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Recovery of gait and other motor functions after stroke: Novel physical and pharmacological treatment strategies*

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Abstract. The gait-lab at Klinik Berlin developed and evaluated novel physical and pharmacological strategies promoting the repetitive practise of hemiparetic gait in line with the slogan: "who wants to relearn walking, has to walk. Areas of research are treadmill training with partial body weight support, enabling wheelchair-bound subjects to repetitively practice gait, the electromechanical gait trainer GT I reducing the effort on the therapists as compared to the manually assisted locomotor therapy, and the future HapticWalker which will allow the additional practise of stair climbing up and down and of perturbations. Further means to promote gait practice after stroke was the application of botulinum toxin A for the treatment of lower limb spasticity and the early use of walking aids. New areas of research are also the study of D-Amphetamine, which failed to promote motor recovery in acute stroke patients as compared to placebo, and the development of a computerized arm trainer, Bi-Manu-T rack, for the bilateral treatment of patients with a severe upper limb paresis.

Keywords: Stroke, hemiparesis, treadmill, gait trainer, armtrainer, botulinum toxin

1. History and introduction

The "gait lab" at Klinik Berlin (Department of Neurological Rehabilitation, Charité, Campus Benjamin Franklin, Berlin, Germany) started its activities in the early nineties. The first observation was that the restoration of gait was of highest priority to wheelchair-bound subjects after stroke, TBI and SCI. The next step was a large gait outcome study on 156 subacute hemiparetic patients after stroke participating in a comprehensive 4-week in-patient rehabilitation programme according to the Bobath concep [16]. Surprisingly, neither gait symmetry (processor variable to assess the aspired gait quality improvement) nor gait function (ground level and stair climbing speed and endurance) had improved considerably during the treatment period. At that time, tone-inhibiting and gait preparatory manoeuvres while lying and sitting were clearly dominating the therapy. Gait itself was practised very little. Some ambulatory patients were even seated in the wheelchair in order to avoid "bad quality" walking, and technical aids such as AFOs and canes were prescribed hesitantly. We therefore concluded that the lack of adequate gait practice was the most likely explanation of the inadequate result of that gait outcome study. At the same time the concept of a task specific repetitive approach emerged in motor rehabilitation as being most favourable approach [1,4]. Accordingly, we coined the slogan: "Those who want to relearn walking should walk". To meet this demand, treadmill training with partial body weight support was introduced for hemiparetic subjects [12] following first positive reports in paraparetic subjects [2, 56]. Harness-secured the wheelchair-bound subjects could practise up to 1000 steps per session as compared

*Conflict of interest: Reha-Stim holds the patent of the gait trainer GT I and the arm trainer Bi-Manu-Track, the company is owned by Dr. Beate Brandl-Hesse, the spouse of the author.

to the much fewer 50 steps during conventional therapy. In the meantime, promising reports on treadmill training for CP-children [49], Parkinson's Disease [41] and hip arthroplasty patients have been published [29].

2. Treadmill training with partial body weight support (BWS)

The patients wore a modified parachute harness to substitute for deficient balance, and the moving belt enforced the locomotion (Fig. 1). A proportion of their body weight was supported with the help of a pulley system, so that the subjects could carry their remaining body weight adequately, i.e. without knee collapse and/or excessive hip flexion. The scientific background of the locomotor therapy was based on experiments in adult spinalised cats and incompletely lesioned primates, showing an entrainment of spinal and supraspinal pattern generators by the repetitive locomotor therapy [38]. Major peripheral drives were the hip extension during the terminal stance phase and the timely correct shifting of the weight. Accordingly, patients are instructed to avoid swinging in the harness, but instead load and deload the weight in a timely correct manner and to extend the hips in the terminal stance phase.

Initially, two or even three therapists assisted the patients' gait placing the paretic limbs and assisting hip extension and weight shifting. For wheelchair-bound subjects, treadmill velocities ranged from 0.25 to 0.5 m/s, and the BWS was less than 30%. A daily therapy of 20 to 30 min of net walking over at least three weeks was targeted to induce motor learning. Minimal inclusion criteria were the ability to sit at the edge of the bed, no fixed joint contractures, and stable cardiovascular conditions.

Gait analysis showed that hemiparetic ($n = 18$) patients walked more symmetrical, and they were less spastic and more efficient on the treadmill with BWS as compared to the floor walking condition [18]. On the other hand, the BWS negatively correlated with the activation of relevant weight bearing muscles, i.e. they became less active when relieving too much, a limit of 30% BWS seemed crucial [15].

First clinical studies, a baseline-treatment ($n = 9$) [12] and two single case design studies ($n = 7$ each), dealt with chronic, non-ambulatory hemiparetic patients, whose stroke stroke had occured at least 3 months earlier [11,22]. The single-case design studies followed an A-B-A design. During the A-phases,

Fig. 1. Treadmill training with partial body weight support of a left hemiparetic subject.

treadmill therapy was applied alone ($n = 7$) or in combination with Functional Electrical stimulation (FES) on the belt ($n = 7$); the patients did not receive any additional single physiotherapy. During the B-phases, the patients received physiotherapy following a very conservative Bobath approach (with tone-inhibiting and gait preparatory manoeuvres while sitting and standing clearly dominating) of the same period of time, with each of the phases lasting 3 weeks. The FES helped to facilitate the movement on the belt. For instance, the stimulation of the N. peronaeus during the swing phase assisted the dorsiflexion of the foot. The results showed that the patients improved their gait ability and ground level walking velocity considerably during the first 3-week A-phase (A1) of exclusive daily treadmill training. During the subsequent period of three weeks of conventional physiotherapy (B) gait ability did not change, whereas the second A-phase further enhanced walking ability (Fig. 2). All subjects who had been wheelchair-bound before therapy became ambulatory at least with verbal support at the end of the study. Other motor functions improved steadily, whereas the muscle tone remained unchanged. Statistics (Friedman test for the ordinal-scaled, and a MANOVA for the con-

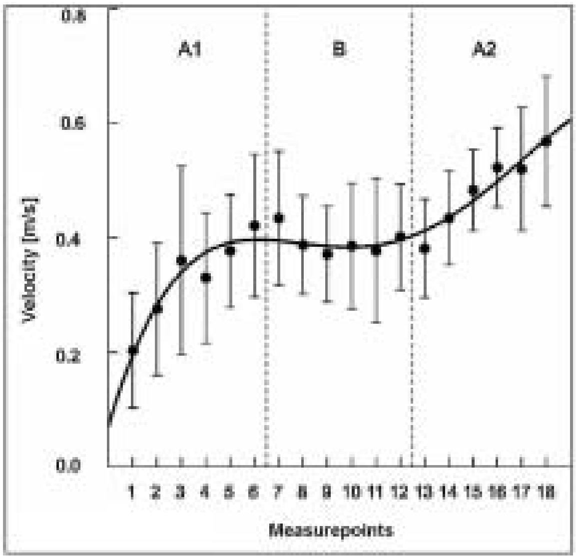

Fig. 2. Mean (SD) walking velocity over time. Treadmill training applied during the A1 and A2 phases was more effective than physiotherapy applied during the B period ($p < 0.05$).

tinuous variables) revealed that the treadmill training was superior to regular physiotherapy with regard to gait ability and walking velocity ($p < 0.05$).

Because the single-case study design was limited by a potential confounding influence of spontaneous recovery, we could not draw any definite conclusions from the study, but the results seemed to confirm the favoured concept of a task-specific repetitive approach, i.e. the practice of up to 1000 gait cycles on the belt during one single session. Four subsequent controlled studies in acute non-ambulatory stroke patients, therefore, we compared the treadmill training with BWS vs. the non-practice of gait but vs. the repetitive gait practice on the floor assisted by braces and technical aids [7,35,37,46]. None of the four studies ($n = 56$, $n = 78$, $n = 13$, $n = 84$) found any difference between the intensive gait practice on the treadmill and on the floor in acute stroke patients with respect to the improvement of gait ability and speed (see also Cochrane Database) [43]. Merely a subgroup of very severely affected subjects, who could not be mobilised on the floor, profited more from the treadmill training in one of the three studies. In summary, repetitive practice was beneficial with gait practice on the treadmill and on the floor yielding comparable results [31].

2.1. *Treadmill training of ambulatory subjects*

Currently, treadmill training of ambulatory stroke patients adopting principles of sport medicine gains attention. Pohl and co-workers elegantly showed that a speed-dependent training in ambulatory hemiparetic patients resulted in a dramatic improvement of walking velocity as compared to conventional therapy or treadmill training with no or little increase of the belt speed [48]. A preceding biomechanical study had already shown the beneficial effect of higher gait speeds on the belt rendering the gait of hemiparetic patients more efficient and facilitating the activity of weight-bearing lower limb muscles [28].

Further, an aerobic training following the guidelines of the American College of Sport Medicine could improve the cardiovascular fitness of nine ambulatory chronic stroke patients as shown in an open study by Macko et al. [40]. Our group most recently completed a controlled study in 60 subacute stroke patients (unpublished). The experimental group significantly walked faster and longer than the control group following a 5-week daily aerobic treadmill training at 0.5 Heart Rate Reserve (HRR). Side effects were not observed.

3. The electromechanical gait trainer GT I

One of the disadvantages of treadmill training was the effort for up to three therapists to assist the gait of severely affected subjects: one or two therapists sitting alongside had to set the paretic limbs and one therapist standing behind the patient assisted weight-shifting, hip extension and trunk erection. Accordingly, fatigue of all participants frequently resulted in too little gait practice in daily routine.

Our group therefore designed the electromechanical gait trainer GT I (Fig. 3) in co-operation with colleagues at Teeside University, Middlesborough, UK [24,26]. The harness-secured and gradually relieved patient was positioned on two footplates whose movements simulated stance and swing in a symmetric fashion. A servo-controlled drive, keeping the chosen cadence constant, supported the patient, and the vertical and horizontal movements of the centre of mass were controlled in a phase dependent manner by ropes attached to the harness. Cadence and step length could be set individually to cover a step length from 34 to 49 cm and a gait speed of 0 to 2 km/h. The height of the subjects could range from 110 cm (for instance CP children) to 195 cm. Optional Functional Electrical Stimulation helped to stabilise the paretic knee during the stance phase.

Gait analysis of hemiparetic gait on the machine and on the manually assisted treadmill revealed similar

Fig. 3. Left hemiparetic patient practising on the electromechanical gait trainer GT I.

sagittal lower limb joint excursion and muscle activation patterns. On the machine, the ankle dorsiflexion and the tibialis anterior activity during the swing phase were less, and the patients carried 10%–20% BWS on the non-paretic limb during its "swing phase", i.e. the y took advantage of the ongoing footplate support to avoid full weight-bearing onto the paretic limb. Further, the gait analysis revealed that the patients walked more symmetrically, less spastic and with a physiological double-sinus CoM movement in the vertical direction on the gait trainer as compared to the treadmill condition.

First results with the machine were so encouraging, that we decided to start-up a spin-off company, Reha-Stim. In the meantime, clinics in 12 European countries and in the Far East successfully apply the gait trainer GT I to the benefit of patients after stroke, TBI, SCI, CP, MS and Parkinsons Disease. The Lokomat, designed by Colombo and co-workers in Zurich, Switzerland, is another solution [6]. The device consists of a treadmill and a powered exoskeleton with programmable drives to flex the hip and knee joints during the swing phase and to move the pelvis up and down in a phase-dependent manner. So far, comparative studies between the two solutions are missing.

For the clinical evaluation of the gait trainer GT I, we firstly conducted a baseline-treatment study including 14 chronic, non-ambulatory hemiparetic subjects [30]. Four weeks of the additionally applied daily gait trainer therapy resulted in a relevant improvement of gait ability ($p < 0.05$, Wilcoxon test) in all patients: seven patients could walk independently, three needed verbal supervision, and three subjects still needed intermittent support after the treatment. Before therapy all patients had displayed little activity of the shank muscles during gait. After therapy in 11 patients the amplitude markedly increased in all patients towards a more physiological pattern (Fig. 4), while three patients exhibited a spasticity associated pattern, characterised by a agonist-antagonist co-activation and a premature activity of the plantar flexors.

A subsequent randomised cross-over study [55] was carried out with 30 non-ambulatory, subacute hemiparetic subjects which were assgined to one of two groups A and B. They either followed an A-B-A (group A) or an B-A-B design (group B) with $A = 2$ weeks gait trainer and $B = 2$ weeks treadmill with BWS. One therapist was required to operate the gait trainer, controlling the paretic knee, while two therapists assisted the patients on the treadmill placing the paretic limbs and controlling the weight shift and hip extension. Gait ability improved steadily in both groups with patients of group A walking significantly better (i.e. more independently) during the last phase. Gait velocity did not differ between groups. At follow-up the effects had diappeared. All but seven patients preferred the gait trainer. They found it less demanding and more comfortable because of less frequently required manipulations during therapy. The other seven patients said that swinging the paretic limb on the tread mill seemed more natural (with or without help) and thus more effective.

Currently we conduct a national multicentre trial ("DEGAS", Deutsche Gangtrainer-Studie) with 5 centres participating. 150 acute hemiparetic patients will be allocated to two groups, the patients either receive the treatment on the gait trainer or physiotherapy of equal intensity with a strong emphasis on gait practice on the floor and on the stairs.

4. Automated motor rehabilitation

The electromechanical gait trainer GT I is in line with the new concept of automated or robot-assisted motor

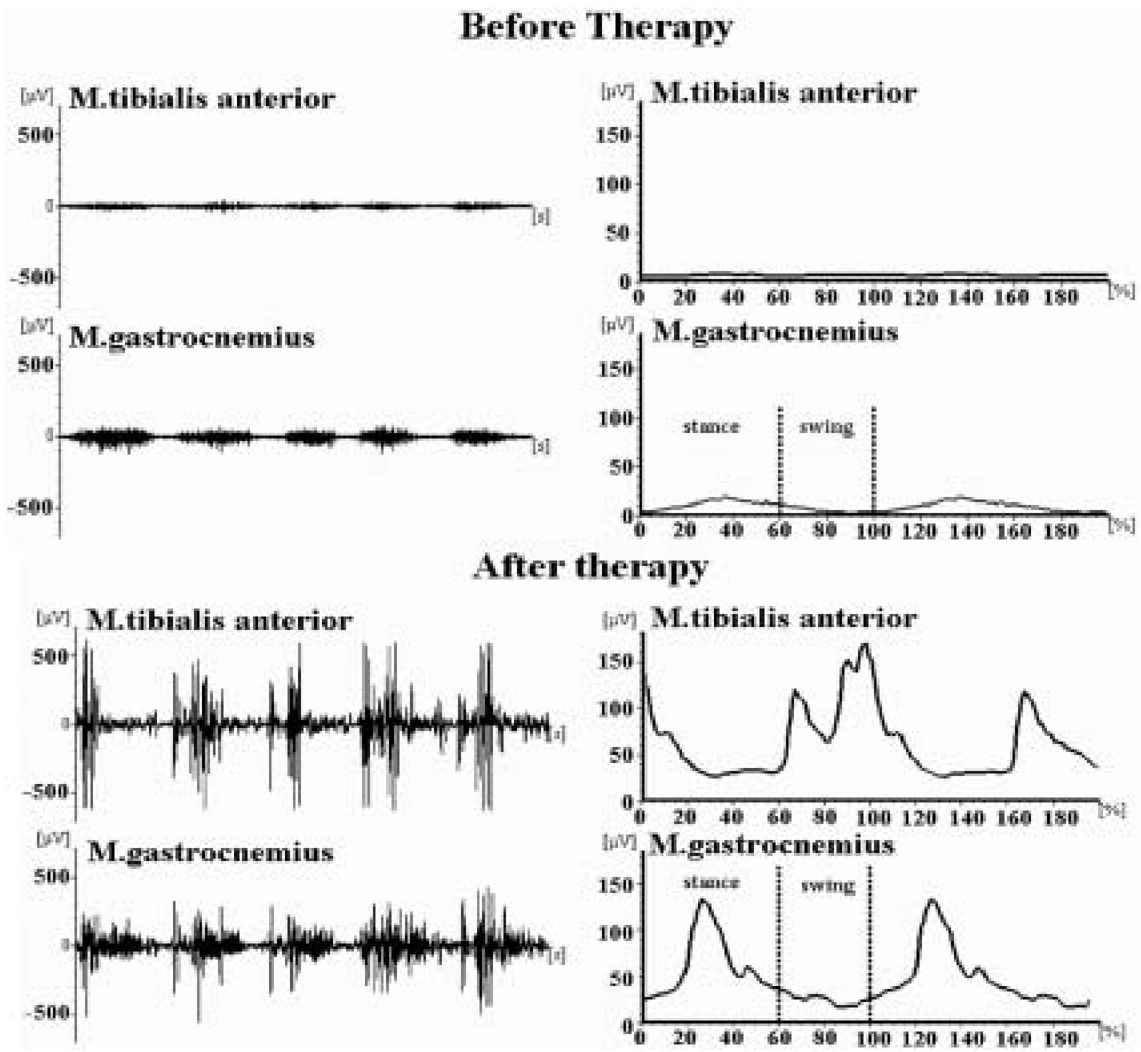

Fig. 4. Raw (left) and rectified, averaged and normalised electromyogram (right) of the tibialis anterior and gastrocnemius muscles of the affected right side of a chronic hemiparetic patient before and after (below) 4 weeks of daily locomotor treatment on the electromechanical gait trainer GT I.

therapy after stroke. Starting with the pioneering work of Hogan et al, who introduced the MIT-MANUS for the upper limb rehabilitation in the mid-nineties [32], this new field has gained more and more attention. The overall advantages of this concept are a more intensive practice, less strenuous effort for the therapists, the possibility of an intelligent man-machine interaction imitating the experienced therapists' hand, and therapy documentation. On the other hand, no machine will ever replace human beings and the multilevel relation between therapists and patients. The devices are and will be an adjunctive tool to primarily intensify the therapy.

In continuation of our activities, we are currently developing a robot-assisted gait trainer, the so-called "HapticWalker" [33]. It addresses the limitations of the electromechanical gait trainer, namely the fixed trajectories of the feet and the lack of a force control. The patients will be positioned on two foot plates, whose trajectories can be adjusted in six degrees of freedom. With this machine the patients not only can practice the gait on the floor but also stair climbing and descending. Further, a force control will provide the sensation of a real swing phase in addition to different floor conditions (asphalt, mud, snow etc.) and sudden perturbations. The combination with virtual reality will be an additional feature. A prototype is on its way and first clinical tests have started at the end of the year 2003.

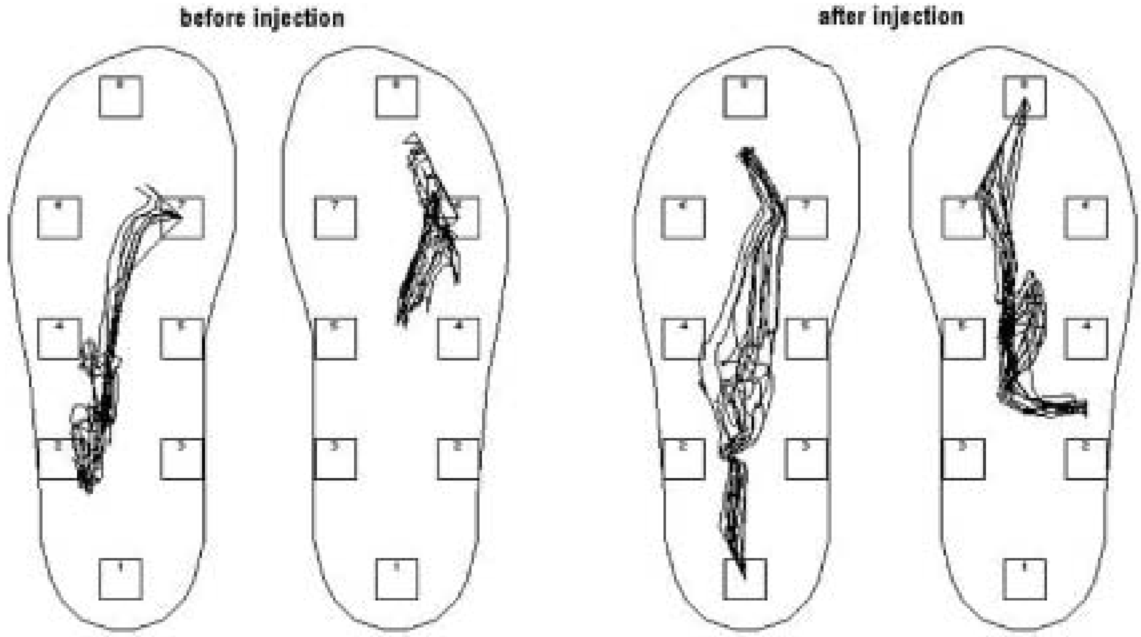

Fig. 5. Trajectories of the force point of action under the non-affected and affceted foot in a right hemiparetic patient before and two weeks after the injection of botulinum toxin A.

Another activity within the concept of automated motor rehabilitation was the design of a computerised arm trainer, the "Bi-Manu-Track" (FIG 5). Following the MIT-MANUS [32,53] and the MIME robot [39], the Bi-Manu-Track enabled severely affected hemiparetic subjects the bilateral practice of two movements: a forearm pro- supination and a wrist flexion - extension movement. Three training modi were implemented: 1) passive – passive with the speed and amplitude adjustable, 2) active – passive with the non-paretic controlling the paretic extremity, and 3) an active – active mode, where the affected extremity had to overcome an initial isometric resistance. The bilateral practice was aimed at facilitating the paretic side via intercallosal fibres [5,44] and the more distal approach took into account the competition between proximal and distal body segments for brain plasticity [45]. So far it turn out that the preferential practice of proximal shoulder girdle movements may even prevent the recovery of the forearm and hand function; instead, the distal functions should be the focus of therapy. A first open study on 12 chronic ($>$ 6 months post ictum) severely affected stroke patients with no volitional wrist or finger activity and moderate to severe spasticity revealed that a 4-week daily therapy with the arm trainer resulted in a relevant muscle tone reduction of the wrist and finger joints. Though 5 subjects improved their motor functions, the disability level, however, remained unchanged [25]. Currently, we conduct a controlled study in subacute, severely affected stroke patients comparing the arm trainer vs. the electrical stimulation of the wrist extensors.

5. Pharmacological strategies

Early in the nineties we started to investigate the potential of Botulinum toxin A (BTX-A) in the treatment of focal spasticity after stroke [8]. Following a first report on the treatment of upper limb spasticity in 1992 [14], work concentrated on the spastic equinovarus deformity impairing gait [19,21]. The injection of BTX-A into the gastrocnemius, soleus and tibialis posterior muscles reduced the muscle tone, relieved spasticity-associated pain and improved the gait pattern of hemiparetic patients (Fig. 6). Dynamic electromyography before and after injection revealed a preferential diminution of the so-called premature activity of the plantarflexors while the functional relevant activity during mid-stance was less affected by the neurolytic agent. At the same time, the tibialis anterior muscle, albeit not injected, could improve its activation pattern from a tonic to a more phasic type. This was robably due to the diminished reciprocal inhibition following the paresis not only of the extra- but also of the intrafusal muscle fibres of the plantarflexors [13]. Two

Fig. 6. The computer-asssited arm trainer Bi-Manu-Track for hemiparetic patients with a severe upper limb paresis.

subsequent randomised controlled trials by Burbaud et al and Pittock et al. could confirm the beneficial effect of BTX-A in the treatment of the equinovarus deformity after stroke [3,47]. In both studies, the injection of 1500 units Dysport® resulted in a muscle tone reduction, pain relieve and a better walking ability. Gait velocity, on the other hand, did not differ between the verum and placebo groups.

Another open question to the BTX-treatment of spasticity was the need for higher doses as compared to the treatment of limb dystonia. Animal experiments (rat-diaphragm preparation) by Hughes et al. suggested that inactivity delayed the onset of paralysis while the electrical stimulation rate directly determined the uptake and the latency of onset of BTX-A [34]. Since in clinical practice spasticity is almost always accompanied by central paresis, the affected muscles are less active, on average, than normal or dystonic muscles. Accordingly, it was plausible to try increasing the activity of the terminal nerve ends of spastic muscles immediately after injection by either encouraging the patients to walk extensively or, if not possible, by the electrical stimulation of the injected muscles. To test this hypothesis, we compared the spasmolytic effect of BTX-A in two groups of hemiparetic patients with lower limb spasticity. Short-term electrical stimulation (ES) of the plantarflexor muscles (6-times 30 min each day for three days) in combination with 2000 units Dysport proved more effective than the injection of BTX-A alone [17]. A subsequent placebo-controlled study with four treatment arms (BTX-A + ES, Placebo + ES, BTX-A, Placebo) for the treatment of upper limb spasticity could confirm the superior treatment effect of the combined approach with respect to muscle tone reduction and functional activities such as putting an arm through the sleeve or cleaning the palm of the hands [23].

Most recently, our group investigated the effect of D-Amphetamine (D-AP) on motor recovery in acute stroke survivors [51]. Following animal experiments, Walker-Batson et al. [10] had shown in 10 acute stroke patients that the oral intake of 100 mg D-AP (10 mg every fourth day) with paired physiotherapy effected a significantly better outcome in ADL and motor competence as compared to placebo [54]. During follow-up, the favourable effects grew even larger. Given the small number of subjects included in the study, we intended to replicate the study. Twenty-four stroke subjects were included in the study. Inclusion criteria were as follows: first-time ischaemic, supratentorial stroke, interval < 40 days, Barthel Index (0–100) ranging from 25 to 50, age < 80 years, stable cardiac condition, controlled hypertension, no hyperthyroidism, no alcohol or drug abuse, no medication with alpha-adrenergics agonists or antagonists, or major tranquillizers. They were randomly assigned to two groups. Patients of group

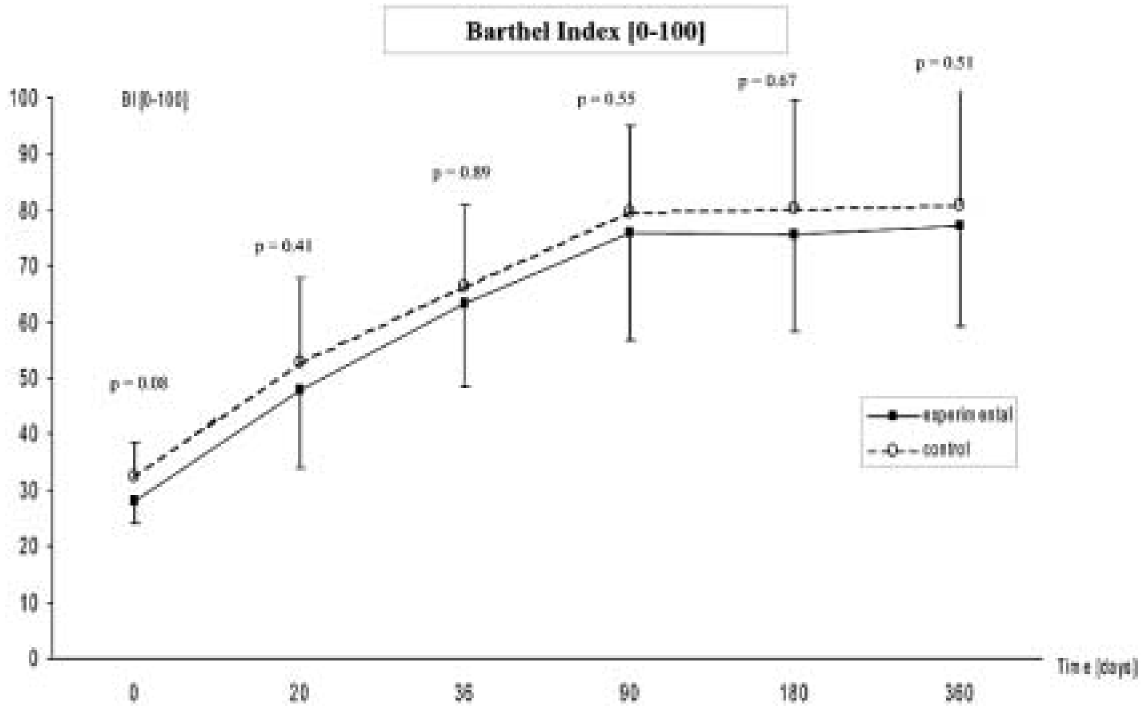

Fig. 7. Mean (SD) Barthel Index (BI, 0-100) of the D-Amphetamine and placebo group on treatment days 0, 20, 36, 90, 180 and 360, p-values of the comparisons between groups are given.

A received 10 x 10 mg D-AP every fourth day with physiotherapy within 60 min after drug intake, patients of group B received a placebo of identical look, also every fourth day. Major outcome variables were the Barthel Index and the motor functions assessed with the help of the three sections of the Rivermead Assessment Score, assessed by a blinded rater at study begin, end and follow-up after 3, 6 and 12 months. At study entry, the patients of both groups did not differ with respect to the clinical data and outcome variables. Drug-related side effects did not occur. All patients improved over the time up to three months after stroke onset, from then on the abilities remained constant. The comparison between groups revealed no difference at any time, i.e. D-AP had no benefit. (Fig. 7). In a previous study, Sonde et al. also had failed to show any beneficial effect of D-AP paired with physical therapy in 37 geriatric stroke patients [50]. For our study we thought that the content of the paired physiotherapy may have put not enough emphasis on the intensive practice of selected motor tasks.

6. Technical aids

Technical aids (TA) are an integral part of the motor rehabilitation of stroke patients. Walking aids and orthoses (AFOs), for instance, render the gait more safely and can thus intensify the independent gait practice. Nevertheless, some therapists are hesitant to prescribe TA out of the fear of a worse gait quality or muscle tone increase when using the TA [9]. To address these concerns (and following our overall intention to intensify the gait practice), we investigated the gait of hemiparetic patients with and without an AFO. With the aid, the patients walked safer, faster, more symmetric and better advanced their body during the stance phase [20], thus confirming previous reports [36,42,57]. The dynamic electromyogram of various lower limb muscles showed a plantarflexor spasticity reduction and a facilitation of the quadriceps muscle as speed-independent AFO effects [27]. On the other hand, the tibialis anterior activity was diminished so that one cannot exclude a disuse-atrophy of the dorsiflexor in the long term. The influence of walking sticks was another concern. Gait analysis revealed that the use of a walking stick of different heights did not render the gait asymmetric nor changed the muscle activation pattern of various lower limb muscles except of the gluteus medius. The abductor muscle was less active when using the walking aid, probably due to a longer lever arm for the hip abductor. Further, Tyson et al [52] had described that the height of the walking stick did not influence the body weight relieve (it was approximately 15% irrespective of the height), nor did it negatively influence the trunk kinematics. Taken together, the studies mentioned could not confirm the therapists concern of a poor gait quality and spasticity increase when using TAs. Rather, they should be prescribed early during the comprehensive gait rehabilitation to allow the independent gait practice as soon as possible, which is in line with the task-specific repetitive approach.

7. Conclusion

In line with the concept of a task-specific repetitive approach ("Those who want to relearn walking should walk"), our group concentrated on the development and evaluation of novel treatment strategies in gait rehabilitation. Treadmill training with partial body weight support and the electromechanical gait trainer GT I enabled wheelchair bound subjects the intensive practice of complex gait cycles, the latter putting less effort on the therapists e.g., when placing the paretic limbs. The future HapticWalker will further allow the training of climbing up and down stairs and of gait perturbations. The focal treatment of equinovarus spasticity with Botulinum toxin A and the gait analysis studies supporte the approach of an early prescription of walking aids and orthoses which are aimed at a higher intensity of gait practice with the stroke patients walking more safely and requiring less therapeutic assistance.

Most recently, the group entered new fields of motor rehabilitation by developing a robot-assisted arm trainer as part of an overall concept of automated motor rehabilitation. In addition, we have studies the effects of drugs such as D-Amphetamine to promote motor recovery. The overall goal of our work is the aspired social and vocational reintegration of the patients, whom we thank for their active participation.

Acknowledgment

We wish to thank the many co-workers who have contributed substantially over the years to our studies and our patients participating in the clinical studies. Hopefully we can pay back some of the credit!

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