DYNAMICS OF INDEPENDENCE AND LOCOMOTOR CAPABILITIES CAUSED BY POWERED EXOSKELETON-INDUCED WALK TRAINING IN PATIENTS WITH SEVERE CHRONIC SPINAL CORD INJURY

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Objective. To evaluate the effectiveness of complex rehabilitation with walk training induced by powered exoskeleton 'ExoAtlet' for the patients with severe chronic paraplegias caused by thoracic or upper lumbar spine injuries.
Material and Methods. Design: prospective monocenter study. Fifty patients with severe spinal cord injuries (ASIA: A – 36, B – 10, C – 4; Frankel: A – 24, B – 16, C – 10) from 6 months to 23 years after complicated thoracic or upper lumbar spine injury underwent two intensive courses of complex neurorehabilitation including 36 sessions/hours of powered exoskeleton-induced walk training. Three areas mostly important for the patients were chosen for the analysis: changes in patient independence (assessed by the SCIM III scale), locomotor capabilities (Hauser's Ambulation Index and tetrapedal tests), and strength and sensitivity indicators (AIS scales). Testing was carried out before and one month after the end of the second course. The frequency of positive changes in each area and their dependence (ANOVA) on the completeness of the spinal cord injury and the duration of the injury were studied.
Results. The increase in independence was observed in 46/50 patients, including by 1–3 SCIM points in 14 (28 %), by 4–9 points in 20 (40 %), and by 10 points and above in 12 patients (24 %). Locomotor capabilities improved in 84 % of patients due to reducing test execution time and the need for care. Progress in sensitivity below the affected area by at least 1 point was detected in 80 % of patients (on average by 6 AIS points), including in 68% in tactile and in 54 % in pain sensitivity. The muscle strength gain was recorded in 7 (14%) patients with incomplete paraplegia (on average by 3.5 AIS points). Within the study group, it was found that the progress achieved in independence, locomotor capabilities and sensitivity did not depend on the completeness of the spinal cord injury as well as on the period after injury.
Conclusion. Rehabilitation with repeated intensive courses of powered exoskeleton-induced walk training increases independence, expands locomotor capabilities and improves sensitivity below the affected area in most patients with complete and incomplete spinal cord injury at different periods after injury.
Key Words: spinal cord injury, rehabilitation, powered exoskeleton for walk training, Spinal Cord Independence Measure SCIM III, locomotor capabilities, tetrapedal tests, ASIA/Frankel classification.
Please cite this paper as: *Shapkova EYu, Emelyannikov DV, Larionova YuE, Kupreev NA, Grigoreva EV. Dynamics of independence and locomotor capabilities caused by powered exoskeleton-induced walk training in patients with severe chronic spinal cord injury. Hir. Pozvonoc. 2020; 17(4):54–67. In Russian. DOI: http://dx.doi.org/10.14531/ss2020.4.54-67.*

Spinal cord diseases and injuries are a complex medical and social problem, the solution or alleviation of which is associated with huge material costs. Each year, spinal cord injury affects 250,000–500,000 people across the world, which corresponds to 40 to 80 cases per million population, with up to 90 % of injuries being associated with traumatic causes [1]. About 80 % of the survivors become category 1 or 2 disabled persons [2].

Clinical manifestations of spinal cord injury (SCI) include partial/complete loss of sensory or motor function of the limbs and body as well as dysfunction of the urinary, gastrointestinal, respiratory, and cardiovascular systems. There is a high risk of secondary complications such as deep vein thrombosis, respiratory and urinary tract infections, osteoporosis, bedsores, and chronic pain syndromes. Up to 30 % of patients with consequences of spinal cord injury have depression symptoms, and the unemployment rate among them exceeds 60 % [1].

Surgical treatment of spinal cord injury (SCI) should be supported by rehabilitation measures at all stages of the traumatic disease. After the disease has become chronic, they do not expect significant neurological improvements: in these cases, the tasks of rehabilitation are to increase the patient's independence and prevent secondary complications associated with physical inactivity.

Until recently, the gold standard for rehabilitation of patients with spinal cord lesions was gait training using a stationary robotic-assisted device (Lokomat and analogs) with partial body weight support [3]. A logical continuation of this technology is gait training using exoskeletons that are active robotic-assisted orthoses providing a vertical posture and real over ground progression of a paralyzed individual in space [4–7]. To date, dozens of exoskeleton models have been developed [8–10], and systematic reviews have shown their safety [11], increasing of independent mobility, and some improvement in health. [5, 12, 13]. However, the efficacy of exoskeleton-induced gait training for SCI rehabilitation is still under discussion [14–17], despite its promising perspectives [18].

In Russia, the ExoAtlet group began developing the first exoskeleton in 2013. In 2016, the exoskeleton was registered as a medical device and was put into clinical practice. Within 2017–2019, as part of a multicenter study, the Ministry of Health of the Russian Federation conducted clinical testing of the protocol 2017-7-11 “A method for rehabilitation of patients with thoracolumbar spine and spinal cord injury” developed at the Novosibirsk Research Institute of Traumatology and Orthopaedics n.a. Y.L.Tsivyan. The authors chose independence of patients assessed by the SCIM III scale, with an average group increase of 4 grade, as the main efficacy indicator; the secondary indicators were locomotor capabilities and changes in neurological state estimated by the Hauser ambulation index [19] and by AIS scales [20].

In this study, we intentionally avoided presenting the full range of conducted tests, including scale and instrumental (neurophysiological and biomechanical) tests, in order to focus on indicators that are significant for the patient. Given the focus of rehabilitation on gait training, we additionally controlled locomotor capabilities of patients using tetrapedal tests [21, 22]. As factors of statistical analysis, we selected spinal cord injury completeness (Frankel grade) and duration of post-trauma period. In fact, the study should answer the question: what is the benefit of exoskeleton-induced gait training to patients with severe chronic spinal cord injury with different completeness of injury and at various times after injury?

The aim of this study was to evaluate the efficacy of complex rehabilitation using ExoAtlet exoskeleton-induced gait training in patients with severe chronic paraplegia caused by thoracic and upper lumbar spine injury.

Material and Methods

Study design: prospective monocentric clinical study.

Inclusion criteria: patients aged 18 to 55 years with an SCI duration of at least 6 months; the neurological status assessed as ASIA grade A, B, or C; the ability to stay in an upright position for at least 30 min without pathological orthostatic reactions; height of 160 to 190 cm; weight of up to 95 kg (exoskeleton technical regulations).

Exclusion criteria 1 (general performance): overweight; severe forms of arterial hypertension; arterial hypotension; hypercoagulability; erythremia; erythrocytosis; unstable diabetes mellitus; pregnancy or lactation; renal failure; malignancies; cytotoxic and immunosuppressive therapy.

Exclusion criteria 2 (specific for exoskeleton-assisted training): clinically significant unresolved mechanical spinal instability, intolerance to physical activity, including verticalization; bedsores or risk of bedsore formation; severe lower limb contractures prohibiting walk; acute or exacerbated chronic inflammatory diseases; lower limb fractures in the post-SCI period; unconsolidated fractures; thrombosis; free-floating thrombus; patient refusal to cooperate.

Patient withdrawal criteria: development of complications that meet the exclusion criteria as well as patient noncompliance with the study protocol.

The total follow-up period was 15 weeks, including two inpatient rehabilitation courses with a break of 4 weeks and a 4-week pause before the final testing. Rehabilitation was carried out in groups of 5–7 patients.

The efficacy of rehabilitation was assessed by comparing the indicators before the 1st course onset and a month after the 2nd course end. The study design is shown in Fig. 1. The causes for withdrawing two patients from the study were exacerbation of chronic bilateral gonitis (1) and inability to comply with the study schedule due to participation in sports competitions (1).

The study was approved by the Scientific Problem Commission and authorized by the Ethics Committee of the Ministry of Health of the Russian Federation (Protocol No. 3 of April 17, 2017). In accordance with Good Clinical Practice (GCP) standard, all patients were minutely informed and gave written consent to participate in the study.

Patients. The study involved 26 males and 24 females aged 18–54 years (mean age, 33.1 ± 8.9 years), including 37 patients with thoracic spine injury (T1–T12), 7 patients with thoracolumbar spine injury (T12–L1), and 6 patients with upper lumbar injury (L1–L2). The mean time after injury was 7.4 years (6 months to 32 years); post-trauma period was less than 2 years (6–18 months) in 8 patients, 2 to 5 years in 23 patients, and over 5 years in 19 patients. Therefore, according to the periodization of traumatic spinal cord disease, 8 patients can be attributed to its late stage, and 42 patients can be attributed to the consequences with sustained neurological symptoms [23, 24].

At the onset of rehabilitation, all patients were wheelchair users; 10 of them could perform several steps using external devices and additional support.

Assessment of pathology, performance and treatment efficacy. The neurological status of participants was assessed according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) developed by the American Spinal Cord Injury Association (ASIA) [20, 25], in particular strength of voluntary movements of the lower limbs using 10 key spinal cord segments innervating the lower limbs (maximum score, 50); pain and touch sensation using 28 segments (maximum score, 112).

Spinal cord injury completeness was classified using both ASIA, based on the preservation/absence of voluntary control and reflex activity of the anus and sensation in the anal area, and according to the Frankel classification (1978) focused on absent/existence of voluntary movements and sensation below to the level of injury [26].

The distribution of patients by severity of spinal cord lesion according to both ASIA and Frankel scales is presented in Table 1.

Independence was assessed by each patient subjectively according to four sections of the Spinal Cord Independence Measure III (SCIM III) scale [27–29]: self-care, respiration and sphincter management, indoor mobility, and outdoor mobility (a maximum total score of 100). The detailing of each ability, provided by the SCIM III key (https://docplayer.ru/68086380-Izmeritel-nezavisimostipripovrezhdeniyah-spinnogo-mozgascim-iii-spinal-cord-independencemeasure-iii.html), enables accurate assessment of the patient's independence in everyday life and its changes (Table 2).

Locomotor capabilities of patients were assessed using the Hauser ambulation index (AI, Table 3) that includes 10 scores [19] characterizing the patient's ability to ambulate: using a wheelchair, walking with unilateral or bilateral support, with allowance for the time taken to walk 8 m and fatigue when walking. At the study onset, 40 out of 50 participants moved only in a wheelchair (AI 8); among patients with adaptive bipedal walking, grade AI 7 was in seven, AI 6 in one, and AI 5 in two participants.

Tetrapedal tests included moving on hands and knees 4 m forward and backward [22] with control of time, steps number, and independence of task performance. All tests were videotaped. The need for assistance was assessed as follows: minimum assistance for partial support or facilitation of movements of one lower limb – 1 point; significant assistance of one person – 2 points; significant assistance of one or two people with walk of less than 4 m – 3 points; completely passive – 4 points. Reducing the initial time of independent test execution by 15 % or decreasing assistance by 1 point or more were considered as significant improvement.

Statistical processing of the data included assessment of descriptive statistics and analysis of variance (ANOVA) of the measured parameters at the beginning and end of the study, and analysis of the rate of neurological improvements for the factors 'completeness of spinal cord lesion'. Due to the sample imbalance, we used a universal linear model in the Minitab 16 software. The significance level of differences was defined as $p = 0.05$. For the factor 'completeness of spinal cord lesion', 2 levels were used: complete lesion – Frankel grade A and incomplete lesion – Frankel grade B and C. According to the factor 'post-trauma period', patients were ranged into 3 levels: up to 2 years (actually 6–18 months), 2 to 5 years, and over 5 years after injury.

Rehabilitation techniques. The powered ExoAtlet exoskeleton provides the ability of getting up from a sitting position, standing, walk in place and forward, turning and slalom walking and walk up and down stairs. The exoskeleton-assisted patient rests on Canadian forearm crutches, coordinating their reposition with leg movements. Balance assistance is provided by operator supporting the patient from behind (Fig. 2). The gait parameters are programmed with adjustment of a step height and length, a pause between steps (0.1–1 s) or its absence. The operator controls the exoskeleton from the tablet (despite of technical possibility to manage exoskeleton by the patient using a screen on a crutch, our patients were not allowed to walk independently). Before each training session, the exoskeleton was adjusted individually according to the participant anthropometric parameters: pelvis width and depth as well as

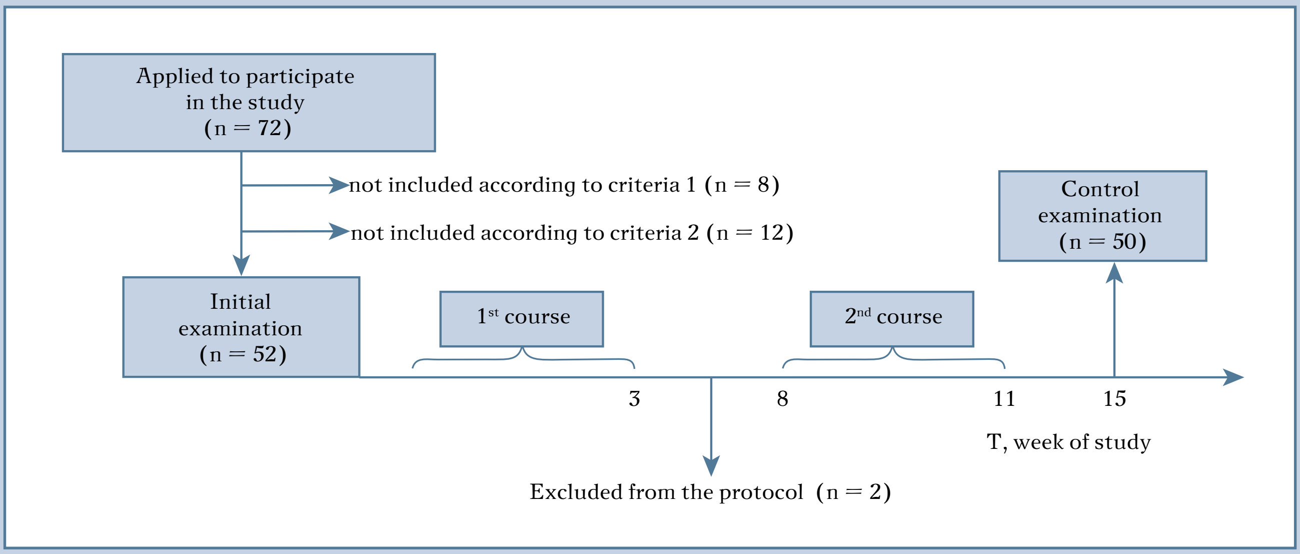

Fig. 1
Study design: two courses of training with control of the efficacy 4 weeks after completion of the 2nd course

length and perimeters of the thigh and shin for each side.

Learning to walk began with getting up from a sitting position, standing with support on Canadian-type crutches, and walking in place. Learning to walk in exoskeleton with external support required from 1 to 5 lessons. By the course end, the technical capabilities of participants expanded due to turns in walking and walking along a curved trajectory. The design, setup, and technique of learning to walk in the exoskeleton of this model are described in detail [30].

Rehabilitation program. The program included 2 stationary courses, 22–24 days long, each comprising at least 18 exoskeleton-induced trainings sessions (totally, 36 h). Additionally, we performed vertical posture training with electrical muscle stimulation – 2 × 20 sessions × 30 min (20 h), pneumatic stimulation of the sole support zones – 2 × 20 sessions × 30 min (20 h), exercises (33 h), and classical manual and mechanical (lymphatic drainage) massages (24 procedures each). Active training techniques amounted to about 140 min/day, passive ones amounted to 60–80 min/day; exoskeleton-induced walk training was performed 6 times a week, and the other procedures were performed 5 times a week. The mean duration of rehabilitation procedures for each patient over two courses was about 141 h.

Results

Dynamics in independence. The integrated indicator of patient independence over the group was 60.9 ± 12.0 (mean ±SD) points before the study onset and 67.7 ± 12.7 a month after completing two rehabilitation courses (Fig. 3a); the differences were statistically significant ($p = 0.001$). Among 50 participants, independence improved by 1–3 points in 14 (28 %) patients, 4–9 points in 20 (40 %) patients, and 10 points and more in 12 (24 %) patients; only 4 (8 %) patients had no changes (Fig. 3b).

An analysis of the rate of a SCIM increase in patients, depending on the post-injury period (Fig. 4a) and spinal cord injury completeness (Fig. 4b), did not reveal statistically significant differences ($p > 0.5$).

An increase in the independence indicators (SCIM) was found in 44 % of the participants after the first course and in 70 % of the participants after the second course; the differences in the efficacy of the 1st and 2nd courses were significant ($p = 0.008$; $F = 7.26$; Fig. 4c).

Dynamics in locomotor capabilities. Bipedal walk. All 10 patients who were initially able to make several steps improved their locomotor capabilities: the Hauser ambulation index improved 6 patients, 4 patients decreased time of 8 m walk with unchanged AI, 6 patients changed the type of additional support, and one begun to walk up and down the stairs. (Table 4). Changes were observed in each course and preserved at follow-up testing at one month. An example of a significant increase in locomotor capabilities is presented in the Clinical Cases Section (Appendix 1 in the electronic version of the article).

Tetrapedal walk. Forty-five patients were admitted to tetrapedal walking tests; five patients were not tested due to ossification in the thigh area (1), recent spine stabilization (1), burns (1), and skin maceration in the knee area (2). Two of the admitted patients were unable to perform both tests, even with significant assistance.

Initially, 30 patients were able to perform independent tetrapedal walk forward, and backward - 23 patients (Fig. 5a). The test execution time widely varied: forward – 4 to 202 s (mean, 40.6 s) and backward – 5 to 147 s (mean, 50.5 s). On control testing, the test execution time decreased for walking forward in 22/30 patients (on average by 41 %) and for walking backward in 18/23 patients (on average by 51 %). The changes revealed a high statistical significance for both tests ($p < 0.03$; Fig. 5b).

On the initial examination, 13 and 20 patients needed assistance in performing forward and backward tetrapedal tests, respectively. Nine and eleven patients reduced the need for assistance in tetrapedal walk forward and backward, respectively; of these, 3 and 5 patients progressed to independent walk. On control testing, the total score of assistance decreased by half (Fig. 5c).

According to tetrapedal tests, a significant increase in locomotor capabilities was detected in 38/45 patients, which amounted to 84 %. Five patients had minimal (2) or no (3) improvements. A video illustration of the changes in locomotor capabilities during the course is presented in Appendix 2 in the electronic version of the article.

Dynamics in neurological state. Changes in touch and pain sensation during the follow-up period were detected in 54 and 68 % of patients, respectively, while an increase in the muscle strength was observed in 7 (14 %) patients with incomplete plegia (Table 5).

The rate of improvements in touch and pain sensation was analyzed by changes in the completeness of spinal cord lesion (Fig. 6a) and the time after injury (Fig. 6b).

Improvement in sensation was more often observed in patients with incomplete SCI; however, the differences were not statistically significant; the differences at different times after injury did not reveal a definite trend.

Therefore, complex rehabilitation with exoskeleton-induced walk training in patients with chronic SCI increased

Table 1

Distribution of patients by severity of spinal cord lesion

Severity of injury	ASIA classification	Frankel classification
Grade A	36	24
Grade B	10	16
Grade C	4	10

Table 2

Spinal Cord Independence Measure III (SCIM III) protocol for assessing independence in spinal pathology

Section	Assessed function	Score
Self care	1. Nutrition	0–3
	2A. Washing (upper body)	0–3
	2B. Washing (lower body)	0–3
	3A. Dressing (top)	0–4
	3B. Dressing (bottom)	0–4
	4. Прическа, бритье, макияж	0–3
	Total	0–20
Respiration and sphincter management	5. Respiration	0–10
	6. Urination control	0–15
	7. Defecation control	0–10
	8. Intimate hygiene	0–5
	Total	0–40
Mobility (room, toilet)	9. In bed	0–6
	10. Bed to chair transfer	0–2
	11. Chair to toilet transfer, chair adaptation	0–2
Indoor/outdoor mobility	12. Moving indoors	0–8
	13. Moving 10–100 m	0–8
	14. Moving more than 100 m	0–8
	15. Walking stairs	0–3
	16. Chair to car transfer	0–2
	17. Floor to chair transfer	0–1
	Total	0–40
Total score		0–100

Table 3

Hauser ambulation index

AI score	Evaluation criterion	Time to walk 8 m
AI 0	Normal walking	–
AI 1	Normal walking. Fatigue during sports or other physical activities	–
AI 2	Abnormal gait or episodic imbalance	10 s or less
AI 3	Walking without assistance or support	20 s or less
AI 4	Walking with unilateral support	25 s or less
AI 5	Walking with bilateral support Walking with unilateral support	25 s or less More than 25 s
AI 6	Walking with bilateral support, use of a wheelchair	More than 25 s
AI 7	Several steps with bilateral support, use of a wheelchair	
AI 8	Restricted to wheelchair, able to transfer self independently	–
AI 9	Restricted to wheelchair, unable to transfer self independently	–

independence (SCIM) in the vast majority of participants; the increase in independence was not associated with the duration of post-trauma period and with completeness of spinal cord lesion.

Exoskeleton-induced walk training improved locomotor capabilities of most patients with severe plegias. In bipedal walk, the effect was manifested by a reduction in the time taken to pass the test distance or by a change in the type of additional support; in tetrapedal walk, the effect was manifested by a reduction in the time taken to walk in one or both directions and by a decrease in the need for external assistance.

Improvement in sensation below the injury level was detected in 80 % of patients (pain sensation, 54 %; touch sensation, 68 %); there was no a statistical correlation between the rate of sensation improvement, completeness of spinal cord lesion, and post- injury period. An increase in the muscle strength was

Fig. 2
Appearance of the ExoAtlet exoskeleton

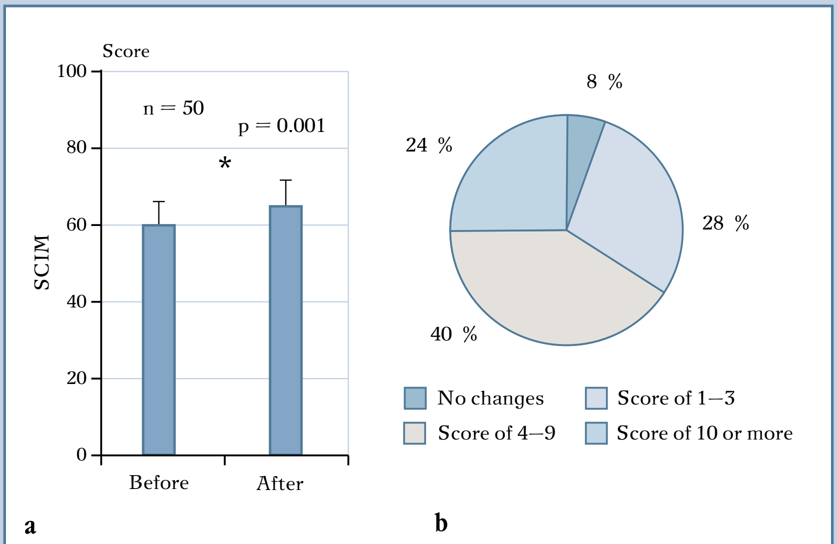

Fig. 3
Changes in mean group **(a)** and individual **(b)** SCIM indicators of independence in spinal pathology during rehabilitation using an exoskeleton

observed in 14 % of patients, only in the case of incomplete plegias.

Clinical cases illustrating the main provisions of this study, including a short medical history, changes in the studied parameters, and video recording of walk change over time in two study participants (with complete and incomplete plegia), are presented in the Appendices in the electronic version of the article on the journal's website.

Discussion

The main question of this study is: What effect does exoskeleton-induced walk training provide to patients with severe chronic post-traumatic spinal cord lesion, and does it depend on the lesion severity/completeness and the length of post-injury period?

Efficacy. Three most patient-related, in our opinion, areas were selected for analysis: independence in everyday life, locomotor capabilities, and basic neurological characteristics such as muscle sensation and strength. The study showed that complex rehabilitation using exoskeleton-induced walk training provides improvements of varying degrees in each area for the majority of participants, with the exception of an increase in the muscle strength. The main task of rehabilitation, to increase the patient's independence, was achieved; the target indicator set in the protocol as a mean group increase in SCIM by 4 points was exceeded by 75 %. An increase in independence was achieved in 92 % of participants; in this case, an individual increase in SCIM reached or exceeded the target level in 64% of patients and was very high in 24 % of patients. Improvement of locomotor capabilities manifested by reduced time taken to perform tetrapedal tests or by reduced need for external assistance was detected in 84 % of patients. All participants who were initially able to walk several steps improved; in particular, two out of 10 patients were able to stop using the wheelchair. During the study period, no wheelchair-dependent patients mastered bipedal walking, but after 3–6 months, four patients reported initiation of walking on parallel bars or with a walker. An increase in one or both types of sensation by 1 or more AIS points was detected in 80 % of the participants, with the mean increase being 5–6 points, and the maximum increase being 23 and 16 AIS points. We associate this effect with total strong afferent load received by patients during forced walking, pneumatic stimulation of the sole

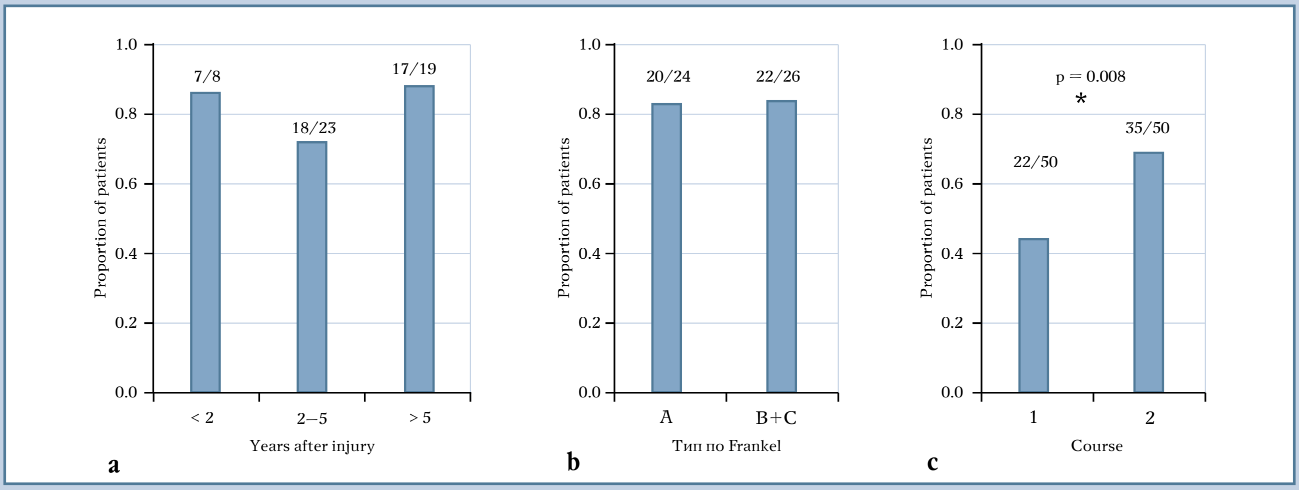

Fig. 4
SCIM changes in patients at different stages of post-injury period (a), in patients with complete and incomplete plegia (b), and during the 1st and 2nd courses of rehabilitation (c)

Table 4
Changes in locomotor capabilities during exoskeleton-induced rehabilitation in patients with compensatory bipedal gait

Patient	Gender	Age, years	Level of injury: in the spine	Level of injury: in the spinal cord	post-injury period, years	AIS	Frankel	AI	Change in support	Shortening time to walk a distance of 10 m	Increase in traveled distance
P3	M	32	T1	D3	4	C	C	7/7	Switch to Canadian crutches	From 112 s to 83 s	–
P5	F	51	L1–L3	D4	24	A	C	7/5	Switch to Canadian crutches, abandoning wheelchair	From 5 m in 49 s to 10 m in 20s	From 5 m to natural walking
P8	M	44	T12	L3	6	C	C	7/6	Switch to Canadian crutches, mastering walking up and down stairs, abandoning wheelchair	42 s	From 25 m to 150–200 m
P9	M	33	T12–L1	L2	15	C	C	7/6	–	From 152 to 136 s	From 3 to 10 m
P12	M	38	T1	D3	10	B	B	7/6	Walkers	139 s	From 4 to 10 m
P15	M	38	T12	L4	10	A	A	5/5	Walkers	18–16 s	From 10 to 30 m
P25	F	21	T11–L1	D5	4	A	B	7/6	Walkers	From 86 to 82 s	From 10 to 30 m
P28	M	45	T12	L2	3	A	C	7/6	Switch to Canadian crutches	From 48 to 40 s	–
P45	M	39	T12–L1	L3	5	B	C	5/5	Switch to Canadian crutches	15 –13 s	From 30 to 200 m
P48	F	31	T12	D12	1,5	A	B	6/6	Switch to Canadian crutches	52 s	From 1.5 to 10 m

Canadian crutches are crutches with forearm support.

support zones [31], and upright posture training with muscle electrical stimulation. Probably, the combination of prolonged exoskeleton-induced walk training (60 min 6 times a week) with large amounts of active and passive stimuli (141 h in total) provided the intensity necessary for initiation of neuroplastic rearrangements.

Repeated courses of exoskeleton-induced walk training in the tested mode were found to provide improvement in a significant part of the patients who met the selection criteria. Obviously, moderate improvements observed in most patients do not cure chronic paralysis and do not enable independent walking in patients. However, even minimal changes within a relatively short period after many years of lack of improvements demonstrate the ability to mobilize the neuroplastic potential and increase the functional capacities of patients.

Contrary to our expectations, the study did not reveal significant differences in the main controlled parameters: the rate of improvements in independence, locomotor capabilities, and sensation between patients with complete and incomplete spinal cord injury. Also, no correlation between these indicators and the post-injury period was found. This necessitates revision of the traditional ideas about the limited capabilities of rehabilitation in clinically complete plegias and in consequences of severe spinal cord injuries of more than two year duration. Probably, the traditional rehabilitation techniques are insufficient for mobilization of the neuroplastic potential in chronic spinal cord injury, which requires a greater amount and intensity of training stimulation for restoring walking.

There is an apparent contradiction between the lack of correlation between the rehabilitation efficacy and the post-injury period, which was found in our study, and the advantage of early initiation of rehabilitation reported in the literature [32]. In our opinion, this is explained by the composition of participants: there were only 7 patients in the intermediate phase (up to 2 years) and no patients in the acute phase of traumatic disease (up to 3–5 months after injury). Perhaps, initiation of exoskeleton-induced rehabilitation in the acute phase of traumatic disease might be even more successful.

The efficacy of restoring the walk pattern varies for different exoskeleton models [33], which is explained by fundamental differences in their design and

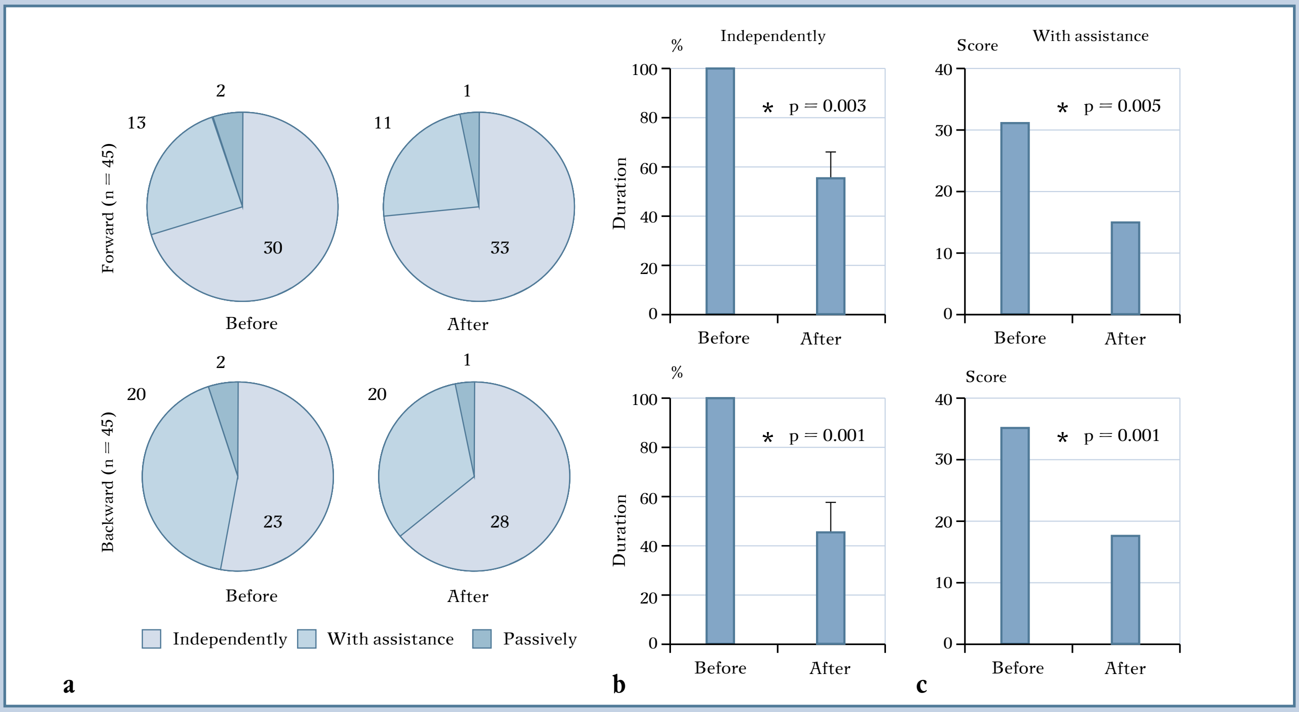

Fig. 5
Tests with tetrapedal walk forward and backward: **a** – in pie charts – the number and proportion of patients who performed tetrapedal walk independently, with assistance and passively before and one month after two courses of rehabilitation using an exoskeleton; **b** – reducing the duration of tetrapedal tests by independent patients (a subgroup with significant improvements is presented); **c** – reducing the need for assistance during tetrapedal tests (total score for the whole subgroup)

Table 5

Changes in neurological indicators (AIS scale) during the follow-up period

Neurological indicator	Cases with improvement, n (%)	Increase in AIS, score	
		range	M ± m
Muscle strength	7 (14)	1–8	3.5 ± 2.6
Pain sensation	27 (54)	1–28	6.2 ± 6.2
Touch sensation	34 (68)	1–16	5.7 ± 4.6

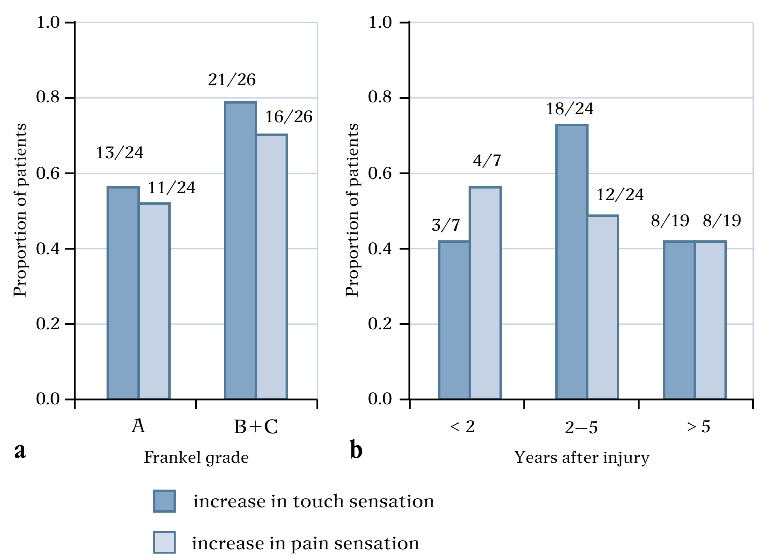

Fig. 6
Proportion of patients with improvements in touch and pain sensation depending on the completeness of spinal cord lesion **(a)** and length of post-injury period **(b)**

control pattern [2, 18]. We attribute success of the applied technology to several causes. First of all, it is a progressive design of the exoskeleton that enables natural-like walking with real movement of a person in space, a shift in the center of mass, and the need to maintain balance. It is instability that mobilizes the patient and provides simultaneous training of not only locomotor but also postural capabilities. Secondly, systematic and comprehensive training is important because it provides a long-term, regularly repeated impact on the motor and sensory parts of the locomotor system. Thirdly, over ground progression, which restores the sensation of real walking, and functional improvements provide a positive emotional mood and motivate for further active rehabilitation. Fourthly, when selecting candidates for training, preference was given to those who were socially active and motivated to functional recovery. This approach ensured active participation of patients in rehabilitation and continuation of self-rehabilitation between courses and after completion of the program.

Prospects for improving the efficacy. The only indicator that had a low increase over the follow-up period (7/50 cases) was muscle strength. Recent publications have noted the efficacy of combining exoskeleton-induced walk training with functional electrical muscle stimulation [2, 34, 35] and epidural [36–38] and percutaneous [39] electrical stimulation of the spinal cord. Conjunction of exoskeleton-forced walk kinematics with artificial muscle activation seems to be very promising.

Efficacy evaluation techniques. Despite an invariable element of subjectivity in assessing independence of patients, the use of the SCIM III scale was a convenient tool, due to a detailed key, that excludes an ambiguous interpretation of the acquired skills. Evaluation of locomotor capabilities using tetrapedal gait testing is available for patients incapable of bipedal locomotion due to a low center of mass, increased support area, no need for knee closure, simplicity, and reproducibility.

Neurological evaluation. Quantification of muscle strength and pain and touch sensation in terms of the ASIA AIS score is a fairly accurate and most recommended tool for testing patients with spinal cord injuries. This standard uses the determination of the completeness spinal cord lesion depending on the presence/absence of voluntary or reflex contraction of the anus and sensation in the anal region as the most caudal region of spinal control, in contrast to the Frankel classification that evaluates completeness of lesion by the presence/absence of movements and sensation below the injury level. In this study, two evaluation techniques (ASIA standard and Frankel scale) were simultaneously used; 10 patients initially capable of limited bipedal walking were distributed according to ASIA as 5A : 2B : 3C (i.e. most patients capable of walking several steps had complete motor and sensory loss); while according to the Frankel scale, the distribution was 1A : 3B : 6C (i.e. in most of these patients, spinal cord injury was incomplete, which seemed more logical). The lack of relationship between ASIA grades and the prognosis of gait recovery was also noted by other authors [40]. We came to the conclusion about an unreasonably broad interpretation of complete spinal cord injury by the ASIA standard and preferential use of the Frankel classification for rehabilitation tasks.

Risks. Initiation of active walk training in patients with severe spinal cord injury is associated with the risk of thrombosis and arthrosis of the lower limbs due to osteoporotic fractures the rate of which ranges from 1 to 34 % [41]. We detected 4 (8 %) serious adverse events (exacerbation of chronic gonitis – 1, foot fractures – 1, fracture of the lower third of the femur – 1); of these, a relationship with training was found only in the case of gonarthrosis. After healing the fractures, the patients completed the rehabilitation program. The number of significant adverse events did not exceed that of complications observed in the natural history of post-traumatic spinal myelopathy. The safety of this technique was ensured by strict adherence to the inclusion/exclusion/withdrawal criteria in selection of patients, availability of medical advisors experienced in working with paralyzed patients, trained non-medical personnel involved in training support, and regular maintenance of the exoskeleton.

Limitations of study validity are associated with scale assessment techniques introducing invariable subjectivity. The second limitation is preliminary selection of patients by age, physical condition, and motivation; therefore, the results cannot be approximated to the entire population of patients with severe post-traumatic myelopathies. In addition, exoskeleton-induced walk training was combined with procedures also aimed at activating locomotor (stimulation of the sole support areas) and postural (verticalization with electrical muscle stimulation) activity, which excludes weighing the contribution of each technique in combined therapy.

Conclusion

Rehabilitation using repeated intensive courses of exoskeleton-induced walk training increases independence, expands locomotor capabilities, and improves sensation below the lesion level in the vast majority of patients with severe chronic (0.5–23.0 years) post-traumatic spinal cord injury. In the study group (n = 50), there was no relationship between the efficacy of rehabilitation and the completeness of spinal cord lesion, as well as the length of post-injury period. The obtained results indicate the efficacy of repeated intensive courses of walk training with a significant amount of locomotor and non-locomotor loads; therefore, the technique may be recommended for rehabilitation of patients with a varying degree of completeness of spinal cord lesion and at various stages of post-injury period, provided that there is a high motivation for recovery.

Acknowledgements

We would like to thank Prof. A.Yu. Mushkin, head of the Center for Spinal Pathology; Dr. N.A. Prokhorovich; Dr. A.I. Berdes; Dr. I.G. Rodnova; neurologists S.A. Kuklina and Yu.V. Didenko; Dr. N.Yu. Basantsov; Dr. O.A. Shakhmetov for assistance in organization and conduction of the study as well as I.A. Yudin and A.V. Andronov who ensured safe management of the trainings. We thank all of the patients for the trust, cooperation, and optimism, which helped conduct this study.

The study was funded by the Ministry of Health of the Russian Federation as part of the clinical trial of protocol 2017-7-11 and in part by a grant from the Saint-Petersburg State University (project No. 51134206).

The authors declare no conflicts of interest.

References

1. World Health Organization: website. URL: https://www.who.int/mediacentre/news/releases/2013/spinal-cord-injury-20131202/ru.
2. **Daminov VD, Tkachenko PV.** Exoskeletons in medicine: world experience and clinical practice of the Pyrogov center. Bulletin of Pirogov National Medical and Surgical Center. 2017;12(4).Pt 2:17–22. In Russian.
3. **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:0.1186/s12984-017-0232-3.
4. **Del-Ama AJ, Koutsou AD, Moreno JC, De-los-Reyes A, Gil-Agudo A, Pons JL.** Review of hybrid exoskeletons to restore gait following spinal cord injury. J Rehabil Res Dev. 2012;49:497–514. DOI: 10.1682/jrrd.2011.03.0043.
5. **Onose G, Cardei V, Craciunoiu T, Avramescu V, Opris I, Lebedev MA, Costantinescu MV.** Mechatronic wearable exoskeletons for bionic bipedal standing and walking: a new synthetic approach. Front Neurosci. 2016;10:343. DOI: 10.3389/fnins.2016.00343.
6. **Sylos-Labini F, La Scaleia F, d'Avella A, Pisotta I, Tamburella F, Scivoletto G, Molinari M, Wang S, Wang L, van Asseldonk E, van der Kooij H, Hoellinger T, Cheron G, Thorsteinsson F, Ilzkovitz M, Gancet J, Hauffe R, Zanov F, Lacquaniti F, Ivanenko YP.** EMG patterns during assisted walking in the exoskeleton. Front Hum Neurosci. 2014;8:423. DOI: 10.3389/fnhum.2014.00423.
7. **Mekki M, Delgado AD, Fry A, Putrino D, Huang V.** Robotic rehabilitation and spinal cord injury: a narrative review. Neurotherapeutics. 2018;15:604–617. DOI: 10.1007/s13311-018-0642-3.
8. **Sanchez-Villamanan MDC, Gonzalez-Vargas J, Torricelli D, Moreno JC, Pons JL.** Compliant lower limb exoskeletons: a comprehensive review on mechanical design principles. J Neuroeng Rehabil. 2019;16:55. DOI: 10.1186/s12984-019-0517-9.
9. **Bao G, Pan L, Fang H, Wu X, Yu H, Cai S, Bingqing Y, Wan Y.** Academic review and perspectives on robotic exoskeletons. IEEE Trans Neural Syst Rehabil Eng. 2019;27:2294–2304. DOI: 10.1109/TNSRE.2019.2944655.
10. **Shi D, Zhang W, Zhang W, Ding X.** A review on lower limb rehabilitation exoskeleton robots. Chin J Mech Eng. 2019;32:74. DOI: 10.1186/s10033-019-0389-8.
11. **He Y, Eguren D, Luu TP, Contreras-Vidal JL.** Risk management and regulations for lower limb medical exoskeletons: a review. Med Devices (Auckl). 2017;10:89–107. DOI: 10.2147/MDER.S107134.
12. **Kozlowski AJ, Bryce TN, Dijkers MP.** Time and effort required by persons with spinal cord injury to learn to use a powered exoskeleton for assisted walking. Top Spinal Cord Inj Rehabil. 2015;21:110–121. DOI: 10.1310/sci2102-110.
13. **Lebedev MA.** Augmentation of sensorimotor functions with neural prostheses. Opera Med Physiol. 2016;2(3-4):211–227. DOI: 10.20388/ OMP.003.0035.
14. **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.
15. **Contreras-Vidal JL, Bhagat NA, Brantley J, Cruz-Garza JG, He Y, Manley Q, Nakagome S, Nathan K, Tan SH, Zhu F, Pons JL.** Powered exoskeletons for bipedal locomotion after spinal cord injury. J Neural Eng. 2016;13:031001. DOI: 10.1088/1741-2560/13/3/031001.
16. **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.
17. **Hornby TG, Reisman DS, Ward IG, Scheets PL, Miller A, Haddad D, Fox EJ, Fritz NE, Hawkins K, Henderson CE, Hendron KL, Holleran CL, Lynskey JE, Walter A.** Clinical practice guideline to improve locomotor function following chronic stroke, incomplete spinal cord injury, and brain injury. J Neurol Phys Ther. 2020;44:49–100. DOI: 10.1097/NPT.0000000000000303.
18. **Gorgey AS.** Robotic exoskeletons: the current pros and cons. World J Orthop. 2018;9:112–119. DOI: 10.5312/wjo.v9.i9.112.
19. **Hauser SL, Dawson DM, Lehrich JR, Beal MF, Kevy SV, Propper RD, Mills JA, Weiner HL.** Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. N Engl J Med. 1983;308:173–180. DOI: 10.1056/NEJM198301273080401.
20. American Spinal Injury Association. Standards for Neurological Classification of Spinal Injury Patients. Chicago, IL: American Spinal Injury Association. 1982. [Electronic resource]. URL: https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet.
21. **Grigorieva EV, Larionova YuE, Emeliannikov DV, Shapkova EYu.** Dynamic assessment of locomotor capabilities of patients with plegias during gait training in the exoskeleton "Exoathlet". New Approaches to Classical Problems: Materials of the 9th All-Russian Conference dedicated to the memory of E.E. Nikolsky. 2019:45. In Russian.
22. **Larionova YuE, Kupreev NA, Grigorieva EV, Emeliannikov DV, Shapkova EYu.** Dynamics of locomotor capabilities of patients with plegias during gait training in an exoskeleton. Motor Control 2020: Materials of 8th All-Russian Conference. Petrozavodsk, 2020:76–77. In Russian.
23. **Konovalov AN, Likhterman LB, Potapov AA.** Neurotraumatology. Moscow, 1994. In Russian.
24. **Amelina OA.** Spinal cord injury. In: Clinical Neurology with the Basics of Medical and Social Expertise, ed. by A.Yu. Makarov. St. Petersburg. 1998:232–248. In Russian.
25. **Schuld C, Franz S, Bruggemann K, Heutehaus L, Weidner N, Kirshblum SC, Rupp R.** International standards for neurological classification of spinal cord injury: impact of the revised worksheet (revision 02/13) on classification performance. J Spinal Cord Med. 2016;39:504–512. DOI: 10.1080/10790268.2016.1180831.
26. **Frankel HL, Hancock DO, Hyslop G, Melzak J, Michaelis LS, Ungar GH, Vernon JD, Walsh JJ.** The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. I. Paraplegia. 1969;7:179–192. DOI: 10.1038/sc.1969.30.
27. Spinal Cord Independency Measure – SCIM III. [Electronic resource]. URL: https://docplayer.ru/68086380-Izmeritel-nezavisimosti-pri-povrezhdeniyah-spinnogo-mozga-scim-iii-spinal-cord-independence-measure-iii.html.
28. **Anderson KD, Acuff ME, Arp BG, Backus D, Chun S, Fisher K, Fjerstad JE, Graves D, Greenwald K, Groah S, Harkema SJ, Horton JA, Huang MN, Jennings M, Kelley KS, Kessler SM, Kirshblum S, Koltenuk S, Linke M, Ljungberg I, Nagy J, Nicolini L, Roach MJ, Salles S, Scelza WM, Read MS, Reeves RK, Scott MD, Tansey KE, Theis JL, Tolfo CZ, Whitney M, Williams CD, Winter CM, Zanca JM.** United States (US) multi-center study to assess the validity and reliability of the Spinal Cord Independence Measure (SCIM III). Spinal Cord. 2011;49:880–885. DOI: 10.1038/sc.2011.20.
29. **Catz A, Itzkovich M, Tesio L, Biering-Sorensen F, Weeks C, Laramee MT, Craven BC, Tonack M, Hitzig SL, Glaser E, Zeilig G, Aito S, Scivoletto G, Mecci M, Chadwick RJ, El Masry WS, Osman A, Glass CA, Silva P, Soni BM, Gardner BP, Savic G, Bergstrom EM, Bluvshtein V, Ronen J.** A multicenter international study on the Spinal Cord Independence Measure, version III: Rasch psychometric validation. Spinal Cord. 2007;45:275–291. DOI: 10.1038/sj.sc.3101960.

30. **Pais-Vieira C, Allahdad M, Neves-Amado J, Perrotta A, Morya E, Moioli R, Shapkova E, Pais-Vieira M.** Method for positioning and rehabilitation training with the ExoAtlet ® powered exoskeleton. MethodsX. 2020;7:100849. DOI: 10.1016/j.mex.2020.100849.
31. Grigor'ev AI, Kozlovskaia IB, Shenkman BS. The role of support afferents in organization of the tonic muscular system. Ross Fiziol Zh Im I M Sechenova. 2004;90(5):508–521. In Russian.
32. Prudnikova OG, Kachesova AA, Ryabykh SO. Rehabilitation of patients in late period after spinal cord injury: a meta-analysis of literature data. Hir. Pozvonoc. 2019;16(3):8–16. In Russian. DOI: 10.14531/ss2019.3.8-16.
33. **Guan X, Kuai S, Ji L, Wang R, Ji R.** Trunk muscle activity patterns and motion patterns of patients with motor complete spinal cord injury at T8 and T10 walking with different un-powered exoskeletons. J Spinal Cord Med. 2017;40:463–470. DOI: 10.1080/10790268.2017.1319033.
34. Kastalskiy IA, Khoruzhko MA, Skvortsov DV. A functional electrical stimulation system for integration in an exoskeleton. Sovremennye technologii v medicine. 2018;10(3):104–109. In Russian. DOI: 10.17691/stm2018.10.3.12.
35. **Ekelem A, Goldfarb M.** Supplemental stimulation improves swing phase kinematics during exoskeleton assisted gait of SCI subjects with severe muscle spasticity. Front Neurosci. 2018;12:374. DOI: 10.3389/fnins.2018.00374.
36. **Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, Beck LA, Sayenko DG, Van Straaten MG, Drubach DI, Veith DD, Thoreson AR, Lopez C, Gerasimenko YP, Edgerton VR, Lee KH, Zhao KD.** Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nat Med. 2018;24:1677–1682. DOI: 10.1038/s41591-018-0175-7.
37. **Wagner FB, Mignardot JB, Le Goff-Mignardot CG, 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, Eberie 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.
38. **Gorgey AS, Gill S, Holman ME, Davis JC, Atri R, Bai O, Goetz L, Lester DL, Trainer R, Lavis TD.** The feasibility of using exoskeletal-assisted walking with epidural stimulation: a case report study. Ann Clin Transl Neurol. 2020;7:259–265. DOI: 10.1002/acn3.50983.
39. **Shapkova EY, Pismennaya EV, Emelyannikov DV, Ivanenko Y.** Exoskeleton walk training in paralyzed individuals benefits from transcutaneous lumbar cord tonic electrical stimulation. Front Neurosci. 2020;14:416. DOI: 10.3389/fnins.2020.00416.
40. **Van Middendorp JJ, Hosman AJ, Pouw MH, van de Meent H.** ASIA impairment scale conversion in traumatic SCI: is it related with the ability to walk? A descriptive comparison with functional ambulation outcome measures in 273 patients. Spinal Cord. 2008;47:555–560. DOI: 10.1038/sc.2008.162.
41. **Schulte LM, Scully RD, Kappa JE.** Management of lower extremity long-bone fractures in spinal cord injury patients. J Am Acad Orthop Surg. 2017;25:e204–e213. DOI: 10.5435/JAAOS-D-15-00686.

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Received 23.11.2020
Review completed 04.12.2020
Passed for printing 11.12.2020

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