Hybrid Assistive Limb Exoskeleton HAL in the Rehabilitation of Chronic Spinal Cord Injury: Proof of Concept; the Results in 21 Patients

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■ INTRODUCTION: **The use of mobile exoskeletons is becoming more and more common in the field of spinal cord injury (SCI) rehabilitation. The hybrid assistive limb (HAL) exoskeleton provides a tailored support depending on the patient's voluntary drive.**

■ MATERIALS AND METHODS: **After a pilot study in 2014 that included 8 patients with chronic SCI, this study of 21 patients with chronic SCI serves as a proof of concept. It was conducted to provide further evidence regarding the efficacy of exoskeletal-based rehabilitation. Functional assessment included walking speed, distance, and time on a treadmill, with additional analysis of functional mobility using the following tests: 10-meter walk test (10MWT), timed up and go (TUG) test, 6-minute walk test (6MWT), and the walking index for SCI II (WISCI-II) score.**

■ RESULTS: **After a training period of 90 days, all 21 patients significantly improved their functional and ambulatory mobility without the exoskeleton. Patients were assessed by the 6MWT, the TUG test, and the 10MWT, which also indicated an increase in the WISCI-II score along with significant improvements in HAL-associated walking speed, distance, and time.**

■ CONCLUSION: **Although, exoskeletons are not yet an established treatment in the rehabilitation of spinal cord injuries, the devices will play a more important role in the future. The HAL exoskeleton training enables effective, body weight–supported treadmill training and is capable of improving ambulatory mobility. Future controlled studies are required to enable a comparison of the new advances in the field of SCI rehabilitation with traditional over-ground training.**

INTRODUCTION

Spinal cord injury (SCI) is a devastating condition usually associated with permanent impairment[1,2] or complete loss of motor-sensory and autonomic functions. Consequently, it has a substantial physical, psychologic, and socioeconomic impact on the lives of those affected.[3,4] The extent of impairment varies and depends on the level and severity of the lesion.[5] Conventional approaches to rehabilitation aim at improving functional tasks. However, the impairment of strength and coordination limits the patients' capacity for over-ground ambulation training[6,7] and therefore the prognosis for partial recovery.[8] By contrast, the desire to walk or stand again ranks among the main priorities of patients who are paraplegic as a result of SCI.[9,10] Although the evidence remains preliminary and insufficient,[11] treadmill training is currently an established and widely used tool in rehabilitation. This is due in part to its ability to enable patients to walk while

Key words
- Body weight–supported treadmill training
- Exoskeleton
- Functional mobility
- Hybrid assistive limb
- Spinal cord injury

Abbreviations and Acronyms
10MWT: 10-meter walk test
6MWT: 6-minute walk test
ASIA/AIS: American Spinal Injury Association/ASIA Impairment Scale
BES: Bioelectrical signals
BWSTT: Body weight–supported treadmill training
DGO: Driven gait orthosis
F: Degrees of freedom of the F-test
HAL: Hybrid assistive limb
LEMS: Lower extremity motor score
rm-ANOVA: repeated measures analysis of variance
SCI: Spinal cord injury
TUG: Timed up and go test
WISCI-II: Walking Index for Spinal Cord Injury II

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giving them partial body weight support (BWSTT), and it is capable of inducing muscle activation and coordinated stepping movements in patients with incomplete and complete SCI.[12] To facilitate BWSTT in SCI patients, robotic driven gait orthoses (DGO) have been developed,[13] which offer many advantages over conventional BWSTT, (e.g., less physical demand on physiotherapists[14] and a more normalized gait pattern than hands-on therapy during BWSTT).[15] However, despite the initial wishful thinking and theoretic potential, neither BWSTT nor robot-assisted gait training have fulfilled their expectations.[11,16] Thus, there is still no evidence that these treatments are superior to over-ground training in improving the functional mobility of walking-impaired patients.[17] Nevertheless, despite this lack of evidence, the use of exoskeletal systems is increasing in the rehabilitation of walking-impaired patients. As a result, various exoskeletons are now available that feature different modes of control.[16,18]

Posture-controlled exoskeletons are particularly effective in enabling patients with neurologic gait disorders to be mobilized by means of direct motion support.[16] Furthermore, use ofthe neurologically controlled exoskeleton hybrid assistive limb (HAL) leads to functional improvements in patients with residual muscular functions in the chronic phase of spinal cord injury, in terms of improved walking abilities.[19]

Building on the results of a preliminary pilot/feasibility study,[19] this trial was conducted to investigate whether body weight–supported treadmill training with the HAL exoskeleton could improve functional mobility in patients with chronic SCI when they do not use the exoskeleton.

METHODS AND MATERIALS

Participants

Twenty-one patients (6 women, 15 men) with chronic SCI, American Spinal Injury Association Impairment Scale (ASIA grades A–D), and a neurologic lesion level between C4 and L3 (paraplegia, n = 18; tetraplegia, n = 3) participated. The mean age ± standard deviation at the time of enrollment was 44.8 ± 13.8 years (range, 16–68 years). The average interval between SCI and

Table 1. Patient Demographics and Clinical Characteristics

Patient	Sex	Age (Years)	Years Since SCI	Cause	Lesion Level	ASIA/ZPP	WISCI-II
1	M	40	13	# T 7/8	T 8	C	13
2	M	63	1	# T 12	L 1	B/L3	6
3	M	36	1,16	# T 11/12	T 12	A/L3	6
4	F	55	1,08	# L 1	L 1	C	13
5	M	42	16	# L 1	L 1	A/L3	9
6	M	52	10	# L 3	L2	A/L3	6
7	F	40	19	# L 1	T 11	A/S1	9
8	M	53	3	# T 12	T 12	D	18
9	M	50	5	# L2-4	T 12	C	8
10	F	32	8	# C 5/6	C7	C	13
11	M	68	19	# T 12	T 12	C	16
12	M	65	6	# T 12	T 12	A/L3	13
13	M	21	3	# T 5/6	T 12	C	13
14	M	16	3,5	# C 4/5	C 6	D	20
15	F	53	6,5	# L 1	L 3	A/L3	13
16	M	45	2	SM	T 10	C	3
17	M	49	2,5	# T 12	T 12	A/L1	1
18	F	31	8	# L 1	L 1	A/L4	13
19	M	37	3	# C ½	C 4	D	16
20	F	58	4	SC-T 10	T 10	A/L3	2
21	M	36	1,5	# L 1	L 1	A/L3	9

A-D classification according to American Spinal Injury Association. A: No motor or sensory function is preserved in the sacral segments S4-S5. B: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5. C: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3. D: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more. E: Motor and sensory function are normal.

ASIA, American Spinal Injury Association; ZPP, zones of partial preservation; WISCI-II, Walking Index for Spinal Cord Injury II; M, male; F, female; #, fracture; SM, syringomyelia; SC, spinal cavernoma; T, thoracic; C, cervical; L, lumbar; S, sacral.

the initiation of the exoskeleton-based body weight–supported treadmill training (HAL-BWSTT) was 6.5 ± 5.8 years (range, 1–19 years).

All the participants were classified according to the ASIA system[20] before the intervention. Eleven patients were classified as motor complete SCI, ASIA grade A (n = 10) or grade B (n = 1), defined as no motor functions below the level of the lesion but with zones of partial preservation between L1 down to S1. Seven were categorized as ASIA grade C and 3 as ASIA grade D (Table 1).

Between June 2013 and April 2015, potentially suitable patients were invited and examined during the course of an initial test training and enrolled if they met the following inclusion criteria: chronic incomplete (AIS B/C/D) or complete (AIS A) paraplegia resulting from lesions of the conus medullaris/cauda equina with zones of partial preservation. To be eligible, patients had to present at least motor function of the hip flexor and knee extensor muscles (Janda ≥2) so they would be able to trigger and control the exoskeleton. In patients with insufficient hip extension flexors, knee flexors, or both, the exoskeleton substitutes their force to yield an upright walking pattern. Exclusion criteria were as follows: complete absence of residual motor function in the lower extremities, severely limited range of motion ≥20° of the hip and knee joints (e.g., contracture, spasticity >4 on Ashworth scale), pressure sores, cognitive impairment, body weight >100 kg, nonconsolidated fractures, epilepsy, and severe insufficiency of the cardiopulmonary system.

Training Paradigm

The patients underwent HAL locomotion training for 12 weeks (5 per week; 60 sessions scheduled). During this period the patients continued their regular physiotherapy. There were no additional concomitant treatments. Eligible patients performed an orientation session to familiarize them with the training conditions and the exoskeleton. The training was conducted on a treadmill (Woodway Inc, Waukesha, Wisconsin, USA) providing a body weight support system (harness). The amount of body weight support was adjusted individually to achieve adequate knee extension during stance and toe clearance during the swing phase. Each training session had 3 components and lasted approximately 90 minutes, divided into 30 minutes for preparation (setup time and preparatory physiotherapy), 30 minutes of functional testing, and 30 minutes of HAL-BWSTT. During the course of the intervention, training intensity was increased progressively by changing walking speed, time, and level of body weight support, depending on each patient's abilities.

Additionally, the training was supplemented by specific task exercises such as downhill/uphill/backwards walking and climbing stairs, using a mobile body weight support system, with the aim of improving the patients' balance and motor coordination (Figure 1).

Hybrid Assistive Limb HAL Exoskeleton

The neurologically controlled HAL exoskeleton (Cyberdyne Inc., Tsukuba, Ibaraki, Japan) is a wearable robot suit, consisting of a frame and robotic actuators placed bilaterally on the hip and knee joints and attached to the patient's lower extremities. Residual muscle functions are detected by electromyography electrodes and are processed to support the patient's motion synchronously by adjusting the level and timing of assistance provided to each joint according to the surface bioelectrical signals (BES).[21,22]

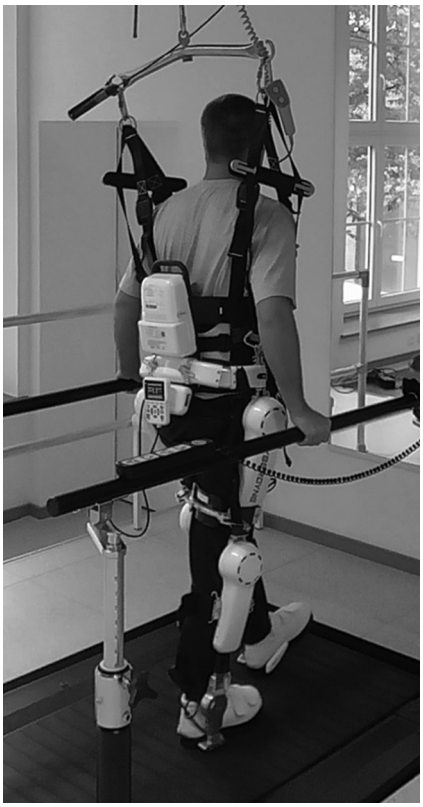

Figure 1. Hybrid assistive limb in use with body weight–supported treadmill training.

The electric motor support at the hip and knee joints can be adjusted gradually according to the patient's remnant flexor and extensor muscle function. This leads to independent, individual, bilateral hip and knee joint motion support in synchrony with the patient's voluntary neurologically controlled drive. This makes individualized and adjustable muscle group locomotion training possible.

This tailored approach allows gait pattern, stride length, and step height to vary so the training can be adjusted to everyday tasks, or even to certain tasks involving obstacles (e.g., doorsteps) that the patients may face in their familiar domestic surroundings (Figure 2).

Outcome Measures

In this study we investigated the effects of 12 weeks of daily HAL-BWSTT (5 per week) on functional outcome in 21 patients with chronic SCI.

To determine the potential increase in muscle strength, the lower extremity motor score (LEMS) was assessed by manual muscle testing according to ASIA over the course of regular biweekly neurologic examinations. The functional walking assessment without the exoskeleton included the 10-meter walk test (10MWT), the 6-minute walk test (6MWT), and the timed up and go (TUG) test. Gait speed, total time, and number of steps were measured with the 10MWT. Therefore, participants were instructed to walk at their preferred speed, and the test was

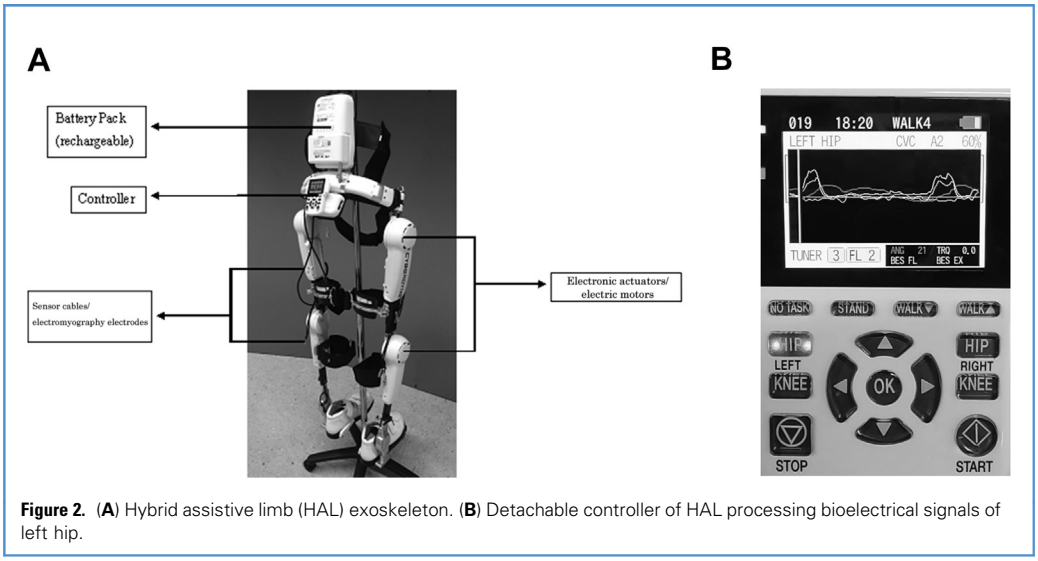

Figure 2. (**A**) Hybrid assistive limb (HAL) exoskeleton. (**B**) Detachable controller of HAL processing bioelectrical signals of left hip.

performed with a "flying start."[23-25] The 6MWT was used to determine gait endurance: the patients walked for 6 minutes at their preferred speed with the option of resting when they felt unable to continue while the ambulated distance was recorded.[26] The TUG test was used to assess the patients' performance in multiple tasks: it established the time required for standing up from the wheelchair, walking 3 meters, turning round, returning to the chair and sitting down again.[27] Furthermore, the treadmill parameters (walking distance, speed, and walking time) were recorded continuously as criteria of the HAL-BWSTT performance. The Walking Index for Spinal Cord Injury II (WISCI-II) was applied to determine the patients' ambulatory walking capacity on the basis of need for physical assistance and assistive devices.[28]

All of the functional walking tests were applied at baseline, 6 weeks midtraining, and 12 weeks after training, without using the exoskeleton.

Statistical Analysis

The frequency distribution was used to record categoric data, demographic details (age, gender), and injury characteristics. The mean ± standard deviation was recorded for continuous variables to provide general information about the study population.

The data were analyzed by repeated measures analysis of variance (rm-ANOVA) with the inner subject factor TIME (baseline, 6-week, and 12-week conditions). Post-hoc analysis (Bonferroni) was used to assess major significant effects. Differences were considered statistically significant at $P < 0.05$. All data were analyzed with the use of SPSS software (version 18.0, SPSS, Chicago, Illinois, USA).

Ethics Statement

All participants in this trial gave written informed consent to participate and to have their anonymized data published. The study protocol was approved by the ethics committee of Bergmannsheil Hospital and the University of Bochum. The study was conducted according to the principles expressed in the Declaration of Helsinki.

RESULTS

Performance on the Treadmill Using the Exoskeleton

Analyzing the treadmill parameters, we noted significant major effects on walking distance (degrees of freedom of the F-test [F]; $F[2,40] = 72.827$; $P \leq 0.001$), walking time ($F[2,40] = 85.83$; $P \leq 0.001$), and walking speed ($F[2,40] = 45.191$; $P \leq 0.001$). The patients improved their walking distance from 196 ± 33.88 meters at baseline to 558.66 ± 67.43 meters at 6 weeks and to 828.95 ± 69.95 meters at 12 weeks, which was significant (baseline to 6 weeks, $P \leq 0.001$; 6 weeks to 12 weeks, $P \leq 0.001$; baseline to 12 weeks, $P \leq 0.001$). Accordingly, the patients significantly extended their walking time from baseline (12.96 ± 1.01 minutes) to 6 weeks (22.94 ± 1.30 minutes; $P \leq 0.001$) to 12 weeks (30.31 ± 1.40 minutes; $P \leq 0.001$) and from 6 weeks to 12 weeks ($P \leq 0.001$). The treadmill speed increased significantly from baseline (0.88 ± 0.076 km/h) to 6 weeks (1.34 ± 0.099 km/h; $P \leq 0.001$), from baseline to 12 weeks (1.63 ± 0.105 km/h; $P \leq 0.001$), and from 6 weeks to 12 weeks ($P \leq 0.001$).

Functional Walking Assessment without the Exoskeleton

At baseline, 20 patients were able to ambulate at least 10 meters over ground with their individual assistive devices, with personal assistance, or both. After the intervention, all of the patients were able to walk a 10-meter distance.

The rm-ANOVA revealed significant changes in the 10MWT performance ($F[2,38] = 30.861$; $P \leq 0.001$). Subsequent post hoc analysis revealed a significant reduction of the time needed from baseline (61.17 ± 44.27 seconds) to 6 weeks (43 ± 31.99 seconds; $P \leq 0.001$), from baseline to 12 weeks (32.18 ± 25.53 seconds; $P \leq 0.001$), and from 6 weeks to 12 weeks ($P = 0.001$).

The rm-ANOVA also indicated significant changes in the number of steps needed to ambulate a 10-meter distance ($F[2,38] = 35.122$; $P \leq 0.001$). Post hoc analysis showed a

significant decrease in the number of steps from baseline to 6 weeks (30.90 ± 8.71 to 24.45 ± 6.47 steps; $P \leq 0.001$), from baseline to 12 weeks (20.70 ± 5.51 steps; $P \leq 0.001$), and from 6 weeks to 12 weeks ($P \leq 0.001$).

The WISCI-II score increased from 10.7 ± 4.95 at baseline to 11.7 ± 4.5 after the intervention. This change was statistically insignificant but corresponds to improved functional walking ability and less dependence on walking aids.

The 6MWT showed a significant increase in mean walking distance ($F[2,40] = 37,41$; $P \leq 0.001$). All patients were assessed before training. At that point, 1 patient did not walk at all. After training, all 21 patients were able to ambulate a certain distance and therefore completed the assessment.

Before the training, the average walking distance covered in the 6MWT was 90.81 ± 110.18 minutes. All patients improved their walking distance significantly to 118.71 ± 134.89 meters (6 weeks, $P = 0.001$) and 149.76 ± 144.28 meters (12 weeks, $P \leq 0.001$). The improvements from midtraining to posttraining were also significant ($P \leq 0.001$).

A significant major effect was also noted in the TUG performance ($F[36,2] = 19.77$, $P \leq 0.001$). Two patients could not perform the TUG before the intervention because of a high risk of falling while turning around and were therefore excluded from assessment and analysis. Statistics revealed significant changes from baseline (53.29 ± 6.84 seconds) to midtraining (44.85 ± 6.54 seconds; $P = 0.002$), from baseline to posttraining (38.75 ± 5.70 seconds; $P \leq 0.001$), and from 6 weeks to 12 weeks ($P = 0.007$). Furthermore, all patients were able to perform the TUG after the 12-week period.

General Results

All included participants underwent HAL-BWSTT according to the training paradigm outlined above. None had to be excluded because of severe adverse events or withdrew from the trial.

There was temporary skin reddening at the site of the skin electrodes, leg cuffs, and shoes in 4 patients, but this adverse event caused no interruption of the training.

Eighteen of the 21 patients reported improvements of their bowel and bladder dysfunctions, and 2 of them were able to discontinue self-catheterization.

Eight patients had spasticity ≤4 according to the Ashworth scale, but this did not interfere with the course of the training. Furthermore, the intervention led to temporary relief after the training sessions, with reversion to the initial state after nightly rest.

The LEMS was used to assess the possible increase of muscle strength attributable to the intervention at the time of enrollment and after the 12-week trial. Every patient showed increased muscle strength, leading to a statistically significant difference in LEMS ($F[1,20] = 64.22$; $P \leq 0.001$) from 22.38 ± 10.7 to 25.71 ± 10.21.

The mean total number of sessions ± standard deviation for all patients was 53.2 ± 5.2 during the 12-week period of HAL-BWSTT.

DISCUSSION

A pilot study showed that HAL-BWSTT is feasible and safe in application and can lead to improved functional mobility and motor functions in patients with chronic paraplegia or tetraplegia.[19] The objective of the present study was to confirm those results by investigating a larger study population of patients with chronic SCI.

The functional assessments reveal highly significant improvements for over-ground walking abilities as assessed by the 10MWT, the 6MWT, the TUG test, and the partial reduction of physical assistance and walking aids in the WISCI-II score. Furthermore, muscle strength measured by the LEMS increased in every patient.

The benefits of locomotion training using a DGO (Lokomat) in patients with chronic SCI has been investigated and deemed promising in several systematic reviews,[29,30] but these studies have not shown that DGOs improve functional outcome, neurologic status, or general application more than conventional body weight–supported treadmill training does.[30] Despite the functional and neurologic outcomes, DGOs permit a more efficient, continuous, and consistent motion pattern to be generated than does conventional BWSTT.

The neurologically controlled exoskeleton HAL represents a substantial advance in rehabilitation devices for SCI patients by depending on the wearer's voluntary drive and simultaneously supporting the patient's movements. To date, there is insufficient evidence, and only a few articles have addressed the main hypothesis of this study: that locomotor training, featuring a neurologically controlled exoskeleton, improves independent walking function for patients with SCI without the exoskeleton.[19,31,32] The present results from 21 patients with chronic SCI imply that HAL-supported locomotion training improves functional walking abilities in terms of speed, gait, distance, along with muscular/motor functions. The normalized motion assistance achieved by the voluntary drive control of HAL results in a proprioceptive feedback loop and further reinforcement of that feedback.[33,34]

The effect of the neurologic control mode of HAL on neuronal plasticity in the primary somatosensory cortex (S1) was recently addressed in a study focusing on functional MRI imaging during HAL-BWSTT. This raised the question whether this specific type of control mode can induce neuronal plasticity and changes of excitability in the S1.[31] This could explain the therapeutic pathway of locomotor training using the HAL exoskeleton.

All 21 enrolled patients were considered to be in a chronic stage, although with an average time since SCI onset of 6.5 ± 5.8 years. All of them improved significantly in respect of treadmill and exoskeleton-associated walking distance and speed, and in exoskeleton-independent functional improvements assessed by standardized over-ground walking tests without HAL.

As limitations of the present study, the following have to be considered: inhomogeneous study population including both complete and incomplete SCI, different levels of lesions, the wide range of time after SCI, and the lack of a control group.

The available literature on locomotor training in the rehabilitation of SCI patients includes several reviews. A Cochrane review by Mehrholz et al.[30] concluded that the results were promising but the evidence remained insufficient owing to the lack of controlled trials. There are still no results from controlled trials concerning robot-assisted locomotors. However, the preinterventional versus postinterventional design of the present study enabled the improvements in the patients' individual functional walking at

baseline to be assessed. All patients were treated in the same facility by the same multidisciplinary team, according to a standardized protocol.

In conclusion, this study confirms the results of the previous pilot study[19] and therefore provides further reliable data and evidence demonstrating the clinical potential of HAL-BWSTT based on voluntary drive in patients with chronic SCI. However, future controlled studies are required to enable comparison of the new advances in the field of SCI rehabilitation with traditional over-ground training.

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