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The value of adding mirror therapy for upper limb motor recovery of subacute stroke patients: a randomized controlled trial

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Background. Upper limb paresis remains a relevant challenge in stroke rehabilitation.
Aim. To evaluate if adding mirror therapy (MT) to conventional therapy (CT) can improve motor recovery of the upper limb in subacute stroke patients.
Design. Prospective, single-center, single-blind, randomised, controlled trial.
Setting. Subacute stroke patients referred to a Physical and Rehabilitation Medicine Unit between October 2009 and August 2011.
Population. Twenty-six subacute stroke patients (time from stroke <4 weeks) with upper limb paresis (Motricity Index ≤77).
Methods. Patients were randomly allocated to the MT (N.=13) or to the CT group (N.=13). Both followed a comprehensive rehabilitative treatment. In addition, MT Group had 30 minutes of MT while the CT group had 30 minutes of sham therapy. Action Research Arm Test (ARAT) was the primary outcome measures. Motricity Index (MI) and the Functional Independence Measure (FIM) were the secondary outcome measures.
Results. After one month of treatment patients of both groups showed statistically significant improvements in all the variables measured (P<0.05). Moreover patients of the MT group had greater improvements in the ARAT, MI and FIM values compared to CT group (P<0.01, Glass's Δ Effect Size: 1.18). No relevant adverse event was recorded during the study.
Conclusion. MT is a promising and easy method to improve motor recovery of the upper limb in subacute stroke patients.
Clinical Rehabilitation Impact. While MT use has been advocated for acute patients with no or negligible motor function, it can be usefully extended to patients who show partial motor recovery. The easiness of implementation, the low cost and the acceptability makes this therapy an useful tool in stroke rehabilitation.

KEY WORDS: Stroke - Mirror neurons - Rehabilitation - Imagery (Psycotherapy).

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The functional impairment of the upper limb is a usual consequence of stroke that affects about 85% of stroke survivors.[1] Various rehabilitative treatments have been introduced to improve the motor control and the functionality of the upper limb, including exercise training of the paretic arm,[2] constraint-induced movement therapy,[3] robotic therapy,[4] neuromuscular electro-stimulation,[5] and bilateral arm training.[6-8] However, for patients with severe to complete upper limb impairment, few therapeutic options exist. Recently, some promising trials of mirror therapy (MT) have been published.[9-13]

Ramachandran, in the rehabilitation of phantom limb pain, was the first to describe a clinical use of MT, observing a significant improvement after treatment.[14] Subsequently, the use of MT has been extended to other pain syndromes, such as complex regional pain syndromes [14] and iatrogenic peripheral nerves damages.[16]

Mirror neurons seem to be involved in the mechanism underlying MT.[17] They are nervous cells with visual-motor properties discovered in the F5 brain area of the macaque.[18-20] This particular type of neurons, also present in human brain, are active both when an action is in progress and when the action is observed being performed by others, mainly if conspecifics.[21]

Only at the end of the 1990s, Altschuler *et al*. introduced MT in the rehabilitation of hemiparetic stroke survivors, showing improvements in their range of motion, speed, and dexterity of the paretic arm.[22]

MT has been utilized to improve upper limb function mainly in chronic stroke survivors,[10, 23, 24] while in the acute phase only one good-quality trial has been published.[9] In this trial authors found a small improvement in the MT group, even if they choose patients with severe to complete motor impairment of the upper extremity.

The aim of the present study was to evaluate if MT, combined with conventional treatment (CT), can improve motor recovery of the upper limb more than CT alone in subacute stroke patients with moderate to severe upper extremity impairment.

Materials and methods

Study population

This study is a prospective, single-centre, single-blinded, randomised, controlled trial. Patients were enrolled among those referred to a Physical and Rehabilitation Medicine Unit between October 2009 and August 2011. The inclusion criteria were: 1) hemiplegia after first stroke episode documented by CT scan and/or available case history); 2) time from stroke < 4 weeks; 3) absence of severe attentive deficit; 4) presence of movements at the three main sites of the upper limb (shoulder, elbow and hand) with a Motricity Index [25] score at upper extremity <77. Exclusion criteria were: 1) hemorragic stroke diagnosis; 2) global aphasia and cognitive impairments that might interfere with understanding instructions for testing, and treatment and/or Mini-Mental State Examination Test <22/30; 3) concomitant progressive central nervous system (CNS) disorders, peripheral nervous system disorders or myopathies. All participants signed an informed consent form before entering the study and the study was conducted in accordance with the Declaration of Helsinki guidelines.

Study design

After enrollment patients were randomly assigned into two groups: 1) conventional treatment; 2) conventional treatment and MT. We allocated patients to one of the two treatment arms using a randomisation scheme generated by a software [26] and one of the investigators (MI), who was not involved in the evaluations, checked correct patient's allocation, according to the randomisation list. All outcome assessments were performed by a physical therapist student, supervised by a senior physical therapist and both were not involved in the treatment of enrolled patients.

Intervention

Both the mirror group and the control group received a four-week conventional stroke rehabilitation program for the upper limb, consisting of five one-hour sessions a week. The CT is patient specific and consists of neurorehabilitative techniques, electrical stimulation and occupational therapy. The mirror group received an additional 30 minutes (for the first two weeks) and one hour (for the last two weeks) per session of a MT program consisting of unaffected upper limb movements. The control group performed the same exercise for the same duration, but the reflecting part of the mirror was covered with paper (sham therapy). Patients had a one-to-one treatment by a physiotherapist, in a separate room from other patients. Physiotherapists were also unaware of patients' assessment results.

Patients were seated on a chair, with the mirror board (65 x 45 cm) positioned between the upper limbs perpendicular to the subject's midline and with the unaffected upper limb facing the reflective surface. Under the supervision of the physiotherapist, the patients observed the reflection of their unaffected upper limb while performing the following movements: flexion and extension of the shoulder, elbow, and wrist and prone-supination of the forearm. The speed of movements was self-selected and no additional verbal feedback was offered.

Outcomes measures

Patients were evaluated at baseline and after four weeks of treatment.

To measure improvements in motor recovery of the upper limb, we included the following evaluations:

— Action Research Arm Test (ARAT),[27] a 19-item measure divided into four subtests (grasp, grip, pinch, and gross arm movement) to assess specific changes in upper limb function and activity level;

— Motricity Index of upper limb (MI),[25] a brief assessment of motor function of the arm throught the Functional Independence Measure (FIM);[28]

ARAT was chosen as the primary outcome measure.

Statistical analysis

The statistical analysis of the data was performed with the 4.0 GraphPad 4 package program (GraphPad Software, Inc., San Diego, CA, USA) and G*Power 3.1.3 (Heinrich Heine Universität Düsseldorf, Germany) for Apple Macintosh OS10.6.

Sample size calculation was based on an effect size of treatment on the primary outcome variable (ARAT) of at least 0.9, which is considered to be highly relevant [29] and for a α error level of 0.05 and for a β error level of 0.4. A sample size of 26 patients (13 per group) was calculated to be necessary.

Differences between single variable measurements in each group were evaluated with Wilcoxon's signed rank test at the end of treatment. Differences between groups were evaluated at baseline and at the end of treatment with the Mann-Whitney U-test.

Glass's Δ effect size was calculated manually implementing the formula in Microsoft Excel for Mac 2008.[30]

Results

From October 2009 to August 2011, 201 stroke patients referred to our Rehabilitation Department were screened. Among these patients, 26 met the inclusion criteria and were enrolled in the study and randomly allocated to receive MT or CT (see CONSORT Diagram, Figure 1).

At baseline patients of both groups showed no significant differences regarding age and time since stroke event (Table I) and ARAT, MI, and FIM scores (Table II). After one month of treatment patients of both groups showed statistically significant improvements in all the variables measured. Moreover, patients who received MT showed greater improvements in MI, ARAT and FIM values compared to CT group.

Both MT and CT were well tolerated and no relevant adverse event was recorded during the study. For ARAT, effect size was 1.18.

A *post-hoc* calculation of power revealed that, with a sample size of 26 patients and an allocation ratio of 1:1.1, the actual power was 0.88. The same calculation with 25 patients (considering that one patient discontinued treatment) revealed a power of 0.87.

Discussion

This study shows that 30-minutes of MT in addition to a conventional rehabilitation program was more beneficial in terms of motor recovery of upper limb than conventional rehabilitative treatment plus 30-minutes of sham therapy in acute post-stroke patients. Moreover, patients of MT group showed a greater improvement in independence, as measured by FIM. These results are in line with those reported in previous studies on chronic [10, 23] and acute [9, 24] stroke survivors.

Furthermore, the improvements in ARAT and FIM observed in the MT group, compared to CT group were not only statistically significant but also clinically meaningful, since they exceeded the Minimal Clinically Important Difference.[31-33]

In our study we evaluated recovery of motor function with the ARAT, while previous works in which MT was utilised patients were evaluated with Fugl-Meyer Assessment. Even if Fugl-Meyer Assessment evaluates upper limb mobility in a more analytical way, both scales are equally sensitive to assess motor recovery after stroke.[34] Moreover, ARAT strongly correlates not only with Fugl-Meyer but also with other motor function evaluation scales for upper limb, as Box&Blocks.[35]

In our study improvements in ARAT were higher than those previously measured by Dohle and colleagues.[9] In fact, their patients had a lesser improvement in absolute term (even if effect size of the modification was quite high, 0.78). Notwithstanding,

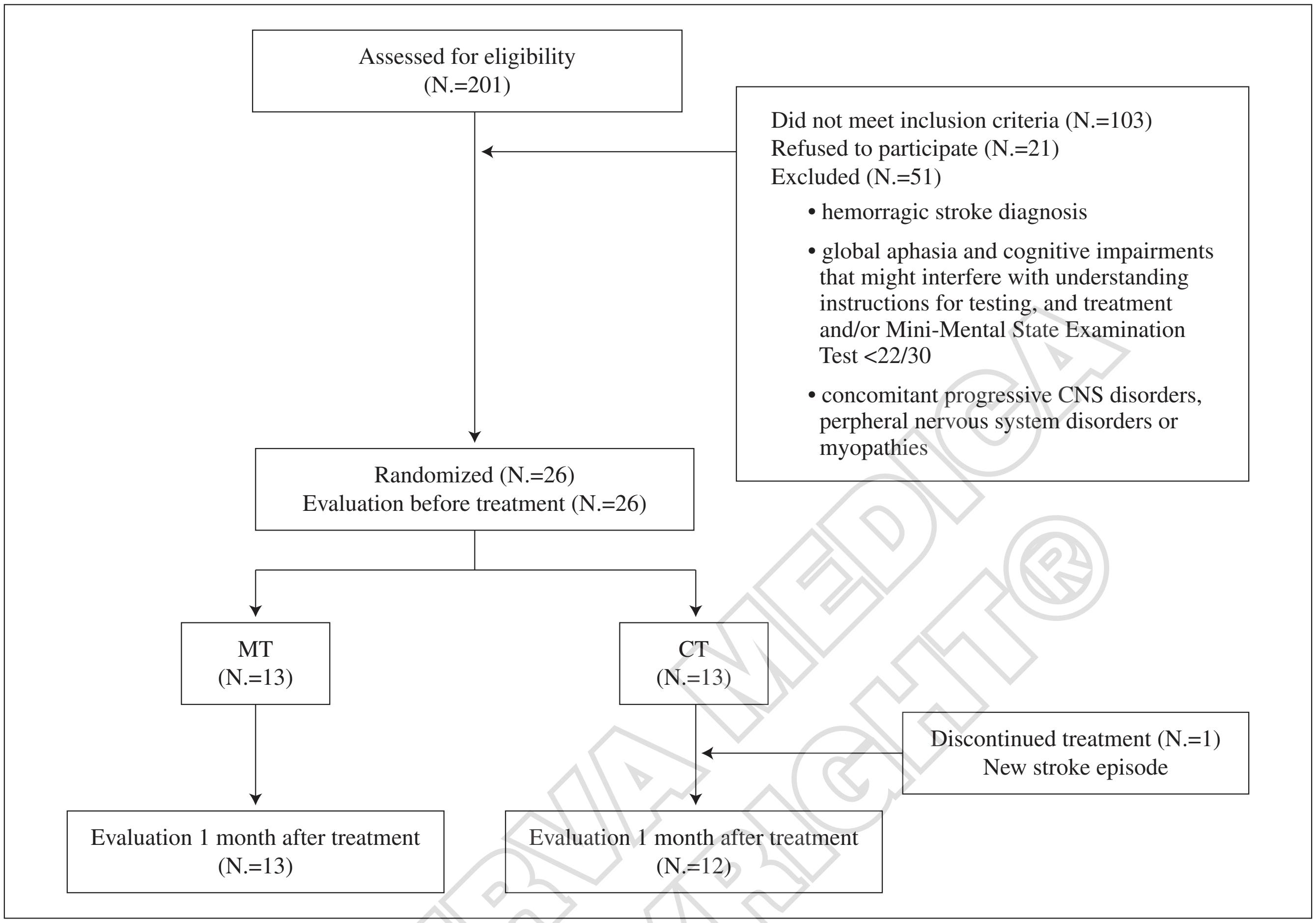

Figure 1.—CONSORT diagram.

TABLE I.—*Patient characteristics at baseline.*

	Mirror Therapy Group	Control Therapy Group
Patients (N.)	13	13
Mean age (years ± SD)	62±25.87	71.1±8.81
Sex (M/F)	9/4	8/5
Hemiparesis (sx/dx)	7/6	6/7
Time since stroke (days ± SD)	22±3	24±2

it should be noted that they enrolled patients with severe paresis at upper extremity and ARAT suffers from floor effect at scores lower than three.[35]

We also observed a significant improvement in FIM scores in both groups, which is straightforward with the pattern of recovery usually seen in stroke patients. Furthermore, patients of MT group had a statistically greater improvement regarding this outcome measure. Lastly, the difference between the MT and CT group is higher that the minimal clinically important difference.[33] However, we should say that, even if the difference is not statistically sig-

TABLE II.—*Outcome measures.*

Outcomes measures	Mirror Therapy Group (Mean ± SD)	Control Therapy Group (Mean ± SD)
FIM (baseline)	52±17.16	45.67±15.79
FIM (after 1 month)	93.18±22.07 *#	67.42±13.19*
ARAT (baseline)	15.90±22.41	21±20.61
ARAT (after 1 month)	47.64±15.19 *#	33.67±20.33*
MI (baseline)	39.27±27.33	36.83±24.34
MI (after 1 month)	76±21.78 *#	51.58±24.74*

FIM: Functional Independence Measure; ARAT: Action Research Arm Test; MI: Motricity Index; *$P< 0.05$ pre-post treatment evaluation; # $P<0.001$ between the two groups.

nificant, at baseline MT group had higher FIM scores compared to CT group.

Many hypotheses have been proposed to explain the motor recovery induced by Mirror therapy in post stroke patients, but the precise mechanisms remain not yet clarified.[9, 17]

Some authors suggested that mirror therapy related to motor imagery and that the mirror creates visual feedback of successful performance of the imagined action with the impaired limb;[22, 36] however, motor imagery itself has proven to be potentially beneficial in the rehabilitation of hemiparesis.[37] As a possible alternative explanation, a recent fMRI study by Mathys *et al*., showed some evidence for MNS activation by reporting increased activation within superior temporal sulcus.[38] This supports the hypothesis that the effect of MT could be due to the activation of the mirror neuron system, since the observation of movements activates the motor areas in the affected hemisphere, facilitating the excitability of M1 area.[39]

However, although superior temporal sulcus is reported to be related to the mirror neuron system,[40] this area has been associated with different behaviours, and its exact function remains poorly understood.[41] Moreover, in the only imaging experiment on inverted visual feedback, lateralized activations were not recorded in the premotor area, but in occipital and posterior parietal regions, assuming that the precuneus region (area V6), rather than superior temporal sulcus, plays a decisive role.[42] This area belongs to the neural network supporting the mental representation of the self,[43] suggesting that premotor areas are activated bilaterally, without lateralisation because of the observed body side.[44] Thus, the beneficial effect of MT is possibly mediated by the visual illusion that actions carried out by oneself are performed normally. However, in a recent work Michielsen *et al*.[45] did not observe mirror related activity in motor or mirror neuron system areas, but showed an increased activity in precuneus and posterior cingulate cortex, areas associated with awareness of the self and spatial attention during bimanual movement.

Finally another theory suggests the possibility that the improvements induced by MT can depend on bilateral training.[46] Bilateral movement training may facilitate rebalancing of the asymmetry of post-stroke hemispheric corticomotor excitability. Typically, the contralesional cortex increases in excitability and the injured cortex decreases. Rebalancing of hemispheric asymmetry occurs because of a change in inhibitory mechanisms including both short interval intracortical inhibition and interhemispheric inhibition. In several bilateral training studies, a decrease in cortical excitability in contralesional motor cortex was associated with an improvement in motor skill of the affected arm.[47, 48]

Even if we treated patients in the acute phase after stroke, as Dohle *et al*.,[9] our patients had better motor function at the upper extremity. On the one hand, this is in contrasts with their observation that the greater improvements were observed in completely plegic patients. On the other hand, our results could be theoretically explained by the fact that a partial lesion of the M1 area can recover its functionality through an activation of the premotor cortex that increases input either to the residual M1 or to the corticospinal tract.[49] Premotor cortex is a critical area for motor control, which role is crucial for motor recovery after brain lesion.[50] In healthy volunteers, MT is able to activate premotor cortex,[51] and this effect may explain the results that we have obtained, compared to previous studies.

However, this remains only a hypothesis, since we did not perform a functional imagery study, but it remains an interesting subject for a further study.

The lack of follow-up is a limitation of this study, because it does not allow to evaluate the possible long-term effects of the treatment. As a further limitation of our work, we did not evaluate modifications in participation and quality of life, even if, since a follow-up evaluation was not planned, measuring these domains during inpatient treatment may be prone to biases.

Conclusions

In conclusion this study shows that MT combined with a CT is a safe, easy and effective treatment to improve motor recovery of the upper limb in subacute post-stroke patients.

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