

No benefit from D-amphetamine when added to physiotherapy after stroke: a randomized, placebo-controlled study

Thomas Treig Neurologisches Therapiezentrum Greifswald, **Cordula Werner** Klinik Berlin, Department of Neurological Rehabilitation, Free University Berlin, **Martin Sachse** Neurologisches Therapiezentrum Greifswald and **Stefan Hesse** Klinik Berlin, Department of Neurological Rehabilitation, Free University Berlin, Germany

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Objective: To assess the effect of D-amphetamine on the recovery of activities of daily living and motor functions after stroke,

Design: Randomized, placebo-controlled study,

Setting: Inpatient rehabilitation centre,

Subjects: Twenty-four stroke survivors after a first ischaemic supratentorial stroke within six weeks before study onset, severely to moderately affected, with a Barthel Index (0-100) ranging from 25 to 50, no severe concomitant internal, neurological or psychiatric diseases, and participating in a comprehensive rehabilitation programme of 10-12 weeks,

Interventions: Ten sessions with 10 mg D-amphetamine (or placebo) every fourth day totalling 100 mg in a time period of 36 days combined with physical therapy according to the neurodevelopmental concept within 60 minutes after drug intake.

Main outcome measures: Barthel Index (0-100) served as the primary outcome measure and the Rivermead Motor Assessment Score with its three sections (gross function, leg and trunk, and arm) as the secondary outcome measure, assessed at days 0, 20, 36, 90, 180 and 360.

Results: The two groups did not differ with respect to clinical data and outcome measures at study onset. All patients improved significantly except for arm function over the intervention period and up to day 90 after study onset. The comparison between groups did not reveal any difference at any time; amphetamine-treated patients did not show any increase in motor function or ADL compared with the control group.

Conclusions: The placebo-controlled study failed to show any effect of D-amphetamine on stroke recovery compared with control. The small number of patients, the timing and content of physical therapy were limiting factors of the present study. Further trials are warranted.

Address for correspondence: Stefan Hesse, Klinik Berlin, Kladower Damm 223, 14089 Berlin, Germany. e-mail: bhesse@zedat.fu-berlin.de

Introduction

Stroke is extremely common in all countries of the world. Two-thirds survive with residual impairments. One of the potential strategies to promote recovery of function is pharmacological.

In animal models it has been reported that D-amphetamine (AMPH) can enhance the beneficial effects of physical therapy after cortical injury.^{1,2} The main mode of action of AMPH is to promote presynaptic release of the monoamines noradrenaline, dopamine and serotonin and inhibition of their reuptake from the synaptic cleft with secondary alleviation of injury-induced functional depression of structures remote from the injury (diachisis).³

Subsequent placebo-controlled clinical studies in subacute stroke victims, however, reported contradictory results. Two studies^{4,5} with eight and 10 patients showed a beneficial effect of D-amphetamine on the competence in daily activities and motor functions, while three papers (with 20, 25 and 39 patients participating) found no effect in subacute stroke patients.⁶⁻⁸ Varying study protocols and different combinations of drug intake and physiotherapy were the most likely explanations of these conflicting results. Feeney *et al.* had pointed out in their pioneering work that D-amphetamine only promoted motor recovery of the stroke animals when given together with 'symptom-relevant experience' (i.e., concomitant training sessions).

Here we report the results of our placebo-controlled study following the protocol of Walker-

Batson and co-workers, who published one of the positive studies.⁵ The authors reported that the five subacute stroke patients receiving 10 mg of D-amphetamine orally every fourth day for 10 sessions paired with physiotherapy had a significantly better outcome at study end than the control group. At follow-up 12 months after study end the effects had grown even larger in favour of the experimental group.

Methods

During the two-year funding period the medical charts of 494 stroke patients admitted to the neurological rehabilitation hospital in Greifswald were screened. Twenty-four hemiparetic subjects (five women and 19 men) participated after informed consent in the study approved by the local ethical committee. Their clinical data are presented in Table 1. A neglect syndrome was assessed with the help of the digit cancellation test and clinical observation. All patients participated in a comprehensive inpatient rehabilitation programme of 10-12 weeks.

The inclusion criteria were:

- first supratentorial ischaemic insult in the territory of the middle or anterior cerebral artery;
- stroke interval before study onset < six weeks;
- age between 18 and 80 years;
- Barthel Index (BI, 0-100) ranging from 25 to 50;

Table 1 Clinical data and initial assessment scores for both groups at study onset

	Experimental	Control
<i>n</i>	12	12
Hemiparesis	6 = left, 6 = right	6 = left, 6 = right
Interval, weeks, mean (\pm SD)	3.58 (\pm 0.39)	3.42 (\pm 1.14)
Sex	F = 1; M = 11	F = 1; M = 11
Age, years, mean (\pm SD)	59.2 (\pm 7.8)	55.0 (\pm 9.4)
Weight, kg, mean (\pm SD)	80.1 (\pm 11.0)	81.3 (\pm 18.7)
Height, cm, mean (\pm SD)	174.1 (\pm 8.1)	177.1 (\pm 7.1)
Neglect (<i>n</i>)	5	4
Initial Barthel Index, 0-100, mean (\pm SD)	27.9 (\pm 4.0)	32.5 (\pm 6.3)
Initial RMS gross function, 0-13, median (IQR)	3.0 (2.0-5.0)	3.5 (2.0-5.0)
Initial RMS leg and trunk, 0-10, median (IQR)	3.0 (1.0-3.0)	2.0 (1.5-2.5)
Initial RMS Arm, 0-15, median (IQR)	0.5 (0.0-1.25)	1.0 (0.0-1.75)

IQR, interquartile range; RMS, Rivermead Motor Score.

- written informed consent.

Exclusion criteria were

- unstable cardiac dysrhythmia;
- hypertension not controlled by medication (>160/100 mmHg);
- untreated hyperthyroidism;
- history of psychiatric illness or excessive alcohol or drug abuse;
- medication with α -adrenergic antagonists or agonists, major tranquillizers;
- terminal medical condition such as cancer or AIDS;
- other coincident neurological disease.

Allocation and drug treatment

The projected sample size was 24 subjects to corroborate a minimum important difference of 10 points of the BI with alpha set at 0.05 and beta at 0.2. Study patients, medical and paramedical staff involved at the NRZ Greifswald were blinded to the treatment type. If a patient met the inclusion criteria and consented, the responsible physician called the external recruiter in Berlin (200 km away from Greifswald), who randomly assigned a number from 1 to 30 to the patient. The patient then received the medication box with the corresponding number. The content of each of the 30 medication boxes (either D-amphetamine or placebo) had been determined previous to study onset by lot. The content of the boxes was thus only known to the recruiter in Berlin (i.e., the team in Greifswald including the assessors were blind with respect to group assignment). Drug treatment was given in form of identical white tablets of 10 mg of either D-amphetamine or placebo 60 minutes before each training session. Patients received a total of 10 drugs administered every fourth day, i.e., the study period lasted for 36 days with the first treatment given on day 0. All side-effects during the intervention period were registered.

Physiotherapy

Both groups received 45 minutes of individual physiotherapy five times a week during the study period of 36 days. The physical therapy, starting within 1 hour after drug intake in the morning at 8.30 a.m., followed the neurodevelopmental (NDT) concept⁹ aiming at the restoration of most

physiological movement control. A typical training session consisted of tone-inhibiting manoeuvres, bridging while lying, balance training while sitting and standing and gait practice along the bench, on the floor or on the stairs. Additionally all patients participated in a so-called 'bilateral group' practising trunk movements with both hands outstretched and folded while sitting. Occupational therapy focusing on ADL competence and arm therapy according to the NDT concept, speech therapy, psychology and physical therapy were administered according to individual needs. After discharge, community-based services provided two to three 30-minute physiotherapy sessions and one to two 30-minute occupational therapy sessions based on the NDT concept per week during the entire follow-up period.

Outcome measures

Activities of daily living were assessed with the 10-item Barthel Index (BI, 0–100) covering self-care, bowel and bladder care and locomotion.¹⁰ The hierarchical Rivermead Motor Score (RMS), with its gross functions, leg and trunk and arm sections, helped to document disabled motor functions.¹¹ Two physiotherapists assessed the BI and RMA at days 0, 20, 36, 90 and 360.

Statistical analysis

Distribution of the variables are given as mean, standard deviation (SD), medians and ranges. Within-group differences were tested for statistical significance with the Wilcoxon test, or the Friedman test for multiple measurement points. Differences between the control and experimental group were tested with the nonparametric Mann-Whitney test. For the primary outcome measure, the BI, alpha was set at 0.05, for the secondary variables, the RMS sections, a Bonferroni correction was considered with an adjusted alpha level of 0.015. Further, the power (1–beta) was calculated for the primary outcome measure.

Results

All patients completed the treatment and showed up at the 90-day follow-up. One patient of the experimental group refused to come at the 180-day and one of the control group at the 360-day follow-up. Hence, 11 patients in the treatment group and 11 in the control group completed the 12 month study (Figure 1). Drug-related side-effects did not occur.

Before treatment, there were no significant differences between the experimental and control group in selected patient characteristics or outcome measures (Table 1).

Both groups improved significantly during the intervention period in all outcome measures except for the arm section of the RMS (Table 2).

From the end of training to follow-up at three months, both groups further improved significantly with respect to the BI and the gross motor functions and leg and trunk sections of the RMS, while the arm score remained stable (Tables 2 and 3).

From 3 to 12 months, all outcome variables remained unchanged (Table 2).

Comparisons between groups showed no difference at any of the measurement points, i.e., neither was superior to the other at any time (Figure 2). The corresponding *p*-values for the comparison of the BI between groups were: *p* = 0.41 (day 20), *p* = 0.89 (day 36), *p* = 0.55 (day 90), *p* = 0.67 (day 180) and *p* = 0.51 (day 360). The power ranged from 0.5 to 0.6.

Discussion

The results of our study did not reveal any difference in ADL competence and motor functions between the amphetamine and control group during the intervention nor at the three- and 12-month follow-up.

Both groups were homogeneous with respect to the clinical characteristics and the motor-function-related outcome measures, the net therapy time during the treatment period was comparable and the amount of outpatient physiotherapy after discharge did not differ markedly.

The mean BI improvement of 35.4 and 33.8 points in the experimental and control group dur-

ing the 40-day intervention period was in keeping with numerous international outcome studies on the BI during the rehabilitation of acute stroke survivors.¹²⁻¹⁴ Also the observed first-degree polynomial time profile of the BI and the RMS over one year corresponded to the curves reported in above-mentioned outcome studies.¹²⁻¹⁴ Furthermore, the least improvement of the arm section of the RMS as compared with the gross functions and the leg and trunk sections was in accordance to the poor prognosis of upper limb recovery of severely affected stroke patients.¹⁵

The missing difference in ADL competence and motor functions between the groups confirmed the negative results of three of the five placebo-controlled studies on AMPH in subacute stroke patients.⁶⁻⁸ In the largest study so far, Sonde *et al.* investigated the effect of 10 sessions with 10 mg of amphetamine combined with physiotherapy within 1 hour after drug intake during a five-week period in 39 geriatric elderly patients.⁸ All patients improved significantly over the time period, but amphetamine-treated patients did not show any increase in motor function or ADL as compared with the control group.

On the other hand, animal studies elegantly showed the beneficial effect of D-amphetamine in combination with physical therapy after artificial stroke,^{1,2} and two small clinical studies could find a positive effect of the drug on motor recovery after stroke.^{4,5} The present study protocol exactly followed the positive paper of Walker-Batson *et al.*⁵ with respect to the drug treatment

Clinical messages

- Ten doses of 10 mg D-amphetamine every fourth day in addition to physiotherapy had no benefit in acute stroke patients compared with placebo.
- The study does not support the clinical use of D-amphetamine to promote motor recovery after stroke,
- Open questions to further studies including larger number of patients are the optimal regime of amphetamine and combined physical therapy.

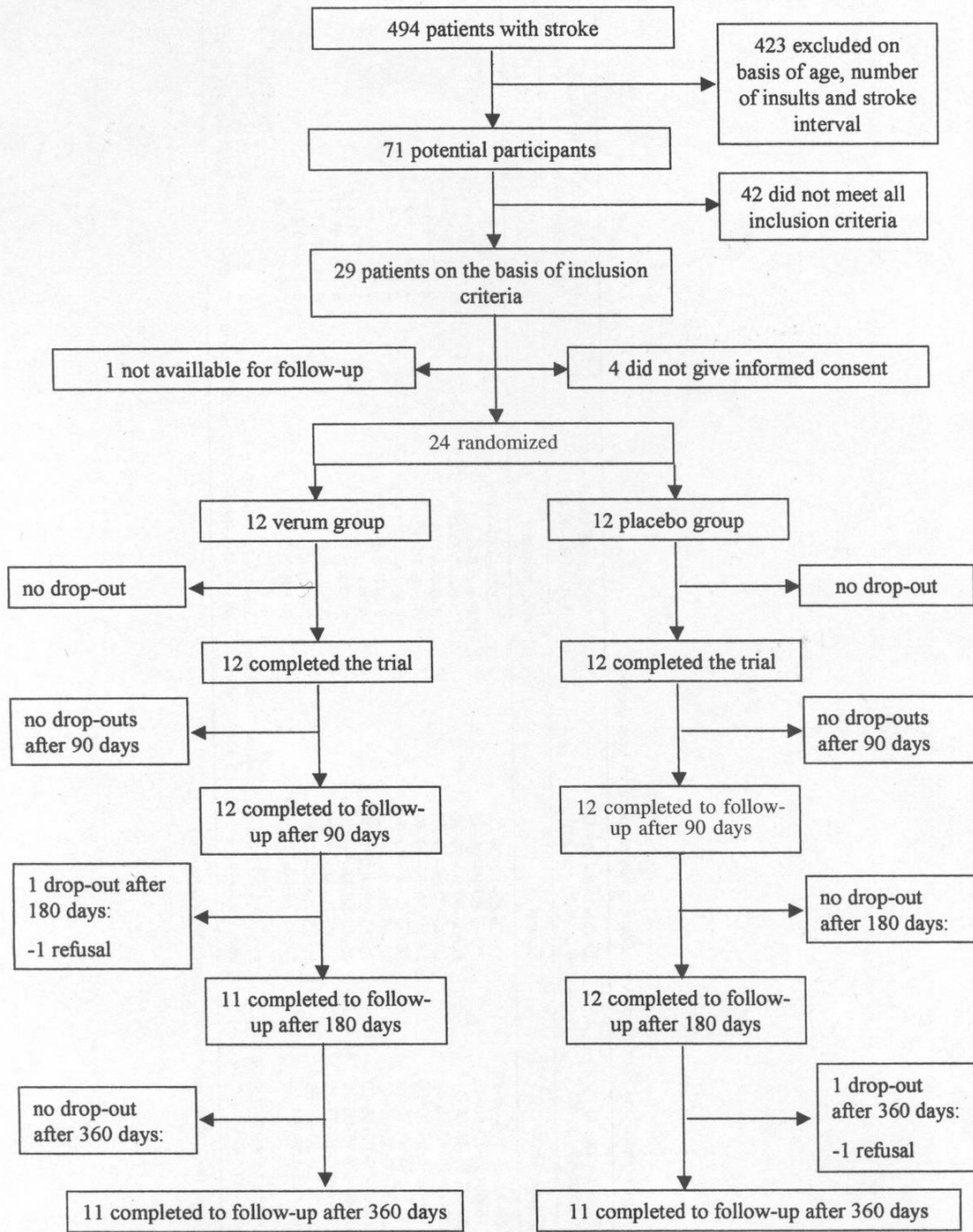


Figure 1 Trial profile.

Table 2 Barthel Index and Rivermead Motor Score (gross function) for both groups

Patient	Barthel Index (0-100) 0-20-36-90-180-360		RMS gross function (0-13) 0-20-36-90-180-360	
	Experimental	Control	Experimental	Control
1	25-40-65-100-90-85	25-55-65-80-80-0	2-5-6-9-10-10	3-6-7-9-9-0
2	25-40-55-70-60-70	35-45-65-90-95-95	2-4-5-6-6-10	2-5-6-10-11-11
3	25-25-25-45-0-0	40-65-80-90-90-90	2-4-4-7-0-0	4-6-8-9-10-10
4	25-45-60-75-75-75	25-25-50-65-75-75	3-6-7-8-9-9	2-5-7-10-10-10
5	25-45-75-95-90-90	35-50-50-60-40-40	5-6-8-10-10-10	1-1-4-4-5-2
6	35-60-75-85-75-90	25-55-65-80-80-80	6-8-11-11-11-10	2-5-7-8-8-8
7	25-30-50-35-45-40	30-45-45-45-45-45	3-3-6-2-3-1	3-6-6-6-6-6
8	30-60-70-80-85-90	40-75-85-100-100-100	5-7-10-11-10-10	5-7-11-11-11
9	25-60-70-85-90-90	25-45-55-80-85-90	2-6-7-9-10-10	4-5-5-7-9-11
10	30-50-65-75-75-75	35-85-90-85-85-85	3-6-8-8-9-9	6-11-11-11-11
11	35-75-80-90-95-95	35-65-75-90-90-90	3-9-10-10-10-10	5-7-8-10-11-11
12	30-45-70-75-50-50	40-55-70-90-100-100	3-7-8-9-8-9-9	2-5-10-10-10-10
Mean	27.9-47.9-63.3-75.8-75.5-77.3	32.5-52.9-63.3-79.6-80.2-80.9	3.0-6.0-7.5-9.0-10-10	3.5-5.5-7.5-10-10-10.5
±SD	±4.0-±14.1-±14.8-±19.0-±17.1-±17.9	±6.2-±15.1-±14.5-±15.6-±19.3-±20.5	2/5-4/7/25-5/75/10-6/75/10.25-6/75/10.8.5/10	2/5-5/7-5.75/10.25-6.75/10.25-8.25/11-9/11

0, absent data; RMS, Rivermead Motor Score; IQR, interquartile range.

Table 3 Rivermead Motor Score (leg and trunk, arm) for both groups

Patient	RMS leg and trunk (0-10) 0-20-36-90-180-360		RMS leg and trunk (0-10) 0-20-36-90-180-360		RMS arm (0-15) 0-20-36-90-180-360	
	Experimental	Control	Experimental	Control	Experimental	Control
1	2-5-5-8-6	2-5-6-6-7-0	2-1-1-0-1	0-2-2-2-3-0	0-2-2-2-3-0	0-2-2-2-3-0
2	3-4-5-4-5	3-4-5-5-7	0-1-1-1-1	1-1-1-1-1	1-1-1-1-1	1-1-1-1-1
3	1-2-3-8-0-0	2-5-5-5-7-6	1-2-3-7-0-0	0-0-1-1-1	0-0-1-1-1	0-0-1-1-1
4	3-5-6-6-5-5	0-4-7-8-9-9	1-2-3-3-3-3	1-1-2-4-4-4	1-1-2-4-4-4	1-1-2-4-4-4
5	3-6-6-8-8-5	1-1-2-2-2-2	0-0-1-1-1-1	0-0-0-0-0-0	0-0-0-0-0-0	0-0-0-0-0-0
6	3-7-9-9-9-5	2-5-6-6-6-6	1-7-8-10-10-10	4-7-7-7-7-7	4-7-7-7-7-7	4-7-7-7-7-7
7	3-2-6-2-3-1	6-6-6-6-6-6	1-2-1-1-1-0	4-7-10-12-14-14	4-7-10-12-14-14	4-7-10-12-14-14
8	5-8-8-8-8-6	5-9-9-9-9-10	3-6-8-9-9-9	0-2-1-1-1-1	0-2-1-1-1-1	0-2-1-1-1-1
9	1-2-5-5-5-4	1-3-4-4-5-5	0-0-0-0-0-0	1-1-1-1-8-8	1-1-1-1-8-8	1-1-1-1-8-8
10	2-4-6-6-6-6	6-9-9-9-9-9	0-2-2-3-3-3	1-1-1-0-0-0	1-1-1-0-0-0	1-1-1-0-0-0
11	3-5-8-8-3-3	2-5-6-7-8-8	0-0-0-0-0-0	0-1-1-0-1-1	0-1-1-0-0-0	0-1-1-0-0-0
12	1-4-4-2-3-3	1-3-7-8-7-7	0-0-1-0-1-1	1-0-1-0-1-0-1-0	1-0-1-0-1-0-1-0	1-0-1-0-1-0-1-0
Median	3.0-4.5-5.5-6.5-6.5-5.0	2.0-4.5-6.0-6.5-7.0-7.0	0.5-1.0-1.0-1.0-1.0-1.0	0/1.25-0/9-0.75/4.25-0/7.5-0/7.5-0/7.5	0/1.75-0.75/3.25-1/3.25-0/4.75-0/7.25	0/1.75-0.75/3.25-1/3.25-0/4.75-0/7.25
IQR	1/3-2/6.25-4.75/8-3.5/8-3/8-3/6	1/5.25-3/6.75-4.75/7.5-4.75/8.25-5/9-5.75/9				

Ø, absent data; RMS, Rivermead Motor Score; IQR, interquartile range.

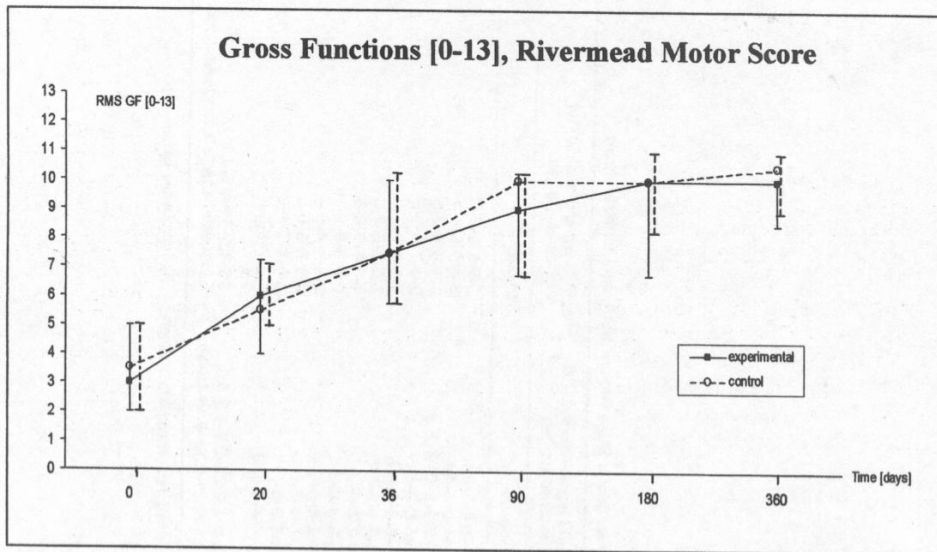
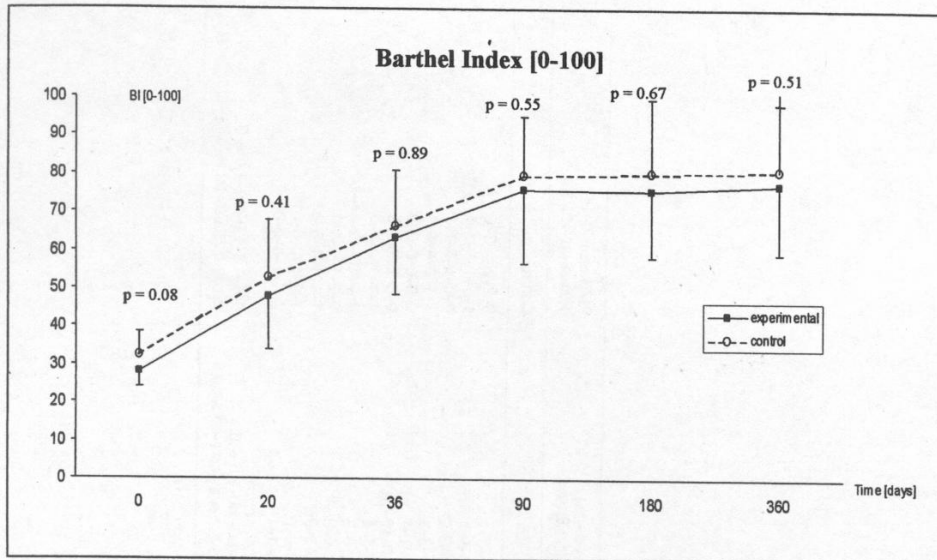


Figure 2 Mean (standard deviation) Barthel Index (BI 0-100) of both groups on treatment days 0, 20, 36, 90, 180 and 360 (above) and median (interquartile ranges) gross function (RMS 0-13), Rivermead Motor Score of both groups on treatment days 0, 20, 36, 90, 180 and 360 (below). *p*-values of the comparisons between groups are given.

and inclusion criteria, and interval from stroke and patient characteristics before study onset were comparable in both studies. What may explain the negative result of the present study? Timing and content of physiotherapy after drug intake seem to be crucial factors. Walker-Batson *et al.* wrote that 'they carefully timed the onset of physical therapy treatment after drug administration to occur during the peak period of drug action'. Unfortunately they did not mention an exact timing in their paper but one cannot exclude that the presently applied protocol of physical therapy onset within 60 minutes after drug intake did not result in an optimum drug promotion effect. Furthermore pharmacokinetic studies revealed that the metabolism of the drug depended on the urine pH-value, which was not controlled in the present study.¹⁶

Another point of concern is the content of therapy. In this study, the therapy followed the NDT programme (which aims at the restoration of a physiological movement pattern) in which tone-inhibiting and manoeuvres while lying and sitting dominated.⁹ Instead of a repetitive exercise of various functional tasks including gait, the so-called quality of movement execution was the primary target. Furthermore, the content of therapy was not standardized and could depend heavily on the individual physiotherapist. Further, due to the low number of subjects included, the statistical power only ranged from 0.5 to 0.6. On the other hand, the observed differences between groups in the BI and RMS scores never met a level of clinical relevance as a difference of at least 15%. One may speculate that this kind of 'quality-oriented' therapy did not meet the criteria of a 'symptom-relevant experience' as postulated by Feeney *et al.* in their paper.¹ Walker-Batson and co-workers applied a uniform approach with rehabilitation tasks attempted in each area addressed by the Fugl-Meyer Motor scale, i.e., the patients obviously practised various motor tasks repetitively.⁵

Furthermore, in healthy subjects, Knecht *et al.* could not show any effect of AMPH as compared with placebo when the subjects only practised a sensory-discrimination task,¹⁷ whereas Buetefisch and co-workers found a positive drug effect when the intake was combined with repetitive motor tasks, namely brisk thumb movements in one

direction in blocks of 5 minutes for a total of 30 minutes at 1 Hz.¹⁸ Correspondingly, future AMPH studies should combine the drug with well-timed, positively evaluated repetitive motor training such as constrained-induced movement therapy¹⁹ for upper or treadmill training with partial body weight support²⁰ for lower limb rehabilitation after stroke.

In summary, the present placebo-controlled study in 24 subacute stroke survivors did not show any additional benefit of 100 mg AMPH, given in 10 sessions over 40 days, as compared with placebo. Future studies in larger number of patients addressing functional aspects such as walking velocity are needed to find the optimal regime of amphetamine and combined physical therapy to promote the recovery after stroke.

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