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ORIGINAL ARTICLE

Early *versus* delayed rehabilitation treatment in hemiplegic patients with ischemic stroke: proprioceptive or cognitive approach?

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ABSTRACT

BACKGROUND: Early/intensive mobilization may improve functional recovery after stroke but it is not clear which kind of "mobilization" is more effective. Proprioceptive neuromuscular facilitation (PNF) and cognitive therapeutic exercise (CTE) are widespread applied in post-stroke rehabilitation but their efficacy and safety have not been systematically investigated.
AIM: To compare PNF and CTE methods in a two different time setting (early versus standard approach) in order to evaluate different role of time and techniques in functional recovery after acute ischemic stroke.
DESIGN: We designed a prospectical multicenter blinded interventional study of early versus standard approach with two different methods by means of both PNF and CTE.
SETTING: A discrete stroke-dedicated area for out-of-thrombolysis patients, connected with two different comprehensive stroke centres in two different catchment areas.
POPULATION: Three hundred and forty consecutive stroke patient with first ever sub-cortical ischemic stroke in the mean cerebral artery (MCA) territory and contralateral hemiplegia admitted within 6 and 24 hours from symptoms onset.
METHODS: All patients were randomly assigned by means of a computer generated randomization sequence in blocks of 4 to one to the 4 interventional groups: early versus delayed rehabilitation programs with Kabat's schemes or Perfetti's technique. Patients in both delayed group underwent to a standard protocol in the acute phase. Primary outcome: disability at 3-12 months. Disability measures: modified Rankin Score and Barthel Index. Safety outcome: immobility-related adverse events. Secondary outcome measures: Six-Minute Walking Test, Motricity Index, Mini-Mental State Examination, Beck Depression Inventory.
RESULTS: Disability was not different between groups at 3 months but Barthel Index significantly changed between early versus delayed groups at 12 months (P=0.01). Six-Minute Walking Test (P=0.01) and Motricity Index in both upper (P=0.01) and lower limbs (P=0.001) increased in early versus delayed groups regardless rehabilitation schedule.
CONCLUSIONS: A time-dependent effect of rehabilitation on post stroke motor recovery was observed, particularly in lower limb improvement. According to our results, rehabilitation technique seems not to affect long term motor recovery.
CLINICAL REHABILITATION IMPACT: These results show a significant effect of time but not of technique that may impact the decision making in the acute phase of care.

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Key words: Brain ischemia - Cerebral stroke - Subacute care - Rehabilitation - Proprioceptive neuromuscular facilitation (PNF) stretching - Cognitive therapy.

Although ischemic stroke represents one of the leading cause of disability worldwide, the optimal schedule and content of rehabilitation in the acute phase of care is still undefined.[1] Recent results of the A Very Early Rehabilitation Trial (AVERT) suggest that early and intensive mobilization may improve functional recovery and accelerate the return to unassisted walking.[2, 3] However, the question about which kind of "mobilization" remain unsolved. Beyond the relevant results of AVERT, only few randomised controlled trials on the efficacy and safety of the various rehabilitation techniques have been published with controversial results because of the small samples and/or the heterogeneity of the case series.[4, 5] Proprioceptive neuromuscular facilitation (PNF) and cognitive therapeutic exercise (CTE) have been widespread applied in post-stroke rehabilitation until today but reports on their efficacy and safety are still not well recognized.[6-11] First developed by professor Hermann Kabat and physical therapist Margaret Knott, PNF is a dynamic approach to the evaluation and treatment of neuromuscular dysfunction that take into account the basic neurophysiologic and kynesiologic principles of the sensory-motor system.[12, 13] By selecting motor elements and developmental components of complex motor patterns, the emphasis is placed upon selective re-education of motor behaviour through training the fundamental skills of trunk and limbs control, stability and coordination. Technically, specific diagonal and spiral motor patterns against an appropriate resistance was sequentially used in order to facilitate and modulate stretch reflex, irradiation and other proprioceptive response toward a motor response in a proximal-distal perspective and in different postural conditions.[14] Conversely, CTE was based on Professor Carlo Perfetti's intuition that movements is a more complex interaction modality with environment that depends on integration of several cognitive functions.[15] Giving a straight relationship between muscular recruitment and perception, motor recovery has been as a consequence considered a learning process in pathological conditions.[16] This method consists in a 4-phase treatment: conversation upon motivation, relaxation through passive mobilization, guided passive mobilization and active mobilization. The third and fourth phases take place with the help of some devices such as soft and hard blocks or panels in order to ensure a correct motor performance.[15, 16] Despite the reliability of theoretical background and basic principles of both techniques, to date their real effect on post-stroke recovery has never been addressed.

The aim of this study was to compare PNF and CTE methods in a two different time setting (early *versus* standard approach) in order to evaluate different role of time and techniques in functional recovery after acute ischemic stroke with hemiplegia. Particularly, we tested the hypothesis that early intervention with specific training modalities such as PNF and CTE positively affects clinical outcome than simple mobilization. We further evaluated whether there are possible differences between the two rehabilitation methods in the long term follow-up.

Materials and methods

The study was approved from the Scientific/Ethical Committees of Neurological Centre of Latium, in line with national legislation and the Declaration of Helsinki. Before written informed consent, all the participants were learned about background and objective of the study, methodologies and the opportunity of withdraw the study at any time.

Design

We designed a prospectical multicenter blinded interventional study of early *versus* standard approach with two different methods by means of both PNF and CTE (Figure 1).

Participants

Between January 2008 and January 2013, we recruited all consecutive patient with first ever sub-cortical ischemic stroke in the mean cerebral artery (MCA) territory and contralateral hemiplegia admitted 6 to

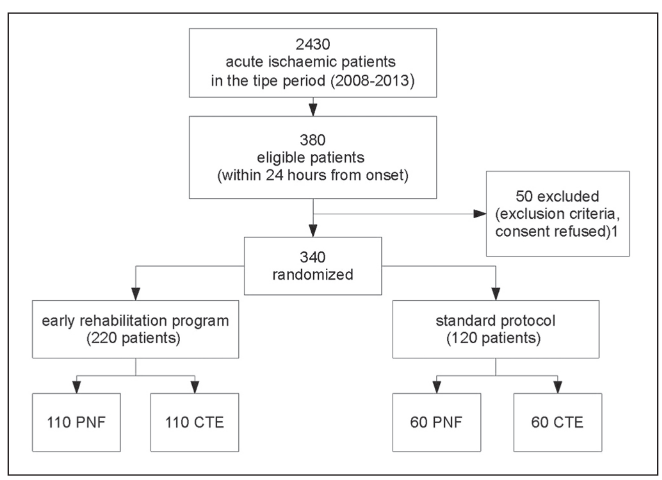

Figure 1.—Study design.

24 hours from symptoms onset to the Operative Unit of Neurology of the Department of Clinical Neurosciences, Neurological Centre of Latium (NCL) and to the Section of Neurology of the Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome – Policlinico Umberto I. A discrete stroke-dedicated area for out-of-thrombolysis patients was present in both hospital wards, connected with two different comprehensive stroke centres in two different catchment areas. An amount of almost 120 acute ischemic stroke patients per year were managed in stroke-dedicated beds of the NCL Operative Unit of Neurology and almost 300 patients per year in the Section of Neurology of the Department of Medical and Surgical Sciences and Biotechnologies. All subjects were excluded from thrombolysis protocols because of inadequate time window and transferred to both acute care wards. Exclusion criteria for study protocol were: Neurological Institute of Health Stroke Scale (NIHSS) <2, aphasia, visual disturbances, neglect and/or other spatial representation defects, disorientation and/or confusional state at onset, ongoing seizures, Mini-Mental State Examination (MMSE) <26, cardiovascular instability defined as uncontrolled hypertension, high frequency arrhythmias, congestive heart failure and concomitant or incident myocardial infarction, neurological instability (worsening and improving stroke), incident haemorrhagic transformation, previous diagnosis of other neurological disease with sensory-motor and cognitive symptoms, chronic inflammatory disease with arthritis and/or neuropathies, psychiatric diseases, amputation, fractures, neoplasms and all the psychological and social causes of unsubscribed informed consent. All patients were stratified for age, sex, cardiovascular risk factors, stroke aetiology according to criteria of Trial of ORG 10172 Acute Stroke Treatment (TOAST),[17] deficit's side, sensitive involvement and National Institutes of Health Stroke Scale (NIHSS) score.

Randomization

Two expert neurologists enrolled the patients at the admission according to inclusion/exclusion criteria. After informed consent, a physical therapists' coordinator randomly assigned all patients by means of a computer generated randomization sequence in blocks of 4 to one in the subsequent 3 groups: early (within 24 hours) rehabilitation program by means of PNF (e-PNF); early (within 24 hours) rehabilitation program by means of CTE (e-CTE); standard rehabilitation schedule (4-days after admission). Patients in standard protocol were further randomized to PNF or CTE extensive treatment regimen (delayed PNF treatment [dPNF] and delayed CTE treatment [dCTE]). The final analysis was conducted upon 4 treatment groups: ePNF *vs.* dPNF, and eCTE *vs.* dCTE.

Intervention

Early rehabilitation programs consist of a daily bedside and out-of-bed 45-minutes intervention with proximal joints passive/active mobilization according to Kabat's schemes in PNF group with subsequent postural alignment and in bed and out of bed positioning (for further 15 minutes) or with guided and passive/active movements during attention task according to Perfetti's technique in the CTE group with subsequent postural alignment and positioning (for further 15 minutes). Thereafter, the specific rehabilitation program with PNF or CTE continued daily (2.15 hours/day) in an intensive rehabilitation unit from the 5th to 60th day after discharge (14 weeks) and after in a day-service setting (1.30 hours/day for 5 days/week) for a mean duration of 38 weeks until the last follow-up according to national legislation. Patients in standard protocol received only postural alignment and in bed and out of bed positioning (for a total duration of 60 minutes in order to resemble the duration of early intervention treatment) during first 4 days after symptom onset and was subsequently transferred in an intensive rehabilitation unit from the 5th to 60th day after discharge where they were further randomized to PNF or CTE treatment regimen (2.15 hours/day for 14 weeks). Thus, they continued the same rehabilitation program in a day-service regimen until the last follow-up (1.30 hours/day for 5 days/week, mean duration of 38 weeks) according to national legislation. All physical therapists were specifically trained for treatment protocols and were unaware of clinical features (including type and subtype of stroke, cardiovascular risk factors, scale grading) and study objective. A physical therapists' coordinator monitored the adherence to and the homogeneity of treatment protocol in all settings.

Outcome measurement

Primary outcome measures were disability grade at 3 and 12 months after stroke. Disability was measured by means of modified Rankin Score (mRS) and Barthel Index (BI). mRS is a commonly used and simple scale for assessing functional outcome in patients with stroke that measures dependence after stroke by categorizing the disability in 6 grades, from 0 to 5, with 0 corresponding to no symptoms and 5 corresponding to severe disability.[18, 19] BI is a consistent disability scale that measures the patient's performance in 10 activities of daily life. The items can be divided into a group that is related to self-care (feeding, grooming, bathing, dressing, bowel and bladder care and toilet use) and a group related to mobility (ambulation, transfers and stair climbing) with a high score of 100 for fully independent patients and a lowest score of 0, representing a totally dependent bedridden state.[20] The safety outcome was immobility-related adverse events (IAEs) at 3 and 12 months post-stroke. Particularly, we clinically addressed the possible onset of the subsequent AE: pressure sores, shoulder pain syndrome, general pain, deep venous thrombosis and infections (pneumonia, urinary tract and bladder infection, other nosocomial infections). Secondary outcome measures were assessed by means of Six-Minute Walking Test (6MWT), Motricity Index (MI), MMSE and Beck Depression Inventory (BDI). 6MWT is a timed walk test first developed for patients with pulmonary disease which measures the distance covered in the specific time interval of 6 minutes and provides a continuous-scale predictive assessment of gait recovery following stroke.[21, 22] MI is a feasible, simple and brief measure of general motor function in upper and lower extremities that can predict the poststroke mobility outcomes.[23] MMSE is a reliable clinician-administered verbal and pencil-and-paper test covering orientation and attention, memory, language and praxis.[24] After correction for age and educational level, the sum of responses provides a rapid estimation of cognitive efficiency and a useful grading of cognitive performance (normal score range: 25-30 out of 30; mild cognitive impairment score range: 21-24; moderate deficit score range: 10-20; severe cognitive impairment score: <10).[25] BDI is a 21-item self-rating mood scale that has been proved to be acceptable screening instruments for post-stroke depression (cut-off values: 14 for mild depression, 20 for moderate depression and 29 for severe depression; maximum score: 63).[26, 27]

All scales were administered at baseline and at 3 and 12 months by two different neurologists who were blinded for treatment.

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Science (SPSS) Version 16. Significance level was set at P=0.05. Descriptive statistics were used to report participant characteristics at baseline. To evaluate the efficacy of both treatment schedule and methods, we performed an intention-to-treat analysis, considering early vs delayed treatment regimens. Dead patients were not excluded and were considered as missing information at follow-up evaluation. Consequently, differences were evaluating according the following groups: early PNF *vs.* delayed PNF and early CTE vs delayed CTE. All values are expressed as median and interquartile range (IQR), mean ± standard deviation (SD), or interval, as appropriate. Statistical differences over time of the scores were analyzed using the univariate analysis of the variance (ANOVA) for repeated measures. Multivariable analyses were used to account for demographic and stroke-related factors known to influence walking and functional independence (age, sex, stroke severity, cardiovascular risk factors) and for treatment effect assessment by means of relative risk (RR) calculation. A cut off value of 60 for BI score was settled in order to define dependence outcome.

Results

340 out of 380 stroke patients were eligible for the study according to inclusion and exclusion criteria and were randomized in the 4 final groups. Clinical and demographic data are shown in Table I. At 3 months follow-up, 38 patients (11.2%) were lost because of death (13 patients) and lack of compliance (25 patients). Further 9 (2.6%) patients were lost at 12 months follow-up because of death (3 patients), recurrence of stroke (4 patients) and lack of compliance (2 patients). The proportion of deaths was not different between groups.

Primary outcome measures at 3 months follow-up are shown in Table II. Both mRS and BI was signifi-

TABLE I.—*Baseline clinical and demographic characteristics of recruited patients.*

	e-PNF N.=110	d-PNF N.=60	e-CTE N.=110	d-CTE N.=60	P
Age	64±14	63±15	63±12	64±13	NS
Male sex	80 (72%)	42 (71%)	81 (73%)	43 (72%)	NS
Time to randomization (hours)	17±2	17±3	18±1	17±1	NS
Left-side ischemic lesion	74 (67%)	41 (69%)	75 (68%)	40 (66%)	NS
Sensitive deficits	36 (33%)	19 (32%)	34 (31%)	20 (33%)	NS
Dysarthria	41 (37%)	23 (38%)	40 (36%)	22 (37%)	NS
2<NIHSS<7	13 (12%)	6 (11%)	11 (10%)	7 (12%)	NS
7<NIHSS<14	83 (75%)	46 (76%)	86 (78%)	45 (75%)	NS
NIHSS>14	14 (13%)	8 (13%)	13 (12%)	8 (13%)	NS
Cardioembolism	63 (57%)	35 (58%)	63 (57%)	34 (56%)	NS
Atherosclerosis	39 (35%)	19 (32%)	38 (34%)	21 (35%)	NS
Unknown	8 (7%)	6 (10%)	9 (8%)	5 (9%)	NS
Hypertension	77 (70%)	42 (70%)	79 (72%)	43 (71%)	NS
Diabetes	54 (49%)	30 (50%)	51 (46%)	29 (48%)	NS
Atrial fibrillation	48 (44%)	28 (47%)	49 (44%)	27 (45%)	NS
Current smoke	39 (35%)	20 (34%)	37 (34%)	22 (37%)	NS
Previous TIA	32 (29%)	18 (30%)	32 (29%)	17 (28%)	NS
MMSE	27.6±1.2	27.4±1.6	27.5±1.5	27.8±1.1	NS
BDI	13±2	12±3	13±3	13±1	NS
Discharge mRS (median)	4 (IQR 1)	4 (IQR 1)	4 (IQR 1)	4 (IQR 1)	NS
Discharge BI (mean)	46±8	47±3	45±8	46±7	NS

TABLE II.—*Primary outcome measures at 3-month follow-up.*

		e-PNF (N.=110)	d-PNF (N.=60)	P	e-CTE (N.=110)	d-CTE (N.=60)	P
mRS - median value (IQR)	Baseline	4±1	4±1	–	4±1	4±1	–
	3-month	3±1	3±1	–	3±1	3±1	–
	P	0.01	0.01		0.01	0.01	
BI - mean value ±SD	Baseline	46±8	47±3	–	45±8	46±7	–
	3-month	63±6	62±9	0.492	62±7	63±5	0.426
	P	0.01	0.01		0.01	0.01	

TABLE III.—*Incidence of immobility-related adverse events at 3-month follow-up*

	e-PNF (N.=110)	d-PNF (N.=60)	P	e-CTE (N.=110)	d-CTE (N.=60)	P
All IAEs	15 (13.6%)	11 (18.3%)	0.17	16 (14.5%)	13 (21.6%)	0.36
Pressure sores	6 (5.4%)	5 (8.3%)	0.26	5 (4.5%)	5 (8.3%)	0.48
Shoulder pain syndrome	1 (0.9%)	4 (6.6%)	0.035	2 (1.8%)	5 (8.3%)	0.031
DVT	4 (3.6%)	1 (1.6%)	0.21	5 (4.5%)	1 (1.6%)	0.26
Infections	4 (3.6%)	1 (1.6%)	–	4 (3.6%)	2 (3.3%)	0.72

cantly different within groups (P=0.01, respectively). No significant differences have been observed between groups. Incidence of all IAEs at 3 months were slightly but not significantly increased in both delayed groups than in two early groups (Table III). Incidence of shoulder pain syndrome was higher in both delayed treatment groups than in the early treatment groups and the difference was slightly significant (respectively, P=0.035 in the PNF groups and P=0.031 in the ECT groups).

Primary outcome measures at 12 months follow-up are shown in Table IV. Both mRS and BI was significantly different within all the groups (P=0.01). BI was stly higher in both early treatment groups than in delayed treatment groups, without differences between the two rehabilitation techniques.

A significant improvement of secondary outcome measures has been observed in all groups across the time with a statistically significant difference at 12 months

TABLE IV.—*Primary outcome measures at 12-month follow-up.*

		e-PNF (N.=110)	d-PNF (N.=60)	P	e-CTE (N.=110)	d-CTE (N.=60)	P
mRS - median value (IQR)	Baseline	4±1	4±1	–	4±1	4±1	–
	3-month	2±1	2±1	–	2±1	2±1	–
	P	0.01	0.01		0.01	0.01	
BI - mean value ±SD	Baseline	46±8	47±3	–	45±8	46±7	–
	3-month	89±2	71±9	0.02	86±7	73±5	0.02
	P	0.01	0.01		0.01	0.01	

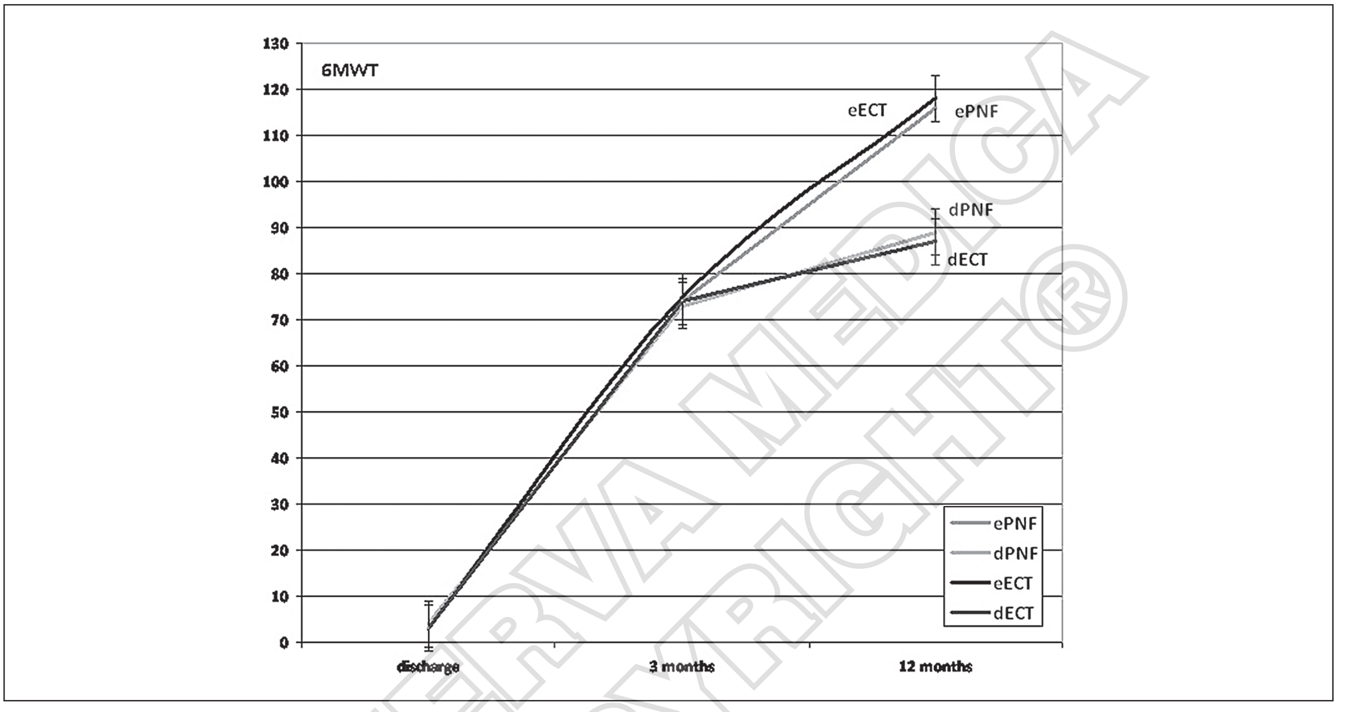

Figure 2.—Time course of 6MWT score.

in 6MWT score between early treatment strategies and delayed treatment protocols (P=0.01) and in MI score in both upper and lower limbs between early treatment strategies and delayed treatment protocols (P=0.01 and P=0.001 respectively) without any significant differences according to post acute rehabilitation program (Figure 2, 3 and 4). MMSE and BDI score were quite similar among all groups.

Lower scores at BI at 12 months follow-up (<60) was independently associated with higher NIHSS at onset (RR: 1.89, 95% CI 1.03-4.86, P=0.01), older age (RR: 2.09, 95% CI 1.11-4.98, P=0.01), diabetes (RR: 2.16, 95% CI 1.21-5.76, P=0.002) and exposure to SP (RR: 1.82, 95% CI 0.96-7.65, P=0.01). Only exposure to SP significantly increased the risk of IAEs (RR: 1.78, 95% CI 0.81-6.98, P=0.02). The presence of sensitive deficits did not affect long-term BI scores.

Discussion

The main result of this study is the time-dependent effect of rehabilitation on post-stroke motor recovery that seems irrespective of the rehabilitation method. Although we did not observe significant differences at short-term follow-up as in some AVERT results, functional recovery was considerably better in patients who underwent early rehabilitation programs at long-term follow-up (12 months).[2] Independently from baseline characteristics and rehabilitation methods, this effect was evident on

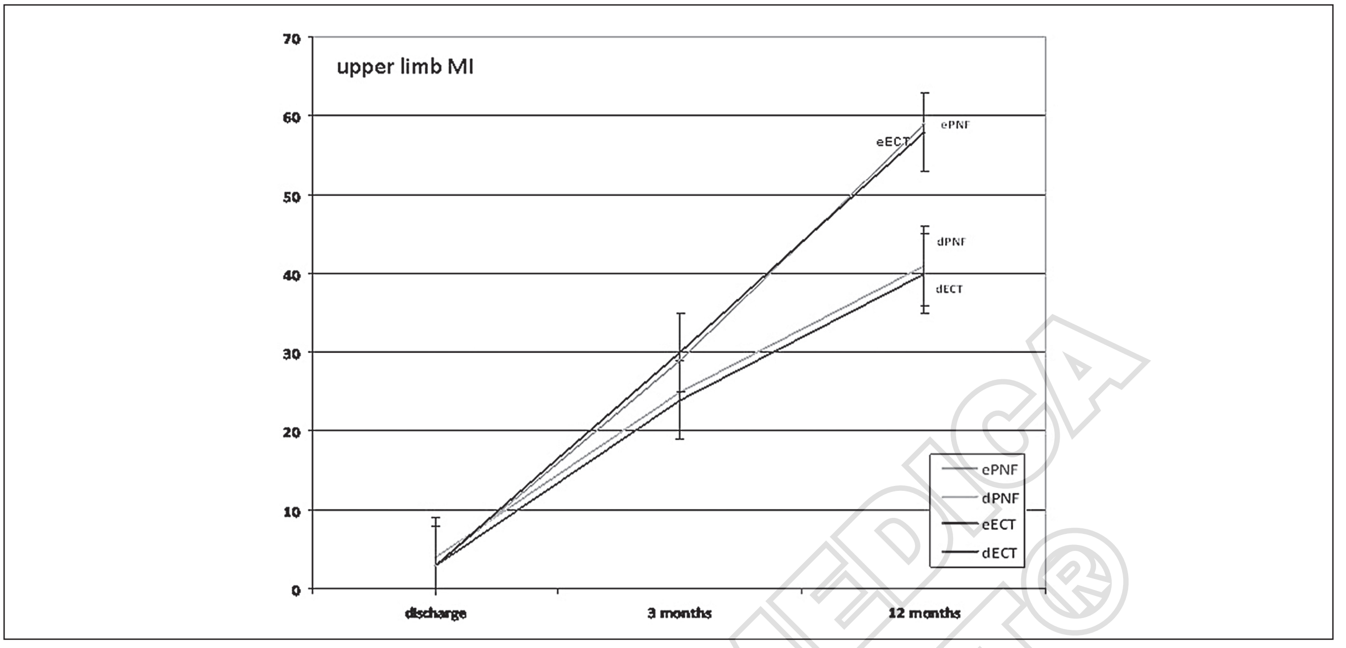

Figure 3.—Time course of upper limb MI score.

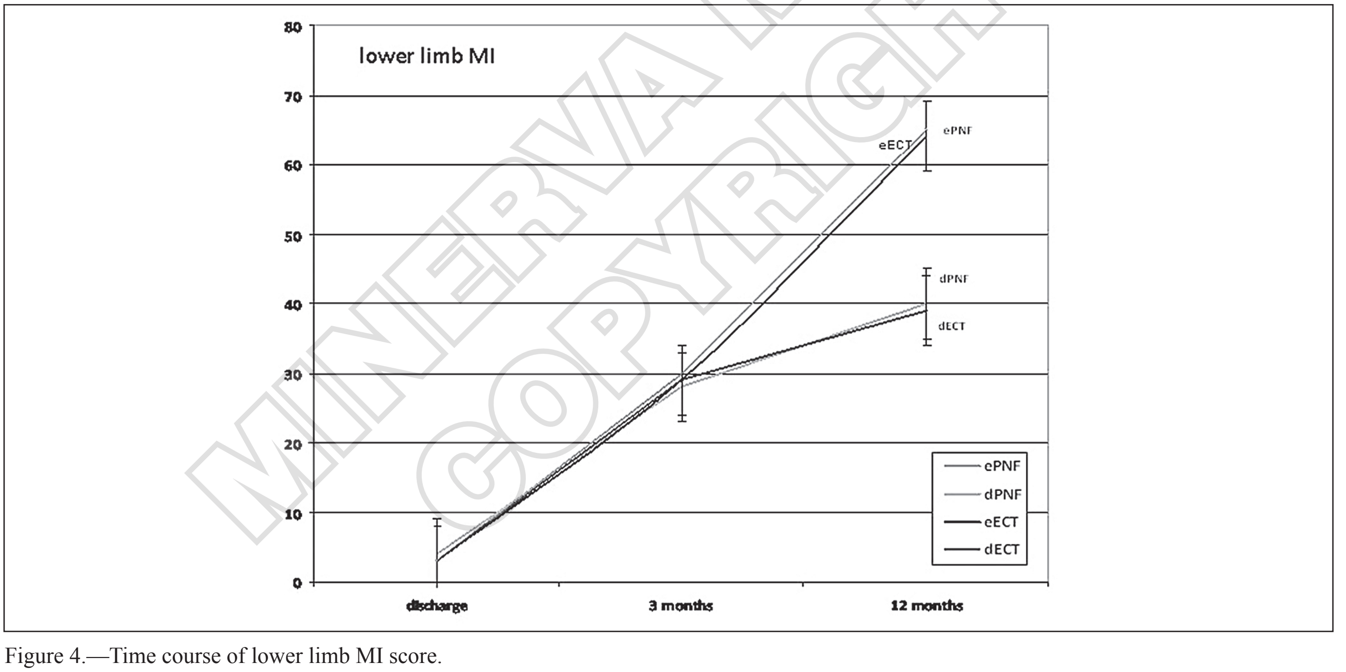

Figure 4.—Time course of lower limb MI score.

both disability measures and motor assessment scales. Moreover, early intervention seems to be unrelated to increasing death and/or morbidity and reduce the risk of adverse events due to immobility, particularly the shoulder pain syndrome. The between-groups differences in primary outcome measures account for a significant impact of time-to-rehabilitation on daily living activities that was more evident in younger patients with lower

NIHSS score at the onset and without diabetes. Stroke severity, age and diabetes were previously associated to an increased odd of a worst functional recovery because of their role in increasing the prevalence of stroke-related complication.[28, 29] In this study, age, NIHSS at onset and a history of diabetes increased the risk of a lower BI and mRS but not of immobility-dependent complications that seems to be independently related only to a delayed rehabilitation program. Although an influence of older age, neurological and metabolic status on functional recovery could be hypotized, some limitations of this study may explain these results. First of all, the sample was highly selected in order to obtain a homogeneous population with subcortical motor stroke that may not resemble the common stroke patients. A further size effect and the high prevalence of patients with moderate stroke severity may account for a lower prevalence of IAEs in older, diabetic and more disabled patients. Beyond the global effect on functional recovery, an early rehabilitation program significantly improved secondary neurological outcome measures such as walking independency and motricity indexes. In this perspective, the days to walk were not measured in this study because of different concept of time-to-walk between the two rehabilitation methods that reduced clinical value of this parameter.[14, 16] Nevertheless, a better walking performance was already evident at 3-month follow-up in early than in delayed treated patients and seems to be associated to a better motricity of the lower limb. This effect becomes more pronounced at 12-months, independently from age, sex and clinical characteristics at baseline. The walking findings indicate that an earlier and intensive mobilization after stroke can accelerate the recovery of some meaningful physical outcomes. Differently from AVERT trial, 12-months activities of daily living were significantly higher in both early treatment groups. Despite the well-known weakness of the BI in discriminating between people at moderate *versus* high levels of function, the significant improves of the both primary outcome measures account for a better performance at 12-months follow-up that may depend on enhanced neurological outcomes.[20] Indeed, an improved MI may contribute to the re-gain of some abilities such as eating, dressing and washing. Moreover, BI score is influenced by walking capacities that are significantly improved in the early intervention groups. A potential explanation for the better return to walking is that both PNF and CTE improved motor performance by earlier and more frequent out-of-bed experiences, also minimizing the muscle loss, immobility-related short and long-term complication and deterioration of neuropsychiatric functioning.[30] Dose-related effectiveness of early rehabilitation is far beyond the aims of this study. In order to reduce confounding factors, the timing of both early intervention and standard mobilization was settled on daily 45 minutes in the acute stage that was similar to AVERT-Phase II trial and to the experience of the Trondheim stroke unit in Norway.[2, 3, 31-33] A higher “dosage” was used in all groups for out-of-bed treatment in intensive and extensive programs in line with national legislation. Further analysis on outcome data, independently for time-to-rehabilitation, did not shown any differences between PNF and CTE in terms of global functional recovery and ability to walk. The observed improvement of MI accounts for the effectiveness of both methods on task performance and quality of movements. Kabat’s approach may induce a recovery of motor function by reducing both learned non-use phenomenon and pathological reflexes or neuromuscular responses.[6, 13] The main goal of reinforcing coordinated link between proximal-distal joints and maintaining an adequate muscular length-straight relationship may bring on a dynamic motor response that was based on stability of proximal elements.[34] Thus, early and repetitive motor reinforcement in different postural conditions would induce a correct relation between trunk stability and limb dynamicity. On the other hand, Perfetti’s method takes advantage of perception phenomena in order to restore an adequate motor response. The guided exercise may integrate the insight of movement to task-oriented movement that could improve the execution of certain tasks by means of the integration of sensory-motor response as a result of a complex cognitive process. In both cases, a motor re-learning could be hypnotized.[10]

Conclusions

Our data support the idea that any intervention that accelerates functional recovery is related to a better outcome. An earlier and more intensive rehabilitation program in the acute phase of stroke is related to a good recovery of walking and functional independence status according to the concept that “time is brain recovery”. Both the neurodevelopmental and the cognitive approaches seem to be safe and effective in ameliorate neuromotor performances and activities of daily living.

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