J. Phys. Ther. Sci. 30: 207–212, 2018

The Journal of Physical Therapy Science

Original Article

Immediate effects of a single session of robot-assisted gait training using Hybrid Assistive Limb (HAL) for cerebral palsy

Mayumi Matsuda, RPT, MS[1, 2]*, Yuki Mataki, MD[3], Hirotaka Mutsuzaki, MD, PhD[2, 4], Kenichi Yoshikawa, RPT, PhD[1], Kazushi Takahashi, RPT[1], Keiko Enomoto, RPT[1], Kumiko Sano, RPT[1], Masafumi Mizukami, RPT, PhD[2, 5], Kazuhide Tomita, RPT, PhD[2, 5], Haruka Ohguro, MD[6], Nobuaki Iwasaki, MD, PhD[2, 4, 6]

1) *Department of Physical Therapy, Ibaraki Prefectural University of Health Sciences Hospital: 4733 Ami, Ibaraki 300-0331, Japan*
2) *Graduate School of Health Science, Ibaraki Prefectural University of Health Sciences, Japan*
3) *Department of Orthopaedic Surgery, Ibaraki Prefectural University of Health Sciences Hospital, Japan*
4) *Center for Medical Science, Ibaraki Prefectural University of Health Sciences, Japan*
5) *Department of Physical Therapy, Ibaraki Prefectural University of Health Sciences, Japan*
6) *Department of Pediatrics, Ibaraki Prefectural University of Health Sciences Hospital, Japan*

Abstract. [Purpose] Robot-assisted gait training (RAGT) using Hybrid Assistive Limb (HAL, CYBERDYNE) was previously reported beneficial for stroke and spinal cord injury patients. Here, we investigate the immediate effect of a single session of RAGT using HAL on gait function for cerebral palsy (CP) patients. [Subjects and Methods] Twelve patients (average age: 16.2 ± 7.3 years) with CP received a single session of RAGT using HAL. Gait speed, step length, cadence, single-leg support per gait cycle, hip and knee joint angle in stance, and swing phase per gait cycle were assessed before, during, and immediately after HAL intervention. [Results] Compared to baseline values, single-leg support per gait cycle (64.5 ± 15.8% to 69.3 ± 12.1%), hip extension angle in mid-stance (149.2 ± 19.0° to 155.5 ± 20.1°), and knee extension angle in mid-stance (137.6 ± 20.2° to 143.1 ± 19.5°) were significantly increased immediately after intervention. Further, the knee flexion angle in mid-swing was significantly decreased immediately after treatment (112.0 ± 15.5° to 105.2 ± 17.1°). Hip flexion angle in mid-swing also decreased following intervention (137.2 ± 14.6° to 129.7 ± 16.6°), but not significantly. Conversely, gait speed, step length, and cadence were unchanged after intervention. [Conclusion] A single-time RAGT with HAL improved single-leg support per gait cycle and hip and knee joint angle during gait, therapeutically improving gait function in CP patients.

Key words: Robot-assisted gait training, Cerebral palsy, Hybrid Assistive Limb

(This article was submitted Aug. 20, 2017, and was accepted Nov. 2, 2017)

INTRODUCTION

Gait disorders including abnormal gait pattern, slow gait speed, and decreased walking endurance are present in over 90% of cerebral palsy (CP) patients[1–3]. Importantly, CP patients with enhanced mobility report improvements in performing activities of daily living and community inclusion[4]. Therefore, if walking ability can be improved by rehabilitation, quality of daily life will increase as a result.

With respect to walking training for CP patients, the effect of body-weight-supported treadmill training (BWSTT) is com-

---

*Corresponding author. Mayumi Matsuda (E-mail: 45070069@ipu.ac.jp)

monly considered as an index of gait speed[5–8]. However, CP patients with severe gait perturbation require manual assistance during walking. Further, it is difficult to objectively set both joint angle and level of assistance during walking.

Much attention has been focused on robot-assisted gait training (RAGT) to automatically control patient gait during walking. Indeed, several walking support robotic devices are commercially available including "end-effector type" like Gait Trainer (Reha-Stim, Berlin, Germany)[9–12] and LokoHelp (Woodway, Waukesha, USA)[13] and "exoskeleton type" like ReWalk™ (ReWalk Robotics, Berlin, Germany)[14, 15] and Lokomat® (Hocoma, Volketswil, Switzerland)[16]. Interestingly, RAGT using Lokomat has been reported as efficacious for CP patients, significantly improving gross motor function measure (GMFM)[17–21], gait speed[17–20, 22], and walking endurance[17–19] and lowering body kinematics parameters[22, 23]. However, Lokomat is a passive robotic gait intervention, with the lower limb joint angle and gait speed set to constant values during treadmill walking.

Conversely, Hybrid Assistive Limb (HAL; CYBERDYNE, Tsukuba, Japan) is a novel robotic device capable of assisting voluntary walking in response to the intention of the wearer. Specifically, proprietary developed sensors and electrodes monitor minimal bioelectrical signals (BES) from the surface of the skin of both the flexor and extensor muscles of the hip and knee joints. Further force-pressure sensors are present in the shoes, biometric information is gathered regarding joint angle, and robotic actuators at the hip and knee joint are driven to assist torque[24]. Importantly, several reports indicate that RAGT using HAL may be an effective therapeutic device for patients with stroke, spinal cord injury, and knee joint deformity. With respect to patient outcomes, RAGT using HAL significantly improved multiple clinical measures including gait speed[25–31], cadence[25, 26], step length[25–29], walking endurance[26, 27, 30], balance function[25], functional ambulation categories (FAC)[31, 32], functional independence measure (FIM)[28, 33] and stroke impairment assessment set (SIAS)[33]. A good clinical practice-adherent clinical trial was conducted in ten facilities for slow, progressive, rare neuromuscular diseases, and HAL is considered to have a certain level of efficacy with acceptable safety from regulatory authority's review report[34, 35]. However, there are only a few reports about the effect of RAGT using HAL for CP patients[36, 37].

Therefore, in this investigation, we performed RAGT using HAL to assist voluntary walking in CP patients and assessed clinical measures of gait function before and following HAL attachment. We hypothesized that RAGT using HAL for CP patients would significantly improve gait function, reduce walking support requirements, and improve independence of ambulation.

The purpose of this investigation was to promote immediate therapeutic effects with respect to gait function with and without HAL attachment, before and after a single 10–20-min session of RAGT using HAL in CP patients.

SUBJECTS AND METHODS

Twelve patients with CP were enrolled in the study between February 2016 and March 2017 (eight males, four females; age range, 9–37 years; average age, 16.2 ± 7.3 years; height, 147.8 ± 12.1 cm; body weight, 40.8 ± 10.8 kg). The severity of the patient's condition was assessed utilizing the gross motor function classification system (GMFCS), with two subjects at GMFCS level I, three subjects at level II, five subjects at level III, and two subjects at level IV. With respect to type of paralysis, nine patients presented with spastic diplegia one patient presented with quadriplegia, and two patients presented with spastic right hemiplegia. In all cases, patients presented with a primary diagnosis of periventricular leukomalacia (PVL) (Table 1). The study protocol was approved by the ethics committee of Ibaraki Prefectural University of Health Sciences (approval number: 682); all patients provided written informed consent.

For this investigation, we utilized HAL for medical use, lower limb type S size (target 145–165 cm) and control mode using Cybernic Voluntary Control (CVC). Further, flexion/extension balance and assist torque at the hip and knee joints were optimized for each patient.

Gait speed was selected by each patient. During walking, patients wearing HAL utilized a walking device (All-in-One Walking Trainer; Healthcare Lifting Specialist, Denmark) with harness for safety. Each patient was assisted by two therapists, with a therapist in front correcting the direction of the walking device and a therapist behind holding the HAL pelvic frame to prevent risk of falling. A single session of RAGT using HAL was performed for 10–20 min, over a 50–200-m distance depending on the condition of the patient (i.e., subject fatigue, facial expression, pulse).

For comparison of gait functions, we examined gait speed (m/s), stride length (cm), and cadence (step/min) during the 10-m walk test (10 MWT) before, during, and after HAL attachment. Specifically, study participants were instructed to walk on a 10-m walkway at a self-selected speed with an assistive device and orthosis (Table 1). When the subject experienced difficulty in walking at 10 m, gait speed was calculated from the video recording. We used a fixed video camera, framed to record the sagittal gait[38]. Markers were attached to the subject's acromion process, greater trochanter, lateral joint line of the knee, and lateral malleolus. We calculated single-leg support during one gait cycle (%), as well as hip and knee joint angle during stance and swing phase over the course of one gait cycle. Before and following HAL attachment, we calculated hip joint angle as acromion process −greater trochanter −lateral joint line of the knee; knee joint angle was calculated as greater trochanter −lateral joint line of the knee −lateral malleolus. During HAL intervention, we calculated hip joint angle as acromion process –hip joint of the HAL −knee joint of the HAL; knee joint angle was calculated as hip joint of the HAL −knee joint of the HAL −ankle joint of the HAL. Further, we utilized Dipp-Motion (DITECT, Dipp-Motion 2D) for gait analysis. Walking style for each subject before and after HAL intervention was categorized as independent walking (n=3), using a

Table 1. Characteristics

Case	Gender	Age	High (cm)	Weight (kg)	Etiology	Movement disordor	Paralysis	GMFCS	Assistive device	Orthosis
1	M	37	165	51	PVL	spactic	Diplegia	II	clutch	AFO
2	M	20	168	64	PVL	spactic	Diplegia	IV	parallel bars	AFO
3	F	19	152	40	PVL	spactic	Diplegia	II	NA	NA
4	M	16	153	49	PVL	spactic	Diplegia	III	walker	AFO
5	F	15	143	35	PVL	spactic	Diplegia	II	clutch	AFO
6	F	15	141	48	PVL	spactic	Diplegia	III	walker	AFO
7	M	15	158	43	PVL	spactic	Diplegia	III	walker	AFO
8	M	14	153	37	PVL	spactic	Quadriplegia	IV	BS walker	AFO
9	M	12	138	27	PVL	spactic	Diplegia	III	walker	AFO
10	F	11	137	35	PVL	spactic	Diplegia	III	walker	AFO
11	M	11	132	32	PVL	spactic	R hemiplegia	I	NA	R AFO
12	M	9	134	28	PVL	spactic	R hemiplegia	I	NA	R AFO

M: male; F: female; PVL: Periventricular Leukomalacia; GMFCS: Gross Motor Function Classification System; NA: not applicable; BS walker: body support walker; AFO: ankle foot orthosis.

clutch (n=2), using a walker (n=6), and using bars (n=1) (Table 1).

Statistical analysis was performed using SPSS ver.22.0 (IBM) for each value obtained before and during HAL attachment, as well as before and after HAL attachment. Changes in gait parameters were assessed using the Wilcoxon test. Results were compared and examined using average values, with p-value <0.05 considered statistically significant.

RESULTS

Gait speed (p=0.004), stride length (p=0.03), and cadence (p=0.003) significantly decreased during RAGT with HAL intervention relative to before values (Table 2).

Conversely, no significant differences were observed during HAL attachment with respect to single-leg support during one gait cycle, hip angle in mid-stance, knee angle in mid-stance, hip angle in mid-swing, knee angle in mid-swing (Table 2).

Single-leg support during one gait cycle (p=0.01), hip extension angle in mid-stance (p=0.04), and knee extension angle in mid-stance (p=0.02) significantly increased immediately after RAGT with HAL intervention relative to before values. Further, knee flexion angle in mid-swing (p=0.02) immediately after HAL intervention significantly decreased compared with measurements obtained before RAGT. Although decreased, hip flexion angle in mid-swing (p=0.14) immediately after HAL intervention was not significantly different (Table 3).

Conversely, no significant differences were observed with respect to gait speed, step length, and cadence before and after HAL intervention (Table 3).

DISCUSSION

Importantly, our study is the first systematic investigation of HAL intervention in CP patients with bilateral lower limb spasticity. Our protocol administered only a single session of intervention. This is to exclude motor learning effects in continuous intervention and purely investigate HAL-specific effects that assist the wearer's voluntary motion intentions. We observed appreciable increases in single-leg support as well as lower limb joint angle during patient gait after HAL attachment; gait speed was not significantly different, during HAL attachment. We believe that the witnessed effects may be attributable to two factors. First, the depressed walking speed with HAL attachment created large joint torque. Second, stability of the single-leg support was increased by the mechanical parts of HAL. Therefore, both single-leg support and lower limb joint angle were significantly different immediately after HAL intervention.

Standing/gait posture and gait pattern also improved during HAL attachment. Therefore, HAL intervention may potentially serve to normalize gait pattern by correcting abnormal gait patterns acquired in response to CP.

Regarding the increase in single-leg support and lower limb joint angle after HAL attachment, previous reports indicate that CP patients demonstrate differences in the degree of right-left paralysis and spasticity, even in the setting of bilateral palsy[39]. Therefore, CP patients demonstrate postural asymmetry during standing and walking. Importantly, HAL adjusts both assist torque and flexion/extension balance separately to both the right and left according to the patient's condition, providing the setting for appropriate intervention performance.

In the normal gait, as gait speed decreases, stride length, cadence, and single-leg support also decrease[40]. Similarly, gait speed during HAL attachment decreased compared to usual gait for all study participants. However, both single-leg support

Table 2. Comparison of gait function before and during HAL intervention

Outcome measurements	before HAL	during HAL
Gait speed (m/s)	0.8 ± 0.4	0.3 ± 0.2**
Stride length (m)	0.5 ± 0.1	0.4 ± 0.1*
Cadence (step/min)	92.4 ± 35.9	55.1 ± 17.5**
Single-leg support phase (%)	64.5 ± 15.8	57.2 ± 15.4
Hip angle of stance phase (°)	149.2 ± 19.0	153.3 ± 17.7
Knee angle of stance phase (°)	137.6 ± 20.2	144.8 ± 18.9
Hip angle of swing phase (°)	137.2 ± 14.6	129.2 ± 13.9
Knee angle of swing phase (°)	112.0 ± 15.5	117.2 ± 18.6

*p<0.05, **p<0.01.

Table 3. Comparison of gait function before and after HAL intervention

Outcome measurements	before HAL	after HAL
Gait speed (m/s)	0.8 ± 0.4	0.8 ± 0.5
Stride length (m)	0.5 ± 0.1	0.5 ± 0.1
Cadence (step/min)	92.4 ± 35.9	92.4 ± 40.0
Single-leg support phase (%)	64.5 ± 15.8	69.3 ± 12.1*
Hip angle of stance phase (°)	149.2 ± 19.0	155.7 ± 20.1*
Knee angle of stance phase (°)	137.6 ± 20.2	143.1 ± 19.5*
Hip angle of swing phase (°)	137.2 ± 14.6	129.7 ± 16.6
Knee angle of swing phase (°)	112.0 ± 15.5	105.2 ± 17.1*

*p<0.05, **p<0.01.

and lower limb joint angle during HAL attachment were maintained relative to the usual gait. Maeshima et al. reported that gait speed decreases during HAL attachment in stroke patients41). Therefore, in slow gait speed, it seems possible to create a large joint angle by HAL assist according to the wearer's voluntary motion intention during HAL attachment (i.e., ease of locomotor control). Additionally, we believe that even if gait speed is reduced by HAL attachment, single-leg support during one gait cycle was not decreased as single-leg support was stabilized by the HAL with integration of foot and pelvis sections. As the wearer can control voluntarily adjustment of gait speed and lower limb joint angle, HAL appears to differ from conventional gait-assist robots without voluntary system control. Walking in CP patients is very unstable and will be refined by supporting one's own body. Walking stability is secured by attaching HAL which is an exoskeleton type walking-assist robot. Therefore, in gait after HAL attachment, the gait pattern such as joint angle and single-leg support during one gait cycle shifted to the gait immediately after HAL attachment despite gait speed returning to almost the same gait speed as before HAL attachment. By repeating this transformation of the gait pattern, improvement in walking ability such as gait speed and stride is expected. In BWSTT, it is said that by repeating walking at a speed faster than usual, gait pattern changes and the Central Pattern Generator (CPG) is activated5–8). However, in this study, in gait training using HAL, the walking stability is secured by the exoskeleton of HAL even at slow walking speed, and in the assist according to the intention, the transformation of gait pattern and activation of CPG can be expected by performing complex articulation repeatedly.

Repetitive stepping exercise is consistent with the motion learning theory, defined as a neuro-rehabilitation inducing the cerebral plasticity with aims of functional recovery42–45). However, the intensity of brain activity, the premise of motion, increases only during conditions where voluntary motion planning and conducted exercise and feedback are combined and does not change with passive exercise or simple repetitive automatic exercise46).

During our investigation, walking intervention using HAL was accepted without resistance in all patients. HAL controls several actuators at the hip and knee joints based on the BES based on the wearer's intention, load distribution of both soles, and hip and knee joint angle information assisting the joint torques during gait47). The greatest characteristic of HAL as compared with conventional gait-assist robots is assisting voluntary gait in response to the wearer's intention.

The conventional robot is an automatic walking-assist device, walking on the treadmill at constant speed, and set to a specific joint angle of the lower limb (i.e., passive walking). In passive walking, it is difficult for the wearer to learn the motor control necessary for proper voluntary walking control, in accordance with the motor learning theory.

HAL already became a medical device to improve neurophysical functions of patients in the European Union and patients with rare neuromuscular disease in Japan34, 35). HAL can utilize voluntary motion intention of the wearer, feedback the results, and contribute to the motor learning theory. In fact, in this investigation, an immediate effect on the gait function was recognized following a single intervention. Therefore, we believe that HAL intervention significantly influences gait function in CP patients even with a single HAL intervention.

Our investigation has several limitations. First, the small number of cases is not sufficient. It will be necessary to obtain future results from controlled trials as compared to conventional rehabilitation to determine the efficacy of RAGT using HAL intervention. Further, it will be necessary to clarify the safety and effectiveness of long-term intervention and treatment adaptation in a larger cohort of patients. Apparently, quantity of training is necessary to produce established improvements in gait function. Further improvement of gait function would be demonstrated by conducting RAGT using HAL in the long term. We expect that walking ability will improve in accordance with the previous study.

In CP patients, a single session of RAGT with HAL intervention significantly improved measures of gait functionality including increasing both single-leg support and lower limb joint angle during gait. Therefore, RAGT using HAL may be an effective option to improve mobility in CP patients.

REFERENCES

1) Hutton JL, Pharoah PO, Rosenbloom L: Effects of cognitive, motor, and sensory disabilities on survival in cerebral palsy. Arch Dis Child, 2002, 86: 84–89. [Medline] [CrossRef]
2) Pharoah PO, Cooke T, Johnson MA, et al.: Epidemiology of cerebral palsy in England and Scotland, 1984–9. Arch Dis Child Fetal Neonatal Ed, 1998, 79: F21–F25. [Medline] [CrossRef]
3) Duffy CM, Hill AE, Cosgrove AP, et al.: Energy consumption in children with spina bifida and cerebral palsy: a comparative study. Dev Med Child Neurol, 1996, 38: 238–243. [Medline] [CrossRef]
4) Lepage C, Noreau L, Bernard PM: Association between characteristics of locomotion and accomplishment of life habits in children with cerebral palsy. Phys Ther, 1998, 78: 458–469. [Medline] [CrossRef]
5) El-hakiem WA, Agha M: Effect of treadmill training with partial body weight support on spine geometry and gross motor function in children with diplegic cerebral palsy. Int J Ther Rehabil Res, 2017, 6: 46–52.
6) Schindl MR, Forstner C, Kern H, et al.: Treadmill training with partial body weight support in nonambulatory patients with cerebral palsy. Arch Phys Med Rehabil, 2000, 81: 301–306. [Medline] [CrossRef]
7) Cherng RJ, Liu CF, Lau TW, et al.: Effect of treadmill training with body weight support on gait and gross motor function in children with spastic cerebral palsy. Am J Phys Med Rehabil, 2007, 86: 548–555. [Medline] [CrossRef]
8) Willoughby KL, Dodd KJ, Shields N, et al.: Efficacy of partial body weight-supported treadmill training compared with overground walking practice for children with cerebral palsy: a randomized controlled trial. Arch Phys Med Rehabil, 2010, 91: 333–339. [Medline] [CrossRef]
9) Hesse S, Uhlenbrock D: A mechanized gait trainer for restoration of gait. J Rehabil Res Dev, 2000, 37: 701–708. [Medline]
10) Hesse S, Uhlenbrock D, Werner C, et al.: A mechanized gait trainer for restoring gait in nonambulatory subjects. Arch Phys Med Rehabil, 2000, 81: 1158–1161. [Medline] [CrossRef]
11) Peurala SH, Tarkka IM, Pitkänen K, et al.: The effectiveness of body weight-supported gait training and floor walking in patients with chronic stroke. Arch Phys Med Rehabil, 2005, 86: 1557–1564. [Medline] [CrossRef]
12) Dias D, Laíns J, Pereira A, et al.: Can we improve gait skills in chronic hemiplegics? A randomised control trial with gait trainer. Eura Medicophys, 2007, 43: 499–504. [Medline]
13) Freivogel S, Mehrholz J, Husak-Sotomayor T, et al.: Gait training with the newly developed ‘LokoHelp’-system is feasible for non-ambulatory patients after stroke, spinal cord and brain injury. A feasibility study. Brain Inj, 2008, 22: 625–632. [Medline] [CrossRef]
14) Esquenazi A, Talaty M, Packel A, et al.: The ReWalk powered exoskeleton to restore ambulatory function to individuals with thoracic-level motor-complete spinal cord injury. Am J Phys Med Rehabil, 2012, 91: 911–921. [Medline] [CrossRef]
15) Zeilig G, Weingarden H, Zwecker M, et al.: Safety and tolerance of the ReWalk™ exoskeleton suit for ambulation by people with complete spinal cord injury: a pilot study. J Spinal Cord Med, 2012, 35: 96–101. [Medline] [CrossRef]
16) Hidler J, Wisman W, Neckel N: Kinematic trajectories while walking within the Lokomat robotic gait-orthosis. Clin Biomech (Bristol, Avon), 2008, 23: 1251–1259. [Medline] [CrossRef]
17) Schroeder AS, Homburg M, Warken B, et al.: Prospective controlled cohort study to evaluate changes of function, activity and participation in patients with bilateral spastic cerebral palsy after Robot-enhanced repetitive treadmill therapy. Eur J Paediatr Neurol, 2014, 18: 502–510. [Medline] [CrossRef]
18) Meyer-Heim A, Borggraefe I, Ammann-Reiffer C, et al.: Feasibility of robotic-assisted locomotor training in children with central gait impairment. Dev Med Child Neurol, 2007, 49: 900–906. [Medline] [CrossRef]
19) Meyer-Heim A, Ammann-Reiffer C, Schmartz A, et al.: Improvement of walking abilities after robotic-assisted locomotion training in children with cerebral palsy. Arch Dis Child, 2009, 94: 615–620. [Medline] [CrossRef]
20) Borggraefe I, Kiwull L, Schaefer JS, et al.: Sustainability of motor performance after robotic-assisted treadmill therapy in children: an open, non-randomized baseline-treatment study. Eur J Phys Rehabil Med, 2010, 46: 125–131. [Medline]
21) Schroeder AS, Von Kries R, Riedel C, et al.: Patient-specific determinants of responsiveness to robot-enhanced treadmill therapy in children and adolescents with cerebral palsy. Dev Med Child Neurol, 2014, 56: 1172–1179. [Medline] [CrossRef]
22) Drużbicki M, Rusek W, Snela S, et al.: Functional effects of robotic-assisted locomotor treadmill thearapy in children with cerebral palsy. J Rehabil Med, 2013, 45: 358–363. [Medline] [CrossRef]
23) Wallard L, Dietrich G, Kerlirzin Y, et al.: Robotic-assisted gait training improves walking abilities in diplegic children with cerebral palsy. Eur J Paediatr Neurol, 2017, 21: 557–564. [Medline] [CrossRef]
24) Suzuki K, Mito G, Kawamoto H, et al.: Intention-based walking support for paraplegia patients with Robot Suit HAL. Adv Robot, 2007, 21: 1441–1469.

25) Kubota S, Nakata Y, Eguchi K, et al.: Feasibility of rehabilitation training with a newly developed wearable robot for patients with limited mobility. Arch Phys Med Rehabil, 2013, 94: 1080–1087. [Medline] [CrossRef]

26) Mizukami M, Yoshikawa K, Kawamoto H, et al.: Gait training of subacute stroke patients using a hybrid assistive limb: a pilot study. Disabil Rehabil Assist Technol, 2017, 12: 197–204. [Medline] [CrossRef]

27) Aach M, Cruciger O, Sczesny-Kaiser M, et al.: Voluntary driven exoskeleton as a new tool for rehabilitation in chronic spinal cord injury: a pilot study. Spine J, 2014, 14: 2847–2853. [Medline] [CrossRef]

28) Fukuda H, Samura K, Hamada O, et al.: Effectiveness of acute phase hybrid assistive limb rehabilitation in stroke patients classified by paralysis severity. Neurol Med Chir (Tokyo), 2015, 55: 487–492. [Medline] [CrossRef]

29) Yoshikawa K, Mizukami M, Kawamoto H, et al.: Gait training with Hybrid Assistive Limb enhances the gait functions in subacute stroke patients: a pilot study. NeuroRehabilitation, 2017, 40: 87–97. [Medline] [CrossRef]

30) Grasmücke D, Zieriacks A, Jansen O, et al.: Against the odds: what to expect in rehabilitation of chronic spinal cord injury with a neurologically controlled Hybrid Assistive Limb exoskeleton. A subgroup analysis of 55 patients according to age and lesion level. Neurosurg Focus, 2017, 42: E15. [Medline] [CrossRef]

31) Nilsson A, Vreede KS, Häglund V, et al.: Gait training early after stroke with a new exoskeleton–the hybrid assistive limb: a study of safety and feasibility. J Neuroeng Rehabil, 2014, 11: 92. [Medline] [CrossRef]

32) Watanabe H, Goto R, Tanaka N, et al.: Effects of gait training using the Hybrid Assistive Limb® in recovery-phase stroke patients: a 2-month follow-up, randomized, controlled study. NeuroRehabilitation, 2017, 40: 363–367. [Medline] [CrossRef]

33) Chihara H, Takagi Y, Nishino K, et al.: Factors predicting the effects of hybrid assistive limb robot suit during the acute phase of central nervous system injury. Neurol Med Chir (Tokyo), 2016, 56: 33–37. [Medline] [CrossRef]

34) The Japan Medical Association Center for Clinical Trials: https://dbcentre3.jmacct.med.or.jp/jmactr/App/JMACTRE02_04/JMACTRE02_04.aspx?kbn=3&seqno=3962 (Accessed Jul. 18, 2017)

35) Pharmaceuticals and Medical Devices Agency: http://www.pmda.go.jp/english/review-services/reviews/approved-information/devices/0003.html (Accessed Jul. 18, 2017)

36) Taketomi T, Yoshiyuki S: Walking Assistance for Cerebral Palsy with Robot Suit HAL. Trans Jpn Soc Med Biol Eng. 2012, 50: 105–111.

37) Tadamitsu M, Ichirou F, Miki T, et al.: Effects of gait training using a robot suit of hybrid assistive limbs on spastic diplegia. DMCN, 2016, Suppl58: 43.

38) Ugbolue UC, Papi E, Kaliarntas KT, et al.: The evaluation of an inexpensive, 2D, video based gait assessment system for clinical use. Gait Posture, 2013, 38: 483–489. [Medline] [CrossRef]

39) Young JL, Rodda J, Selber P, et al.: Management of the knee in spastic diplegia: what is the dose? Orthop Clin North Am, 2010, 41: 561–577. [Medline] [CrossRef]

40) Bejek Z, Paróczai R, Illyés A, et al.: The influence of walking speed on gait parameters in healthy people and in patients with osteoarthritis. Knee Surg Sports Traumatol Arthrosc, 2006, 14: 612–622. [Medline] [CrossRef]

41) Maeshima S, Osawa A, Nishio D, et al.: Efficacy of a hybrid assistive limb in post-stroke hemiplegic patients: a preliminary report. BMC Neurol, 2011, 11: 116. [Medline] [CrossRef]

42) Nudo RJ, Milliken GW, Jenkins WM, et al.: Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. J Neurosci, 1996, 16: 785–807. [Medline]

43) Nudo RJ, Plautz EJ, Frost SB: Role of adaptive plasticity in recovery of function after damage to motor cortex. Muscle Nerve, 2001, 24: 1000–1019. [Medline] [CrossRef]

44) Nudo RJ: Plasticity. NeuroRx, 2006, 3: 420–427. [Medline] [CrossRef]

45) Fu M, Yu X, Lu J, et al.: Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. Nature, 2012, 483: 92–95. [Medline] [CrossRef]

46) Perez MA, Lungholt BK, Nyborg K, et al.: Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. Exp Brain Res, 2004, 159: 197–205. [Medline] [CrossRef]

47) Kasaoka K, Sankai Y: Predictive control estimating operator's intention for stepping-up motion by exoskeleton type power assist system HAL. In Intelligent Robots and Systems. Proceedings 2001 IEEE/RSJ International Conference on. 2001, 3: 1578–1583.