Milan, 6th August 2013

Effectiveness of mirror therapy in upper limb rehabilitation early after stroke

Introduction

Stroke is one of the major causes of disability in occidental world (1-3) and upper limb paresis is among the most disabling consequences (4). Intensive rehabilitation programs, especially if started early, may promote upper limb functional recovery (5-6) and cortical reorganization (7-9). However, when the sensory-motor deficit is severe, intensive rehabilitation programs are difficult to bring to a successful conclusion. The reduction of the patient's active motor participation alters the cortical representation of the involved limb and interferes with the recovery induced by neurorehabilitation. A rehabilitation program, based on the stimulation of the mirror neuron system, could provide a valid way to deal with and partially overcome these limits (9-13).

Mirror neurons, in particular those of the parietal-frontal network, are activated not only when a movement is performed, but also by the act of observing a motor action performed by others (14). It has been noticed that the activation of the premotor cerebral areas determined by the observation of a motor act, can foster a facilitating effect on the activation of the brain areas responsible for the execution of the same movement (14-17).

Mirror Therapy (MT) is a rehabilitation approach that uses a mirror placed aside the patient's trunk, hiding the paretic upper limb and reflecting the contralateral healthy arm. In this way, moving one half of the body and looking into the mirror, it is possible to have the illusion that gestures are carried out by the contralateral half, covered and not visible. Specifically, in pathological conditions, such as hemiparesis, the mirror covers the injured limb and reflects the sound one. In this way, when moving the sound hand, the patient sees his/her impaired limb moving. MT was first tested in phantom pain treatment with excellent results (18).

Subsequently, thanks also to the new scientific assumptions offered by the discovery of mirror neurons, attempts were made to apply MT also in post-stroke neurorehabilitation, both for upper limb motor recovery and for the treatment of spatial neglect (19-25).
The studies conducted so far have yielded interesting results, however only a few works have been performed with a significant number of participants and with appropriate experimental designs. Among the most important works, Yavuzer and colleagues (21) completed a study on 40 post-stroke patients in the subacute phase (within 12 months after stroke), reporting a better recovery on upper limb function in patients treated with MT compared to untreated patients. In another randomized trial involving 36 patients, Dhole and colleagues (19) showed that even in the post-acute phase (starting from 6 weeks after stroke), MT seemed to induce a greater recovery of upper limb function in patients with severe hemiparesis. In this study, no effects of MT on spatial neglect, nor an impact of the presence of spatial neglect on motor recovery using MT were found. However, according to Ramachadran and colleagues (20) and to our working group (21), spatial neglect can have an impact on the ability to observe a body image reflected into a mirror and, consequently, on the correct execution of a MT protocol.

In conclusion, although the results obtained so far using MT are encouraging, an optimal MT protocol for patients with hemiparesis, who can present or not spatial neglect, is not available. Furthermore, although there are many evidences regarding the efficacy of starting neurorehabilitation immediately after a cerebral accident, no studies on MT have been performed in the early post-acute phase.

Aim

The aim of the present study is to demonstrate the efficacy of MT in a selected group of patients and to propose an optimal protocol for treatment specifically designed for this clinical population. Thanks to a targeted recruitment and to the accurate control of various clinical-instrumental variables that can play a decisive role in the effectiveness of a rehabilitative therapy, it will be possible to demonstrate the efficacy of MT in the functional recovery of the hemiplegic patient.
The primary objective focuses on the motor recovery of the upper limb. We also propose as a secondary objective to demonstrate that MT can promote a global functional improvement of the patient in daily living activities.

Materials and methods

Trial design

Single-blind, randomized controlled trial with the aim of evaluating the effect of MT, added to a standard neurorehabilitation protocol, in a selected population of post-acute patients.

Participants

We will consecutively recruite all post-stroke patients admitted to our neurorehabilitation clinic.

Inclusion criteria are as follows:

- Ischemic/hemorrhagic stroke, which determines hemiparesis or hemiplegia.
- Time post onset no longer than 4 weeks
- Age between 18 and 80 years.
- First stroke or stroke recurrence without previous functionally evident motor outcomes.
- MMSE (Mini Mental State Examination) ≥ 24 (29-30)
- Absence of global aphasia. Comprehension deficit, when present, should be minimal, mild or moderate (Token Test score, Aachener Aphasie Test < 40) (33-34)
- Spatial neglect (can be present or not)
- Ideomotor apraxia (can be present or not)
- No other pathologies (e.g., upper limb joint-muscle) that could interfere with motor recovery
- No other seriously invalidating clinical conditions (cardiopathies, bronco pneumopathies)

The recruitment will take place according to the following specifications: during the daily clinical briefing of each Operative Unit of our Centre, physicians inform the physiotherapist coordinators about the patients admitted for post-stroke hemiparesis and coordinators, in turn, inform the physician and the physiotherapists responsible for the study.

1- Clinical Screening

The Medical Specialist in charge of the project will: (i) verify that the patients accomplish with the clinical and neuroimaging inclusion criteria in order to access the study; (ii) obtain the informed consent signed;

(iii) fill in the registration form and (iv) refer the patient to the neuropsychologist responsible for the project.

2- Neuropsychological screening with integrated cognitive evaluation

The neuropsychologist will perform a deep cognitive evaluation investigating: global cognitive functioning (Mini Mental State Examination) (29-30); presence of aphasia (Token Test, Aachener Aphasie Test, 33-34; oral naming, Batteria per l'Analisi dei Deficit Afasici, 35); spatial neglect (line and bell cancellation, 31-32; , 38; complex figure copy 39, 40; clock drawing test, 40; test for personal neglect, 41); ideomotor apraxia (movement imitation test, 36), and mood disorders (Hamilton Depression Rating Scale, 37). Patients will be randomly assigned to the MT or control group (CT).

Interventions

Treatment:

During the study period and regardless of randomization, patients will perform a standard rehabilitation program consisting of neuromotor therapy, physics, occupational therapy, speech therapy and cognitive rehabilitation, according to the patient's clinical needs.

The patients included in the MT group will complete a structured protocol lasting for 45 minutes a day, for a minimum of 30 days. Patients will have to execute movements of increasing complexity using the non-paretic upper limb:

Simple movements - with the pronated forearm: flexion-extension of the elbow, flexion-extension of the wrist, flexion of the wrist with proximal and distal extended fingers, opening and closing of the fist, finger tapping;

Complex movements- with the elbow flexed at 45° or flexed and lifted from the table: for example flexion-extension of the fingers, closing of the fist, finger tapping, flexion of the forearm on the arm with simultaneous prone-supination of the forearm itself;

Functional movements - that consist in taking, lifting or moving objects of variable shape and weight: a pen, a plastic cup, a full aluminum can, a playing card, a tennis ball, a ball, a coin, all according to the instructions of the operator.

During the execution of the exercises the patients have to look at the movements performed in the mirror. At the same time they instinctively should imagine that they are executing those movements with the paretic upper limb.

Patients included in the Control Therapy (CT) will perform for 45 minutes a day, for a minimum of 30 days a protocol of exercises similar to that performed by the MT patients, but with a non-reflecting surface, in place of the mirror.

The physiotherapist will monitor the patients' level of attention during the course of the MT (concentration in looking in the mirror) giving a score between 0 (no attention) and 2 (maximum attention). If in the first two weeks of treatment (or 10 sessions) the total score of the attention scale is < 6, the patient will exit the

trial, unless there will be a clear trend of improvement in attention levels in the last sessions. Records of patients that will not show a sufficient level of sustained attention during therapy will be consider in the analysis of possible factors that affect the efficacy of MT rehabilitation.
The mirror intervention both for the study group and for the control group will be in add-on modality and standard rehabilitation activity will be regularly plan.

Outcome measures

Functional evaluation

Four physiotherapists, after performing a joint training of 2 months, will deal alternatively and on randomized assignment with the functional assessment or treatment. Therefore, the physiotherapist who deals with the treatment will not be the same that will evaluate the patient both at T0 (baseline) and at T1 (after treatment).

The functional evaluation performed at T0 and T1 will be based on the following scales, which will constitute the outcome measures.

- Fugl-Meyer Asessment (FMA): a specific complex scale for stroke. In our study, we will use a part of the scale, specifically the 33 items used to evaluate motor function, coordination, somatic sensitivity and excursion of the joints of the upper limb (27). The administration of the scale will involve the execution of gestures with increasing complexity, pure or finalized engines. The score is based on the direct observation of the patient's performance in relation to the latter's ability to complete the item (score 2), to partially execute it (score 1), not to do it at all (score 0). The final score is given by the sum of the scores of all the items (from 0 to 66). The administration of the scale takes 35-40 minutes.

- Action Research Arm Test (ARAT): scale for the study of the functionality of the upper limb. It consists of 19 items grouped into 4 subtests (28). The items allow analysing both simple and finalized motor acts with variable difficulty. The score is based on the direct observation of the patient's performance: from the ability to complete the task on time (score 3), to the possibility of completing the task in a longer time than expected (score 2), to perform the task in an incomplete way (score 1), up to the total impossibility to complete the task (score 0). The score can therefore be between 57 and 0. The administration of the scale takes 10 minutes.

- FIM (Functional Independent Measure): 18-voice scale that analyses different activities of daily life. The score in each item varies from 1 (complete dependence) to 7 (complete self-sufficiency), thus offering a cumulative score and a score profile in the various items. In this way the degree of self-sufficiency in performing elementary functional activities such as personal care, sphincter control, mobility, locomotion (motor area) and communication and social interaction (cognitive area) is measured. The administration of this scale will take about 10 minutes.

The primary outcome consists in the motor recovery of the upper limb, evaluated using the Fugl-Meyer scale (27). Secondary outcome are a specific physiatrist scale for the upper limb, the Action Research Arm Test (ARAT, 28), and a generic functional scale, the Functional Independent Measure (FIM, 26).

Sample size and randomization

Data analysis will be performed by a biostatistics, blind with respect to the treatments performed. The sample size will be constituted of 40 patients (randomized in 20 for the experimental group, MT, and 20 for the control group, CT).

Randomization will be performed according to the block randomization procedure, which allows to balance the quantitative asymmetry of the patients assigned to the two groups. The "block" is a sequence of the randomization list, which contains the same number of patients to be assigned to patients treated with MT and to controls (CT). For example, a block of 4 generates six different sequences, each of which assigns two patients to the MT group and two to the CT: MT-MT-CT-CT, MT-CT-MT-CT, CT-CT-MT-MT, CT-MT-CT-MT, MT-CT-CT-MT, CT-MT-MT-CT. Thanks to the progressive balanced assignment, block randomization guarantees a similar number of patients enrolled in the two groups.

Statistical analysis

It was calculated to have a power of 0.80 and to demonstrate an effect size of .90 (difference between the two treatments equal to 90% of the variability of the phenomenon) to a Student t test for independent data, performed at a significance level of 0.05 (two-tailed test).

Considering that the model of the analysis of covariance (ANCOVA), used for inferential analysis, has a greater expected efficiency (less residual variability) of at least 30%, it can be considered that the aforementioned sample size will allow to highlight also an effect size of around 0.7. The variables will be described by mean, median, standard deviation (quantitative variables) and absolute frequency and relative percentage (qualitative variables). Furthermore, for the differences between before and after treatment for the variables detected for each group, the 95% confidence intervals will be calculated. The analysis of the main and secondary variables will be carried out by analyzing the covariance (satisfied assumptions) with the base value as a covariate, the treatment group as a factor and inserting the variables relevant to the response to the treatment, which presented an unsatisfactory balance between the two groups at baseline. The effectiveness of the therapeutic intervention will be reported also in terms of effect size (difference between the variations of the scores in each group in relation to the total variance).

Expected results

The functional outcomes of stroke and the pathophysiological characteristics of the patients affected can be extremely variable. The standardization of patient groups is an extremely delicate moment in the design of efficacy studies of rehabilitation treatments. We believe that in this study a scrupulous standardization of the sample, the process of randomization, the separation of information between those responsible for patient assessment and data processing and analysis, may be the appropriate approach for the study of a correctly selected and homogeneous population.

Indeed, MT presents the scientific and physiological assumptions to positively impact on the patient's functional recovery with post-acute early-onset stroke. However, in order to highlight this aspect, it is necessary that the treatment is designed in strict relation with the patient's characteristics and that possible biases and interfering factors are carefully controlled.

Hopefully, with the careful execution of the proposed study design, it will be possible to demonstrate the efficacy of MT in the functional recovery process of the paretic upper limb of hemiplegic patients. This effective results will be expressed through the score improvement of the specific scales employed in the study.

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