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Effects of amphetamine and/or L-dopa and physiotherapy after stroke – a blinded randomized study

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Objectives – Major therapeutic advances in the rehabilitation of subacute stroke are lacking. A promising approach is treatment with facilitating drugs like amphetamine or levodopa in combination with physiotherapy. *Methods* – In a randomized, double-blind, placebo-controlled clinical trail, the effect of 10 sessions with either 20 mg of D-amphetamine, 100 mg of L-dopa or 10 mg of D-amphetamine + 50 mg of L-dopa combined with physiotherapy during a 2-week period was investigated in 25 patients admitted to a stroke rehabilitation unit. Motor function (Fugl–Meyer score) and activities of daily living (Barthel's index) were assessed. *Results* – All patients improved significantly over the intervention period. Drug-treated patients did not show any additional increase in motor function or ADL. *Conclusion* – It is feasible and safe to perform larger clinical trials with this type of four-arm design. However, the lack of significant effects could be because of type, dosage, and time of drugs as well as the physical intervention strategy.

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Introduction

Until very recently, the only therapeutic option for motor recovery after stroke was physiotherapeutic training. Experiments have shown that practice-induced plasticity can be modulated in adult animals by systemic (1) or intraventricular (2) amphetamines and norepinephrine (3), but only when given together with training (afferent stimulation). Human studies with administration of amphetamines in addition to exercise have been shown to increase recovery with suggested benefits on motor as well as language functions (4–6). We earlier reported that amphetamine-treated patients did not show any increase in motor function or ADL when compared with a control group, which could be because of factors as dosage and interval and intensity of exercise (7). Also single doses of L-dopa have been reported to enhance motor function after stroke (8, 9). Moreover, dementia occurring after stroke, post-stroke dementia, is about 30% and the incidence of new onset after stroke is reported to be 7% the first year post-stroke (10). Whether cognition is affected by norepinephrine-stimulating drugs is not fully understood.

The objective of our study was to investigate the effect of 10 sessions of an oral dose of either amphetamine, L-dopa, amphetamine or L-dopa combined with physiotherapy, starting 5–10 days after stroke with regard to motor function, ADL and cognition.

Materials and methods

In a randomized, double-blind, placebo-controlled trial 30 primary stroke patients were consecutively enrolled from the geriatric rehabilitation ward at Karolinska University Hospital, Huddinge ($n = 25$) and the geriatric rehabilitation ward at Malmö University Hospital ($n = 5$). Patients were examined by the physician in charge. The medical examination included a medical history, assessment of somatic and neurological status, laboratory analysis and a CT scan.

Patient selection

Geriatric patients (65 years or over) with a paretic arm and/or leg following a stroke which had occurred 5–10 days previously and who could follow instructions were included. The presence of hemiplegia was defined as an arm motor score 0–50 and a leg motor score of 0–30 on the Fugl–Meyer (FM) motor scale at baseline screening. Patients were excluded if they had had an earlier cerebral lesion with a documented need for care and remaining paretic symptoms and/or a serious disease, as assessed by the responsible physician. Patients receiving alfa-adrenergic antagonists or agonists, neuroleptics, benzodiazepines or antidepressants were also excluded. Patients were included in the study after their informed consent had been obtained.

Drug administration and randomization

Study patients and all other people involved were blinded to the treatment type. In a four-group intervention model, drug treatment was given in the form of identical white tablets of 4×5 mg of either D-amphetamine or placebo and a capsule with either 1×100 mg L-dopa or 1×50 mg L-dopa or placebo 60 min before the training session (see Fig. 1). The pharmacological company Recip AB, Stockholm, Sweden, supplied the drugs. The amphetamine/L-dopa/placebo was randomly distributed in boxes labeled 1–30. Patients received the boxes in consecutive order. All side-effects during the intervention period were registered.

AMPH-group **Amphetamine 20 mg** **+** **L-dopa-placebo** **+** **Physiotherapy**	*L-Dopa-group* **L-Dopa 100 mg** **+** **Amphetamine-placebo** **+** **Physiotherapy**
AMPH/L-Dopa-group **Amphetamine 10 mg** **+** **L-Dopa 50 mg** **+** **Physiotherapy**	*Placebo-group* **Amphetamine-Placebo** **+** **L-dopa-Placebo** **+** **Physiotherapy**

Figure 1. The four-group intervention model.

Physiotherapy

The physiotherapy intervention was based on functional movements including balance training, transfer training and more specific motor function training of the paretic arm/leg. Because of the clinical setting, the content but not the volume of the training varied from each patient depending of the severity of his or her paresis. Patients received drugs or placebo five times a week (every working day) for 2 weeks together with 30 min of physiotherapy 1 h after drug or placebo intake. The first of the 10 study sessions took place within 5–10 days from the onset of stroke.

The Ethical Committee of Karolinska University Hospital approved the study.

Assessments

Motor function and activities of daily living (ADL) were assessed by the responsible physiotherapist at baseline, at the end of the 10th session (after 2 weeks) and at follow-up, 3 months after stroke onset. Baseline motor scores were obtained 1 day before study initiation in all patients. The score at the end of the treatment was determined the day after the 10th session. The FM motor performance score was used to evaluate changes in motor function. On this scale, a score of 0 means no motor function and a score of 100 indicates normal motor function (divided into 66 points for normal arm motor function and 34 points for normal leg motor function). This test is often used in stroke research and its reliability and validity are both well documented (11, 12). Autonomy in ADL was evaluated with Barthel's index (13, 14). This scoring system involves a weighted scale, ranging from 0 to 100 in five-point increments, that measures performance in terms of self-care (feeding, bathing, personal toilet, dressing, bowel and bladder care), as well as locomotion (for instance, moving between bed, wheelchair and toilet, ambulation and stair climbing). A score of 100 does not imply normality but rather that the patient is functionally independent in most ADL.

At follow-up, the cognitive function was assessed using the Mini Mental State Examination (MMSE), where 11 subtasks were assigned points to a total of 30 (15). A score of less than 24 suggested cognitive dysfunctions.

Study size and power

The variance and effect size needed to calculate the number of patients were estimated from the study of Walker-Batson et al. (5) This revealed that a

sample of 32 patients was necessary to achieve an 80% chance (power = 0.80) of detecting a mean difference of 20 points in improvement between two groups in the main outcome measure (FM score) with a 5% significance level. This difference was in line with the knowledge of clinically relevant improvements in stroke patients.

Statistics

The data are given as mean ± SD. The non-parametric Mann–Whitney *U*-test was used to analyze the FM and Barthel's data. At follow-up, a classical intention-to-treat analysis was used, including the last observation available for each subject (Fig. 2).

Results

Table 1 shows the characteristics of the 25 patients who were treated during the 2-week period. Drug treatment was started on average 8 days after the onset of stroke in all groups (range 7.6–9.3 days). For the remaining five patients, the treatment was discontinued after three to six sessions and data for these patients were not included in the analysis. Three patients (two in L-dopa, one in AMPH/L-dopa) were excluded because of general health deterioration. All of them had low scores in FM and Barthel at start. Two patients were excluded because of confusion of study medication by the nurses at the ward (one in L-dopa, one in placebo group respectively). These two patients had FM and Barthel scores above average at the start.

There were no adverse side-effects in any of the patients.

Placebo-treated patients showed higher FM scores (arm and leg) at baseline but the differences were not significant. All patients improved significantly in motor function over the intervention period (Figs 3 and 4). However, drug-treated

Table 1 Demographic data of drug-treated patients (three groups) and placebo-treated controls

	AMPH ($n = 7$)	L-dopa ($n = 4$)	AMPH/L-dopa ($n = 7$)	Placebo ($n = 7$)
Mean age, years (SD)	78.3 (9.1)	78.8 (3.9)	76.9 (8.4)	77.6 (5.7)
Range	67–91	75–84	65–86	68–84
Male/female	4/3	2/2	1/6	5/2
Infarct/hemorrhage	5/2	4/0	6/1	5/2
Right/left paresis	3/4	1/3	3/4	3/4
FM arm motor score, mean (SD)	16.3 (9.1)	7.0 (7.8)	11.0 (10.6)	26.9 (23.7)
FM 0–15*	4	3	5	3
FM 16–30	2	1	1	1
FM 31–50	1	0	1	4
FM leg motor score, mean (SD)	10.0 (8.2)	13.8 (15.3)	11.4 (10.0)	15.1 (6.1)
FM 0–10*	4	2	5	2
FM 11–20	1	1	0	3
FM 21–30	2	1	2	2
Barthel's ADL index, mean (SD)	35.7 (16.9)	48.8 (25.6)	31.4 (9.4)	43.6 (13.4)
Barthel 0–30*	4	1	4	1
Barthel 35–65	2	2	3	6
Barthel 70-	1	1	0	0
MMSE, median	24.5	28.0	28.0	26.5
Range	13–30	19–30	16–29	25–29

*Stratified, number of patients.

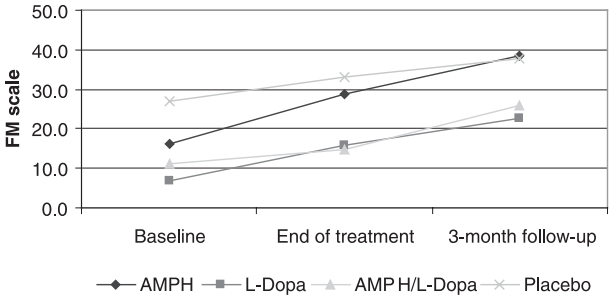

Figure 3. Mean FM motor performance scale score (arm) in patients treated with either amphetamine, L-dopa, amphetamine and L-dopa or placebo.

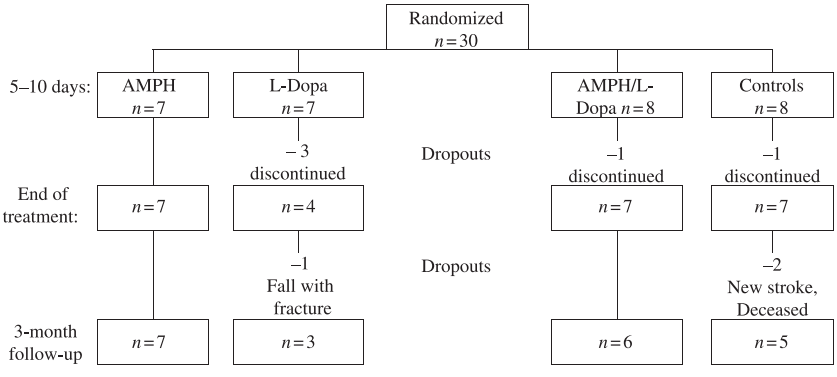

Figure 2. Flow chart describing the subjects included and randomized in the drug treatment study.

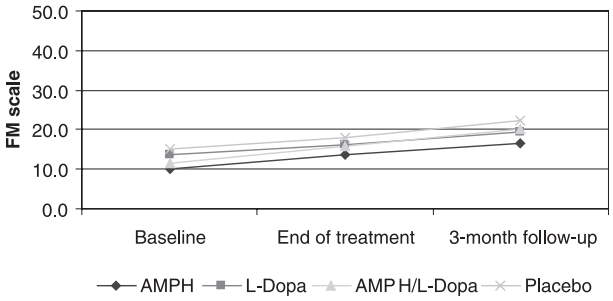

Figure 4. Mean FM motor performance scale score (leg) in patients treated with either amphetamine, L-dopa, amphetamine and L-dopa or placebo.

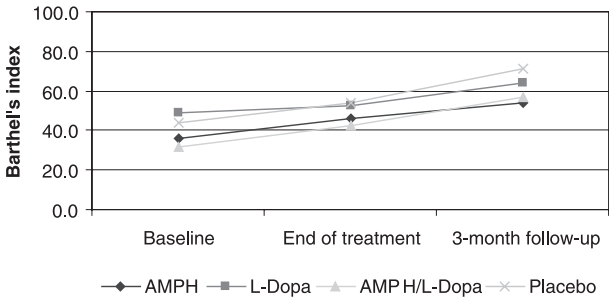

Figure 5. Mean Barthel's index score in patients treated with either amphetamine, L-dopa, amphetamine and L-dopa or placebo.

groups did not show a greater increase in motor function over the intervention period even though AMPH-treated patients at follow-up had caught up to similar arm mean scores compared with controls (38.6 ± 21.7 vs 37.6 ± 23.6) (Fig. 3).

Activities of daily living functions graded on Barthel's index improved over the intervention period, but the improvements were similar in drug-treated groups and controls.

Mini Mental State Examination scores assessed at follow-up showed neither a general cognitive deterioration in patients nor a significant cognitive worsening in medication groups compared with placebo (Fig. 5).

Discussion

In this randomized, controlled study with norepinephrine facilitating drugs in stroke patients recovering during rehabilitation, we found a trend towards greater improvement in the amphetamine group compared with placebo. All patients improved as expected over the 3-month follow-up period as most post-ischemic patients showed some signs of recovery over time (16). It could be that the somewhat better, but not significant, scores in the placebo group compared with the other groups, could be expected to give them more recovery potential. However, the amphetamine group starting on lower scores improved more and reached the same levels as the placebo group after 3 months.

Although the mechanisms of recovery are controversial, data exist that support long-term recovery in humans and that the adult brain has considerable potential for plasticity (17). New imaging techniques with positron emission tomography on humans who have recovered motor function after stroke show significant increases in regional cerebral blood flow induced by movement of the recovered limb in the sensorimotor cortex contralateral to the injury (18). Similar changes in the contralateral hemisphere of patients recovering motor function after stroke have also been demonstrated with functional MRI (19). Taken together these findings suggest that norepinephrine simulating therapy may exert its impact on recovery through effects on processes in the contralateral hemisphere as well as on the neuronal reorganization in the ipsilateral hemisphere.

Results of earlier human studies have been inconsistent with no clear evidence of benefits in the face of potential cardiovascular or dependence risks of patients (20). The importance of our study is that the design with four treatment arms is to our knowledge new. Use of established instruments and scales for possible effects makes it possible to collocate them in future meta-analyses, and we did not find any side-effects. The shortcoming was the small number of patients and that no regard, like in other studies, has been taken to the size and localization of the ischemic lesion. It might also be that the amounts of study drugs were too small and/or for a too short time and/or that the intensity of physiotherapy was too light and/or short and/or that the timing was not optimal, i.e. within 10 days after stroke onset. Another possible bias is the well-known ceiling effects in the scales used. The highest scoring patients have naturally limited or no possibility to improve their high or maximum scores. The recruitment of patients excluded patients with arm and leg FM-scores more than 50 and 30, respectively, attempting to eliminate this problem.

However, our study has shown that it is feasible to perform larger clinical trials where one must bear in mind the type, dosage, and time of administration of drugs as well as the physical intervention strategy together with a targeting of appropriate patients who may benefit from this type of intervention.

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