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Original article

Three by three weeks of robot-enhanced repetitive gait therapy within a global rehabilitation plan improves gross motor development in children with cerebral palsy – a retrospective cohort study

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ABSTRACT

Aim: To assess the improvement in gross motor function following three blocks of a three-week, intensive robot-enhanced treadmill therapy (ROBERT-Program).

Method: retrospective chart review in a before-after interventional trial in children with cerebral palsy attending a university hospital outpatient rehabilitation centre. Patients received three blocks of a three-week, 12 sessions ROBERT-Program over a mean period of 24 months. Outcome measures were block specific and cumulative improvement in GMFM 66, D and E. Longterm GMFM 66 improvements were compared to the individuals' expected increment as derived from previously published GMFM-66 percentiles. 95% confidence intervals (CI) and paired t-test were calculated.

Results: 20 children (8 GMFCS Level II; 12 GMFCS Level III, mean age 5.9 years (CI: [5.0; 6.7])) were treated. For each block a significant increase in motor performance in similar size could be observed without deterioration between blocks. The cumulative improvement during 21 months observation period was: 6.5 (CI: [4.8; 8.2]) in GMFM 66, which represents a clinically meaningful effect size of 3.6 (CI: [1.4; 5.8]) above the expected improvement.

Interpretation: Progressive clinically meaningful improvement in motor performance for three blocks of ROBERT-Program was observed. Cumulative GMFM 66 improvements exceeded the individuals' age-specific expected course.

Abbreviations: AACPDM, American Academy on Cerebral Palsy and Developmental Medicine; ARTIC, Advanced Robotic Therapy Integrated Centers; CI, confidence interval; CP, cerebral palsy; DIST 6 MWT, distance in the 6 Minute Walking Test; LMU, Ludwig Maximilian University of Munich; MCID, minimum clinically important differences; ROBERT-Program, ROBot-Enhanced-Repetitive-Therapy-Program; SSWS 10 MWT, self-selected and maximum walking speed in the 10 Meter Walk Test walking test.

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1. Introduction

Spastic movement disorders such as cerebral palsy (CP) are the most frequent reason for impairment of gross motor function in childhood.[1] The age, when children with CP reach 90% of their maximal gross motor performance varies by GMFCS level e.g. 4; 11 years for GMFCS level II and 3; 2 years in level III. After reaching peak motor ability, a clinically relevant decline in motor ability is characteristic in patients with GMFCS levels III-V beginning already within the first decade of life (for GMFCS Level III at 7; 11 years of age).[2] For independently ambulant patients with CP (GMFCS Level I-II) a decline in gait function has been reported to occur in about 25% during transition from adolescence to adulthood.[3]

Task-specific therapeutic interventions (e.g. functional gait therapy) within their standard of care individualised global rehabilitation plan may improve the natural course in these patients. Recently, the American Academy on Cerebral Palsy and Developmental Medicine (AACPDM) highlighted the value of task-specific gait therapy in patients with CP in a systematic review. They concluded that "*there is promising evidence that functional gait training is a safe, feasible, and effective intervention to target improved walking ability in children and young adults with CP. The addition of virtual reality and biofeedback can increase patient engagement and magnify effects*".[4] Unfortunately, studies on robot-enhanced gait therapy were not considered in this comprehensive review. In the accompanying comment Eva Swinnen[5] criticized the exclusion of robotic assisted gait therapy studies and emphasized that the global rehabilitation plan in children and young adults should include gait rehabilitation irrespective of device used. Taking both publications into account, there appears to be a need to assess the benefit of robotic assisted gait training within a global rehabilitation plan over a longer period of time. The superiority of robot-enhanced treadmill therapy as compared to manually guided gait therapy has so far only been shown in early rehabilitation of gait in adult post stroke survivors.[6] The undoubted advantage in children as well as adults is a better standardisation of the intervention and the ability to allow the therapist to focus on active engagement of the patient during the task, instead of guiding the (leg-) movements. Due to smaller absolute numbers - compared to adult stroke - and heterogeneity in patients with CP superiority of robot-enhanced treadmill therapy has not been shown by now. Therefore, an international cooperation - Advanced Robotic Therapy Integrated Centers (ARTIC) - has been established in order to pave the way for a better understanding of the true value of robotic medicine for improving gait function in children with CP.[7]

At Munich University Hospital, we have established a three-week (Monday-Friday, weekends to recover) intensive treadmill therapy program including 12 sessions of 30–60 min actively engaged gait training including virtual reality biofeedback for outpatients (ROBot-Enhanced-Repetitive-Therapy-Program: ROBERT-Program) using robotic assistance (Pediatric Lokomat®, Hocoma, Volketswil, Switzerland).

Since 2006, several patients in our database have had multiple treatment blocks as part of their global rehabilitation plan. We therefore had the opportunity to assess the impact of repeated three-week ROBERT-blocks on gross motor development in these children. For patients with three blocks of ROBERT-Program we addressed the issues: 1) does each block improve gross motor performance, 2) is there a decline in response to the treatment by number of blocks, 3) how does the overall change in gross motor function compare to the individuals' expected course.

2. Material and methods

2.1. *Therapy device*

The ROBERT-Program was conducted using the commercially available (Pediatric) Lokomat® product (Hocoma Inc., Volketswil, Switzerland). The Lokomat® consists of two exoskeletons, which are adjustable to the anthropomorphics of the patient. Several braces allow joining of the patient to the exoskeleton. The exoskeletons are connected to the frame of a body weight support system, which provides vertical stability. For body weight support, a counter system with a harness is used. Foot lifting belts passively position the ankle joints. Body weight support, step length, guidance force of the exoskeleton, as well as walking speed during therapy can be adjusted to the child's personal abilities via a personal computer interface using the Lokocontrol® software.

This study was performed using the first version of the pediatric Lokomat® including augmented reality, which requires 90–100% guidance force, but allows maximal engagement in walking by navigating an avatar within the virtual reality. Therapists did not need to guide the legs of the patient – as required in manually guided treadmill therapy, but had time to continuously interact with and stimulate the patient to engage actively in the serious gaming scenario. During the second part of the therapy session patients were not playing in the augmented reality environment while therapists reduced guidance force to the individuals' minimal supportive level while walking, thereby aiming to stimulate the subcortical/spinal gait patterns.

2.2. *Participants and intervention*

The ROBERT-Program consists of 12 therapy sessions in the (pediatric) Lokomat® during a three week period. It is performed on an outpatient basis at the department of Paediatric Neurology, Ludwig Maximilian University of Munich (LMU), Germany. Any child or adolescent with cerebral palsy (CP) is eligible for taking part in the ROBERT-Program, unless they met the predefined exclusion criteria for the use of the system. These are significant hip flexion- or knee flexion contractures of more than 20°, joint or bone instability, other medical devices within the body, severe epilepsy, and impaired tolerance of the device. The walk duration and treadmill speed during the ROBERT sessions is adjusted to the patient's ability to participate actively during therapy (30–60 min/day). Body weight support and guidance force are supported by the Lokomat® as much as necessary with the goal of individually adapted weight reduction during therapy progress. The therapist continuously encourages the patient to step actively and attempts to raise the child's awareness for active participation. Commercially available virtual reality biofeedback in a child friendly gaming design is included in the Lokomat® system to enhance active hip and knee flexion/extension.

The individual global rehabilitation plan (e.g. outpatient functional therapies, botulinum toxin, orthotics, splints, surgery, etc.) in each child was kept stable during the three weeks of ROBERT-Program and adapted to the patients' multidisciplinary management between blocks as clinically needed. There were 135 patients with at least one ROBERT block. In order to achieve homogeneity, we confined our analysis to children with bilateral spastic cerebral palsy (BS-CP), GMFCS level II or III and three blocks. The selection process of patients for the study is depicted in Supplementary Fig. 1.

Patients and/or their care givers had given informed consent to the research and the publication of the results. The study was approved by the local ethics committee (Ludwig-Maximilians University, Munich; Re # 222-07).

2.3. *Study design and outcome measures*

This is a retrospective chart review in a before-after intervention trial design. The main outcome parameters were the change in GMFM-66 total score (WHO-ICF domain of activity; representing overall gross motor abilities), GMFM-D score (standing abilities) and GMFM-E score (walking, running and jumping abilities). The assessments were performed the day before and two days after each three-week ROBERT block.

2.4. *Statistical analysis*

To identify possible selection bias, Pearson's chi[2]-test or t-test were calculated to compare the characteristics of included children with at least three ROBERT blocks with those children with less than three ROBERT blocks. Mean values with the respective 95% CI's for each outcome parameter and for the delta values for the increments achieved during each session and between pre-ROBERT 1 and post ROBERT 3 were calculated. We additionally calculated paired t-test to identify significant change during treatment.

In order to disentangle ROBERT specific improvements from the predicted course of development we estimated the patients' predicted course from the GMFM-66 reference percentiles as published by Hanna et al.[2,8] The patient's GMFM-66 percentile at baseline at first ROBERT block was identified. The patients expected course up to the end of his treatment period (end of third ROBERT block) was determined in accordance to the percentile at baseline. The expected improvement of GMFM-66 score was determined by subtracting the patient's baseline score from his percentile specific expected value. For all patients we added up the improvements in GMFM-66 observed throughout the entire treatment period and subtracted the expected increments of GMFM-66 in the respective patients. The difference between the observed minus expected increment yielded the individual's as well as the total group's mean increase in GMFM-66 exceeding the expected course. Two were older than 12 years after ROBERT 3. Therefore expected values could only be calculated for 18 cases as the Hanna et al. percentiles only extend to the age of 12 years. The mean and 95% CI of these increments was calculated.

Significant changes (two sided) were assumed for a p-value <0.05 as well as for non-overlapping 95% confidence intervals. All statistical tests were calculated using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. *Patients*

One hundred thirty five patients finished at least one block and 30 patients had three blocks of ROBERT Program. For the analysis, we had to exclude eight patients due to missing values in the GMFM 66 data. We further excluded one patient with ataxic CP and one patient with hereditary spastic paraparesis (SPG4) leaving a cohort of 20 patients over three ROBERT blocks (Supplementary Fig. 1). All children had a diagnosis of bilateral spastic cerebral palsy (BS-CP) due to perinatal hypoxaemia of the brain. Eight patients had GMFCS level II and twelve patients GMFCS level III. Comparison of a wide range of covariates including the presented outcome measures in children with three therapy blocks and those with less than three therapy blocks ($N = 66$) only yielded significant differences for age and consequently the distance walked per session.

The mean age of the patients with three ROBERT blocks at beginning of ROBERT 1 was 5.9 years (CI: [5.0; 6.7]) versus 8.6 years (CI: [7.5; 9.7]) in the patients with less than three blocks (Table 1). Fifteen patients received at least one treatment with botulinum toxin prior to their ROBERT block. One of these treatments was combined with casting to treat pes equinus contracture inhibiting heel contact during gait prior to ROBERT. One patient received soft tissue surgery during the observational period. Detailed single subject data is shown in Table 2a.

3.2. *Therapy*

The mean time interval between ROBERT 1 and ROBERT 2 was 7.4 months (CI: [5.6; 9.2]) and 11.2 months (CI: [7.7; 14.7]) between ROBERT 2 and ROBERT 3. Adding 3×3 weeks for the three ROBERT blocks, the mean duration from the beginning of ROBERT 1 to the end of ROBERT 3 was 21 months. Mean guidance force of the exoskeleton was 69% during the first block, 56% in the second block and 59% during the third ROBERT Block. Detailed single subject data is show in Table 2b.

3.3. *Outcomes*

The mean total increase from pre ROBERT 1 to post ROBERT 3 was 6.5 (CI: [4.8; 8.2]) in GMFM 66, 21.6 (CI: [13.9; 29.3]) in GMFM D and 13.0 (CI: [7.0; 19.0]) in GMFM E. There were no increments in between ROBERT 1 and ROBERT 2 (mean GMFM 66 change score −0.1), as well as between ROBERT 2 and ROBERT 3 (mean GMFM 66 change score of +0.4) (Fig. 1). There was no significant difference in the increments in GMFM 66, GMFM D and GMFM E comparing the three blocks as indicated by similar mean values with widely overlapping 95% confidence intervals (Fig. 1).

The mean increment on GMFM 66 scale in the treated patients compared to their age-adjusted expected individual course with standard of care during the intervention period is depicted in Table 3. The improvements in GMFM 66 score exceeded the expected improvement in all 18 patients participating in three ROBERT blocks. The mean excess on the GMFM 66 scale above the expected course was similar for children with GMFCS level II and III accounting for an highly clinically meaningful effect size of +3.6 points [1.4; 5.8] (Table 3).

4. Discussion

In children with cerebral palsy GMFCS Level II and III, and a mean age of 5.9 [5.0; 6.7] years at the first ROBERT block, each of three blocks of robot-enhanced treadmill therapy resulted in a similar increase in gross motor performance as measured by the GMFM-66, GMFM-D (Standing abilities) and GMFM-E (walking, running and jumping abilities) during the observational period of 21 months. Additionally, there was no decline in gross motor performance in the intervals (7.3 months and 11.8 months respectively) between blocks. The increment in GMFM-66 achieved over the mean observation period of 21 months significantly exceeded the expected values reported in a large population based cohort from Canada.[8]

To our knowledge, the effect of three blocks of intensive gait-therapy has not yet been evaluated in children with BS-CP. Similar improvements after each block provides a strong argument for repetitive treatments of task-specific gait therapy.

Although for children with GMFCS Level III peak motor performance was reported to start declining with the age of 7; 11 years and older, we did not observe such a decline following the blocks of ROBERT. This finding is in line with our previous findings regarding sustainability of ROBERT for a minimum of 6 months[9] and extends this knowledge on sustainability up to 11.8 months after ROBERT for children with bilateral spastic CP GMFCS Level II and III in this age group.

Recent studies on robotic assisted gait therapy using the Lokomat® have only documented short-term effects comparing before and after blocks in uncontrolled[10] as well as controlled, randomized trials.[11,12] All studies show benefits in WHO-ICF domains of “Structure and Function” and “Activity”.[13] Unfortunately, heterogeneity of therapy protocols does not allow for a conclusive meta-analysis and there are only expert-based practical recommendations to guide the application of robot-assisted treadmill therapy in clinical practise.[10] In particular data regarding the impact of robotic assisted gait therapy embedded within a global rehabilitation plan are lacking.

The observed increments in GMFM-66, GMFM-D, and GMFM-E in this study represent a “large effect size in minimum clinically important differences (MCID)” according to Oeffinger et al..[14] This was true for both, the single-block improvements and the overall improvement compared to the expected course within a standard care setting.[8]

4.1. *Limitations*

From the patient's perspective, the value of inclusion of task-specific interventions into his/her global rehabilitation plan is the potential impact on motor performance during the life course of CP. Here we can only provide observational data on a limited period of 21 months. However, this appears to be a long-term observational period compared to the periods considered in published randomized trials.[11,12]

Institutional and selection bias might be an issue. Our institution is one among five therapeutic centres for children with CP serving the Munich region in Germany. All institutions offer conventional therapeutic interventions for children with CP, GMFCS Level II and III, within a global rehabilitation plan. Two centres offer robotic enhanced gait therapy. All children with bilateral spastic CP (GMFCS Level II and III) in our cohort were offered to participate in the ROBERT

Table 1 – Comparison of characteristics in study population with 3 ROBERT blocks versus patients with <3 ROBERT blocks in our institution.

Characteristics	Cases 3 ROBERT blocks Mean [CI]	Cases < 3 ROBERT blocks Mean [CI]	p-value
n	20	105	
Age	5.9 [5.0; 6.7]	8.6 [7.5; 9.7]	0.001
GMFCS Level at baseline			0.337
II n=	8 (40.0%)	18 (27.3%)	
III n=	12 (60.0%)	48 (72.7%)	
Distance walked per session (m)	845.3 [764.8; 925.8]	960.1 [897.4; 1022.8]	0.063
Distance walked within 12 sessions total (km)	10.1 [9.2; 11.1]	11.5 [10.8; 12.3]	0.063
Duration walked per session (min)	37.2 [34.3; 40.1]	39.0 [37.6; 40.3]	0.237
Duration walked within 12 sessions total (h)	7.4 [6.9; 8.0]	7.8 [7.5; 8.1]	0.237
Mean treadmill-velocity within 12 sessions (km/h)	1.4 [1.2; 1.6]	1.5 [1.4; 1.6]	0.390
GMFM 66 pre	55.6 [52.0; 59.2]	54.6 [52.2; 57.0]	0.660
GMFM D pre	46.7 [35.2; 58.1]	45.1 [38.3; 51.9]	0.823
GMFM E pre	29.2 [20.6; 37.8]	28.1 [22.4; 33.9]	0.856

Abbreviations: CI: 95% confidence interval; GMFCS: Gross Motor Function Classification System; GMFM: Gross Motor Function Measure.

Table 2a – Individual patients' data.

Patient ID	Diagnosis	Gestational age; aetiology	Brain pathology	GMFCS prior to 1st ROBERT block	Age at 1st ROBERT	Age at 3rd ROBERT	GMFM Percentile pre 1st ROBERT block	GMFM Percentile post 3rd ROBERT block	Body weight 1st ROBERT block (kg)	Body weight 3rd ROBERT block (kg)	Body length 1st ROBERT block (cm)	Body length 3rd ROBERT block (cm)
1	BS-CP	29. WGA	PVL	III	5.0	6.3	40	70	15.0	19.0	101.0	105.0
2	BS-CP	31. WGA	PVL	III	6.2	9.2	20	55	22.0	29.0	121.0	130.0
3	BS-CP	33. WGA	PVL	II	4.5	5.5	95	97	18.0	25.0	100.0	111.0
4	BS-CP	26. WGA	ICH III° with PVL	III	6.8	9.6	97	97	23.0	30.0	108.0	128.0
5	BS-CP	term; asphyxia	PVL	III	10.8	13.7	50	*	32.0	45.0	137.0	155.0
6	BS-CP	31. WGA	PVL	II	5.6	7.1	70	80	15.0	22.0	100.0	122.0
7	BS-CP	29. WGA	PVL	II	4.4	5.9	75	95	17.0	20.0	110.0	117.0
8	BS-CP	29. WGA	PVL	III	10.2	12.7	55	*	28.0	42.0	140.0	152.0
9	BS-CP	32. WGA	PVL	II	5.7	6.9	55	45	20.0	21.0	117.0	118.0
10	BS-CP	28. WGA	PVL	III	4.5	6.1	65	75	16.0	21.0	101.0	108.0
11	BS-CP	term; conn. CMV infection	cysts & maldevelopment right > left	II	4.1	4.8	70	97	12.0	13.0	104.0	104.0
12	BS-CP	29. WGA	ICH III° with PVL	III	5.2	6.7	60	75	14.5	18.0	101.0	107.0
13	BS-CP	33. WGA	PVL	II	6.2	7.9	80	65	25.0	34.0	120.0	128.0
14	BS-CP	28. WGA	ICH III° with PVL	III	7.5	9.9	10	30	18.5	36.0	118.0	129.0
15	BS-CP	26. WGA	ICH III° PVL	II	5.1	7.3	95	90	16.0	19.5	104.0	117.0
16	BS-CP	30. WGA	PVL	III	5.3	7.6	50	80	15.0	16.5	95.0	105.0
17	BS-CP	30. WGA	PVL	III	4.6	6.2	85	85	16.0	17.0	98.0	109.0
18	BS-CP	32. WGA	PVL	III	5.7	7.0	60	75	12.5	16.5	112.0	121.0
19	BS-CP	term, prenatal	PVL	II	4.0	5.1	50	95	20.0	19.0	105.0	110.0
20	BS-CP	31. WGA	PVL	III	4.7	5.9	10	50	15.0	18.0	98.0	116.0
Mean values					5.9	7.7			18.5	23.7	109.8	119.4

Table 2b – Individual therapy data.

Patient ID	BoNT within 8 weeks prior to 3 ROBERT blocks	Casting post BoNT	Soft tissue surgery within 16 week prior to 3 ROBERT blocks	Mean guidance force of exoskeleton during all ROBERT blocks (%)	Total distance all ROBERT blocks (km)	Total duration all ROBERT blocks (hrs)	GMFM 66 Delta post-pre (during observational period)	GMFM 66 Delta post-pre (netto ROBERT blocks: 3 × 3weeks)	Mean walking speed/ session during all ROBERT blocks (km/h)
1	1/1/–	–	–/–/–	80.0	30.6	19.0	6.7	3.9	1.6
2	1/1/–	–	–/–/–	80.0	36.6	20.5	7.2	5.0	1.8
3	–/–/–	–	–/–/–	50.0	54.9	31.2	9.4	8.3	1.8
4	–/–/–	–	–/–/–	60.0	35.2	21.0	6.2	7.2	1.7
5	–/–/–	–	–/–/–	70.0	31.1	18.4	2.8	4.3	1.7
6	–/–/1	–	–/–/–	60.0	30.0	21.7	7.0	4.8	1.4
7	–/1/1	–	–/–/–	60.0	32.4	23.7	12.0	8.7	1.4
8	–/–/1	–	–/–/–	90.0	26.6	20.4	2.2	3.0	1.5
9	–/–/–	–	–/–/–	70.0	36.1	24.2	3.1	5.5	1.5
10	1/1/1	–/–/1	–/–/–	40.0	32.7	24.7	4.1	3.8	1.3
11	–/–/1	–	–/–/–	50.0	36.3	26.1	13.1	7.7	1.4
12	1/–/1	–	–/–/–	50.0	29.7	23.8	4.0	4.5	1.3
13	–/1/–	–	–/–/–	60.0	30.3	26.3	3.3	2.2	1.2
14	1/1/–	–	–/–/–	70.0	30.1	23.7	7.3	10.9	1.3
15	1/–/–	–	–/–/–	40.0	32.1	27.1	6.1	4.5	1.2
16	–/1/–	–	–/–/1	60.0	25.8	23.5	6.5	3.5	1.1
17	–/1/–	–	–/–/–	50.0	25.7	23.5	3.4	5.6	1.1
18	1/1/–	–	–/–/–	50.0	34.3	27.5	3.8	6.8	1.2
19	1/–/1	–	–/–/–	70.0	27.0	24.4	13.4	11.8	1.1
20	–/–/–	–	–/–/1	80.0	25.8	25.2	9.7	13.4	1.0
Mean Values				60.0	32.2	23.8	6.5	6.3	1.4

Abbreviations: GMFCS: Gross Motor Function Classification System; GMFM: Gross Motor Function Measure; ROBERT: Robot-enhanced repetitive treadmill therapy; BoNT: botulinum neurotoxin; BS-CP: bilateral spastic cerebral palsy; WGA: weeks of gestational age; CMV: cytomegaly virus; PVL: periventricular leukomalacia; ICH: intracranial haemorrhage.

program during the observational period, yet 2/3 of our population were not able to participate, because of personal or environmental factors (ICF), such as distance to our institution or care givers, who could not organize 12 outpatient sessions within a 3 weeks of daily therapy within their daily life activities. Additionally, patients with three ROBERT blocks did not differ from those obtaining only one block in our centre. Therefore, a selection bias is unlikely.

The population in the Hanna and Rosenbaum studies[8,15] might not be the ideal comparator, because of differences in time and place. Undoubtedly, Ontario area is not the Munich area and the Hanna & Rosenbaum data was recruited about 10 years earlier. The regional difference would be relevant if access to healthcare differed. This is not the case since free access to health care is equally offered in Canada and Germany. Regarding time, the mayor improvement during the 10 years pertains to the task specific gait therapy using robots, which is in the focus of our paper. The size of the reference group is considerable. Hanna and colleagues used GMFM 66 scores from a total of 1940 motor measurements in 650 children with CP acquired over a period of 4 years to calculate gross motor development percentiles stratified by age and GMFCS level I–V. For GMFCS Level II 80 children were assessed 269 times at a mean age of 7.3 years (SD 2.5 years). For GMFCS Level III 119 children were assessed 363 times at a mean age of 7.7 years (SD 2.2 years).[8] Therefore, the subgroup of children with CP in the Ontario cohort used for the reference percentiles have a very similar age range as our reported population. There are further aspects of the control group, which need careful discussion. During the observational period, the participants received standard of care therapy as part of their global rehabilitation, but without access to task-specific gait therapy. Because the 19 Canadian participating centres served the majority of eligible children in its treatment area, Rosenbaum et al. argued that the sample was closely representative of the population of children with CP in Ontario.[15] The authors concluded, that with this data, evidence based prognostication about gross motor progress in children with CP is possible, and that interventions could be judged over time, as we now have presented in comparison.[15] It has to be kept in mind, that the global rehabilitation plan within the Ontario reference population assessed from 1996 to 2001 contained a range of not in detail described developmental therapies and services, including physical therapy, occupational therapy, speech-language therapy, and recreational therapy, which is difficult to quantify objectively during such long observational period. As the multidisciplinary global rehabilitation plan was not assessed in detail in both cohorts, we could not stratify for the intensity of therapy in between the three ROBERT blocks. Interestingly, increments within the two inter-block-intervals did not deviate significantly from the expected changes in the reference percentiles (see details in result section). This might be an

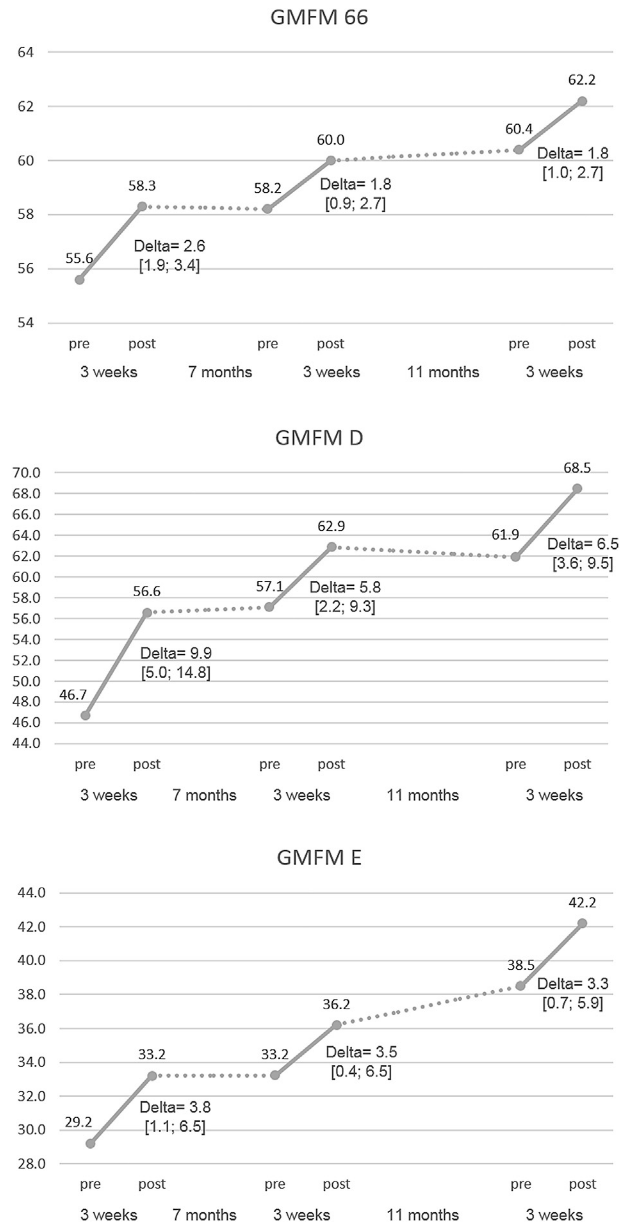

Fig. 1 – Gross Motor Function Measure increments during and in-between three blocks of treatment with robot-enhanced repetitive treadmill therapy in 20 patients with cerebral palsy. Delta indicates the mean increments [95% confidence interval]. Months indicate the mean time span between the blocks. GMFM 66: total score of the GMFM test; GMFM D: Standing; GMFM E: Walking, Running, Jumping. Abbreviations: GMFM: Gross Motor Function Measure.

indicator that the overall effect of interventions of the global rehabilitation plan (besides ROBERT program) was similar. Children from the reference population were excluded if they had ever received botulinum toxin in the lower limbs or dorsal rhizotomy (SDR) or were currently receiving intrathecal baclofen (ITB).[15] All of the here reported children did not receive ITB or SDR prior or during the observational period of 24 months. Yet the majority (15/20) received at least one concomitant BoNT injection within 8 weeks prior to participation in the ROBERT Program. We cannot rule out, that add on BoNT prior to ROBERT might have positively affected the responsiveness to ROBERT. However, as we were able to analyse in a previous study on 83 children receiving their first ROBERT block, additional BoNT therapy in 24 children did not affect the GMFM 66 total score.[16]

Therefore, using the Ontario population as a reference population maybe the second best approach if a randomized controlled study was not feasible as in our setting.

Our cohort study is reporting children GMFCS Level II and III with an age range of 4.1–10.8 years (mean 5.9 [5.0; 6.7]). Therefore, we cannot claim, that the here reported population is similar to all children with CP. However, the ROBERT specific exclusion criteria (fixed knee contracture > 20°, bone instability, etc.) generally do not pertain to children with CP, GMFCS Level II and III in the reported age group and all children within this subpopulation of CP treated at our institution were eligible for participation in the ROBERT-Program. Therefore, non-participation in the ROBERT program was mainly due to organisational reasons (WHO ICF personal or environmental factors) within the patients' and families individual environment (e.g. not being able to come to the centre 12 times in three weeks, etc.). Patients given access to three ROBERT blocks, however, differed in age from those receiving less than three blocks. Age represents a relevant influencing factor on gross motor improvement, especially when using the GMFM 66 outcome measures. We recently showed that the effect of the ROBERT-Program on standing abilities is better in children at a younger age.[17] Since this age effect was confined to improvements in GMFM-D, it may be an explanation for the considerable improvements in GMFM-D in this study.[17] Regarding the improvement from before block 1 to the end of block 3 the effect of age was accounted for by referencing each child to the age-specific expected course as derived from his reference percentile.

The paucity of outcome measures might be a further limitation. Our outcome measures did not pertain to the ICF component of “Participation”.[13] Previously, however, we have shown in a controlled clinical trial, that improvements on “Activities” level (GMFM-66) in ROBERT-Program correlate with improvements on “Participation” level as measured using the COPM (Canadian Occupational Performance Measure).[16]

Finally, sample size with 20 included patients is small and the 95% CI's around the observed improvements are wide reflecting the imprecision of our findings. Although we could not identify bias in validating our findings a confirmation is mandatory. A higher level of evidence might be achieved in multi-centre, long-term randomized trials. Since these are not easy to perform, the Advanced Robotic Therapy Integrated Centers (ARTIC) – Network has been established to make the best use of available evidence. Recently first data on 208 children with CP receiving robotic assisted treadmill therapy using the Lokomat was published.[7] Extension of this database may offer the opportunity to investigate (i) different application protocols as

Table 3 – Comparison of the expected increment in GMFM 66 based on the age and GMFCS-specific reference percentiles by Hanna et al. and the observed mean of the individual increments in 18 patients with cerebral palsy during the intervention period of 24 months including 3 × 3weeks of ROBERT.[8]

Characteristics	expected increment [CI]	observed increment [CI]	delta observed − expected [CI]	Large effect size for MCID according to[14]
GMFCS level II (n = 8)	5.0 [3.4; 6.7]	8.2 [4.0; 12.4]	3.2 [−2.0; 8.3]	>1.5
GMFCS level III (n = 10)	1.3 [0.6; 2.0]	5.3 [3.5; 7.1]	**3.9 [1.9; 6.0]**	>1.2
Total (n = 18)	3.0 [1.8; 4.2]	6.6 [4.6; 8.6]	**3.6 [1.4; 5.8]**	>1.3

Significant effects are printed in bold (delta excluding null-effect); two patients had to be excluded, as they were too old for percentile referencing at the end of ROBERT 3.
Abbreviations: CI: 95% confidence interval; GMFCS: Gross Motor Function Classification System; MCID: Minimum Clinically Important Difference.

well as (ii) short- and (iii) long-term effectiveness of robotic rehabilitation technologies across (iv) different diagnoses and (v) lifespan.

5. Conclusion

In children with CP, GMFCS level II and III, with a mean age of 5.9 years, repeated administration of intensive therapy blocks of robot enhanced gait therapy appear to be beneficial to improve gross motor activity as measured with GMFM 66. The reported improvements show that the increments exceed the expected course of gross motor development in children with CP in a clinically meaningful effect size. Whether these improvements represent motor learning of gait on spinal level (spinal gait pattern generators) or supra spinal level needs to be assessed in the future.

Conflicts of interest

None.

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Appendix A. Supplementary data

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