10.1016/S0140-6736(11)60547-3.
47. **Young W.** Electrical stimulation and motor recovery. Cell Transplant. 2015;24:429–446. DOI: 10.3727/096368915X686904.
48. **Calvert JS, Grahn PJ, Strommen JA, Lavrov IA, Beck LA, Gill ML, Linde MB, Brown DA, Van Straaten MJ, Veith DD, Lopez C, Sayenko DG, Gerasimenko YP, Edgerton VR, Zhao KD, Lee KH.** Electrophysiological guidance of epidural electrode array implantation over the human lumbosacral spinal cord to enable motor function after chronic paralysis. J Neurotrauma. 2019;36:1451–1460. DOI: 10.1089/neu.2018.5921.
49. **Taccola G, Sayenko D, Gad P, Gerasimenko Y, Edgerton VR.** And yet it moves: Recovery of volitional control after spinal cord injury. Prog Neurobiol. 2018;160:64–81. DOI: j.pneurobio.2017.10.004.
50. **Barolat G.** Epidural spinal cord stimulation anatomical and electrical properties of the intraspinal structures relevant to spinal cord stimulation and clinical correlations. Neuromodulation. 1998;1:63–71. DOI: 10.1111/j.1525-1403.1998.tb00019.x.
51. **Wagner FB, Mignardot JB, Goff-Mignardot CJL, Demesmaeker R, Komi S, Capogrosso M, Rowald A, Seanez I, Caban M, Pirondini E, Vat M, McCracken LA, Heimgartner R, Fodor I, Watrin A, Seguin P, Paoles E, Van Den Keybus K, Eberle G, Schurch B, Pralong E, Becce F, Prior J, Buse N, Buschman R, Neufeld E, Kuster N, Carda S, von Zitzewitz J, Delattre V, Denison T, Lambert H, Minassian K, Bloch J, Courtine G.** Targeted neurotechnology restores walking in humans with spinal cord injury. Nature. 2018;563:65–71. DOI: 10.1038/s41586-018-0649-2.
52. **Huang H, He J, Herman R, Carhart MR.** Modulation effects of epidural spinal cord stimulation on muscle activities during walking. IEEE Trans Neural Syst Rehabil Eng. 2006;14:14–23. DOI: 10.1109/TNSRE.2005.862694.
53. **Hamid S, Hayek R.** Role of electrical stimulation for rehabilitation and regeneration after spinal cord injury: an overview. Eur Spine J. 2008;17:1256–1269. DOI: 10.1007/s00586-008-0729-3.
54. **Wenger N, Moraud EM, Gandar J, Musienko P, Capogrosso M, Baud L, Le Goff GG, Barraud Q, Pavlova N, Dominici N, Minev IR, Asboth L, Hirsch A, Duis S, Kreider J, Mortera A, Haverbeck O, Kraus S, Schmitz F, DiGiovanna J, van den Brand R, Bloch J, Detemple P, Lacour SP, Bezard E, Micera S, Courtine G.** Spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after spinal cord injury. Nat Med. 2016;22:138–145. DOI: 10.1038/nm.4025.
55. **Popovic MR, Kapadia N, Zivanovic V, Furlan JC, Craven BC, McGillivray C.** Functional electrical stimulation therapy of voluntary grasping versus only conventional rehabilitation for patients with subacute incomplete tetraplegia: a randomized clinical trial. Neurorehabil Neural Repair. 2011;25:433–442. DOI: 10.1177/1545968310392924.
56. **Shah PK, Lavrov I.** Spinal epidural stimulation strategies: clinical implications of locomotor studies in spinal rats. Neuroscientist. 2017;23:664–680. DOI: 10.1177/1073858417699554.
57. **De Andres J, Reina MA, Hernandez-Garcia JM, Carrera A, Oliva A, Prats-Galino A.** Role of spinal anatomical structures for neuromodulation. Region Anesth Pain M. 2011;36:E130–E137.
58. **Moreno-Duarte I, Morse LR, Alam M, Bikson M, Zafonte R, Fregni F.** Targeted therapies using electrical and magnetic neural stimulation for the treatment of chronic pain in spinal cord injury. NeuroImage. 2013;85 Pt 3:1003–1013. DOI: 10.1016/j.neuroimage.2013.05.097.

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