Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2003;16:338–345
DOI: 10.1159/000072555

Received: December 30, 2002
Accepted: February 28, 2003

Intensive Early Physiotherapy Combined with Dexamphetamine Treatment in Severe Stroke: A Randomized, Controlled Pilot Study

Louise Martinsson[a] Staffan Eksborg[b] Nils Gunnar Wahlgren[a,c]

[a]Institution of Clinical Neurosciences, Karolinska Institutet, [b]Department of Woman and Child Health, Childhood Cancer Research Unit, Karolinska Institutet and Karolinska Pharmacy, [c]Department of Neurology, Karolinska Hospital, Stockholm, Sweden

Key Words
Cerebral infarction · Dextroamphetamine · Recovery of function · Rehabilitation

Abstract
Background: The most severely disabled stroke patients are often excluded from studies evaluating effects of physiotherapy. This study intended to investigate the effect of an increased intensity of physiotherapy in combination with dexamphetamine the first week after ischemic stroke in patients with an impaired level of consciousness and severe motor dysfunction. ***Methods:*** Thirty patients were enrolled within 96 h after onset of symptoms. Patients were randomized to 30–45 min of physiotherapy twice daily or to maximally 15 min per day for 5 days. All patients received dexamphetamine to achieve alertness. Functional outcome measures were assessed at baseline, the day after treatment discontinuation, and 3 and 12 months after stroke onset. Residence of living was registered at long-term follow-ups. ***Results:*** No statistically significant differences were seen between groups in the outcomes measured at any time point. However, both groups improved over time in all outcomes at 3 and 12 months ($p < 0.05$), except for sensory functions at 3 months and motor functions at 12 months. The number of patients needed to treat (NNT) to achieve the desired improvement in Lindmark motor score was 8, with the 95% CI being NNT(harm) 10 to NNT(beneficial) 3. The fraction of patients who died was the same in both treatment groups, 47% (95% CI 28–65%). ***Conclusions:*** An increased intensity of physiotherapy in combination with dexamphetamine during the first week after stroke onset did not affect short- or long-term outcome in this limited sample of patients with severe stroke.

Introduction

Patients with stroke receiving more physiotherapy achieve a better recovery [1, 2]. An early start of intensive physiotherapy has also been suggested to be an important aspect of expert care [3, 4] as well as early mobilization [5]. Information about the amount of physiotherapy needed and how early therapy should start to achieve better recovery is, however, still scarce, as is information about which patients benefit from 'more and early' treatment. The most severely disabled patients are often excluded from studies evaluating physiotherapy because they seem less likely to recover and are regarded to be too ill to receive rehabilitation [6].

The present study reports results from a randomized, controlled, single-blind study carried out in a group of patients with ischemic stroke and impaired conscious-

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/03/0164–0338$19.50/0

Accessible online at:
www.karger.com/ced

Louise Martinsson
Stroke Research Unit, R2:03, Department of Neurology
Karolinska Hospital
SE–171 76 Stockholm (Sweden)
Tel. +46 8 517 756 00, Fax +46 8 736 61 58, E-Mail louise.martinsson@ks.se

ness. Dexamphetamine (d-amph) treatment was administered to all patients to make them alert [7]. We were primarily interested in comparing motor function between patients receiving two different intensities of physiotherapy the day after treatment discontinuation and at 3 and 12 months after stroke. We were also interested in evaluating differences in mobility, balance, sensation, neurological function and activities of daily living (ADL) at the same time points as stated above, and in residence of living 3 and 12 months after stroke.

Patients and Methods

Patient Selection

Patients with first as well as recurrent stroke admitted to the Department of Neurology, Karolinska Hospital, Stockholm, Sweden, were screened for inclusion during a period from February 1997 to December 2000. During March–September 1998, no inclusion was made due to administrative reasons. Patient recruitment was made by one of the authors (L.M.). The following inclusion criteria were used: (1) clinical diagnosis of acute hemispheric cerebral infarction within the carotid supplying area, confirmed by CT scan to exclude hemorrhagic stroke; (2) onset of symptoms $\leq$96 h before the start of treatment; (3) a score between 0 and 100 on the Lindmark motor assessment chart (LMAC) part A + B (motor score) [8, 9], which indicates severe deficit [9]; (4) a level of consciousness classified as grade 2 (drowsy – responsive to light stimulation) on the Reaction Level Scale (RLS85) [10]; (5) Katz Index of Activities of Daily Living (ADL) grade A–B [11]; (6) age 55–85 years, and (7) informed consent provided. The diagnosis of stroke was based on the medical history and clinical examination of the patient according to the WHO criteria [12]. Exclusion criteria were other serious diseases reducing the expected remaining lifetime to less than 1 year and known alcohol or drug abuse. Patients with posterior circulation infarcts once included in accordance with the protocol were also included in the analysis, even if it was found later that the stroke had been in the posterior circulation.

The study was performed in accordance with the Declaration of Helsinki. The protocol was approved by the local ethics committee at Karolinska Hospital and by the Medical Products Agency in Sweden. All patients or their relatives gave informed consent.

Randomization Procedure and Study Design

A prospective, randomized, controlled, single-blind approach was used. Patients were randomized either to the 'intensive treatment group' (ITG) or the 'standard treatment group' (STG). A person not involved in the study prepared the sealed, numbered envelopes used. The randomization allocation remained unknown to the evaluators until all patients had been included and attended their last follow-up. The Karolinska Pharmacy produced the d-amph capsules. Serious adverse events were evaluated by an external neurologist (J.E.O.).

Treatment

Patients received d-amph and ITG or STG for 5 consecutive days (the treatment period). The two different treatment regimes were started the day after baseline assessments (on the same day when patients were randomized to the ITG or the STG).

The first 10 patients received 5–10 mg d-amph once or twice daily, depending on the level of consciousness. The remaining patients were given 10 mg of d-amph twice daily independently of their consciousness level during the treatment period.

The research physiotherapist (L.M.) treated both groups. Training was conducted when the patients were alert, i.e. assessed as level 1 according to the RLS85. In the ITG, patients were scheduled for 30–45 min of physiotherapy twice daily. Training was conducted with emphasis on the patients actively taking part in transfer from supine to lying on the side, to sitting up, standing with support and finding their balance in these positions. The training encouraged patients to actively move the paretic side in supine and sitting positions. Patients with inattention problems were stimulated verbally and tactically to attend the neglected side. STG patients were scheduled for maximally 15 min of daily training, consisting of passive movements and mobilization to a sitting position.

After the treatment period the authors did not influence quantity or type of physiotherapy.

Assessments

Demographic details, medical and cerebrovascular history, general characteristics of the present stroke, ECG and laboratory tests were collected at baseline.

Baseline assessments were performed 1–3 days after stroke onset. The following measures were used at baseline: LMAC [8, 9] part A + B (motor score), part C (mobility score), part D (balance score), part E (sensation score); the National Institute of Health Stroke Scale (NIHSS) [13], and the Activity Index (AI) [14] (psychiatric, ADL, and motor score). The LMAC and AI were assessed mainly by two physiotherapists (M.K. and M.N.) and the NIHSS by a senior neurologist (N.G.W.). Systolic and diastolic blood pressure (BP) as well as heart rate were recorded every 15 min for the first 2 h after d-amph administration. The paretic arm was used for registration, using a Datascope Accutorr 3 (Datascope Corporation, Montvale, N.J., USA). Body temperature was measured in the ear with a Thermo-Scan pro 1 (Thermoscan Inc., San Diego, Calif., USA) once daily before therapy started. Level of consciousness was recorded with the RLS85 scale at least every 30 min for the first 2 h after d-amph administration. Patients with slight disorientation but fully awake were accepted within reaction grade 1, since assessments focused on the level of consciousness rather than cognitive functions. The quantity of physiotherapy and adverse events were recorded daily during the treatment period.

The stroke was classified into embolic and non-embolic and into various syndromes on the basis of clinical symptoms according to the Oxfordshire Community Stroke Project (OCSP) [15]. A senior neurologist (N.G.W.) identified the infarct territory by CT scan.

Follow-Up

Patients were scheduled for follow-ups on the first weekday after the intervention period (day 7), and at 3 and 12 months after their stroke. The patients were reassessed by means of LMAC, NIHSS and AI. The assessors were the same as at baseline whenever possible. They were blinded to treatment allocation and the treatment given. The residence of present living was noted at 3 and 12 months. The physiotherapist responsible for the patient was asked to give information about the amount of physiotherapy the patient had received since the intervention period. Whenever possible, the follow-up was

Table 1. Demographic and medical history by group

Characteristic	STG n = 15	ITG n = 15	p
Median age, years (IQR)	79 (72–82)	78 (69–83)	0.595
Sex, female/male	11/4	8/7	0.256
Living alone	8	8	1.000
Median weight, kg (IQR)	75.5 (64–78)	77 (64–84)	0.983
Median height, cm (IQR)	162 (160–173)	167 (160–178)	0.236
Cigarette smoking	5	2	0.195
Diabetes mellitus	2	4	0.361
Hypertension	8	6	0.464
Atrial fibrillation	4	3	0.666
Myocardial infarction	2	3	0.624
Cardiac failure	2	1	0.543
Angina pectoris	0	2	0.143
Previous stroke	4	2	0.573
Previous TIA	2	4	0.361

Table 2. Baseline characteristics of present stroke

Characteristic	STG n = 15	ITG n = 15	p
Left side affected	6	10	0.272
Aphasia	10	5	0.143
Neglect	15	13	0.483
Hemianopia	15	12	0.224
Urinary incontinence	15	15	NA
OSCP classification			
TACI	15	12	0.224
PACI	0	3	
CT abnormal on admission	15	15	NA
Localisation			
Middle cerebral artery	13	15	0.343
Posterior cerebral artery	1	0	
Other	1	0	
Diagnosis			
Cardioembolic infarction	4	6	0.700
Noncardioembolic infarction	11	9	
Median time from onset until treatment start, days (IQR)	2 (1–2)	2 (2–3)	0.436
Functional median score (IQR)			
LMAC motor score (0–210)	79 (73–89)	87 (84–91)	0.187
LMAC mobility score (0–27)	3 (0–5)	2 (0–6)	0.744
LMAC balance score (0–21)	2 (0–3)	3 (1–4)	0.436
LMAC sensory score (0–52)	26 (26–26)	26 (26–27)	0.512
NIH stroke scale (0–47)	27 (22–29)	21 (18–27)	0.029
AI psychiatric score (0–32)	13 (11–24)	20 (16–24)	0.186
AI motor score (0–24)	12 (10–14)	13 (11–16)	0.331
AI ADL score (0–36)	11 (8–13)	12 (10–12)	0.505

TACI = Total anterior circulation infarct; PACI = partial anterior circulation infarct.

held at the hospital, but if the patient for some reason could not visit the hospital, the patient was assessed at the present stay (at home or in a nursing home).

Statistics

Non-parametric statistical procedures were used throughout this study. Associations were established by the Spearman rank correlation coefficient. The Mann-Whitney U test and sign test were used for the comparison of two independent populations and Wilcoxon matched-pairs signed-ranks test for the comparison of two related samples. For repeated measurements, the Kruskal-Wallis analysis of variance by ranks was used for comparison of several independent samples and the Friedman analysis of variance by ranks for comparison of several related samples. Dunn's post hoc test was used for repeated measurements. Classified data from two independent populations were compared by the Fisher's exact test. p values <0.05 were considered statistically significant. The main analysis of efficacy data was performed on surviving patients who completed the 5 days treatment protocol. All outcome scores were also transformed according to a previously used algorithm [16]. The transformed scores ranged from −100 (maximal deterioration) to +100 (maximal improvement).

Analyses were carried out with Statistica version 6.0 (Statsoft Inc., Tulsa, Okla., USA) and GraphPad InStat version 3.05 (GraphPad Software Inc., San Diego, Calif., USA).

Results

Patient Recruitment and Baseline Characteristics

Thirty-two patients fulfilled the inclusion criteria and were asked to participate in the trial; of these, 30 gave informed consent for participation and were randomized to the trial. In 1 ITG and 1 STG patient treatment was discontinued due to signs of cerebral herniation. The other 28 patients were treated according to the study protocol. Demographic and medical history are summarized in table 1 and baseline characteristics in table 2. In 2 patients the CT scan prior to inclusion in the study showed no signs of cerebral ischemia or other cause of neurological symptoms. CT scans performed later showed cerebral infarcts in the posterior cerebral artery territory in 1 patient and in both the middle and the posterior cerebral artery territory in the other. Both patients were included in the analysis according to the intention-to-treat principle. The ITG group had a better NIHSS score ($p = 0.029$). Please note that for the NIHSS, increasing score indicates a decrease in neurological function. Otherwise differences were not significant.

Amount of Physiotherapy

Treatment Period. The median amount of physiotherapy in the ITG was 80 min/day [interquartile range (IQR) 73–85] and 15 min/day (IQR 13–19) in the STG ($p <$

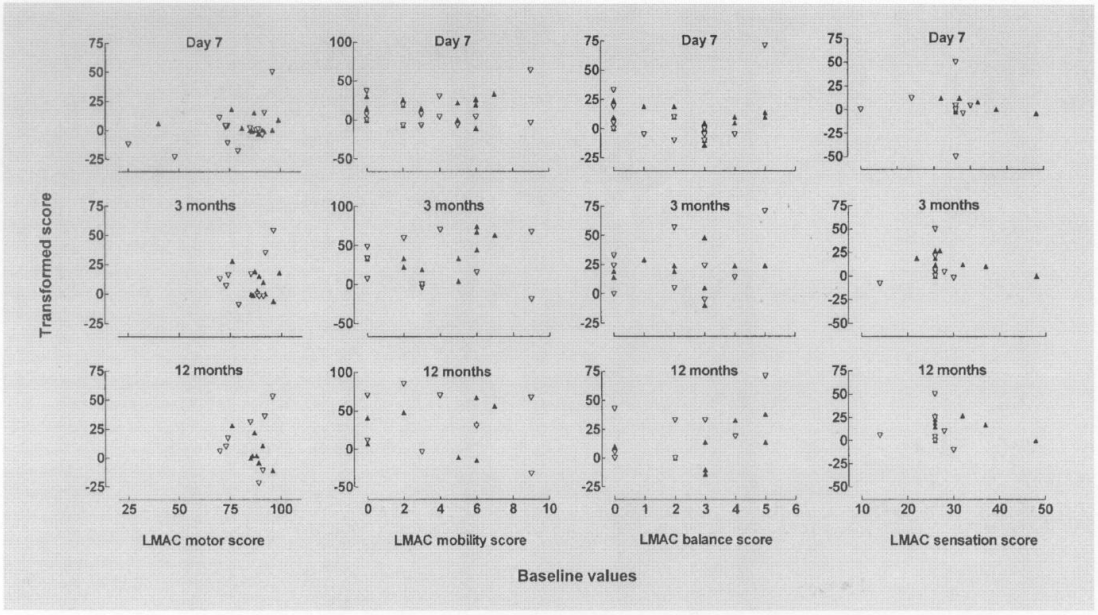

Fig. 1. Outcome, expressed as transformed scores (i.e. relative change) on day 7 and 3 and 12 months of the LMAC motor, mobility, balance and sensation scores as a function of the baseline score. ▽ = STG patients; ▲ = ITG patients.

0.001). After the treatment period until follow-up at 3 months, the ITG received a median total amount of 790 (IQR 65–1,625) min of physiotherapy and the STG 373 (IQR 105–1,655) min [difference not significant (n.s.)]. Between follow-ups at 3 and 12 months, the median total amount of physiotherapy was 1,125 min (IQR 0–1,740) in the ITG and 415 min (IQR 0–1,195) in the STG (n.s.).

The amount of physiotherapy during the treatment period was not correlated with outcome at any time point, nor was the amount of physiotherapy during the period from day 6–3 months at the follow-ups at 3 or 12 months. There were significant positive correlations between the amount of physiotherapy during 3–12 months and the AI ADL-transformed score ($p = 0.014$) and the AI psychiatric-transformed score at 12 months ($p = 0.033$). The correlation with LMAC balance-transformed score was borderline significant ($p = 0.057$).

Amount of Dexamphetamine

The ITG group received a median of 20 mg (IQR 17.5–20) and the STG 20 mg (IQR 12–20) during the treatment period (n.s.).

Efficacy

There were no statistically significant differences between treatment groups in outcome (LMAC motor, mobility, and balance scores, NIHSS, AI psychiatric, ADL, or motor scores) at any time point (day 7, 3 and 12 months). This also applied to the analysis including all patients, independently of whether absolute or transformed scores were used. The outcomes for individual patients were not predictable from the initial LMAC subscores, as shown in figure 1, or from the initial NIHSS and AI subscores (fig. 2).

Significant differences between baseline and outcome were seen when analyzing all patients as a single group ($p = 0.0184$ to $p < 0.0001$). All scores, except LMAC sensory score at 3 months, were significantly better compared to baseline ($p < 0.05$ to $p < 0.001$). Significant improvements from baseline until 12 months were seen for all scores except LMAC motor score and AI motor score ($p < 0.05$ to $p < 0.001$). The relative changes from baseline until follow-up for all individual different outcomes assessed, irrespective of treatment, are shown in figure 3. The clinical goal was defined as an improvement of 50

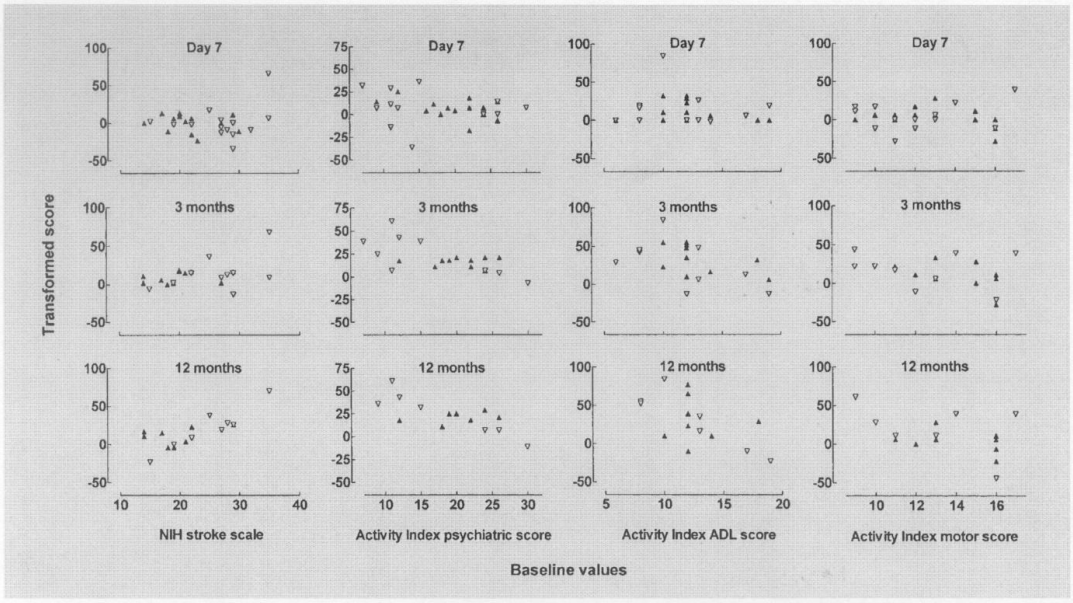

Fig. 2. Outcome, expressed as transformed scores (i.e. relative change) on day 7 and 3 and 12 months of the NIHSS, AI psychiatric, ADL and motor scores as a function of the baseline score. ▽ = STG patients; ▲ = ITG patients.

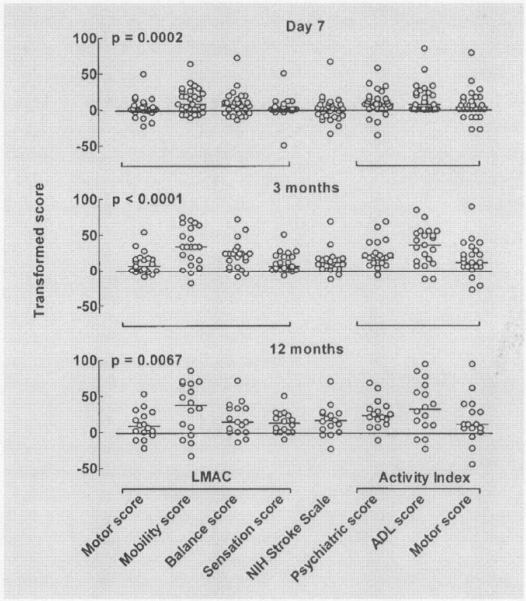

Fig. 3. Assessment of the transformed scores (i.e. relative changes) from baseline to follow-up for all individual outcomes, irrespective of treatment. Data from all outcomes at day 7 (n = 28), 3 months (n = 21) and 12 months (n = 16) are plotted for LMAC, NIHSS, AI and ADL. Medians for each outcome are indicated by small horizontal lines. Improved patients' data are plotted above the horizontal zero lines, deteriorated patients' below. p values indicate results of Friedman analysis of variance.

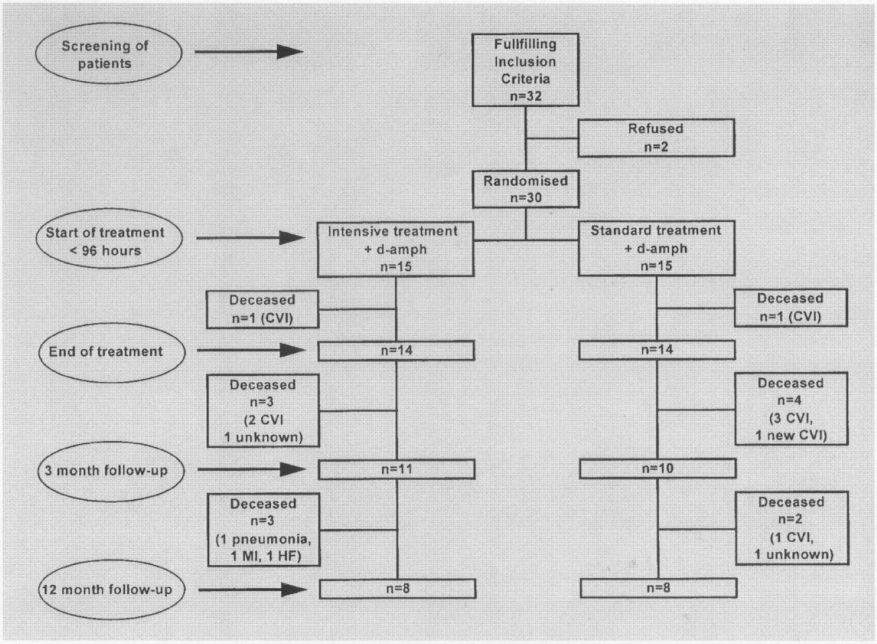

Fig. 4. Flow chart describing the patients included and randomized in the study. Causes of death are shown in parentheses. CVI = Cerebral vascular infarction; MI = myocardial infarction; HF = heart failure.

LMAC motor scores or more from baseline until follow-up at 12 months. One patient in the ITG and 3 in the STG improved >50 points on the LMAC motor score (n.s.). The fraction of patients in the present study improving >50 points was 13% (95% CI 5–31%). The number of patients needed to treat (NNT) to achieve this effect was 8, with a 95% CI of NNT(harm) 10 to NNT(beneficial) 3 [17].

Residence of living did not differ between treatment groups at 3 or 12 months (n.s.). Seven patients in each treatment group died during the 12 months of follow-up. Of the 8 patients in the ITG alive at 12 months, 4 were in nursing homes, 1 in a serviced flat and 3 patients were living at home. In the STG the corresponding numbers for the 8 patients alive were 2, 1, and 5 patients, respectively. Patients with a spouse at baseline were more likely to be living at home at 12 months, while no patient living alone at baseline lived at home at 12 months ($p = 0.033$).

Physiological Parameters

Body temperature, systolic or diastolic BP and heart rate during the course of measurements where similar in both treatment groups (n.s.).

Level of Consciousness

The median time until response in RLS85 grade after amphetamine administration was 33 min (IQR 23–59) in the ITG and 35 min (IQR 6–35) in the STG (n.s.).

Adverse Events and Mortality

During the treatment period 1 patient in each treatment group hallucinated and 1 patient in each group was diagnosed with pneumonia. One ITG and 2 STG patients showed signs of restlessness, 1 single ITG patient had insomnia, headache, sweating and rashes, and 1 other ITG patient had stomach pain. Adverse events did not differ between treatment groups (n.s.).

A flow-chart of the patients included and randomized in the trial (including causes of death) is shown in figure 4.

Table 3. Primary causes of death during treatment and follow-up period

	STG	ITG
Treatment period, days 1–5		
Number of patients	15	15
Cerebral infarct	1	1
Follow-up at 3 months		
Number of patients	14	14
Cerebral infarct	3	2
New cerebral infarct	1	0
Unknown cause	0	1
Follow-up at 12 months		
Number of patients	10	11
Cerebral infarct	1	0
Pneumonia	0	1
Myocardial infarction	0	1
Heart failure	0	1
Unknown cause	1	0

One patient in each group died during the treatment period and 6 patients in each of the groups died after treatment discontinuation (table 3). Overall mortality was 47% (95% CI 28–65%). There was no significant difference between groups regarding the causes of death. The risk for death at 12 months was higher with increased age ($p = 0.044$), in females ($p = 0.026$) and in patients living alone at baseline ($p = 0.007$). The female patients were older, with a median age of 80 (IQR 78–84) versus 72 years (IQR 67–78) in men ($p = 0.002$). Patients with a baseline NIHSS score of < 25 were more likely to be dead at 12 months than patients with an initial score of ≥ 25 ($p = 0.057$).

Discussion

An increased amount of physiotherapy in combination with d-amph treatment during the first week after cerebral infarct in a limited group of patients with severe stroke did not improve outcome. The baseline differences in favor of the ITG strengthen this conclusion. These results do, however, not exclude a benefit from physiotherapy or from an increased amount of physiotherapy at a later stage, since an increased amount of physiotherapy after 3 months resulted in an improved outcome at 12 months. The patients improved significantly over time (fig. 3), and several of the patients in both groups were able to return to their previous living. It was, however, not possible to predict outcome from the initial clinical status (fig. 1, 2). Previous observations that patients with impaired consciousness due to large cerebral infarcts are unstable in their neurological and overall status during the first week after stroke were confirmed in this study. Increased physiotherapeutic intervention should probably wait until patients are more stable. However, early mobilization [5] and passive motion to prevent contractures [18] are likely to be of value in the acute phase.

Just over half of the patients included were still alive at the 12-month follow-up. The mortality rate was not unexpectedly high, considering the proportion of total anterior circulation infarct (TACI) patients included in the study. In a large sample, the 1-year mortality rate for TACI patients was 60% [19]. In the present study we could not observe any signs of increasing lesions with early training or interference with recovery with early forced use as has been reported earlier in rat models [20, 21]. However, the 95% CI of NNT indicated that a disadvantage of early intensive treatment for this group of patients cannot be excluded.

Comorbidity, for instance old myocardial infarction, heart failure, and angina pectoris, is probably a limiting factor to intensive treatment in the acute phase, as is fatigue. In our experience, severe cognitive dysfunctions are the main limiting factors for active participation in the physiotherapy sessions in this group of patients treated with d-amph. We did not experience that patients were unable to actively take part in the training due to fatigue, most likely due to the effects of d-amph treatment. It should, however, be of further interest to investigate the effects of early intensive physiotherapy in younger patients (<65 years), who probably suffer less comorbidity. Six of the patients had suffered a previous stroke. They were ADL independent prior to the last stroke, but of course it cannot be ruled out that they had a worse prognosis than the other patients.

The aim of administering d-amph was to make the patients alert enough to be able to actively take part in the physiotherapy sessions instead of being passive receivers. The effects of amphetamine (amph) on stroke recovery in combination with physiotherapy have been evaluated in previous clinical studies [22–25]. In these studies, all patients received physiotherapy while the patients were randomized to amph or placebo. This is in contrast to the present study, where all patients received d-amph but patients were randomized to different intensities of physiotherapy. Of course, the effects of d-amph per se cannot be evaluated with this study design, nor the effects of physiotherapy per se.

During the course of the study the study protocol was changed regarding d-amph administration. In the first 10 patients, d-amph was adjusted to the individual patient's alertness. The experience from this dosing regimen was that a dose of 10 mg given twice daily with an interval of about 4 h results in adequate levels of consciousness. However, the time to response and the time the response lasted varied much between patients, which made timing of the physiotherapy during alertness more difficult.

Several patients, and especially the relatives, appreciated the alerting effect of the d-amph treatment and wanted us to continue the treatment after drug discontinuation since they noticed the improvement in the contact they (patient-relative) could get. This was an unexpected effect of treatment and not further evaluated.

Conclusion

Outcome was not affected by the increased intensity of physiotherapy, but patients and relatives responded positively to the alerting effect of d-amph. The effect of d-amph on the impaired level of consciousness should be further evaluated from a quality-of-life perspective. Further studies are also needed to evaluate the efficacy of different intensities of physiotherapy after severely disabling stroke in a more subacute and stable phase and also in younger patients in the very acute stage.

Acknowledgments

This study would not have been possible without the dedicated cooperation of the patients and their families or the physiotherapists 'out in the field'. We also gratefully acknowledge the physiotherapists at the Department of Neurology, Karolinska Hospital, especially Marie Kierkegaard and Malin Nässén, the staff at the Stroke Research Unit, especially Anita Hansson-Tyrén and Lena Lundqvist, for their assistance with data collection, the personnel at the Stroke Ward for assistance with patient management and Prof. Jan-Edvin Olsson for safety monitoring.

The trial was supported by grants from the Vårdal foundation and funds from the Karolinska Institutet (Nämnden för Vård and Forskningsnämnd Vård) and the Swedish Stroke Association.

References

1 Langhorne P, Wagenaar R, Partridge C: Physiotherapy after stroke: More is better? Physiother Res Int 1996;1:75–88.
2 Kwakkel G, Wagenaar R, Koelman T, Lankhorst G, Koetsier J: Effects of intensity of stroke rehabilitation. A research synthesis. Stroke 1997;28:1550–1556.
3 Kwakkel G, Wagenaar R, Twisk J, Lankhorst G, Koetsier J: Intensity of leg and arm training after primary middle artery stroke: A randomised controlled trial. Lancet 1999;354:191–197.
4 Paolucci S, Antonucci G, Grasso MG, Morelli D, Troisi E, Coiro P, Bragoni M: Early versus delayed inpatient stroke rehabilitation: A matched comparison conducted in Italy. Arch Phys Med Rehabil 2000;81:695–700.
5 Indredavik B, Bakke F, Slørdahl SA, Rokseth R, Håheim LL: Treatment in a combined acute and rehabilitation stroke unit. Which aspects are most important? Stroke 1999;30:917–923.
6 Gladman JRF, Sackley CM: The scope for rehabilitation in severely disabled stroke patients. Disabil Rehabil 1998;20:391–394.
7 Rang HP, Dale MM, Ritter JM: Pharmacology, ed 4. Edinburgh, Churchill Livingstone, 1999.
8 Lindmark B, Hamrin E: Evaluation of functional capacity after stroke as a basis for active intervention. Presentation of a modified chart for motor capacity assessment and its reliability. Scand J Rehab Med 1988;20:103–109.
9 Lindmark B, Hamrin E: Evaluation of functional capacity after stroke as a basis for intervention. Validation of a modified chart for motor capacity assessment. Scand J Rehab Med 1988;20:111–115.
10 Stålhammar D, Starmark J-E, Holmgren E: The reaction level scale (RLS 85). Manual and guidelines. Acta Neurochir (Wien) 1988;91:12–20.
11 Katz S, Ford A, Moskowitz R, Jackson B, Jaffe M: Studies of illness in the aged: The Index of ADL. A standardized measure of biological and psychosocial function. J Am Med Assoc 1963;185:914–919.
12 WHO: Stroke – 1989. Recommendations on stroke prevention, diagnosis, and therapy. Stroke 1989;20:1407–1431.
13 Goldstein L, Bertels C, Davis J: Interrater reliability of the NIH stroke scale. Arch Neurol 1989;46:660–662.
14 Hamrin E, Wohlin A: Evaluation of the functional capacity of stroke patients through an activity index. Scand J Rehab Med 1982;14:93–100.
15 Bamford J, Dennis M, Sandercock P, Burn J, Warlow C: The frequency, causes and timing of death within 30 days of a first stroke: The Oxfordshire Community Stroke Project. J Neurol Neurosurg Psychiatry 1990;53:824–829.
16 Gelmers HJ, Gorter K, Weerdt CJD, Wiezer HJA: A controlled trial of nimodipine in acute ischemic stroke. N Engl J Med 1988;318:203–207.
17 Altman DG: Confidence intervals for the number needed to treat. BMJ 1998;317:1309–1312.
18 Barnes M, Ward AB: The value of rehabilitation; in Barnes M, Braithwaite B, Ward A (eds): Medical Aspects of Personal Injury Litigation. London, Blackwell Science, 1997, pp 17–46.
19 Bamford J, Sandercock P, Dennis M, Burn J, Warlow C: Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337:1521–1524.
20 Risedal A, Zeng J, Johansson B: Early training may exacerbate brain damage after focal brain ischemia in the rat. J Cereb Blood Flow Metab 1999;19:997–1003.
21 Humm J, Kozlowski D, James D, Gotts J, Schallert T: Use-dependent exacerbation of brain damage occurs during an early post-lesion vulnerable period. Brain Res 1998;9:286–292.
22 Crisostomo E, Duncan P, Propst M, Dawson D, Davis J: Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients. Ann Neurol 1988;23:94–97.
23 Martinsson L, Wahlgren NG: Safety of dexamphetamine in acute ischemic stroke – a randomized, double-blind, controlled, dose-escalation trial. Stroke 2003;34:475–481.
24 Sonde L, Nordström M, Nilsson C, Lökk J, Viitanen M: A double-blind placebo-controlled study of the effects of amphetamine and physiotherapy after stroke. Cerebrovasc Dis 2001;12:253–257.
25 Walker-Batson D, Smith P, Curtis S, Unwin H, Greenlee R: Amphetamine paired with physical therapy accelerates motor recovery after stroke. Further evidence. Stroke 1995;26:2254–2259.