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CASE STUDY

Impact of locomotion training with a neurologic controlled hybrid assistive limb (HAL) exoskeleton on neuropathic pain and health related quality of life (HRQoL) in chronic SCI: a case study*

Oliver Cruciger[1], Thomas A. Schildhauer[2], Renate C. Meindl[1], Martin Tegenthoff[3], Peter Schwenkreis[3], Mustafa Citak[2], and Mirko Aach[1]

[1]Department of Spinal Cord Injuries, [2]Department of General and Trauma Surgery, and [3]Department of Neurology, BG University Hospital Bergmannsheil, Bochum, Germany

Abstract

Chronic neuropathic pain (CNP) is a common condition associated with spinal cord injury (SCI) and has been reported to be severe, disabling and often treatment-resistant and therefore remains a clinical challenge for the attending physicians. The treatment usually includes pharmacological and/or nonpharmacological approaches. Body weight supported treadmill training (BWSTT) and locomotion training with driven gait orthosis (DGO) have evolved over the last decades and are now considered to be an established part in the rehabilitation of SCI patients. Conventional locomotion training goes along with improvements of the patients' walking abilities in particular speed and gait pattern. The neurologic controlled hybrid assistive limb (HAL®, Cyberdyne Inc., Ibraki, Japan) exoskeleton, however, is a new tailored approach to support motor functions synchronously to the patient's voluntary drive. This report presents two cases of severe chronic and therapy resistant neuropathic pain due to chronic SCI and demonstrates the beneficial effects of neurologic controlled exoskeletal intervention on pain severity and health-related quality of life (HRQoL). Both of these patients were engaged in a 12 weeks period of daily HAL®-supported locomotion training. In addition to improvements in motor functions and walking abilities, both show significant reduction in pain severity and improvements in all HRQoL domains. Although various causal factors likely contribute to abatement of CNP, the reported results occurred due to a new approach in the rehabilitation of chronic spinal cord injury patients. These findings suggest not only the feasibility of this new approach but in conclusion, demonstrate the effectiveness of neurologic controlled locomotion training in the long-term management of refractory neuropathic pain.

➤ Implications for Rehabilitation

- CNP remains a challenge in the rehabilitation of chronic SCI patients.
- Locomotion training with the HAL exoskeleton seems to improve CNP in chronic SCI.
- HAL locomotion training is feasible and safe in the rehabilitation of chronic SCI patients.

Keywords

Chronic neuropathic pain, exoskeleton, health related quality of life, locomotion training, spinal cord injury

History

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Introduction

Approximately 1200 people suffer from traumatic spinal cord injury (SCI) every year alone in Germany. SCI especially affects young adults and 80.6% occur among males [1]. Due to the traumatic lesion of the central nervous system, up to 90% of the patients experience pain for a variable length of time [2]. A systematic review published in 2009 by Dijkers et al. concerning the prevalence of chronic pain after traumatic SCI including a meta-analysis of 42 studies, reported a pain prevalence that ranged from 26% to 96% among those patients [3]. Other studies revealed that approximately 70% experience chronic pain manifestations [4–6] and furthermore are considered refractory to treatment in 5–37% of the patients [7]. Because of the challenging management, a diversity of treatments has been established with different rates of success [8,9]. The treatment remains empirical including pharmacological and non-pharmacological approaches. Antidepressants, especially tricyclic antidepressants and anticonvulsants, most notably gabapentin are considered first-line drugs in the treatment [9]. Analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDS) or opiods have not been identified as consistently helpful in relieving neuropathic pain and are more useful for musculoskeletal pain problems [10], which are a common complaint in SCI patients [11]. A survey study by Cardenas

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Address for correspondence: Oliver Cruciger, Bürkle de la Camp-Platz 1, 44789 Bochum, Germany. Tel: +49 234 302 3270. Fax: +49 234 302 6704. E-mail: oliver.cruciger@bergmannsheil.de

et al. with 117 participants suffering from traumatic SCI reported chronic pain manifestations, investigated patients with severe pain, report relief due to physical exercise [9]. Conventional rehabilitation regimen in particular locomotion training and body weight supported treadmill training (BWSTT) are capable of improving the patient's locomotor functions, gait pattern and performance in functional tasks, the chronic neuropathic pain (CNP) however remains and substantially affects the patient's quality of life and furthermore impairs the potential of rehabilitation [12,13]. In the last decade, locomotion training has evolved due to the development of motorized driven gait orthosis (DGO) [14]. The advantages over conventional BWSTT are less effort for attending physiotherapists, longer duration of the training and a more physiological gait pattern [15]. Several studies provide clear and consistent evidence that DGO training improves the over ground walking abilities [16–18]. However, significant effects on often present neuropathic pain have not been well described and appear inconsistent to date. More recently, the neurologic controlled exoskeleton HAL® (Cyberdyne Inc., Ibraki, Japan) allows, in opposite to the other available exoskeletons (Re-Walk®, Rex® and Ekso®) with predefined gait patterns, an intention-based walking support. This enables voluntary machine supported range of motion of incomplete and complete (with zones of partial preservation, ZPP) SCI patients by using minimal bioelectrical signals (BES) recorded and amplified from hip and knee flexor and extensors [19–21]. Exercising of chronic SCI patients with the HAL® exoskeleton (Cyberdyne Inc., Ibraki, Japan) seems to significantly improve functional outcome in regard to overground walking and mobility [22] including partial reduction of physical assistance and required walking aids in the WISCI II score [23]. This case series focused on describing the decrease of CNP and the changes of the health related quality of life (HRQoL) subsequent to intensive locomotor training with the HAL® exoskeleton in two patients, drawn from a series of 10 patients, suffering from chronic SCI and CNP.

Methods

Design

The study has been approved by Ethical Board Committee of the BG University Hospital Bergmannsheil Hospital and the University of Bochum and followed strictly the declaration of Helsinki.

All patients provided written informed consent. The study represents a pretest/posttest, uncontrolled design by repetitive assessments of the same patients.

Population

Ten patients with chronic SCI have been enrolled in the study. Two out of the 10 subjects additionally presenting CNP were encompassed in this case study. A 52-year-old male (patient #1) with complete SCI after a fracture of the 3rd lumbar vertebrae 10 years post-trauma. According to the American Spinal Injury Association/ASIA Impairment Scale (ASIA/ASI) with zones of partial preservation to L3 (LEMS = 16, pin prick score = 83 and light touch score = 90) and furthermore a 40-year-old female (patient #2) suffering from complete SCI after a fracture of the 1st lumbar vertebrae 19 years ago. At the time of enrollment, according to the ASIA-Impairment Scale (ASIA/ASI) with zones of partial preservation (S1) (LEMS = 28, pin prick score = 84 and light touch score = 83).

Eligible patients were at least 18 years of age with moderate/severe therapy-resistant (pharmacological and non-pharmacological treatment) CNP attributable to SCI, numerical rating scale (NRS) ≥ 4 (weekly average), chronic SCI ≥ 12 months post-trauma. Exclusion criteria were as follows: body weight > 100 kg, severe limitation of range of motion (ROM) of hip and knee joints, or non-consolidated fractures.

Both patients characterized the CNP as burning and disabling. Medical treatments at baseline of the two patients were as follows: amitriptyline 150 mg/day, metamizole (5×30 drops) and tramadol 300 mg/day (patient #1) and tetrazepam/benzodiazepine (not available in the US) 300 mg/day (patient #2). Both patients reported a long history of many different treatments without significant or persistent pain relief but intolerable side effects, or a combination of both.

Metamizole → Metamizole, or dipyrone, is a ampyrone sulfonate analgesic, antispasmodic and antipyretic drug, similar to paracetamol in that it has minimal anti-inflammatory effects and is most commonly given orally or parenterally. Maximum dose of 120 drops/4000 mg/day.

Tramadol → is a centrally acting atypical opioid analgesic with additional serotonin-norepinephrine reuptake-inhibiting effects and is used to treat moderate to severe pain. Maximum dose of 400 mg/day.

Tetrazepam → is a benzodiazepine derivative with anticonvulsant, anxiolytic, hypnotic and muscle relaxant properties. Tetrazepam has relatively little sedative effect at low doses while still producing useful muscle relaxation and anxiety relief. Maximum dose of 400 mg/day. Tetrazepam is not available in the US.

Hybrid assistive limb (HAL®) exoskeleton

The voluntary neurologic controlled HAL® exoskeleton consists of a frame and robotic actuators attached to the patients' lower extremities. The movement/step is voluntarily initiated by the patient. Therefore minimal BES are recovered via emg-electrodes from extensor and flexor muscles of the hip and knee regions. The BES are amplified and trigger the support of the robotic actuators synchronously to the voluntary drive of the patient.

Intervention

The patients performed a BWSTT using the HAL® exoskeleton five times a week for a period of 12 weeks. The intervention was scheduled in addition to the patients' regular physiotherapy. No further additional concomitant treatments (nonpharmacological interventions or self management strategies) have been applied. During the intervention neither minor nor severe adverse events occurred.

Training

The patients were scheduled for 60 sessions of treadmill training using the HAL® exoskeleton. The training was performed on a treadmill (Woodway USA, Inc., Waukesha, WI) including a body weight support system (harness).

Depending on the patients' abilities, the intensity of the training, regarding walking speed, distance and time has been adapted individually. The mean number of sessions was 54.5. Reasons for non-attendance were holidays or absence due to illness. Sessions lasted approximately 90 min, subdivided into 30 min of preparation, 30 min of functional testing and 30 min of actual treadmill-training. At all time the training was supervised by a physiotherapist, providing assistance and instructions for the patient and a medical doctor in charge of documentation and supervision.

SF-36-questionnaire (SF-36)

The Short Form-36 (SF-36) questionnaire was used to assess the HRQoL. SF-36 is a well-accepted, self-administered scoring system to measure the patients' QoL [24,25]. The use of the

SF-36-questionnaire has been recommended especially for patients suffering from chronic pain to measure their QoL [26] and is also suitable for elderly patients [27].

It consists of eight independent domains that can be distinguished in two major dimensions. The eight multi-item scales include physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). Five scales (PF, RP, BP, GH and VT) are summarized into the physical health dimension and the other three scales (SF, RE and MH) into the mental health dimension [24].

Numerical rating scale (NRS-11)

The numerical pain rating scale (NRS-11) [28] was applied to assess the severity of pain before each training session. The NRS-11 requires patients to rate their pain from 0 to 10 (11-point scale), with the understanding that 0 represents the absence of pain and 10 represents the worst pain possible. The value selected represents the pain-intensity score. The scores obtained throughout a week were used to calculate a weekly average of the NRS for each of the two patients.

The validity of NRS has been verified and indicates positive and significant correlations with other assessments tools of pain intensity [29]. Furthermore, the pain medication and corresponding dosage were documented on every training day.

Functional testing

Assessment of functional mobility was carried out, using established mobility tests. The 10-meter walk test (10MWT) without the exoskeleton and the walking distance on the treadmill with HAL® are specified exemplarily for both patients of this case study. The values are expressed as means ± standard deviation (SD).

Results

The two patients of this case series experienced moderate/severe CNP below the level of lesion in addition to their SCI at the time of enrollment. Both subjects reported an excessive and long history of pain medication and concomitant treatment prior to the beginning of the trial. The average pain intensity (NRS) of both patients reported in the 1st week of the training has been 4.3 (range of maximum values from 3 to 8). After completing the 12 weeks of training the severity (NRS) decreased to an average of 0.6 between the two patients.

The mandatory pain medication at baseline has been reduced, due to decreasing pain intensity, to an on demand medication at the 4th week of the trial. Initially after the reduction, the pain intensity increased, to shortly after decrease again. The relief of pain persisted even after the training was terminated. In a one-year follow up, both patients reported neither recurrence of pain nor need for medication.

At baseline patient #1 reported an intake of 150 mg amitriptyline/day, 5×30 drops/day of metamizole and 300 mg/day of tramadol. Due to the excessive and mandatory use of painkillers the patient experienced persistent elevated liver values (ALT: 121 U/l and γ-GT: 145 U/l). Throughout the intervention the patient was able to completely stop the medication (4th week) and the liver values normalized within one and a half years.

Patient #2 reported at baseline a daily intake of 300 mg tetrazepam/benzodiazepine per day and achieved a reduction of her medication to 50 mg on demand regimen. Due to the reduction, she reported fewer side effects such as persistent fatigue and lack of concentration.

To evaluate the impact of the intervention on HRQoL the patients completed the SF-36 at baseline and after the period of 12 weeks. Both subjects experienced substantial improvements concerning their HRQoL according to the SF-36 questionnaire.

Compared to baseline, both patients reported a significant pain relief and increase in HRQoL subsequent to locomotion training with HAL® exoskeleton. In addition to the beneficial effects on CNP and HRQoL both subjects of this case study improved in terms of ambulation, subsequent to 12 weeks of HAL®-BWSTT. The mean time needed to walk a 10 m distance without the exoskeleton decreased from 85.6 ± 56.9 s to 44.3 ± 34.6 s. The distance ambulated on the treadmill increased from 122.5 ± 0.71 m to 1032 ± 45.2 m.

Both patients showed minor improvements in the ASIA examination. The lower extremity motor score (LEMS) increased marginal from 16 to 18 for patient #1 and from 28 to 29 for patient # 2. The sensory functions did not differ to the findings at baseline for both patients.

Discussion

It is well accepted that the loss of afferent drive for example due to SCI is followed by functional reorganization of the primary somatosensory cortex (S1) [30,31]. Henderson et al. proposed that the cortical reorganization in humans results at least in part from changes in cortical anatomy, such as axonal sprouting. Contrary to Henderson's results, Björkman et al. state that S1 reorganization can occur within a short period of time, and therefore supporting the existence of dormant synapses [32]. Although the mechanism of cerebral plasticity remains uncertain and needs further investigation the results concerning functional mobility due to locomotion training are widely accepted. Recent research indicates that cortical reorganization may be reversible and responsible for functional improvements in these patients [33]. Although the reduction of pain severity may be explained by cortical reorganization, the upright position and therefore the more physiological alignment of the spine during the training may be taken into account. Prolonged static sitting increases the incidence of musculoskeletal disorders [34], representing an aggravating factor for pain in the lower back [35,36]. Ergonomists agree that regular movements preserve spinal health and prevent musculoskeletal disorders [37].

However, significant effects on often present neuropathic pain have not been well described and appear inconsistent to date. Kressler et al. reported reduction of pain in three out of three complete SCI patients due to Overground Bionic Ambulation (OBA) [38]. Esquenazi et al. only reported reduction for five out of 12 patients, while one subject reported increased pain due to OBA [39]. Our findings reveal reduction in overall pain severity (Figure 1) during the course of the intervention compared to the 1st session for both subjects.

Concerning the impact of CNP on HRQoL a review containing 52 articles by Jensen et al. provides strong evidence that the presence and severity of neuropathic pain are associated with greater impairments of HRQoL domains [40]. According to Jensen et al. the HRQoL-domains mainly affected throughout the 52 clinical trials are physical and emotional role. Their findings suggest, based on the evidence showing the negative effects of pain on HRQoL, despite of focusing on pharmacologic treatments and invasive interventions, psychosocial treatments may also improve the situation of the patient. The patient thereby is able to regain the sense of control over the pain again and therefore easing the feeling of helplessness [41]. As the HRQoL domains are not only associated to pain but also to each other, improving one domain is most likely to cause improvements in the others [40]. Similarly, both patients of this case report a beneficial impact on every domain measured by the SF-36.

The small number of patients ($n = 2$) presents a limitation of this case study. 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

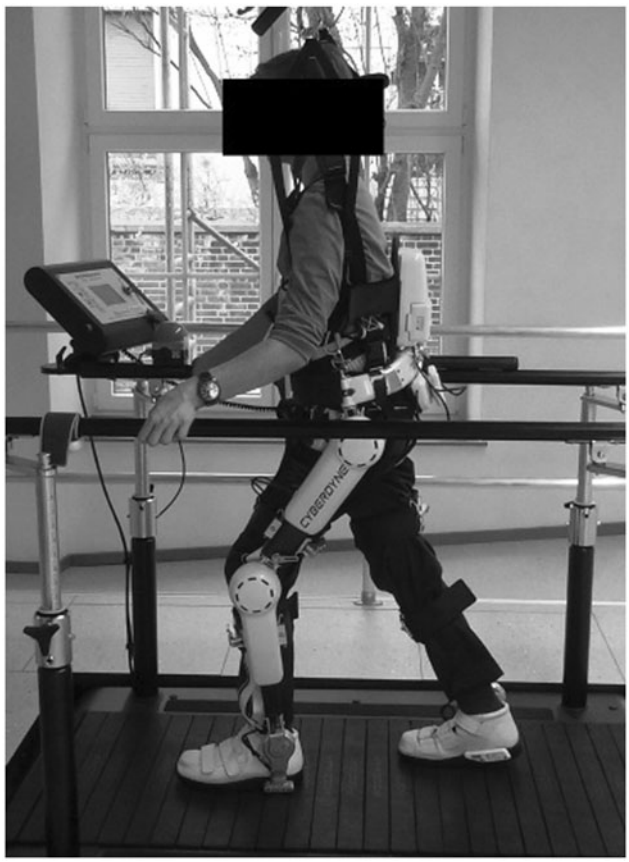


Figure 1. Patient performing locomotion training with the HAL exoskeleton.

Table 1. Patient characteristics.

Case	Sex	Age	Time since trauma (years)	Etiology	Level	ASIA/ZPP	NRS
1	M	52	10	# L 3	L2	A/L3	5
2	F	40	19	# L 1	T 11	A/S1	8

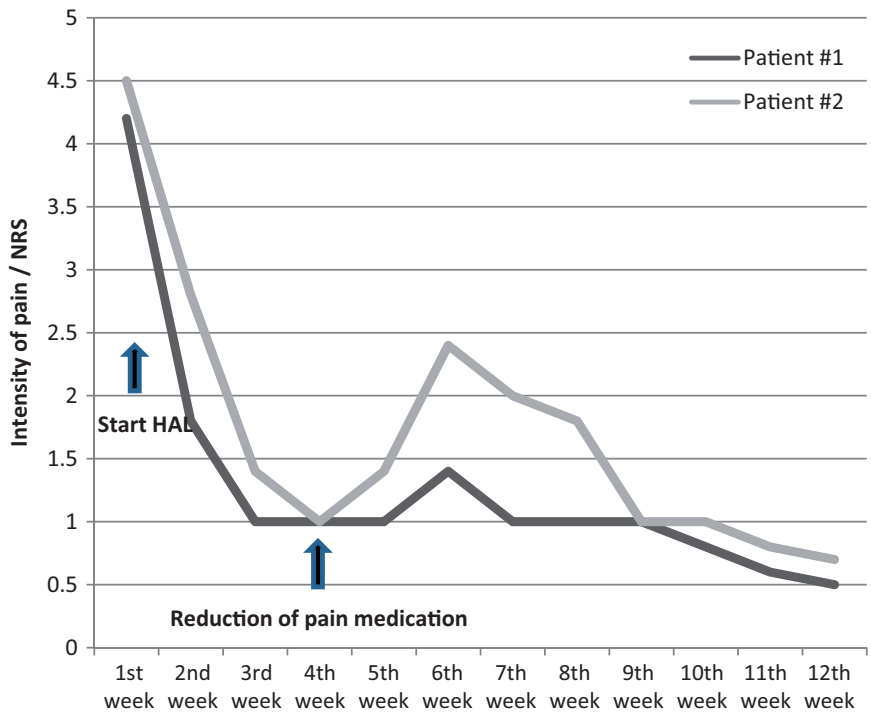
M, male; F, female; #, fracture; ZPP, zones of partial preservation; T, thoracic; L, lumbal; S, sacral; NRS, numerical rating scale.

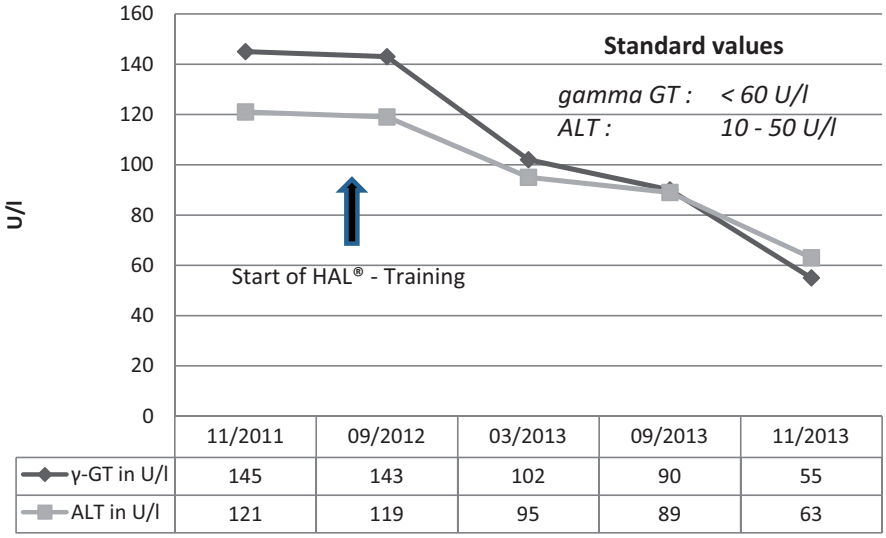
Table 2 Changes in HRQoL domains.

Patient #1	Baseline	Post	Change
PF	5	10	+5
RP	0	25	+25
BP	0	62	+62
GH	10	30	+20
VT	40	70	+30
SF	12.5	62.5	+50
RE	0	66.6	+66.6
MH	40	36	+36
Patient #2	Baseline	Post	Change
PF	35	95	+60
RP	0	100	+100
BP	20	51	+31
GH	30	80	+50
VT	25	65	+40
SF	12.5	75	+62.5
RE	33	100	+67
MH	44	68	+24

PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; SF, social functioning; RE, role emotional; MH, mental health.

Figure 2. Intensity of pain in the course of the training.





	11/2011	09/2012	03/2013	09/2013	11/2013
γ-GT in U/l	145	143	102	90	55
ALT in U/l	121	119	95	89	63

Figure 3. Levels of gamma GT and GPT in the course of the training. γ-GT: gamma-glutamyl transpeptidase; ALT: alanine transaminase; HAL®: hybrid assistive limb.

data demonstrating the beneficial impact of HAL®-locomotor training on CNP in chronic SCI patients.

Conclusion

CNP remains an unconquered challenge for SCI patients and their attending physicians. Intensive locomotion training with the exoskeleton HAL® provides evidence to be a useful adjunct to the variety of existing SCI- rehabilitation programs and has shown a beneficial impact on the severity of pain accompanied by improvements of all HRQoL domains, besides improvements of functional mobility. This study invites further investigations to circumstantiate the beneficial effect of HAL®-training on CNP and HRQoL due to SCI. Questions regarding long term effects and whether this new method is capable of inducing cortical reorganization remain to be answered in follow-up studies.

Declaration of Interest

The author(s) report no conflict of interest with respect to the research, authorship, and/or publication of this article.

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