SPONSOR FEATURE

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New medical technology: Cybernic treatment as a functional regenerative treatment

CYBERDYNE, Inc. develops products and services based on cybernic technologies in the fields of medicine, welfare, personal care, business and labour support. CYBERDYNE, Inc. was founded in 2004 by Yoshiyuki Sankai, of the University of Tsukuba in Ibaraki Prefecture, Japan, who established cybernics, a field that is defined as the fusion of humans, robots and information systems. Under the philosophy that technology exists for humans and society, the company promotes social innovation with innovative cybernic systems. One of its novel products, the world's first cyborg-type robot, HAL®, can be controlled by intention-based bioelectrical signals generated by neural activity to regenerate, improve, support and expand the wearer's physical, brain and nerve functions.

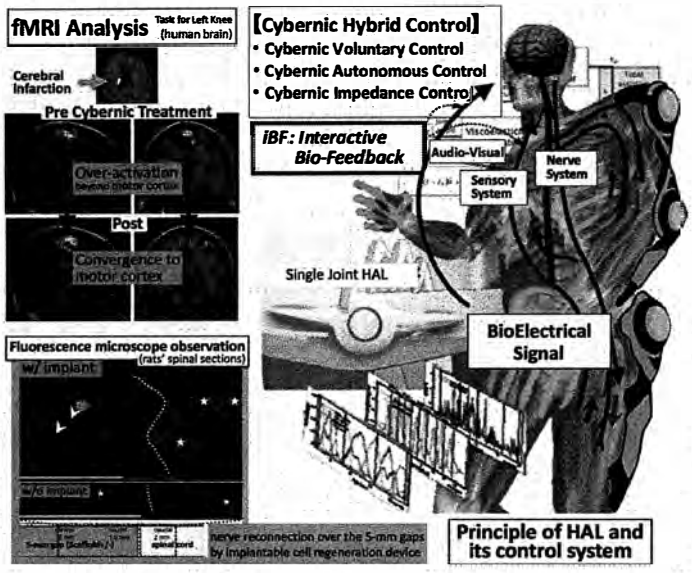

Figure 1. The principle of HAL. Clear differences in the active areas of (top left) the brain of a person with cerebral infarction and (bottom left) spinal sections of the implant and control rats.

The cyborg-type robot HAL is a cybernic system developed for the purpose of regenerating and improving patients' brain–neuro–physical functions. HAL is equipped with the cybernic treatment control system and includes the following: cybernic voluntary control, which is a function based on bioelectrical signals derived from a person's brain and nervous system that reflect an intended movement; cybernic autonomous control, which is a function based on processing by artificial intelligence; cybernic impedance control, which is a function that adjusts to the wearer's individual characteristics; and a cybernic hybrid control system that combines all three functions.

The world's first robotic treatment device, medical HAL, was demonstrated in a good clinical practice-adherent clinical trial[1] led by Takashi Nakajima of the National Hospital Organization, Niigata National Hospital in Japan. The trial was conducted in ten facilities to target slow, progressive, rare neuromuscular diseases: spinal muscular atrophy, spinobulbar muscular atrophy, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease, distal myopathy, inclusion body myositis, congenital myopathy and muscular dystrophy. The world's first robotic treatment to be paid for using public health insurance began in Japan in September 2016. In Germany, clinical evaluations targeting spinal cord injuries were conducted using results from research led by Thomas Schildhauer. Public worker's compensation insurance in Germany has been covering the treatment for people with spinal cord injuries since August 2013.

In the treatment using HAL, clear differences in the active areas of the brain were observed before and after treatment. Cybernic treatment can be categorized as a functional regenerative treatment and has been made possible only by HAL's ability to simultaneously realize informational and physical interactions between the human and HAL to functionally integrate humans and robots. HAL's presence between the patient's brain and his or her nervous and musculoskeletal systems allows the establishment of interactive biofeedback (iBF). The iBF adjusts or strengthens the synaptic connections between the brain, nervous system and musculoskeletal system, and promotes neuroplasticity to restructure the connectome, which is the network of neural connections in the human brain.

Medical technology developed using cybernics is known as medical cybernics. New treatment methods that include combinations of HAL and regenerative medicine, HAL and implanted devices, and HAL and pharmaceuticals are being developed.

The combination of HAL and regenerative medicine, which we call cybernic treatment with stem cells, will combine cutting-edge medical technologies. For example, when used to treat people with a spinal cord injury the physical reparation effects of regenerative medicine and the functional regeneration effects of HAL are expected to be more effective in combination than if each treatment were to be used alone. Such promising regenerative medicine includes, but is not limited to, autologous bone marrow-derived mesenchymal stem cells (in research led by Osamu Honmou), Muse cells (in research led by Mari Dezawa) and surgically transplanted autologous stem cells.

The combination of HAL and pharmaceuticals is called cybernic treatment with drugs. Botox injections were administered to patients who experience severe contractures because of stroke or encephalomyelitis. The use of HAL when the botox injection was providing relief from the contractures resulted in the reestablishment and improvement of the patients' voluntary movements (in collaborative research with Ryuji Kaji).

To study cybernic treatment with devices, which combines HAL and implanted devices, basic science research on nerve connectivity was conducted on rats that had 5 mm of their spinal cords removed. By implanting a three-dimensional scaffold structure made of nanofibre hydrogel and a honeycomb-structured collagen sponge, the nerves were successfully reconnected covering this 5 mm gap (Figure 1, ref. 2). We are planning to use HAL in the next step to confirm the effects of this combination.

HAL can extract faint information from the brain and nervous system that reflects the intent of the wearer, process the input and output, and monitor the state of the patient's nervous and musculoskeletal systems. In other words, HAL is able to cover both the treatment and evaluation aspects of medicine and has the potential to take over medicine for patients with brain, nerve and muscle diseases. Through the next generation of medical technology, such as HAL's combination with regenerative medicine, implanted devices and pharmaceuticals, and through the development of cybernic treatment as the future of medicine, energetic physicians, researchers and business entrepreneurs are creating markets in the medical field and starting a new era of medical innovation.

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Voluntary driven exoskeleton as a new tool for rehabilitation in chronic spinal cord Injury – A pilot study

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Voluntary driven exoskeleton as a new tool for rehabilitation in chronic spinal cord Injury – A pilot study

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Voluntary driven exoskeleton as a new tool for Rehabilitation in chronic SCI – A pilot study

Abstract

Background context: Treadmill training after traumatic SCI has become an established therapy to improve walking capabilities. The hybrid assistive limb (HAL®) exoskeleton has been developed to support motor function and is tailored to the patients´ voluntary drive.

Purpose: To determine whether locomotor training with the exoskeleton HAL® is safe to use and can increase functional mobility in chronic paraplegic patients after SCI.

Design: Involved Departments: Dept. of Spinal Cord Injury, Neurology and General and Trauma Surgery at the University Hospital Bergmannsheil Bochum, Germany.

A single case experimental A-B (pre-post) design study by repeated assessments of the same patients. The subjects performed 90 days (5 times per week) of HAL® exoskeleton body weight supported treadmill training (BWSTT) with variable gait speed and body weight support.

Patient Sample: 8 patients with chronic SCI classified by the ASIA Impairment Scale (AIS) consisting of ASIA A (ZPP L3-*S1*) *n=4*, ASIA B (with motor ZPP L3-*S1*) n=*1* and ASIA C/D n=3 who received full rehabilitation in the acute and sub acute phase of SCI.

Outcome Measures: Functional measures including treadmill associated walking distance, -speed and time with additional analysis of functional improvements, using the 10-m-walk test (10 MWT), timed-up-and-go test (TUG test), 6-minute-walk test (6 MWT) and the WISCI II score. Secondary physiologic measures including the AIS with the LEMS, the Spinal spasticity (Ashworth Scale) and the lower extremity circumferences.

Methods: Subjects performed standardized functional testing prior to and after the 90 days of intervention.

Results: Highly significant improvements of HAL®-associated walking time, -distance, -and speed. Furthermore significant improvements have been especially shown in the functional abilities without the exoskeleton for over ground walking obtained in the 6MWT, TUG-Test and the 10MWT, including an increase in the WISCI II score of three patients. Muscle strength (LEMS) increased in all patients accompanied by a gain of the lower limb circumferences. A conversion in the AIS was ascertained in one patient (ASIA B to ASIA C). One patient reported a decrease of spinal spasticity.

Conclusion: HAL® exoskeleton training results in improved over ground walking and leads to the assumption of a beneficial effect on ambulatory mobility. However evaluation in larger clinical trials is required.

Introduction

About 1.200 people suffer a traumatic spinal cord injury (SCI) each year in Germany. Recent statistics indicate that more than 50% of these injured patients have a motor incomplete lesion.[1] In patients with initial motor incomplete SCI, at least 75% regain some kind of ambulatory function. Better functional outcome is associated with age, level of lesion and the classification in the American Spinal Injury Association (ASIA) Impairment Scale.[2] In the first two month after initial SCI approximately half of the recovery occurs. Within the following four month a decreasing rate of recovery has been observed. One year after injury, neurologic recovery is assumed to be nearly complete.[3] Although conventional rehabilitation programs enhance the performance of functional tasks, the loss of strength and coordination substantially limits one's capacity for over ground ambulation training.[4] In the past two

decades, body weight supported treadmill training (BWSTT) has been proposed as a useful adjunct to enhance locomotor function after motor incomplete SCI.[5] In patients with incomplete or complete SCI, a bilateral leg muscle activation combined with coordinated stepping movements can be induced in partially unloaded patients, standing on a moving treadmill. BWSTT enables early initiation of gait training, integration of weight-bearing activities, stepping and balance by the use of a task-specific approach and a systematic gait pattern.[6] To facilitate the delivery of BWSTT in SCI patients, the locomotor training evolved over the last twelve years and a motorized robotic driven gait orthosis (DGO) has been developed.[7] The advantages over conventional BWSTT methods are considered to be less effort for attending physiotherapists[8], longer duration, more physiological and reproducible gait patterns and the possibility to measure a patients´ performance. Several studies pointed out that DGO training improves over ground walking.[9-13] However, there was no reported difference in the outcome of DGO training compared to conventional training. A significant switch in the ASIA classification has not been found.[14,15]

Over the last five years exoskeletal systems became available for SCI patients. These systems offer different possibilities. Three exoskeletons (Ekso®, Rex® and Re-Walk®) allow SCI patients to stand up, walk with a defined pattern and even climbing stairs mainly on a basis of passive range of motion (ROM). The exoskeleton HAL® (Cyberdyne Inc., Japan) offers the possibility of getting connected with the SCI patient through emg-electrodes on the skin at the extensor/flexor muscle region of the lower extremities. This allows voluntary machine supported ROM of incomplete SCI patients by using minimal bioelectrical signals recorded and amplified from hip and knee flexors and extensors.[16-18] More recently, these various exoskeletal systems allow patients mobilization outside the treadmill. A former study by Kawamoto et al. concerning locomotion improvement using hybrid assistive limb (HAL) in

chronic stroke patients, emphasized the feasibility for rehabilitation of these particular patients.[19]

The aim of this pilot study was to evaluate the possibilities of exoskeletal locomotor training (HAL®, Cyberdyne Inc.) under voluntary control and to identify beneficial effects on functional mobility of the patients. The hypothesis was that exoskeleton treadmill training is feasible and safe in application and capable of improving ambulatory mobility in chronic SCI patients.

Materials and Methods

Patients

We enrolled 8 patients (two females, six males). The mean ± standard deviation (SD) age at the time of enrolment was 48±9,43 years. All patients were in the chronic stage of traumatic spinal cord injury according to time since injury of 1 to 19 years (97,2±88,4 months). Inclusion criteria were traumatic SCI with chronic incomplete paraplegia (ASIA B/C/D) or complete paraplegia (ASIA A) after lesions of the conus medullaris/ cauda equine with zones of partial preservation (ZPP). Independent of ASIA classification the enrolled patients must present motor functions of hip and knee extensor and flexor muscle groups in order to be able to trigger the exoskeleton. Exclusion criteria were as follows: Non traumatic SCI, pressure sores, severe limitation of range of motion (ROM) regarding hip and knee joints, cognitive impairment, body weight > 100kg, non consolidated fractures and mild or severe heart insufficiency. Two patients suffered from an incomplete thoracic SCI (ASIA C/D) since 3 to 13 years. 2 patients suffered from an incomplete lumbar SCI (ASIA B/C) since 12 to 13 months and 4 patients had a complete SCI with ZPP in L3-S1 after lesions of the conus medullaris. The classification according to the American Spinal Injury Association was

carried out before the treadmill training was initiated. The study was approved by Ethical Board Committee of Bergmannsheil Hospital and the University of Bochum and followed strictly the declaration of Helsinki.

All patients provided written informed consent. The study design was a single case experimental A-B (pre-post) design by repeated assessments of the same patients.

[Table 1]

Intervention

During this study the patients underwent a body weight supported treadmill training (BWSTT) five times per week using the HAL® exoskeleton (Cyberdyne Inc., Japan). The study was performed between June and September 2013 in the BG University Hospital Bergmannsheil, Bochum.

Neither adverse nor severe adverse events occurred during the intervention.

The Exoskeleton: The HAL® robot suit (Cyberdyne Inc., Japan) is an exoskeleton with a frame and robotic actuators that attach to patients´ legs. The joint movement is supported by electric motors. Voluntary initiated minimal bioelectrical signals recovered from extensor and flexor muscles of hip and knee are detected via emg-electrodes.

[Figure1]

Through a cable connection between exoskeleton and patient this system allows voluntary robotic supported ROM (CVC mode). Also a passive, non voluntary ROM (CAC mode) is possible.

[Figure 2]

The Treadmill: The treadmill system (Woodway Inc.) includes a body weight support system with a harness. The speed can be adjusted from 0 km/h to approximately 4,5 km/h. During treatments, the velocity of the treadmill was set individually between comfortable and maximum speed tolerated by the patients. Approximately 50 % of each patient's body weight needed to be supported by the harness system, individually reduced during the following sessions as tolerated without substantial knee buckling or toe drag.

The training: The patients underwent a 90 days period of HAL® exoskeleton (Cyberdyne Inc.) training (5 per week) , including a mean number of sessions of 51.75±5.6. The training was performed on a treadmill with individually adjustable body weight support and speed, recording walking speed, walking time and walking distance. It included a 10-m-walk-test before and after each session, regular physiotherapy and lasted approximately 90 min. The training was supervised by a physiotherapist and a medical doctor.

Measurements

Walking capabilities and neurological status: All patients were assessed upon admission by medical doctors involved in this trial. The outcomes were assessed by physiotherapists neither involved in study design nor analysis after 45 days and upon discharge from the training period. An assessment through the ASIA classification was already done upon admission and upon discharge from the spinal cord injury department Bergmannsheil Bochum within the initial therapy after acute SCI. The 10-m-walk-test (10MWT), done before and after each session, detected the needed time, the number of steps and the required assistance to walk a 10 m distance.[20,21] The timed-up-and-go-test (TUG-Test) describes the time and assistance required for standing up from the wheelchair, walk 3 meter, turn around, walk back and sit down. It was performed every 2 weeks. The 6-minute-walk-test (6MWT) was done at the

beginning, at half time and at the end if possible, depending on the patient. It evaluates the distance and assistance while walking 6 minutes.[22] The main outcome was the functional motor assessment by the walking index for SCI II (WISCI II).[23,24] The WISCI II score is a 20 item scale measuring the walking capabilities of a patient based on the requirements of assistance due to walking aids, personal assistance or braces. Grade 0 means that the patient has neither standing nor walking abilities. Grade 20 means that no assistance is needed to walk a distance of 10 meters. The neurological status was assessed using the ASIA Impairment scale modified from the Frankel classification and classifies motor and sensory impairment that results from a Spinal Cord Injury (SCI).[3] The lower extremity motor score (LEMS) acquired in this study was obtained by addition of the impairment scores (0-5) of the lower extremity key muscles of both sides. Muscle volume was assessed by manual measurements 20/10 cm above and 15 cm below inner knee gap.

Statistical analysis: Descriptive analysis of the demographic and injury characteristics was done using frequency distribution for categorical data, and mean for continuous variables. Differences between pre- and post-training sessions were assessed by a paired t-test (for continuous variables). Treatment effects on functional performance as the WISCI II are all ordinal scales, medians were used as descriptive statistics for these outcomes, and non-parametric tests were used to assess the relative effect of the treatments.

Results were considered statistically significant when the P-value was ≤ 0.05.

Study funding

There has been no monetary study funding. The study was supported by a grant and has been supervised by the staff of BG University Hospital Bergmannsheil Bochum.

Conflict of Interest

YS is a founder, shareholder and the CEO of Cyberdyne Inc. which produces the HAL. Cyberdyne was neither involved in study funding, design, data collection, analysis, nor writing or submitting this article, therefore concluding in no specific influence on the trial. We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated.

Results

Treadmill associated results:

All patients improved in treadmill training by using HAL® (Cyberdyne Inc., Japan). The mean walking speed increased from 0.91±0.41 m/s (0.5-1.8 m/s) in the first session up to 1.59±0.5 m/s (0.8-2.1 m/s) in the last session after three month. The progress in speed in the period after 6 weeks of training was lower than in the first weeks. The range was located between 0 km/h and 0.8 km/h. The mean walking time at the beginning was 12.37±4.55 min. The average walking time at the end was 31.97±9.45 min. The mean ambulated distance at the first session was 195.9±166.7 m and increased to 954.13±380.4 m upon discharge.

[Figure 3]

Functional outcome:

Although the mean improvement concerning the WISCI II score was not statistically significant, three patients showed functional improvements in gait abilities. Two subjects needed braces, a walker and support by a physiotherapist at the beginning, and were able to walk after the training series only with a walker and braces (WISCI II score increased from 6 to 9). One Patient increased from 9 to 12 and therefore was able to walk with two crutches and a brace compared to a walker and a brace before the training. At baseline the mean

WISCI II score was 10±4.3. At the end of the 90 days trial the mean WISCI II was 11.13±6.68. Improvements in speed and endurance in over ground gait assessments in all participants have been achieved. The 10MWT showed a significant increase in mean gait speed at the end of the training period compared to baseline (0.28±0.28 m/s vs. 0.50±0.34 m/s).

[Figure 4]

The improvement corresponded to a 44 % faster walking than in initial evaluation. It includes also the reduction of support needed detected by the WISCI II score. The mean number of steps decreased from 29.8±7.85 to 19.4±3.16. We observed significant increase in gait speed from pre training to mid training and from mid training to post training assessments. Similar results were detected for the TUG-Test. The mean time needed for the TUG-Test decreased from 55.34±32.2 sec to 38.18±25.98 sec. The 6MWT was done with a constant walking time of 6 minutes without any break. Only three patients were able to perform the 6MWT before the training with a mean walking distance of 187±162.2 m. The subjects in this subgroup improved their performance and increased the walking distance to 287.3±229.4 m. After completing the training, all eight patients could be evaluated, therefore the overall mean distance increased from 70.1±130 m to 163.3±160.6 m.

[Table 2]

The LEMS increased in all patients. The mean LEMS before the training increased significantly from 21.75±8.3 to 24.38±7.6 after the intervention.

[Figure 5]

One patient switched in the ASIA Scale from ASIA B to C, he was at the beginning of the training 12 months post trauma.

Others:

To describe muscle volume, measurements of the circumferences 10/20 cm cranial of the inner knee joint gap and 15 cm distal of it have been done before and after the 90 days of training. Seven participants showed a gain of muscle circumference from 5 mm up to 50 mm. In one participant with edema in his lower legs we observed a loss of circumference up to 25 mm. One patient suffering from a thoracic SCI presented a significant spinal spasticity. For spastic motor behaviors, we used the modified Ashworth scale to evaluate the involuntary resistance to passive stretch of the quadriceps muscle group. At pre training evaluation he showed an extensor spasm with high resistance to passive stretch according to Ashworth 4. After the training sessions the resistance was reduced according to Ashworth 2. This level lasted for about 6-8 hours with a new maximum level at the next morning. All other patients showed no spastic motor behaviors.

Discussion

The objective of the study was to determine whether locomotor training with the exoskeleton HAL® is feasible and safe in application, improves functional mobility and increases motor functions in chronic paraplegic patients after SCI. The results obtained, reveal a highly significant improvement for over ground walking abilities evaluated by the 10-m-walk-test (10MWT), the 6-minute-walk-test (6MWT) and the timed-up-and-go test (TUG test), as well as the partial reduction of physical assistance and walking aids in the WISCI II score. Muscle strength, measured with the lower extremity motor score (LEMS) increased in all patients.

The results acquired in this clinical trial imply that HAL®-supported locomotion training can improve walking abilities in terms of speed, gait and distance. Furthermore it improves motor functions.

Thus far there is insufficient evidence and only a few articles addressing the main hypothesis of this study that locomotor training improves walking function for patients with SCI.[26]

The present study is according to the knowledge of the authors the first to investigate the impact of hybrid assistive limb-supported locomotor training in chronic SCI patients where referring to the current state of knowledge no further functional improvements are to be expected.

In the subject population consisting of 8 patients including patients suffering from SCI from 1 up to 19 years (8.03 ± 7.4 years), all patients improved significantly regarding treadmill associated walking distance and speed, as well as functional improvement detected in the over ground walking tests.

Although no significant influence was seen on the requirements of assistance in the 10MWT,

3 patients attained improvement in walking abilities according to the WISCI II, under condition of a comfortable and stable gait. A further reduction of assistance was not forced due to more pathologic gait or higher risk of falling.[25]

Although the evidence is still insufficient, the effectiveness of automated locomotor training using the DGO in patients with chronic SCI is being investigated and considered promising in several systematic reviews including a Cochrane review.[26,27] The results mentioned above add to the wealth of that data presuming that HAL®-assisted locomotion training is useful in terms of functional mobility and a safe adjunct to the treatment of patient with chronic spinal cord injury.

Our study had several limitations: the relatively small number of patients (n=8), as well as the mixture of complete and incomplete SCI.

However all the patients were treated in the same facility by the same multidisciplinary team, according to a standardized protocol.

In summary, our study provides the first data demonstrating the clinical potential of HAL®-locomotor training based on voluntary drive in patients suffering from chronic SCI.

It was proven to be a safe device for locomotion therapy as neither adverse nor severe adverse events occurred.

However, continued research in the form of large randomized trials to compare the efficacy of HAL®-assisted training with well established, conventional therapies is necessary.

Conflict of interest

YS is a founder, shareholder and the CEO of Cyberdyne Inc. which produces the HAL.

YS and Cyberdyne as the manufacturer of the device provided exclusively technical and advisory support.

Abbreviations

HAL: Hybrid assistive limb (Cyberdyne Inc., Japan); CVC: Cybernic voluntary control; CAC: Cybernic autonomous control; 10MWT: 10-meter-walk-test; 6MWT: 6-minute-walk-test; TUG: Timed-up-and-go-test; WISCI II: Walking index for spinal cord injury; SCI: Spinal cord injury; ROM: Range of motion

Authors' contributions

MA and OC carried out the experiments and data analysis as well as drafting of the manuscript. RCM, PS and MT helped with the experimental set up. MSK and OH contributed to the data analysis.

TAS participated in study design and coordination of the study.

YS as the CEO of Cyberdyne, has been involved exclusively in terms of an advisory capacity, regarding technical support and the limitations of the exoskeleton. Therefore the inclusion and exclusion criteria have been modified (e.g. body weight and contractures). YS and Cyberdyne was neither involved in the course of the study, data collection and analyses, writing nor submitting this article.

All authors read and approved the final manuscript.

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Figure Legends

Figure 1 -Positioning of the emg-electrodes on the knee extensor and flexor muscles .

Figure 2 - Patient performing treadmill locomotion training with body weight support and hybrid assistive limb (HAL®) exoskeleton.

Figure 3 - Changes in walking distance treadmill associated in pre, -mid and -post evaluation.
***m* median**
***pre-post difference, P<0,05.**

Figure 4 - Changes in 10MWT in pre, -mid and -post intervention evaluation.
***10MWT* 10 m-walk-test**
***m* median**
***pre-post difference, P<0,05.**

Figure 5 - LEMS in pre and post evaluation.
***m* median**
***pre-post difference, P<0,05.**

Table 1

Subject demographics, clinical characteristics

Case	Sex	Age	Time since trauma, years	Etiology	Level	ASIA / ZPP	WISCI II	Ashworth
1	M	40	13	# T 7/8	T 8	C	13	4
2	M	63	1	# T 12	L 1	B / L3	6	0
3	M	36	1,16	# T 11/12	T 12	A / L3	6	0
4	F	55	1,08	# L 1	L 1	C	13	0
5	M	42	16	# L 1	L 1	A / L3	9	0
6	M	52	10	# L 3	L2	A / L3	6	0
7	F	40	19	# L 1	T 11	A / S1	9	0
8	M	53	3	# T 12	T 12	D	18	0

***M* male, *F* female, # fracture, *ZPP* zones of partial preservation, *T* thoracic, *L* lumbal, *S* sacral**

Table 2

Table 1 Comparison of pre, - post intervention

Outcome measurements		Before training	After training	n
10MWT	Speed (m/s)	0.28 ± 0.28	0.5 ± 0.34*	8
	Number of steps	29.88 ± 7.85	19.38 ± 3.16*	8
6MWT	Distance (m)	70,1±130	163,3±160,6*	8
TUG (s)		55.34 ± 32.20	38.18 ± 25.98*	8
Distance (m)		195.88 ± 166.71	954.13 ± 380.35*	8
WISCI-II		10 ± 4.34	1 1.12 ± 3.68	8

Values are means ±standard deviation.

***10MWT* 10-m walk test, *TUG* Timed-up and go Test**

***pre-post difference, P<0,05.**