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The effects of a robot-assisted arm training plus hand functional electrical stimulation on recovery after stroke: a randomized clinical trial.

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Abstract

Objective: To compare the effects of unilateral, proximal arm robot-assisted therapy combined with hand functional electrical stimulation to intensive conventional therapy for restoring arm function in subacute stroke survivors.

Design: This was a single blinded, randomized controlled trial. **Setting:** Inpatient Rehabilitation University Hospital. **Participants:** Forty patients diagnosed with ischemic stroke (time since stroke <8 weeks) and upper limb impairment were enrolled. **Interventions:** Participants randomized to the experimental group received 30 sessions (5 sessions/week) of robot-assisted arm therapy and hand functional electrical stimulation (RAT + FES). Participants randomized to the control group received a time-matched intensive conventional therapy (ICT). **Main outcome measures**: The primary outcome was arm motor recovery measured with the Fugl-Meyer Motor Assessment. Secondary outcomes included motor function, arm spasticity and activities of daily living. Measurements were performed at baseline, after 3 weeks, at the end of treatment and at 6-month follow-up. Presence of motor evoked potentials (MEPs) was also measured at baseline.

Results: Both groups significantly improved all outcome measures except for spasticity without differences between groups. Patients with moderate impairment and presence of MEPs who underwent early rehabilitation (<30 days post stroke) demonstrated the greatest clinical improvements.

Conclusions: A robot-assisted arm training plus hand functional electrical stimulation was no more effective than intensive conventional arm training. However, at the same level of arm impairment and corticospinal tract integrity, it induced a higher level of arm recovery.

Keywords: rehabilitation; stroke; robotics; transcranial magnetic stimulation; upper extremity

Abbreviations:

ANOVA: analysis of variance

BBT: Box and Block Test

BI: Barthel Index

FES: functional electrical stimulation

FMA-UE: Fugl-Meyer Assessment – Upper Extremity

ICT: intensive conventional therapy

MAS: Modified Ashworth Scale

MCID: minimal clinically important difference

MEPs: motor-evoked potentials

OP: opponent muscle

OSP: optimal scalp position

RAT: robot-assisted therapy

rMT: resting motor threshold

TMS: transcranial magnetic stimulation

WMFT: Wolf Motor Function Test

INTRODUCTION

The first 10 to 12 weeks post-stroke represent the time window when most of the functional arm recovery occurs.[1,2] Recently, stroke rehabilitation has recognized the importance of a timely intensive, task specific therapy to foster motor recovery;[2,3] however evidence supporting the superiority of one intervention over another is very scarce in subacute stroke clinical trials,[4] probably due to the spontaneous functional recovery that acts as prime confounder in this rehabilitation phase. The use of technology-aided interventions, such as robotics and electrical stimulation devices has been rapidly introduced into clinical settings with the aim of increasing repetitions of motor tasks and promoting the restoration of motor function after stroke. Both arm robotics and hand FES devices have been previously tested in stroke survivors, providing mixed results.[5–9] Arm robotics failed to demonstrate its superiority on task-oriented training, usual therapy or even if applied at a very early stage.[5–7] A more comprehensive recommendation was given in a recent update of the Cochrane review concluding that arm robotics was effective in increasing activities of daily living, even in the subacute stroke subgroup.[10] Jonsdottir et al.[8] reported a beneficial effect of FES in addition to a task-oriented approach and it seems to improve activities of daily living in the subacute phase after stroke.[9] Nevertheless, a combination of the two interventions using commercialized devices had not been tested so far.

Considering the positive effects on motor recovery of arm robotics and hand FES, we explored the effects of the combination of a shoulder-elbow robotic device[11] with a hand FES neuroprosthesis on the whole arm recovery.[12,13] The primary aim of this study was to test the hypothesis that a proximal arm robot-assisted therapy with the additional use of hand functional electrical stimulation (RAT + FES) during the subacute phase of rehabilitation could have higher benefit, compared with intensive conventional therapy (ICT) alone, in arm and hand function in subacute stroke patients. Moreover, we explored the role of several factors on arm motor recovery after rehabilitation and at 6-month follow-up.

METHODS

This was a prospective, randomized, single-blinded, control study. This trial was approved by local Ethics Committee and a written consent was provided. All procedures were conducted according to the ethical standards of the Declaration of Helsinki. The trial protocol has been registered on ClinicalTrials.gov (NCT02267798). The data that support the findings of this study are available from the corresponding author upon reasonable request. Inclusion criteria were: males and females, aged 18-80 years with diagnosis of first, single unilateral ischemic stroke verified by brain imaging <8 weeks. To be enrolled in the study patients had to have an upper limb motor impairment defined by an upper extremity score >11 and <55 on the Fugl-Meyer Assessment (FMA-UE). Patients were excluded if they presented with neurological conditions in addition to stroke that may affect motor function, other medical conditions likely to interfere with the ability to safely complete the study protocol, impaired cognitive functioning (score <21 on the Mini Mental Status Examination), or severe upper-limb pain defined as >7 on the Visual Analogue Scale. Participants were randomized to the two groups through a block randomization approach. The randomization scheme was generated using the website http://www.randomization.com. The random list was managed by an administrator external to the research groups to prevent selection bias.

The experimental group received 1 hour and 40 minutes of hand FES+ RAT for each session (5 times/week over 6 weeks); the control group received the same amount of conventional therapy.

The primary outcome for this study was to detect arm motor recovery. We chose the Fugl-Meyer motor Assessment score, which is the most sensitive to therapeutic change early after stroke in stroke patients with arm paresis.[14–16] The score ranges from 0-66. Moreover, arm motor function was tested with the Wolf Motor Function Test (WMFT) that encompasses single or multiple joint movements and functional tasks and that has been successfully used in subacute and moderate to severely affected stroke patients.[17–20] Gross motor function was evaluated using the Box and Block Test (BBT) where the number of blocks that can be transported from one compartment of a box to another compartment within 1 minute is counted.[21] Arm spasticity was assessed with the Modified Ashworth Scale (MAS).[22] Furthermore, ADL independency was measured with the Barthel Index

(BI).[23] All patients were evaluated before intervention (T0), after 3 weeks (T1), at the end of treatment (T2) and at 6-month follow-up (T3) by an investigator blinded with regards to the treatment group.

The presence/absence of TMS-induced motor-evoked potentials (MEPs) was measured as a possible prognostic factor of recovery at baseline. Focal TMS was performed by means of a 70-mm figure-of-8 stimulation coil (standard Magstim plastic-covered coil), connected to a Magstim Bistim (The Magstim Company, Carmarthenshire, Wales, UK)[a], producing a maximum output of 2 T at the coil surface (pulse duration, 250 ls; rise time, 60 ls). The resting motor threshold (rMT), defined as the lowest stimulus intensity able to evoke 5 of 10 MEPs with an amplitude of at least 50 μV, was determined by holding the stimulation coil over the optimal scalp position (OSP), defined as the position from which MEPs with maximal amplitude were recorded for opponent (OP) muscle. The patient was classified as MEP+ if MEPs were observed with a consistent latency in response to at least 5 stimuli, with OP latencies ≈ 20 – 40 ms; MEP- if MEPs were not observed at rest with 100% maximum stimulator intensity.

The experimental group received 1 hour and 40 minutes of arm rehabilitation. Specifically, a 40 minute-session of hand FES was delivered through a battery-powered programmable stimulator and a forearm-wrist-hand orthosis containing 5 electrodes positioned to provide reliable activation of the following muscles: extensor digitorum communis, extensor pollicis brevis, flexor pollicis longus, flexor digitorum superficialis, and thenar muscles (H200, Bioness, CA)[b]. The intensity of stimulation was set to a level that provided comfortable and consistent activation of the extensor and flexor muscles to achieve whole hand opening and functional grasping. Participants were instructed to coordinate their actions with the pre-timed stimulation patterns programmed in the device so as to synchronize the user's intention with FES assistance. Although the stimulation cycles were fixed, participants needed to engage actively in the tasks to produce the synergistic muscle actions throughout the upper limb required for effective task performance. The therapist set up activities to involve each subject in functional exercises specific to their personal needs, such as reaching, grasping, holding and releasing or daily activities with upper limb engagement. The voluntary contraction during electrical stimulation increases motor cortical excitability in the agonist muscle.[24] After FES training, patients received 60 minutes of RAT with an end-effector device (Reo Therapy System, Motorika Medical Ltd, Israel)[c] which focused on repetitive tasks that incorporate multidirectional reaching actions. In this robot-assisted therapy a robot manipulator applied forces to the paretic arm during goal-directed movements. During the session the patient's affected hand was placed on or strapped onto a robotic arm and she/he was instructed to either actively reach predefined reach points, or to be guided while the robotic arm led the arm towards these reach points.

The control group received the same time of conventional arm therapy (100 minutes). Specific exercises for the affected upper limb included active, passive and sensory exercises or functional tasks.

In addition to arm rehabilitation, all patients received multidisciplinary rehabilitation based on an individualized approach.

Baseline characteristics were reported as mean and standard deviation, median and inter-quartile range or frequency and percentage, according to variables distribution and compared among groups to confirm the quality of randomization, using unpaired t-test, Wilcoxon-Mann-Whitney test or Pearson’s Chi-Squared test, as appropriate. To investigate time effects (T0, T1, T2 and T3) within groups we applied both Analysis of variance (ANOVA) and the alternative non-parametric Friedman test as a confirmatory analysis; results were reported as mean and 95% CI. To underline between-group differences, unpaired t-tests were performed. Since stroke encompasses a wide spectrum of characteristics, linear models were used to analyse the effect of several factors (age, sex, stroke type, affected hemisphere, comorbidities, cognitive and sensory deficits, stroke onset, MEPs presence/absence and arm impairment at baseline) on motor recovery. An intention-to-treat analysis was carried out on all outcome measures, handling missing data with the last observation carried forward approach. Statistical analysis was performed using STATA 13 (StataCorp, College Station, TX) software. Significance was recognized when $p < 0.05$.

We were interested in detecting a between-group difference equal to the minimal clinically important difference (MCID) value for FMA-UE which is 9 ± 8.8 points given a power of 80% and α of 5%.[25] Therefore, the sample size needed resulted of at least 34 patients (17 in each group); however, an increase of 20% to 40 patients was adopted to account for possible drops-out.

RESULTS

391 consecutive patients with ischemic stroke were screened between January 2014 and September 2016 and 40 were enrolled in the study (median age 68 (58-73), 61.5% males, 37 (21-60) median days from stroke onset). One subject in the RAT + FES group did not receive the allocated treatment due to a post-randomization drop-out, whereas one patient in the ICT group did not receive the allocated treatment due to an organizational error. All participants concluded the rehabilitation protocols, except for a subject in the RAT + FES group who withdrew for medical issues. The 17.5% (5 in the RAT + FES group and 2 in the ICT group) did not return to the hospital for the 6-month follow-up for personal reasons (overall attrition rate 22.5 %). The study flow diagram is reported in Figure 1.

[INSERT FIGURE 1 ABOUT HERE]

The two groups were similar in demographic and clinical characteristics, as summarized in Table 1 and 2.

[INSERT TABLE 1 and 2 ABOUT HERE]

Both groups significantly improved all outcome measures (FMA-UE, BBT, WMFT, BI) over time ($p < 0.001$) except for spasticity (MAS). The effects were highlighted since T1 (mid-treatment assessment). Results were reported in Table 3.

[INSERT TABLE 3 ABOUT HERE]

Between-group differences were not found for any variables, leading to the conclusion that RAT + FES was not superior than ICT in increasing motor recovery after stroke in a subacute phase.

We run a linear regression model to analyse the influence of several demographic or clinical factors on FM-UE improvement after rehabilitation or on FM-UE at 6-month follow-up. The first one was predicted by stroke onset (β = -0.15; p = 0.005) and FMA-UE at baseline (β = -0.18; p = 0.05), whereas arm motor function at 6 months was influenced by stroke onset (β = -0.30; p = 0.013), FM-UE at baseline (β = 1.0; p < 0.001) and MEPs (β = 13.47; 0.036). Given that arm severity at baseline and time since stroke can be considered as possible confounders, we categorized our sample into subgroups according to these variables: ≤ 30 days since stroke (early rehabilitation) or > 30 days since stroke (late rehabilitation) and ≤ 21 points FM-UE (severe), > 21 points FM-UE (moderate to mild).[26] See Table 4 and Figure 2.

[INSERT TABLE 4 ABOUT HERE]

[INSERT FIGURE 2 ABOUT HERE]

Moderate and early rehabilitation subgroups achieved the greatest clinical improvements after rehabilitation compared to the severe and late rehabilitation subgroups. Specifically, it was statistically significant in the ICT group for severity (+ 15.5 FM-UE points in the moderate group compared to + 4.4 FM-UE points in the severe group; p = 0.02) and in the RAT + FES group for time since stroke (+13.7 FM-UE points in the early rehabilitation group compared to + 6.3 FM-UE points in the late rehabilitation group; p = 0.01).

Our analysis revealed that only 15.79% of the patients who were enrolled within 30 days after stroke had a severe arm paresis, compared with 47.62% who started arm rehabilitation after 30 days post stroke (Chi2 4.60; p = 0.032). Thus, severity and time since stroke were not independent factors. To better explore the effects of treatments, arm severity and time since stroke on arm recovery, a mixed-effects linear model was run, showing that only arm severity significantly influenced FM-UE score (β = -22.89; p < 0.0001) with a positive interaction severity*time (at T2 β = - 5.96; p = 0.02), whereas neither time since stroke nor treatment reached statistical significance. See Figure 3.

[INSERT FIGURE 3 ABOUT HERE]

We found that, in addition to severity, treatment and MEPs significantly influenced arm motor recovery over time. Patients who were allocated to RAT + FES reached a higher level of arm recovery (β= + 5.93; p = 0.016) compared to ICT, considering same impairment level and MEPs; whereas patients with MEP+ obtained a greater arm recovery at 6-month follow-up (β=4.35; p=0.011). See Figure 4.

[INSERT FIGURE 4 ABOUT HERE]

We observed the amount of practice during therapy sessions (n=35) in a convenience sample. During ICT (n=16) the amount of movement practice was observed and categorized according to Lang et al.[27] into active exercise, passive exercise, sensory and functional. We reported 376.06 ± 36.12 repetitions /each ICT session with 55.70% of functional tasks (209.5 ± 24.8) compared to 794.68 ± 318.50 repetitions/each RAT + FES session (p<0.001). The session consisted of 630.47 ± 284.90 RAT repetitions and 164.21 ± 68.34 FES repetitions.

DISCUSSION

This clinical trial failed to demonstrate the superiority of an arm robotics plus hand FES training on a time-matched ICT in a subacute stroke population. Both groups equally improved their arm impairment, arm function and activities of daily living after an intensive arm rehabilitation and reached further gains at 6-month follow-up. Arm motor recovery, measured with the FMA-UE, was clinically significant at the end of both treatments, considering an MCID of 9-10 points. Similarly, arm function improvement measured with the WMFT Function score reached the MCID of 1.2 points in both groups after 15 sessions.[28] The independence in activities of daily living, monitored with the BI, clinically improved after 15 sessions, considering a MCID value of 1.85 points.[23]

This trial confirmed the potential role of several factors (intensity, time, arm severity and integrity of the corticospinal tract) on arm motor recovery after stroke, outlining potential recovery trajectories that can be modulated by intensive arm rehabilitation. Regarding intensity, the proposed interventions were both more intense (~200 repetitions/session in ICT and ~ 700 repetitions/session in RAT + FES group) compared to usual arm rehabilitation reported by Lang at al. who observed a mean of 32 functional repetitions during a usual physiotherapy session.[27] However, a dose-response effect of task-specific upper limb training in chronic stroke patients has not been proved.[29]

The first 30 days after stroke represent a critical time-window for starting rehabilitation, when the interaction between treatment and spontaneous recovery process can be more effective;[2] however, only 6% of stroke motor rehabilitation RCTs have enrolled all patients during the first month after stroke.[30] In our trial we enrolled patients within 8 weeks after stroke with a mean of 37 days. An association between time since stroke and arm motor recovery has been highlighted, confirming the importance of early rehabilitation for stroke outcome.

Initial arm severity is the most important predictor of arm recovery after stroke and the majority of stroke patients shows a fixed arm proportional recovery of about 78%.[31,32] Patients who present an initial severe paresis usually do not follow this rule and, for these patients, the study of the integrity of the corticospinal tract by TMS in the first days after stroke can be useful to predict recovery.[33–35] In this scenario, the role of arm rehabilitation might be that of accelerating and optimizing this time-dependent, dynamic process, through a modulation of the spontaneous recovery mechanisms.[4,36]

In our study, we confirmed the association between baseline arm severity and functional recovery, even if baseline assessment was not done in the first few days after the stroke, as studies of stroke recovery recommended.[31,35] The mixed-effects linear model outlined that given a fixed level of arm severity and integrity of the corticospinal tract, the RAT + FES group presented a higher arm recovery over time, suggesting a potential role of these interventions to promote recovery during rehabilitation.

Study Limitations

In this 3-year study we enrolled subacute ischaemic stroke survivors with arm paresis defined by a FMA-UE score of 12-54, within 8 weeks from stroke. With this inclusion criteria, we had a recruitment rate of 10% which is in line with other subacute stroke trials;[37,38] however a low proportion of patients recruited limits the generalizability of results to the entire stroke population. Even though we reached the predetermined sample size, our hypothesis on groups difference was too optimistic and further analyses on bigger samples are needed. Another limit is that our two intensive interventions were time-matched, instead of dose-matched. Both groups received more therapy compared to usual arm therapy, however a significant difference was highlighted in favor of the experimental group.[27] However, it is possible that more than repetitions, the quality and salience of movements trained are essential to induce motor recovery. Finally, a potential reason for the overall negative results, is that, at this stage, we characterized our sample only based on clinical outcomes and the integrity of the corticospinal tract. Including markers of biology, imaging, neurophysiology or a combination of these might improve knowledge on the effects of arm rehabilitation on stroke recovery.[39]

CONCLUSION

An intensive arm training that combined RAT and hand-FES, seems to not be superior to a time-matched intensive conventional arm training, even though people who received RAT + FES, at the same level of arm impairment and corticospinal tract integrity, reached a higher level of arm recovery.

Disclosures

The Authors declare that there is no conflict of interest.

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Suppliers:

a. Magstim Bistim (The Magstim Company, Carmarthenshire, Wales, UK)

b. H200 (Bioness, CA)

c. Reo Therapy System (Motorika Medical Ltd, Israel)

Figure captions:

Figure 1: CONSORT flow diagram.

Figure 2: Scatterplots showing effects of stroke onset and arm severity at baseline on arm recovery after rehabilitation (T0-T2) and at follow-up (T3) (♦ and dotted line for ICT group; ○ and continuous line for RAT + FES group).

Figure 3: predicted arm recovery (FM-UE) as a function of severity and stroke onset (♦ and continuous line for RAT+FES moderate early, ♦ and dotted line for ICT moderate early; ▲ and continuous line for RAT+FES moderate late, ▲ and dotted line for ICT moderate late; ■ and continuous line for RAT+FES severe early, ■ and dotted line for ICT severe early, ● and continuous line for RAT+FES severe late, ● and dotted line for ICT severe late).

Early = ≤ 30 days since stroke; late = > 30 days since stroke; moderate = > 21 points FM-UE; severe = ≤ 21 points FM-UE [26]

Figure 4: predicted arm recovery (FM-UE) as a function of corticospinal tract integrity and severity (♦ and continuous line for RAT+FES moderate MEP+, ♦ and dotted line for RAT+FES moderate MEP-; ▲ and continuous line for ICT moderate MEP+, ▲ and dotted line for ICT moderate MEP-; ■ and continuous line for RAT+FES severe MEP+, ■ and dotted line for RAT+FES severe MEP-, ● and continuous line for ICT severe MEP+, ● and dotted line for ICT severe MEP-).

Moderate = > 21 points FM-UE; severe = ≤ 21 points FM-UE [26]

Table 1. Participants Characteristics at Baseline.

	RAT + FES (n = 19)	ICT (n = 20)	Total (n = 39)	*p*
Age, years*	68 (56-71)	68 (58.5-73)	68 (58-73)	0.715
Gender, no. male (%)	12 (63.2)	12 (60.0)	24 (61.5)	0.839
Type of stroke				
Subcortical, no. (%)	9 (47.4)	10 (50.0)	19 (48.7)	0.344
Cortical, no. (%)	6 (31.6)	9 (45.0)	15 (38.5)	
Brainstem, no. (%)	4 (21.0)	1 (5.0)	5 (12.8)	
Time since stroke, days*	39 (21-62)	32.5 (20-51)	37 (21-60)	0.574
Affected hemisphere, no. left (%)	13 (68.4)	14 (70.0)	27 (69.2)	0.915
Sensory impairment, no. (%)	4 (25.0)	5 (27.8)	9 (26.5)	0.855
Cognitive impairment, no. (%)	4 (23.5)	6 (35.3)	10 (29.4)	0.452
Comorbidities, no.*	1.5 (1-3)	2 (1-3)	2 (1-3)	0.384
MEPS n (%)†	7 (50.0)	9 (60.0)	16 (55.2)	0.588

Abbreviations: RAT + FES, Robot Arm Training + Functional Electrical Stimulation; ICT, Intensive Coventional Therapy; *p*, level of significance.

*Median (interquartile range).

† FDI-TMS was performed in 14/19 RAT + FES subjects and 15/20 ICT subjects

Table 2. Baseline characteristics of subacute ischemic stroke who received RAT + FES or ICT.

	RAT + FES (n = 19)	ICT (n = 20)	Total (n = 39)	*p*
Fugl-Meyer Assessment Upper Extremity (FMA-UE)				
Total score *	28.8 ± 13.3	31.4 ± 12.3	30.1 ± 12.7	0.529
Proximal score*	17.4 ± 8.4	20.4 ± 7.1	18.9 ± 7.8	0.246
Distal score*	7.8 ± 5.7	7.6 ± 6.5	7.7 ± 6.0	0.902
Impairment level				
Mild (score 66-49) no. (%)	1 (5.3)	1 (5.0)	2 (5.1)	
Moderate (score 48-22) no. (%)	10 (52.6)	14 (70.0)	24 (61.5)	
Severe (score 21-0) no. (%)	8 (42.1)	5 (25.0)	13 (33.3)	
Modified Ashworth Scale, total score †	1 (1-4)	1.75 (1-2.5)	1.5 (1-3)	0.819
Box and Block Test affected arm, total score †	7 (0-20)	6 (0-18.5)	7 (0-20)	0.728
Wolf Motor Function Test				
Functional Ability Scale score *	31.9 ± 19.6	31.2 ± 22.1	31.5 ± 20.6	0.918
Task rate ‡, no. *	12.5 ± 10.4	17.3 ± 12.3	15.0 ± 11.5	0.190

Barthel Index, total score [b]	80 (40-90)	75 (52.5-90)	75 (45-90)	0.724

Abbreviations: RAT + FES, Robot Arm Training + Functional Electrical Stimulation; ICT, Intensive Coventional Therapy; *p*, level of significance.

[*] Mean (standard deviation).

†Median (interquartile range)

‡ Task rate = 60(s)/Performance Time (s)[28]

Table 3. Effects of RAT+FES or ICT on primary and secondary outcome measures reported as mean (95% CI).

		Δ T0-T1	Δ T0-T2	Δ T0-T3	*p*
FMA-UE, total score	RAT + FES	7.0 (4.0-10.0)	9.8 (6.6-13.0)	13.2 (8.3-18.1)	<0.001
	ICT	7.9 (4.9-10.8)	12.8 (9.2-16.3)	16.5 (11.9-21.1)	<0.001
	p	0.674	0.200	0.308	
FMA-UE, proximal score	RAT + FES	3.3 (1.2-5.4)	4.8 (2.9-6.8)	6.6 (3.9-9.3)	<0.001
	ICT	3.7 (2.1-5.3)	5.9 (4.1-7.7)	6.5 (4.3-8.7)	<0.001
	p	0.760	0.404	0.937	
FMA-UE distal score	RAT + FES	3.5 (1.9-5.2)	4.5 (2.7-6.3)	5.1 (3.1-7.1)	<0.001
	ICT	5.2 (3.0-7.4)	5.7 (3.7-7.7)	7 (4.7-9.3)	<0.001
	p	0.220	0.351	0.197	
MAS, total score	RAT + FES	0.13 (-0.88-1.14)	-0.24 (-1.41-0.93)	0.37 (-0.95-1.69)	0.651
	ICT	-0.30 (-0.89-0.29)	-0.60 (-1.18- -0.02)	-0.78 (-1.55- -0.01)	0.106
	p	0.446	0.564	0.127	
BBT affected arm, total score	RAT + FES	7.4 (1.7-13.0)	8.4 (3.2-13.6)	10.5 (4.6-16.5)	<0.001
	ICT	7.0 (3.1-10.8)	10.3 (5.2-15.4)	13.6 (7.6-19.5)	<0.001
	p	0.898	0.590	0.456	

WMFT Functional Ability Scale score	RAT + FES	8.0 (3.5-12.5)	11.2 (5.2-17.2)	15.7 (7.3-24.1)	<0.001
	ICT	11.9 (7.0-16.8)	17.1 (11.4-22.8)	23.6 (16.1-31.1)	<0.001
	p	0.232	0.142	0.150	
WMFT Task rate*, no.	RAT + FES	7.7 (3.6-11.8)	10.4 (5.5-15.3)	12.4 (5.6-19.1)	<0.001
	ICT	6.6 (3.3-9.9)	10.2 (5.1-15.2)	13.6 (7.8-19.4)	<0.001
	p	0.669	0.945	0.767	
BI, total score	RAT + FES	10.5 (3.5-17.6)	16.1 (6.7-25.4)	22.6 (12.1-33.1)	<0.001
	ICT	9.8 (2.9-16.6)	19.3 (12.0-26.5)	24.3 (13.0-35.5)	<0.001
	p	0.869	0.572	0.828	

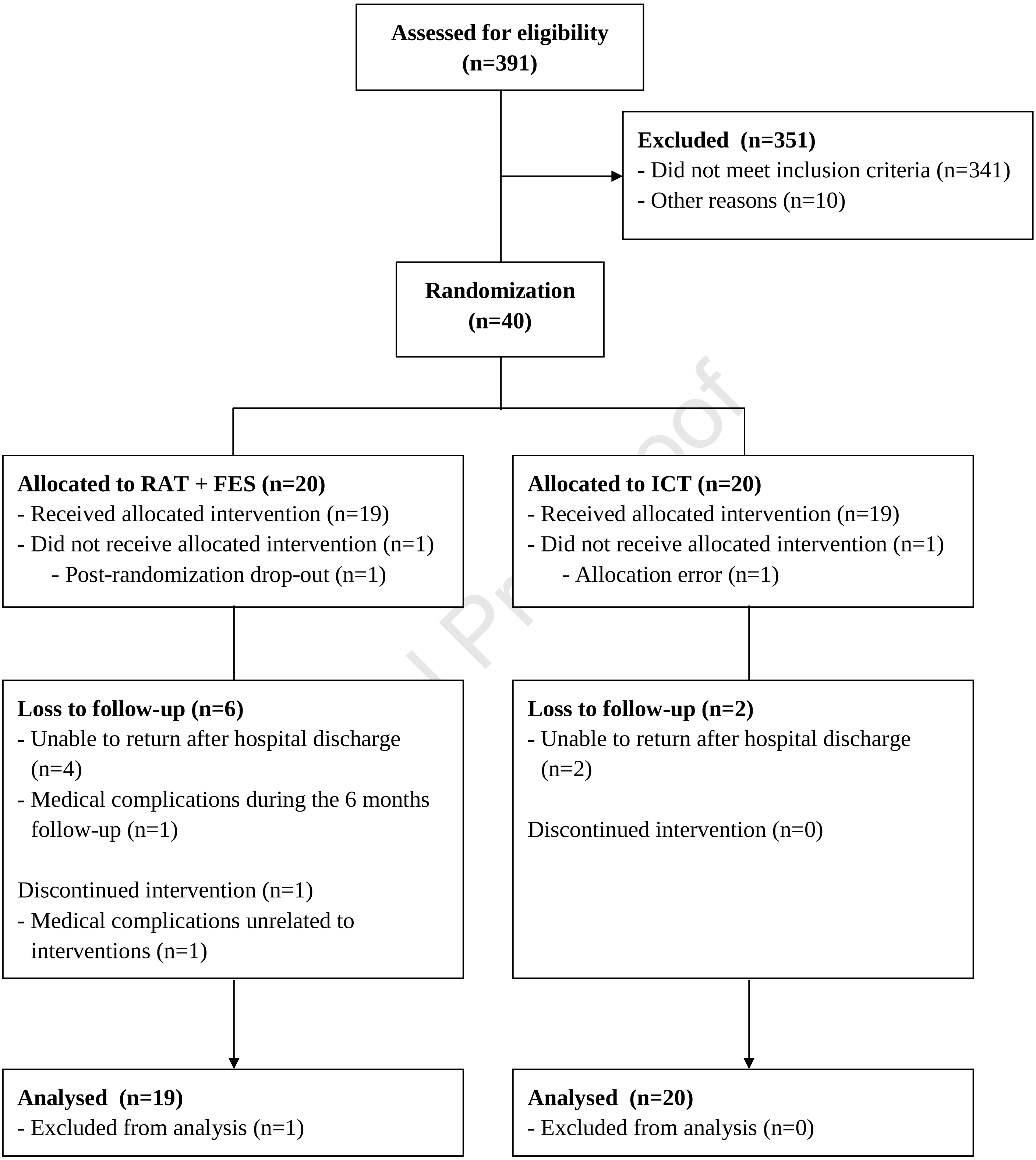
Abbreviations: RAT + FES, Robot Arm Training + Functional Electrical Stimulation; ICT, Intensive Coventional Therapy; T0, assessment before treatment; T1, assessment after 3 weeks of treatment; T2, assessment after the end of treatment; T3, assessment at 6 months follow-up; *p*, level of significance over time (Friedman Test); FMA-UE, Fugl-Meyer Assessment Upper Extremity; MAS, Modified Ashworth Scale; BBT, Box and Block Test; WMFT, Wolf Motor Function Test; MAL, Motor Activity Log; BI, Barthel Index; * Task rate = 60(s)/Performance Time (s) [28]

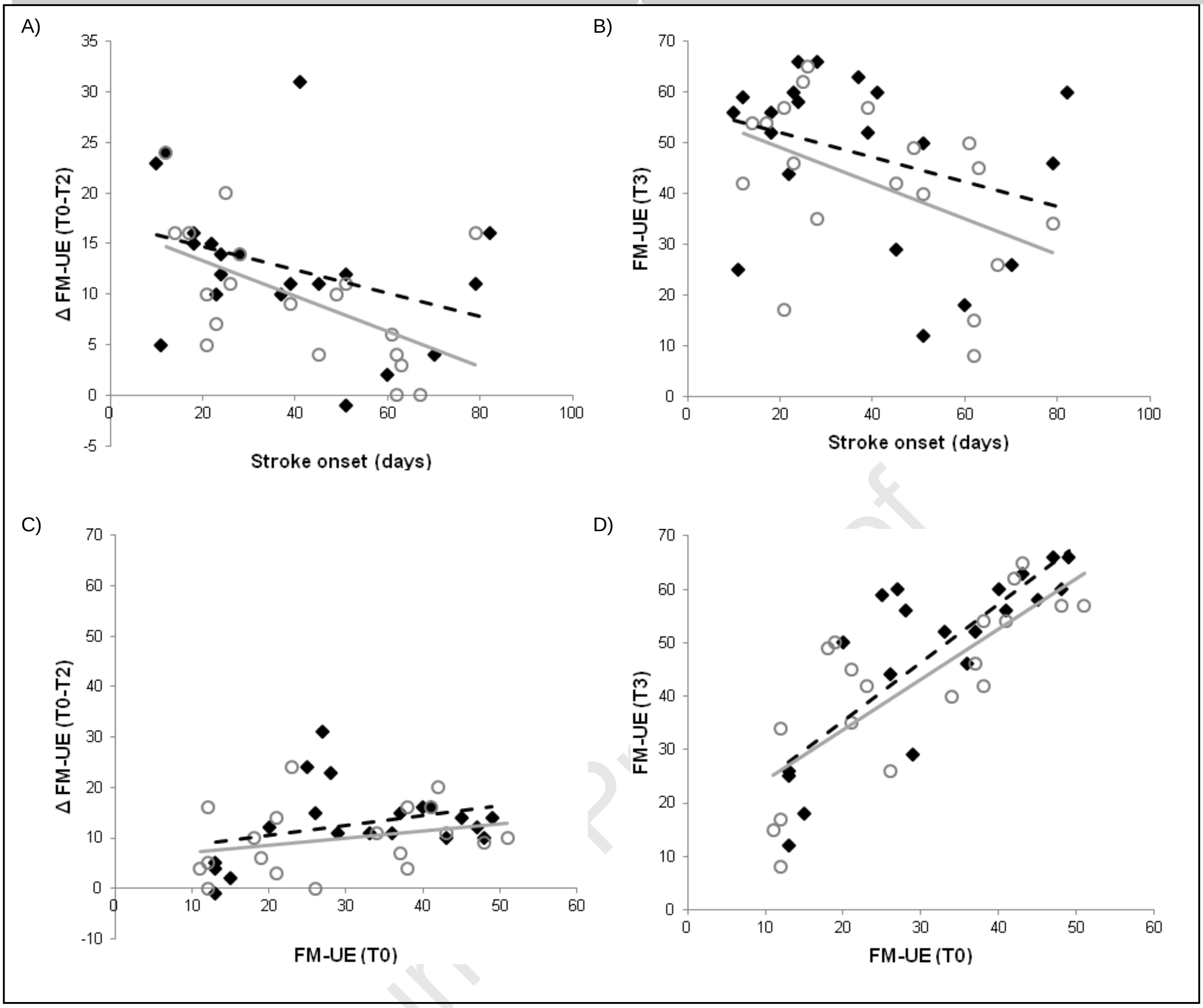
Table 4. Effects of RAT + FES or ICT on primary outcome in subgroups stratified for arm impairment and time since stroke reported as mean (standard error).

	Impairment level			Time since stroke		
	Moderate[a]	Severe[b]	*p*	≤ 30 days	> 30 days	*p*
RAT + FES	(n=11)	(n=8)		(n=9)	(n=10)	
Δ T0-T2	+11.6 (2.1)	+7.3 (2.0)	0.161	+13.7 (2.0)	+6.3 (1.6)	0.011
Δ T0-T3	+11.3 (2.2)	+15.9 (4.7)	0.341	+13.8 (2.0)	+12.7 (4.1)	0.819
ICT	(n=15)	(n=5)		(n=10)	(n=10)	
Δ T0-T2	+15.5 (1.5)	+4.4 (2.1)	0.002	+14.8 (1.8)	+10.7 (2.8)	0.230
Δ T0-T3	+18.2 (2.2)	+11.4 (5.3)	0.184	+18.3 (2.3)	+14.7 (3.7)	0.424

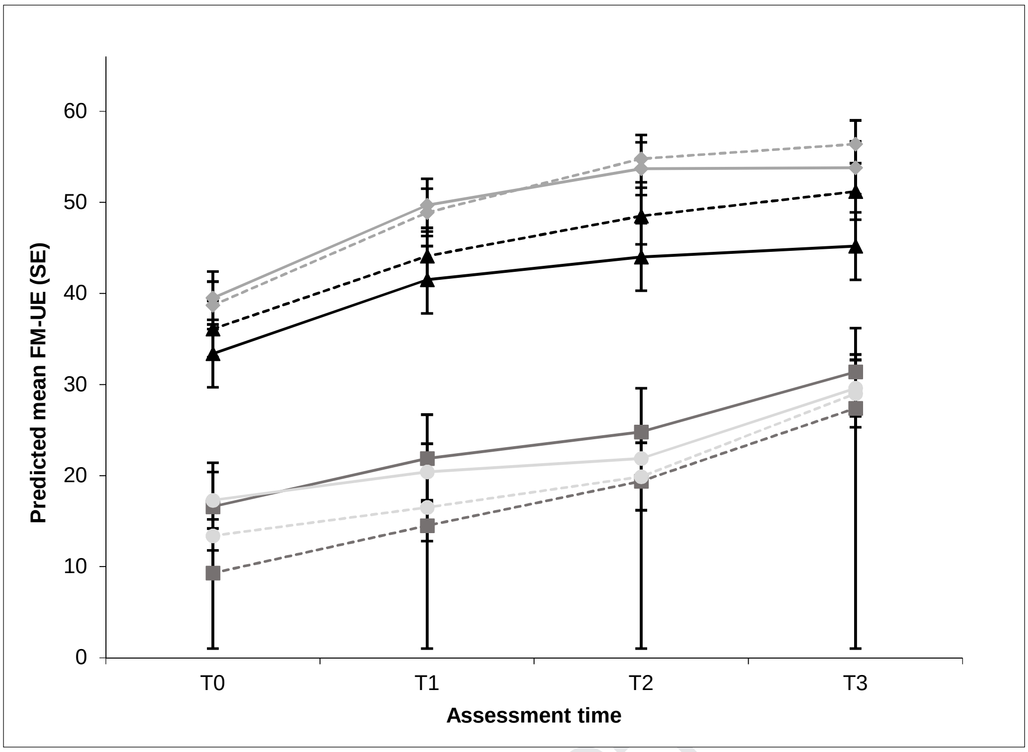
Abbreviations: RAT + FES, Robot Arm Training + Functional Electrical Stimulation; ICT, Intensive Conventional Therapy; T0, assessment before treatment; T1, assessment after 3 weeks of treatment; T2, assessment after the end of treatment; T3, assessment at 6 months follow-up; *p*, level of significance.

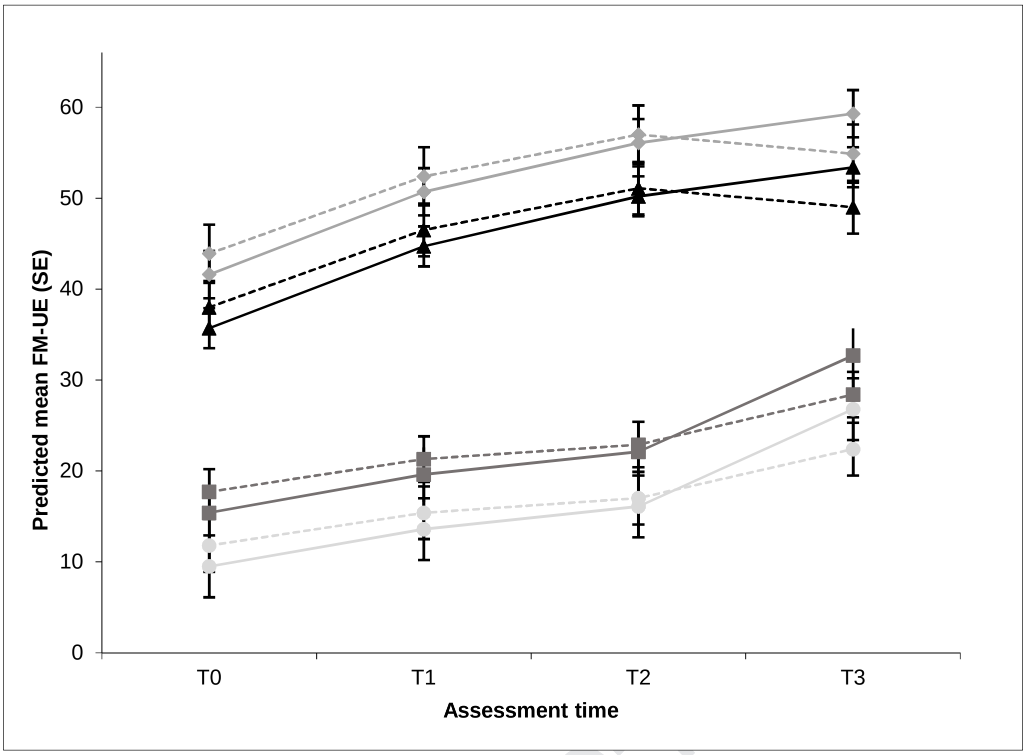
[a] > 21 points FM-UE; [b] ≤ 21 points FM-UE[26]


Assessed for eligibility (n=391)
Excluded (n=351)
- Did not meet inclusion criteria (n=341)
- Other reasons (n=10)
Randomization (n=40)
Allocated to RAT + FES (n=20)
- Received allocated intervention (n=19)
- Did not receive allocated intervention (n=1)
- Post-randomization drop-out (n=1)
Allocated to ICT (n=20)
- Received allocated intervention (n=19)
- Did not receive allocated intervention (n=1)
- Allocation error (n=1)
Loss to follow-up (n=6)
- Unable to return after hospital discharge (n=4)
- Medical complications during the 6 months follow-up (n=1)
Discontinued intervention (n=1)
- Medical complications unrelated to interventions (n=1)
Loss to follow-up (n=2)
- Unable to return after hospital discharge (n=2)
Discontinued intervention (n=0)
Analysed (n=19)
- Excluded from analysis (n=1)
Analysed (n=20)
- Excluded from analysis (n=0)



A)
Δ FM-UE (T0-T2)
Stroke onset (days)
B)
FM-UE (T3)
Stroke onset (days)
C)
Δ FM-UE (T0-T2)
FM-UE (T0)
D)
FM-UE (T3)
FM-UE (T0)


Predicted mean FM-UE (SE)
0
10
20
30
40
50
60
T0
T1
T2
T3
Assessment time


Predicted mean FM-UE (SE)
0
10
20
30
40
50
60
T0
T1
T2
T3
Assessment time